

Melatonin, sleep and circadian rhythms in critical care patients

Richard Stanley Bourne

Submitted in total fulfilment of the requirements of
the degree of Doctor of Philosophy

Academic Unit of Clinical Pharmacology

University of Sheffield

August 2008

Volume 1

Abstract

Critical care patients commonly experience sleep fragmentation, in which sleep quality is poor and distributed throughout the 24 hour cycle. This irregular sleep wake pattern is a form of circadian rhythm sleep disorder. The causes of sleep disturbances are multifactorial and contribute to patient morbidity. Conventional hypnotic treatment is often ineffective and, indeed, may cause delirium and reduced sleep quality.

Administration of exogenous melatonin has been shown to re-enforce circadian rhythm disorders and improve sleep in other patient groups.

An open evaluation of 5 mg oral melatonin was undertaken in a group of 12 critical care patients exhibiting sleep disturbances resistant to conventional hypnotics.

Melatonin significantly increased observed sleep quantity by night 3, compared to baseline.

An oral solution of melatonin was formulated to allow administration by enteral feeding tubes. It was shown to have a 1 year shelf life when refrigerated and protected from light.

A randomised controlled trial was undertaken in 24 critical care patients weaning from mechanical ventilation. Melatonin 10 mg orally increased nocturnal bispectral index sleep quantity over nights 3 and 4 compared to placebo. Agreement of the other sleep measurement techniques with the bispectral index was poor. Actigraphy was not a useful measure of sleep in critical care patients and nurse observation overestimated sleep quantity.

The clearance of melatonin appeared to be decreased in critical care patients compared to that in healthy subjects. Doses of 1-2 mg should be used in future critical care studies.

Acute administration of melatonin did not have a significant effect over placebo on rest-activity rhythms, which remained delayed, fragmented and reduced. Similar disturbances were present in plasma melatonin and cortisol rhythms, which were no longer phase locked.

Melatonin therapy may prove beneficial in the treatment of sleep and circadian rhythms in critical care patients, and further larger studies should be pursued.

Acknowledgements

I have been fortunate to have had the support and assistance of a number of people during the course of this thesis, to whom I wish to acknowledge my gratitude.

Firstly, to Professor David Edbrooke for taking me to the European Society of Intensive Care Medicine annual conference in 1999, and challenging me to undertake research into the care of the critically ill patient. I am very grateful to my research supervisors for their continuous support, advice and guidance over the whole research period. Dr Gary Mills and Professor Edbrooke who provided almost constant advice on my research development in our day to day working. Professor Geoff Tucker, who made significant contributions to my understanding of pharmacokinetics and helped mould this thesis into a more coherent work. He continued to provide prompt and constructive advice even after his retirement from the University of Sheffield.

Special thanks to Dr Cosetta Minelli who provided valuable statistical advice which greatly improved the presentation of the results. Her drive and enthusiasm for this work, most of which was conducted over the phone and by e-mail, provided great encouragement.

To my colleagues in Sheffield Teaching Hospitals who supported me throughout my research, including the time needed to undertake this work. Specifically to Mr John McLaughlin, for his high performance liquid chromatography expertise and the conduction of the melatonin oral solution stability assays. Mr Roger Brookes, for providing moral support, the facilities of the pharmacy manufacturing unit, and assistance in securing funding from the Pharmacy Department which allowed further thesis development. I am also grateful to Mrs Perm Wilson and her colleagues in Clinical Chemistry for allowing me to conduct the melatonin RIA within their

Department, and patiently answering my many questions. To Mr Neil Smith (Department of Clinical Chemistry), for undertaking the plasma cortisol assays. The critical care nursing staff who completed the nurse sleep assessments; in particular to those individuals who actively supported the research studies.

I appreciate the efficient and professional assistance provided throughout the development of this thesis by the University of Sheffield Health Services Librarians. I acknowledge the graphic design skills of Professor Milagros Figueroa-Ramos (University of California), which assisted with the presentation of sleep mechanisms, and her continued interest in the areas of sleep and delirium in critical care patients. To my parents for their unrelenting support and encouragement in everything I have done.

Most importantly to my wife Karen, without whose love and support I would not have been able to complete this work - thank you. To our children, Alexander and Jennifer, who have patiently put up with daddy's "home work". Hopefully we will now be able to spend a lot more time together.

Presentations and publications

Invited presentations

Thames Valley Critical Care Network “Weaning Event”. Oxford, England. June 2005.

Sedation monitoring techniques affecting weaning from mechanical ventilation.

British Association of Critical Care Nurses, 21st Annual Conference. Newcastle upon Tyne, England, September 2006.

Detection, prevention and treatment of delirium in critically ill patients.

Mid and South Trent Intensive Care Society “State of the Art” Meeting. Nottingham, England, September 2006.

The use of melatonin for night sedation on ICU.

Society of Critical Care Medicine, 36th Critical Care Congress. Orlando, Florida, USA, February 2007.

Drug therapy for sleep disruption in the critically ill.

Association of Teaching Hospital Chief Pharmacists. Sheffield, England, May 2007.

Research into melatonin in the critically ill.

Alzheimer’s Society and NHS South Central, “The Delirium Dilemma” meeting. Oxford, England, August 2007.

How do we prevent delirium?

Manchester Critical Care Network and Association of North West Intensive Care Units, “Delirium and Cognitive Impairment in Critical Care” meeting, Manchester, England, August 2007.

Guidelines on the detection, prevention and treatment of delirium.

European Delirium Association, 2nd Scientific Meeting, Limerick, Ireland, November, 2007.

Drug treatment of delirium - the evidence base.

Conference poster presentations

27th International Symposium on Intensive Care and Emergency Medicine. Brussels, Belgium. March 2007.

Bourne RS. Assessment of melatonin, cortisol and rest-activity rhythms in critically ill patients weaning from mechanical ventilation.

Critical Care 2007; **11** (Supplement 2): S71.

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Critical Care 2008; **12** (Supplement 2): S200.

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Intensive Care Medicine 2001; **27** (Supplement 2): S293

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Book chapters

Borthwick M, **Bourne RS.** Agitation and confusion. In Oxford Desk Reference—Critical Care. Eds Waltermann K, Soni, N & Rhodes, A. Oxford University Press, Oxford UK. (In press).

Abbreviations

6-SMT	6-sulfatoxymelatonin
dBA	A-weighted decibels
ABW	Actual body weight
APACHE II	Acute physiology and chronic health evaluation II
ARDS	Acute respiratory distress syndrome
ACTH	Adrenocortrophic hormone
ASPS	Advanced sleep phase syndrome
ALT	Alanine Transaminase
AUC	Area under the curve
AUC(0-24)	Area under the plasma concentration-time curve between 0 and 24 hours
AUC(0-Infinity)	Area under the plasma concentration-time curve between 0 and Infinity
AAS	Ascending arousal system
ASB	Assisted spontaneous breathing
ADHD	Attention deficit hyperactive disorder
F	Bioavailability
BIPAP	Biphasic positive airway pressure
BIS	Bispectral index
BMI	Body mass index
CNS	Central nervous system
Cl	Clearance
M10 Onset	Commencement of 10 hour period of most activity
L5 Onset	Commencement of 5 hour period of least activity
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CPAP	Continuous positive airway pressure
C/R	Controlled release
CRH	Corticotrophin releasing hormone
CYP1A2	Cytochrome P450 1A2
DSPS	Delayed sleep phase syndrome
DLMO	Dim light melatonin onset
D	Dose
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electro-oculogram
GABA	Gamma aminobutyric acid
GC-MS	Gas chromatography-mass spectroscopy
GM-CSF	Granuloctye macrophage-colony stimulating factor
G-CSF	Granulocyte-colony stimulating factor

HPLC-F	High performance liquid chromatography - fluorescence
6-SMT	6-sulfatoxymelatonin
HPLC-MS	High performance liquid chromatography-mass spectroscopy
HAD	Hospital anxiety and depression scale
IBW	Ideal body weight
ICU	Intensive care unit
IL	Interleukin
C_{max}	Maximum plasma concentration
MRT	Mean residence time
Mesor	Midline estimating statistic of rhythm
M/R	Modified release
NAT	N-acetyltransferase
NREM	Non-rapid eye movement
NNH	Number needed to harm
PVN	Paraventricular nucleus
%CV	Percent coefficient of variation
$C_{(08)}$	Plasma concentration at 0800 hours
$t_{1/2}$	Plasma half-life
PTSD	Post traumatic stress disorder
RIA	Radioimmunoassay
REM	Rapid eye movement
RHT	Retinohypothalamic tract
RCSQ	Richards-Campbell sleep questionnaire
SAS	Sedation agitation scale
SSRIs	Selective serotonin reuptake inhibitors
SQI	Signal quality index
SAHS	Sleep apnoea/ hypopnoea syndrome
SE	Sleep efficiency
SEI	Sleep efficiency index
SL	Sleep latency
SWS	Slow wave sleep
SCN	Suprachiasmatic nucleus
S/R	Sustained release
SIRS	Systemic inflammatory response syndrome
t_{max}	Time to maximum plasma/ serum concentration
TST	Total sleep time
TNF_{α}	Tumour necrosis factor alfa
VLPO	Ventrolateral preoptic nucleus
VSH	Verran/ Synder-Halpern Sleep Scale
VAS	Visual analogue scale
Vss	Volume of distribution at steady state

Table of Contents

ABSTRACT	II
ACKNOWLEDGEMENTS	IV
PRESENTATIONS AND PUBLICATIONS	VI
INVITED PRESENTATIONS	VI
CONFERENCE POSTER PRESENTATIONS	VI
CONFERENCE ORAL PRESENTATIONS	VII
JOURNAL PUBLICATIONS	VII
BOOK CHAPTERS	VII
ABBREVIATIONS	VIII
<u>1 INTRODUCTION</u>	<u>1</u>
INTRODUCTION	2
BACKGROUND	3
RESEARCH AIMS	3
KEY RESEARCH QUESTIONS	4
THESIS STRUCTURE	5
<u>2 BACKGROUND LITERATURE</u>	<u>6</u>
NORMAL SLEEP	7
NORMAL SLEEP ARCHITECTURE	7
NEUROPHYSIOLOGY OF SLEEP AND WAKEFULNESS	10
PHARMACOLOGY OF SLEEP AND WAKEFULNESS	12
THE SLEEP-WAKE CYCLE	15
SLEEP DISORDERS	16
MEASUREMENT OF SLEEP	18
Polysomnography	18
Actigraphy	19
Nurse assessment	20
Subjective assessment	20
Bispectral index	21
SLEEP IN THE CRITICALLY ILL	22
SLEEP ARCHITECTURE IN CRITICALLY ILL PATIENTS	22
CONSEQUENCES OF DISRUPTED SLEEP IN THE CRITICALLY ILL	23
Respiratory effects	23
Cardiovascular effects	25
Neurological effects	25
Immunological effects	27
Long-term effects	28
CAUSES OF SLEEP DISRUPTION	29
Environment	29
Noise	29
Light	31
Care activities	32
Acute illness	33
Respiratory considerations	33
Drugs used in intensive care	36
Sedative agents	37
Non-opioid analgesics	38

Cardiovascular Drugs	38
Gastric protectors and antiemetic agents	40
Anti-asthma therapy	40
Antimicrobial agents	41
Antidepressants	42
Anticonvulsants	42
Miscellaneous Drugs	43
Drug Withdrawal Reactions	44
TREATMENT OF SLEEP DISORDERS IN CRITICALLY ILL PATIENTS	49
SLEEP <i>VERSUS</i> SEDATION	49
NON-PHARMACOLOGICAL TREATMENT	49
PHARMACOLOGICAL TREATMENT	50
Benzodiazepines	53
Non-benzodiazepine GABA _A agonists	54
Propofol	55
Antidepressants	55
Tricyclics	55
Miscellaneous antidepressants	56
Chloral hydrate	57
Alcohol	57
Antipsychotics	58
Alpha-2 agonists	59
Antihistamines	59
Melatonin	60
MELATONIN	61
CIRCADIAN RHYTHM	61
PHARMACOLOGY	62
INFLUENCE OF LIGHT ON MELATONIN SECRETION	65
THE PHARMACOKINETICS OF EXOGENOUS MELATONIN	69
MELATONIN THERAPY FOR SLEEP DISORDERS	70
Jet lag	71
Night Shift	72
Insomnia	73
Other circadian rhythm disorders	75
THE POTENTIAL EFFECTS OF ACUTE ILLNESS ON MELATONIN	77
Intra and post-operative disturbances in melatonin turnover	77
Melatonin and sleep disruption in the critically ill patient	81
Melatonin in septic patients	82
Melatonin and delirium	84
ADVERSE EFFECTS	86
PRECAUTIONS	87
DRUG INTERACTIONS	88
DOSAGE AND ADMINISTRATION	91
CONCLUSIONS	93

3 PRELIMINARY EVALUATION OF MELATONIN THERAPY IN INTENSIVE CARE PATIENTS REFRACTORY TO CONVENTIONAL HYPNOTIC THERAPY

94

INTRODUCTION	95
MATERIALS AND METHODS	99
PATIENTS	100
STATISTICAL ANALYSIS	101
RESULTS	102

DISCUSSION	107
CONCLUSIONS	114
<u>4 FORMULATION OF AN ORAL MELATONIN SOLUTION</u>	<u>115</u>
INTRODUCTION	116
MATERIALS AND METHODS	119
MATERIALS	119
METHODS	120
Chemical stability	122
Statistical analysis	122
RESULTS	123
PH STABILITY	123
CHEMICAL STABILITY	123
DISCUSSION	126
CONCLUSIONS	130
<u>5 METHODS</u>	<u>131</u>
METHODOLOGICAL DEVELOPMENT	132
STUDY DESIGN	132
PATIENT SELECTION	132
STUDY ENDPOINTS	132
STUDY SIZE	135
MELATONIN DOSE	135
MEASUREMENT OF PLASMA MELATONIN	136
Melatonin RIA procedure	137
PHARMACOKINETIC ANALYSIS	137
CIRCADIAN RHYTHM ANALYSIS	138
Cortisol assay procedure	139
NEUROMUSCULAR STRENGTH ASSESSMENT	139
ENVIRONMENTAL CONTROL	139
PEER SUPPORT	140
FUNDING	141
ETHICS COMMITTEE APPROVAL	141
FINAL STUDY PROTOCOL	143
SCHEMA	143
STUDY OBJECTIVES	144
Primary end point	144
Secondary end points	144
PATIENT ELIGIBILITY CRITERIA	144
PATIENT RANDOMISATION	145
TREATMENT SCHEDULE	145
SLEEP MEASUREMENT	145
PLASMA SAMPLES	146
STATISTICAL ANALYSIS	146
Sleep and Circadian Rhythm analysis	146
Agreement	147

<u>6</u>	<u>MELATONIN THERAPY TO IMPROVE NOCTURNAL SLEEP IN CRITICALLY ILL PATIENTS</u>	149
INTRODUCTION		150
METHODS		152
RESULTS		153
DISCUSSION		158
CONCLUSIONS		167
<u>7</u>	<u>KINETICS OF ORAL MELATONIN IN CRITICAL CARE PATIENTS</u>	168
INTRODUCTION		169
METHODS		180
RESULTS		180
DISCUSSION		184
CONCLUSIONS		190
<u>8</u>	<u>SLEEP MEASUREMENT IN CRITICAL CARE PATIENTS. RESEARCH AND CLINICAL IMPLICATIONS</u>	191
INTRODUCTION		192
METHODS		193
LITERATURE REVIEW		193
RESULTS		194
LITERATURE REVIEW		194
AGREEMENT BETWEEN SLEEP MEASUREMENT TECHNIQUES IN THE MELATONIN INTERVENTION STUDY		194
OBJECTIVE MEASUREMENTS OF SLEEP		211
POLYSOMNOGRAPHY		211
BISPECTRAL INDEX		215
ACTIGRAPHY		217
SUBJECTIVE MEASUREMENTS OF SLEEP		219
Patient assessment		220
Verran/Synder-Halpern Sleep Scale		220
Richards-Campbell Sleep Questionnaire		220
Nurse assessment		222
METHODOLOGICAL PROBLEMS OF REVIEWED STUDIES		224
CONCLUSIONS		227
<u>9</u>	<u>MELATONIN, CORTISOL AND REST-ACTIVITY RHYTHMS IN CRITICALLY ILL PATIENTS</u>	228
INTRODUCTION		229
METHODS		231
RESULTS		232
CORTICOSTEROID EXPOSURE		232
EFFECT OF MELATONIN ON REST-ACTIVITY RHYTHMS		234
PLASMA MELATONIN RHYTHM ANALYSIS		237
PLASMA CORTISOL RHYTHM ANALYSIS		242
EFFECT OF MELATONIN ON PLASMA CORTISOL LEVELS		249

RELATIONSHIP BETWEEN PLASMA MELATONIN AND CORTISOL LEVELS	250
RELATIONSHIP BETWEEN PLASMA MELATONIN AND CORTISOL RHYTHMS AND REST- ACTIVITY RHYTHMS	251
DISCUSSION	252
CONCLUSIONS	262
<u>10 CONCLUSIONS AND SUGGESTIONS FOR FURTHER RESEARCH</u>	263
REFERENCES	271
APPENDICES	305
APPENDIX 1 GUIDELINES ON MELATONIN USE IN INTENSIVE CARE	305
APPENDIX 2 PRELIMINARY MELATONIN THERAPY EVALUATION FORM	307
APPENDIX 3 ENVIRONMENTAL DISTURBANCES LOG	308

Tables

TABLE 2-1 ELECTROENCEPHALOGRAM CHARACTERISTICS OF NON-RAPID EYE MOVEMENT AND RAPID EYE MOVEMENT SLEEP PHASES	9
TABLE 2-2 NEUROTRANSMITTER EFFECTS ON SLEEP AND WAKEFULNESS	13
TABLE 2-3 DRUGS COMMONLY USED IN ICU AND THEIR EFFECTS ON SLEEP ARCHITECTURE	48
TABLE 2-4 DRUGS WITH POTENTIAL TO AFFECT MELATONIN METABOLISM BY INHIBITION OR INDUCTION OF CYTOCHROME P450 1A2	89
TABLE 2-5 DRUGS KNOWN TO AFFECT MELATONIN SECRETION OR EXCRETION	90
TABLE 3-1 INTENSIVE CARE SOCIETY SEDATION SCORE	100
TABLE 3-2 PATIENT HYPNOTIC ADMINISTRATION PRIOR TO MELATONIN ADMINISTRATION	102
TABLE 3-3 NURSE OBSERVATION OF NOCTURNAL TOTAL SLEEP TIME AT BASELINE AND AFTER MELATONIN ADMINISTRATION	103
TABLE 3-4 DIFFERENCES IN OBSERVED TOTAL SLEEP TIME MEANS COMPARED TO BASELINE	103
TABLE 3-5 SUBJECTIVE NURSE ASSESSMENT OF BENEFIT NIGHT 1 COMPARED TO SUBSEQUENT NIGHTS	105
TABLE 3-6 NOCTURNAL INTENSIVE CARE SOCIETY SEDATION SCORE OVER THE STUDY PERIOD	105
TABLE 4-1 ROYAL HALLAMSHIRE HOSPITAL PHARMACY PRODUCTION WORKSHEET FOR A 0.5 MG/ ML ORAL MELATONIN SOLUTION	121
TABLE 4-2 PH OF 0.5 MG/ML ORAL MELATONIN SOLUTION OVER TIME	123
TABLE 4-3 STABILITY OF MELATONIN IN THE 0.5 MG/ ML SOLUTIONS	124
TABLE 6-1 BASELINE PATIENT CHARACTERISTICS	156
TABLE 6-2 EFFECT OF MELATONIN ON NOCTURNAL SLEEP EFFICIENCY ON NIGHTS 3 & 4, DETERMINED USING DIFFERENT OUTCOME MEASURES	157
TABLE 7-1 SUMMARY OF STUDIES REPORTING BLOOD MELATONIN CONCENTRATIONS AFTER ORAL DOSAGE (STUDIES IN ADULTS AND PUBLISHED IN ENGLISH)	179
TABLE 7-2 SUMMARY OF MELATONIN PHARMACOKINETIC DATA AFTER A 10 MG ORAL DOSE IN CRITICAL CARE PATIENTS (MEAN (SD))	181
TABLE 7-3 ASSOCIATIONS BETWEEN POTENTIAL CO-VARIATES AND MELATONIN EXPOSURE	182

TABLE 7-4 CORRELATIONS BETWEEN MARKERS OF MELATONIN EXPOSURE AND BIS MEASURES OF SLEEP	183
TABLE 7-5 ASSOCIATIONS BETWEEN MELATONIN ORAL CLEARANCE AND ADMINISTRATION OF DRUGS AFFECTING CYP1A2 ACTIVITY	183
TABLE 8-1 SUMMARY OF METHODS USED IN CRITICAL CARE FOR SLEEP MEASUREMENT	199
TABLE 8-2 POLYSOMNOGRAPHY STUDIES OF SLEEP IN CRITICAL CARE PATIENTS	204
TABLE 8-3 ACTIGRAPHY AND BIS STUDIES OF SLEEP IN CRITICAL CARE PATIENTS	205
TABLE 8-4 SUBJECTIVE STUDIES OF SLEEP IN CRITICAL CARE PATIENTS	207
TABLE 8-5 SUMMARY OF MISSING DATA FROM THE MELATONIN INTERVENTION STUDY	208
TABLE 9-1 PATIENT CORTICOSTEROID EXPOSURE	233
TABLE 9-2 REST-ACTIVITY ANALYSIS BY TREATMENT ALLOCATION	234
TABLE 9-3 REST-ACTIVITY ANALYSIS FOR ALL CRITICAL CARE PATIENTS	235
TABLE 9-4 COSINOR ANALYSIS OF PLASMA MELATONIN LEVELS	240
TABLE 9-5 COSINOR ANALYSIS OF INDIVIDUAL PATIENT PLASMA CORTISOL LEVELS	247
TABLE 9-6 COSINOR ANALYSIS OF PLASMA CORTISOL LEVELS	248
TABLE 9-7 EFFECT OF MELATONIN ON PLASMA CORTISOL AREA UNDER THE CONCENTRATION TIME CURVE FOR A 24 HOUR PERIOD	249
TABLE 9-8 COMPARISON OF MELATONIN AND CORTISOL ACROPHASES IN PLACEBO PATIENTS	250

Figures

FIGURE 2-1 HISTOGRAM REPRESENTING NOCTURNAL SLEEP STAGES IN A HEALTHY YOUNG ADULT	8
FIGURE 2-2 ASCENDING AROUSAL SYSTEM MAINTAINING WAKEFULNESS	11
FIGURE 2-3 VENTROLATERAL PREOPTIC-NUCLEUS MAINTAINING SLEEP	12
FIGURE 2-4 TWO PROCESS MODEL OF SLEEP REGULATION	15
FIGURE 2-5 PROPOSED APPROACH TO THE DRUG TREATMENT OF SLEEP DISORDERS IN CRITICALLY ILL PATIENTS	52
FIGURE 2-6 EFFECT OF AGE ON PLASMA MELATONIN VERSUS TIME	61
FIGURE 2-7 SYNTHESIS OF MELATONIN IN THE PINEAL GLAND	64
FIGURE 2-8 REGULATION OF MELATONIN SECRETION BY LIGHT	65
FIGURE 2-9 LIGHT PHASE RESPONSE CURVE	67
FIGURE 2-10 MELATONIN PHASE RESPONSE CURVE	71
FIGURE 3-1 PROPORTION OF NIGHTS IN WHICH NURSE PERCEPTION OF OBSERVED SLEEP QUALITY DURING MELATONIN ADMINISTRATION WAS RANKED AS “BETTER” THAN BASELINE HYPNOTIC TREATMENT	104
FIGURE 4-1 CHROMATOGRAM SHOWING THE SEPARATION OF MELATONIN FROM ACID DECOMPOSITION PRODUCTS AFTER AUTOCLAVING AT 121-124°C FOR 15 MIN IN 0.1M HYDROCHLORIC ACID	124
FIGURE 4-2 CHROMATOGRAM OF THE 0.05% W/V MELATONIN SOLUTION AFTER STORAGE AT 25°C FOR 450 DAYS	125
FIGURE 5-1 FINAL STUDY PROTOCOL	143
FIGURE 6-1 PATIENTS RECRUITMENT ANALYSIS	155
FIGURE 7-1 PLASMA MELATONIN CONCENTRATIONS (MEAN ± SD) AFTER ORAL ADMINISTRATION OF A 10 MG DOSE IN SOLUTION AT 2100 HOURS TO CRITICAL CARE PATIENTS	181
FIGURE 8-1 SCATTER PLOTS COMPARING THE RESULTS FROM FOUR DIFFERENT TECHNIQUES USED TO MEASURE NOCTURNAL SLEEP EFFICIENCY IN THE MELATONIN INTERVENTION STUDY	209
FIGURE 8-2 BLAND-ALTMAN PLOTS FOR THE FOUR DIFFERENT TECHNIQUES USED TO MEASURE NOCTURNAL SLEEP EFFICIENCY IN THE MELATONIN INTERVENTION STUDY	210
FIGURE 9-1 EXAMPLES OF REST-ACTIVITY ACTOGRAMS IN (A) HEALTHY VOLUNTEER AND CRITICAL CARE PATIENTS DEMONSTRATING A MODERATE (B) AND LIMITED (C) CIRCADIAN RHYTHM ACTIVITY VARIATION	236

FIGURE 9-2 FITS OF THE SINGLE COSINOR MODEL PLASMA MELATONIN CONCENTRATIONS IN INDIVIDUAL PATIENTS RECEIVING PLACEBO	239
FIGURE 9-3 FIT OF THE SINGLE COSINOR MODEL TO PLASMA MELATONIN CONCENTRATIONS IN ALL PATIENTS RECEIVING PLACEBO	239
FIGURE 9-4 PLASMA MELATONIN AREA UNDER THE CURVE FOR A 24 HOUR PERIOD IN ELDERLY CONTROLS [387] AND CRITICAL CARE PATIENTS	241
FIGURE 9-5 FITS OF THE SINGLE COSINOR MODEL TO PLASMA CORTISOL LEVELS IN INDIVIDUAL PATIENTS	245
FIGURE 9-6 FITS OF THE SINGLE COSINOR MODEL TO PLASMA CORTISOL LEVELS IN (A) PLACEBO PATIENTS, (B) MELATONIN PATIENTS AND (C) ALL PATIENTS	246
FIGURE 9-7 PLASMA CORTISOL AREA UNDER THE CURVE FOR A 24 HOUR PERIOD IN THE MELATONIN AND PLACEBO GROUPS	249

1 INTRODUCTION

Introduction

The use of sedatives in critical care is an every day occurrence. Medical, nursing and pharmacy staff of all grades working in this unique environment are experienced in the common indications, clinical and adverse effects of these agents. Almost as common are the remarks of nursing staff highlighting yet another patient who has not slept well last night. The general response to this plea is the prescription of a night-time sedative drug. In the case of an unsatisfactory response, then a larger dose or another sedative agent is added. This approach seems to work in some patients (*i.e.* they appear to be asleep for more of the night shift), but clearly does not help in all cases and, indeed, may complicate matters. In late 1999, whilst discussing one such patient I was asked about the potential value of melatonin supplementation in this scenario by one of the medical consultants. Dr David Edbrooke, a seasoned traveller who had recently supplemented his pre-flight whisky with melatonin to then discover that he arrived at his destination in a “blink of an eye”. Like any self respecting pharmacist, my initial reaction was to express my views that this area was the subject of over zealous reporting by the lay press, that there would be difficulties obtaining a pharmaceutical product and recommended that we just try some nocturnal amitriptyline instead. The patient received their additional sedative agent that night but, on reflection, the discussion prompted me to undertake an unexpected journey that was to dominate much of my subsequent waking life and which has resulted in this thesis.

Background

The primary role of intensive care is to provide organ support to acutely ill patients while attempts to diagnose and then treat the underlying condition(s) are undertaken. Assuming the patient is successfully resuscitated, stabilised and appropriate treatment commenced, organ support is eventually weaned, and survivors are subsequently discharged to a ward or intermediate care facility. However, this process underestimates important aspects of recovery. In recent years there has been a greater appreciation of the long term implications for survivors of critical illness requiring intensive care [1-3]. The consequences for patient morbidity, including quality of life and functional status, has even led to a plan by the National Institute of Clinical Excellence to guide specialised follow up services to meet the needs of patients. How we identify sub-groups of patients to receive this care and, indeed, how we actually reduce the actual requirement, remains poorly understood. Sleep during recovery from a critical illness is an example of an issue that may be regarded as of minor significance in the overall care of an intensive care patient. However, sleep disturbances and treatments may ultimately have affects on medium and longer term outcomes [4].

Research Aims

This research aims to review:

1. The current literature on normal sleep mechanisms.
2. How critical illness and intensive care therapy affects patients sleep.
3. The efficacy and safety of drug therapy routinely used to treat sleep disorders in intensive care patients.

4. The basis of relevant circadian rhythms, the role of melatonin, and the theoretical basis for melatonin therapy in critical care patients.

On this basis, studies are described that:

- I. Investigate the efficacy of melatonin on nocturnal sleep quantity in patients recovering from critical illness.
- II. Make recommendations for future oral melatonin dosing strategies in critical care patients.
- III. Investigate the degree of circadian rhythm disturbances in intensive care patients as well as the acute effects of melatonin administration.
- IV. Make recommendations for future research including guidance on alternative sleep measurement techniques for clinical and research use.

Key Research Questions

1. What is the theoretical basis for melatonin therapy in patients recovering from critical illness?
2. What oral melatonin product can be used to dose intensive care patients?
3. Does melatonin improve sleep quantity and quality in intensive care patients?
4. How does critical illness affect the kinetics of melatonin and what dose should be recommended in future studies?
5. How should sleep be measured in intensive care patients, both in clinical practice and research studies?
6. Do patients recovering from critical illness demonstrate disturbed circadian rhythms, and does acute melatonin therapy improve rhythms?
7. Do plasma melatonin and cortisol maintain their phase relationship in critical illness?

Thesis Structure

Chapter 2 describes the background literature on the problem of sleep disturbances in critical care patients, mechanisms, potential interventions and adverse effects including the relationship with delirium. It also introduces the basis of circadian rhythm disturbances, the importance of melatonin and the application of melatonin therapy. In Chapter 3 a description is given of a service evaluation designed to examine if there was any merit in the use of oral melatonin to aid sleep in intensive care patients. The development and stability of a melatonin oral solution is described in Chapter 4. Chapter 5 develops what was learnt in the preliminary evaluation and background literature review to describe the methods used in a randomised control trial of melatonin in patients recovering from critical illness. Chapter 6 evaluates the results of melatonin therapy on nocturnal sleep quantity and Chapter 7 describes the kinetics of melatonin in the study subjects. Chapter 8 comments on the degree of agreement between some of the measures of nocturnal sleep, and makes recommendations for clinical application and research studies. Chapter 9 discusses the circadian rhythm disturbances found in critical care patients, including the relationship between melatonin and cortisol. Chapter 10 presents the final conclusions, explores the limitations of the research, the challenges of studying sleep in critical care patients and makes recommendations for further research.

2 BACKGROUND LITERATURE

Normal Sleep

“Sleep is a reversible behavioural state of perception disengagement from and unresponsiveness to the environment” [5]. Early concepts of sleep regarded it as a passive process (*i.e.* a cessation of wakefulness), whilst modern sleep research has shown that sleep is a dynamic process that requires the activity of elaborate mechanisms involving numerous areas of the brain. To date, the complete mechanism of sleep regulation and its importance to human health has not been fully deciphered. However, the intensity of sleep after waking is proportional to the duration of wakefulness, which emphasises the necessity of recovery during sleep. The proposed functions of sleep are biochemical (metabolic rate slows during sleep); physiological (positive effects on the immune system); neurological (neurodevelopment, memory), psychological (memory consolidation, creative mental activity, problem solving capabilities, emotions) and social.

Normal sleep architecture

Sleep occurs in two distinct phases, involving rapid eye movement (REM) and non-rapid eye movement (NREM). NREM sleep comprises four subdivisions (1-4) with increasing sleep depth. The more restful sleep of stages 3 and 4 represents slow wave sleep (SWS). REM is also a restful period of sleep but has a lower threshold for awakening than SWS. Dreaming normally occurs during periods of REM sleep. Normal sleep architecture is described by a continuous cycle during the night between NREM and REM sleep; the cycle lasts approximately 90 minutes (Figure 2-1). REM periods of the sleep cycle become more prolonged the further into the total sleep episode.

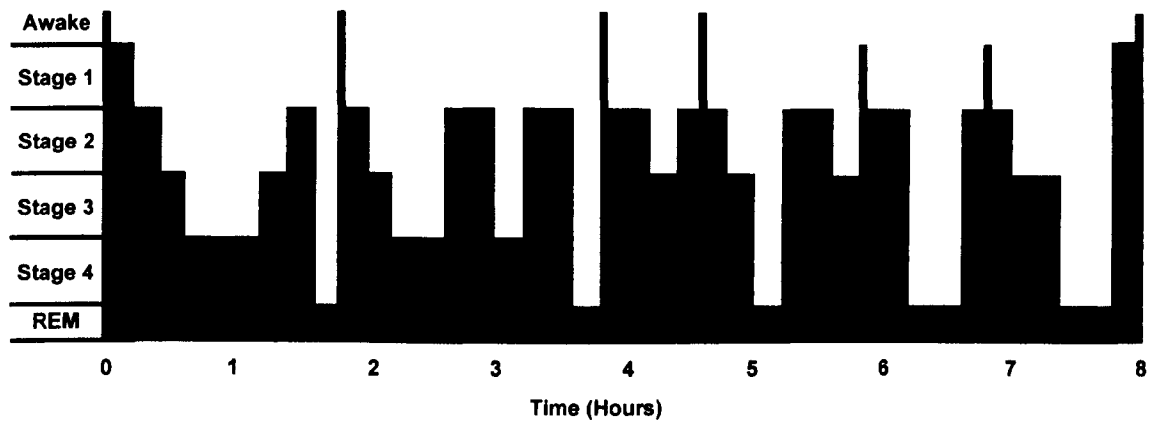


Figure 2-1 Histogram representing nocturnal sleep stages in a healthy young adult
 REM: Rapid Eye Movement

The NREM sleep stage is characterised by the frequency and amplitude of the electroencephalogram (EEG), the presence of sleep spindles and K-complexes in combination with electro-oculogram (EOG) and electromyogram (EMG) patterns. In REM sleep desynchronised EEG frequencies with loss of EMG and characteristic rapid eye movements emphasise the intense cerebral cortical activity that occurs during this sleep phase (Table 2-1).

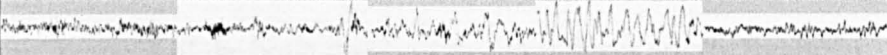
Characteristics	Sleep Stages			
	NREM			REM
	Stage 1	Stage 2	SWS	
EEG				
% TST	2-5%	45- 55%	10-15%	20-25%
Wave	Low voltage. Mixed frequency activity. Alpha waves.	Gradual high voltage of slow wave activity. Intermittent “sleep spindles” and “K-complexes”.	High voltage slow waves. Delta waves. Delta activity: 20-50% (Stage 3); >50% (Stage 4).	Low-voltage amplitude. High frequency. Sawtooth wave. Slow alpha activity.

Table 2-1 Electroencephalogram characteristics of Non-Rapid Eye Movement and Rapid Eye Movement Sleep Phases

EEG: Electroencephalogram; TST: Total Sleep Time; NREM: Non-Rapid Eye Movement Sleep; SWS: Slow Wave Sleep; REM: Rapid Eye Movement Sleep
 (Adapted from MI Figueroa-Ramos with permission)

Neurophysiology of sleep and wakefulness

Within a 24 hour period, a healthy individual cycles wakefulness, NREM sleep and REM sleep. Recent work has consolidated our understanding of the sleep and wakefulness process. Regions of the brain involved in wakefulness are the forebrain, reticular formation, thalamus and hypothalamus [6]. The ascending arousal system (AAS) originates from the upper brain stem and projects to the basal forebrain and thalamus [7]. Cortical arousal results from two pathways, namely a dorsal route through the thalamus and a ventral route through the hypothalamus and basal forebrain. This interaction between the ventrolateral preoptic nucleus (VLPO) and components of the arousal systems has been demonstrated to be mutually inhibitory, and has been compared to an electronic “flip-flop” switch [7] (Figure 2-2). State dissociation may become more prominent if one side of the switch becomes weakened and, therefore, less able to resist the dominance of the other [7].

The hypothalamus and brain stem are closely involved with the regulation of sleep [5]. Within the hypothalamus the suprachiasmatic nucleus, lateral hypothalamus, VLPO, tuberomammillary nucleus and pineal gland help to orchestrate sleep. The VLPO neurons are primarily active during sleep [7] (Figure 2-3).

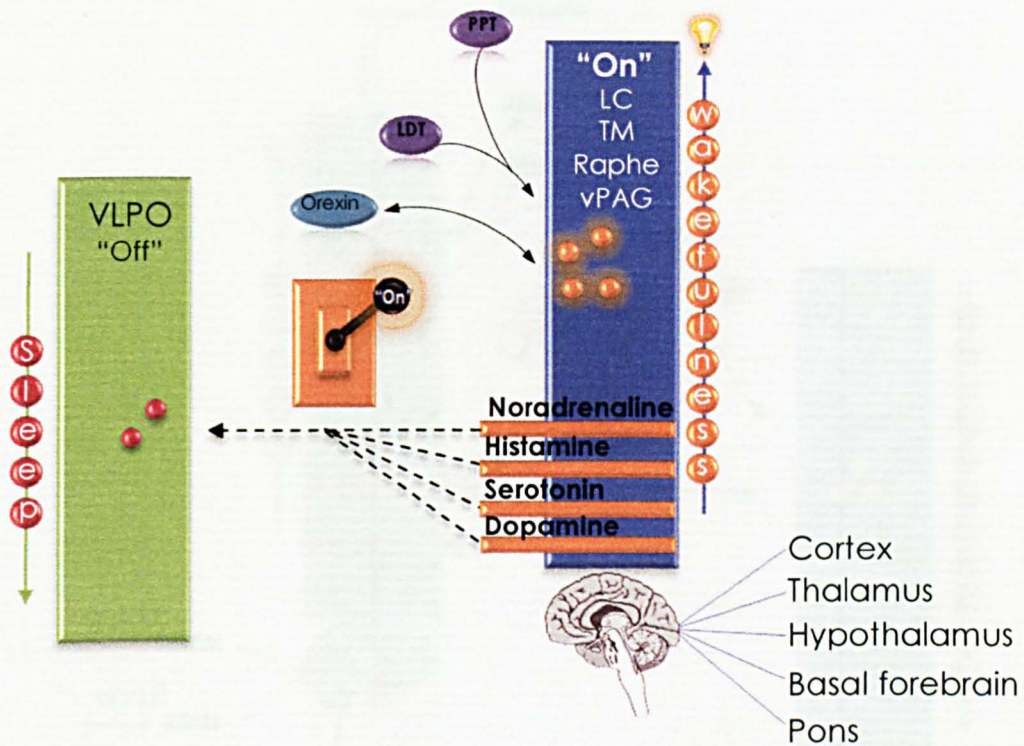


Figure 2-2 Ascending arousal system maintaining wakefulness

VLPO: Ventrolateral Preoptic Nucleus; PPT: Pedunculopontine; LDT: Laterodorsal Tegmental; LC: Locus Coeruleus; TM: Tuberomammillary Nucleus; vPAG: ventrolateral periaqueductal grey; Inhibition: ----; Activation: —

(Adapted from MI Figueroa-Ramos with permission)

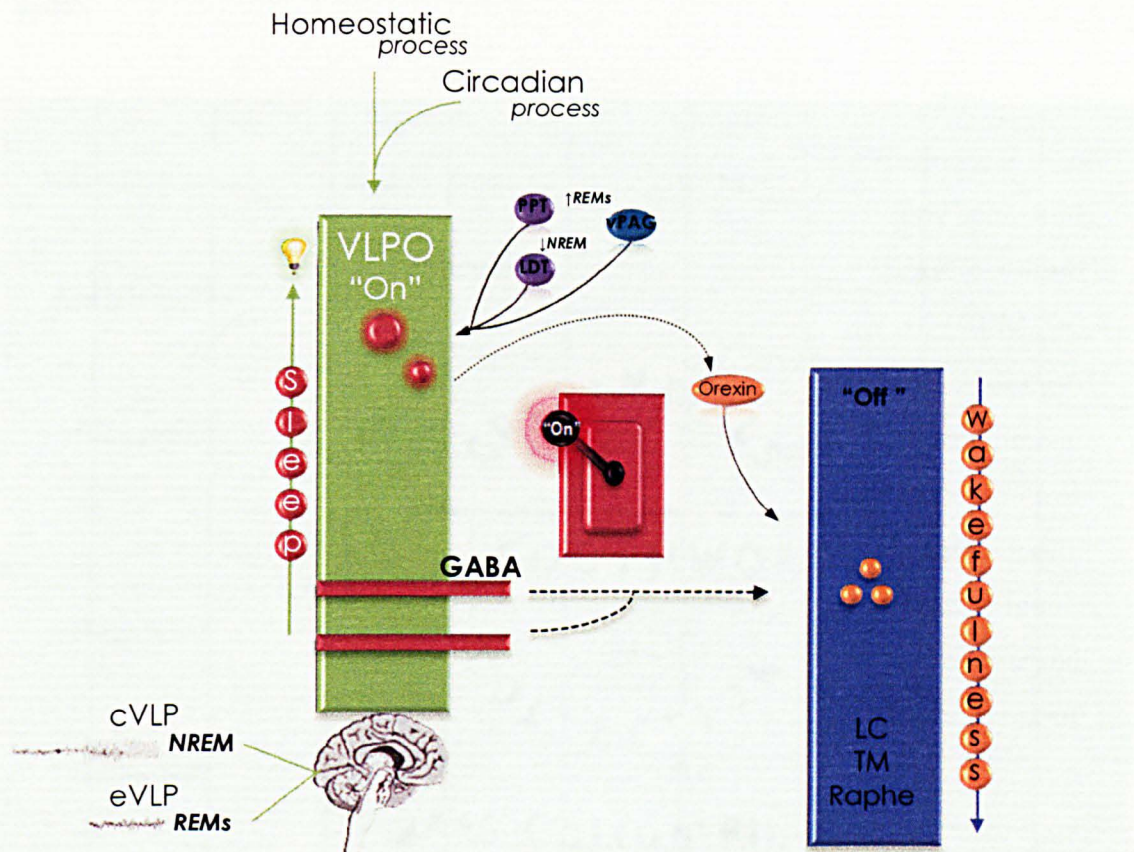


Figure 2-3 Ventrolateral preoptic nucleus maintaining sleep

VLPO: Ventrolateral Preoptic Nucleus; LC: Locus Coeruleus; TM: Tuberomammillary Nucleus; Raphe: Dorsal Raphe Nucleus; PPT: Pedunculopontine; LDT: Laterodorsal Tegmental; cVLP: VLPO cluster ; eVLP: VLPO extended; vPAG: ventrolateral periaqueductal grey; REM: Rapid Eye Movement; NREM: Non-Rapid Eye Movement; Inhibition: ----; Activation: —
 (Adapted from MI Figueroa-Ramos with permission)

Pharmacology of sleep and wakefulness

The sleep-wake cycle and sleep stages are regulated by a complex interplay of neurotransmitters including noradrenaline, serotonin, acetylcholine, dopamine, histamine and gamma aminobutyric acid [8] (Table 2-2). The activity of neurotransmitters themselves is affected by cotransmitters which may alter the sensitivity of the receptor and, *via* neuromodulation, also affect transmitter synthesis and release. Other sleep factors such as hypnotoxins, somnogens and sleep regulatory

substances also interact with intrinsic neurotransmitter control of the sleep-wake cycle.

	Promotes	Inhibits	Other
Noradrenaline	Wakefulness	REM	Influences mood and behaviour
Acetylcholine	Wakefulness REM		Motor inhibition in REM
Serotonin	Wakefulness	REM	Influences mood, behaviour and motor control
Dopamine			Influences thoughts, emotions, behaviour and motor control
Histamine	Wakefulness	REM	
GABA	NREM	REM	

Table 2-2 Neurotransmitter effects on sleep and wakefulness

REM: Rapid Eye Movement; GABA: Gamma Aminobutyric Acid; NREM: Non-Rapid Eye Movement Sleep

(Adapted from Shneerson [9])

Noradrenaline is involved in controlling wakefulness and in the inhibition of REM sleep. The cholinergic system is also involved in the generation of REM sleep and sleep-wake regulation. The role of serotonin is complex but overall it appears to promote wakefulness [9]. 5HT_{1A} and 5HT_{2A} have the most impact on sleep and inhibition of the latter receptors promotes REM sleep. The effects of dopamine (D₂) agonists and antagonists on sleep and wakefulness are affected by neuromodulation [9]. Dopamine promotes alertness and disturbances in dopamine activity induce diurnal sleep. Histamine has a role in the control of wakefulness and limitation of REM sleep. Gamma aminobutyric acid (GABA) is an important inhibitory

neurotransmitter; its release within the VLPO inhibits aminergic induced wakefulness [9].

Many other amino acids, hormones, cytokines and prostaglandins are also involved in the regulation of sleep and wakefulness. Adenosine is probably an important sleep regulatory substance, and accumulation of this purine nucleoside accounts for some of the homeostatic sleep drive. Pituitary hormones may be of functional significance in the maintenance and quality of sleep [8]. The neurohormone melatonin is also important in regulating the sleep-wake cycle in humans [10]. Prostaglandin D₂ (PGD₂) induces NREM and REM sleep while PGE₂ promotes wakefulness.

Cytokines may also act as sleep factors. Interleukin-1 (IL-1) promotes NREM sleep and Tumour Necrosis Factor alfa (TNF_α) increases SWS sleep while reducing REM sleep [11, 12]. Raised IL-6 plasma concentrations are associated with reduced sleep quality [13]. Abrupt changes in the levels of these cytokines during a systemic inflammatory response syndrome (SIRS) or sepsis will, therefore, have adverse effects on sleep regulation [14]. Orexins (hypocretins) are important in maintaining wakefulness and disturbances in their secretion occur in some disorders such as the obstructive sleep apnoea syndrome [15].

Clearly, as long as they penetrate the blood brain barrier, drugs that have an effect on neurotransmitters and hormones may influence normal sleep architecture. Sleep stage classification and spectrum analysis using polysomnography (continuous polygraph of multiple physiological variables during sleep) can provide detailed information on the adverse effects of drugs on sleep [16]. However, few data are available, especially in relation to critically ill patients.

The sleep-wake cycle

The sleep-wake cycle is governed by two distinct types of process – homeostatic (“sleep drive”) and circadian [17]. During wakefulness accumulation of sleep factors (e.g. adenosine) increases the propensity for sleep while the circadian process counteracts this drive (preventing sleep intrusion) until a threshold when the “sleep gate” is opened. The latter probably follows the surge in plasma melatonin concentration. The homeostatic drive during sleep is eventually depleted as the circadian drive for wakefulness returns (low plasma melatonin levels) and awakening occurs.

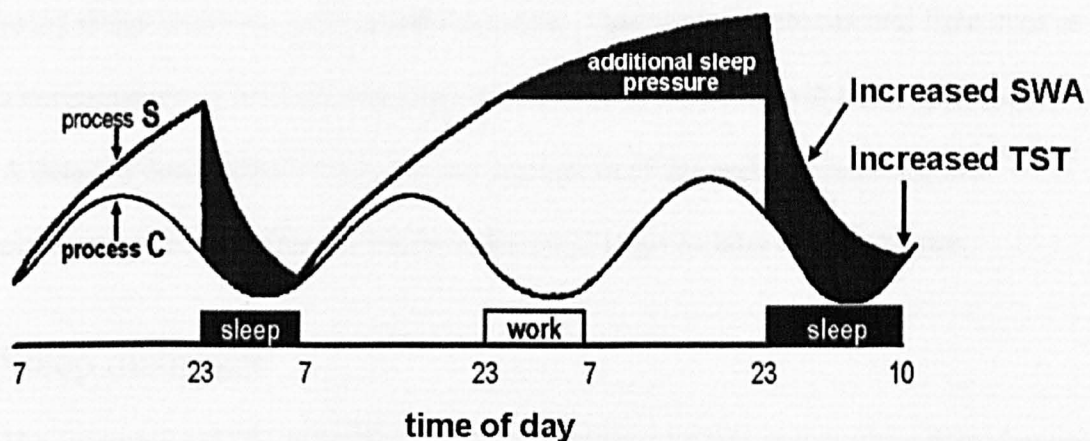


Figure 2-4 Two process model of sleep regulation

Sleep drive is a function of homeostatic and circadian processes. The second 24 hour period represents a period of sleep deprivation (due to nocturnal work) with subsequent accumulation of sleep drive which eventually results in increased recovery sleep [17].

Process S: Homeostatic process; Process C: Circadian process; SWA: Slow wave activity; TST: Total sleep time

The sleep-wake cycle is the most visible human circadian rhythm. The biological clock is entrained to a 24-hour rhythmicity by retinal transmission of the effect of environmental light. Light is the most important zeitgeber (time cue) in the entrainment of the biological clock.

Disorders of the sleep-wake cycle occur in the form of advanced sleep phase syndrome (ASPS), delayed sleep phase syndrome (DSPS) and irregular sleep-wake rhythm. International travel (jet lag) and the demands of shift work also affect the sleep-wake cycle.

Drugs have the potential to affect the timing of the biological clock by stimulation or inhibition of the neural pathway of the suprachiasmatic nucleus (SCN). Thus, those that are capable of crossing the blood brain barrier have the potential to phase advance or delay the biological clock depending on the individual receptor type they interact with and whether they are agonists or antagonists. Clearly, critically ill patients will have acute changes in endogenous neurotransmitters and are exposed to many drugs under stressful conditions. Also, changes in environmental light cues as a consequence of institutionalisation in the critical care area will have an influence. A detailed description of the role and regulation of the endogenous zeitgeber melatonin with regard to the sleep-wake cycle is given later in this chapter.

Sleep disorders

The International Classification of Sleep Disorders (2005) groups sleep disturbances into four categories [18]. These are dyssomnias, parasomnias, sleep disorders associated with mental, neurologic or other medical disorders and proposed sleep disorders. Dyssomnias are disorders that affect the initiation or, maintenance of sleep, and include insomnia, which is one of the most common symptoms of a sleep disorder encountered in general practice. Insomnia is characterised by difficulty in falling asleep (increased sleep latency) and/ or difficulty in maintaining sleep and/ or early awakening. Although insomnia is often an acute problem associated with a trigger such as stress, it may become chronic. Insomniacs frequently experience increased autonomic activity either at night, in anticipation of problematic sleep, or

during sleep itself. This autonomic activity is responsible for increases in blood pressure and heart rate, muscle tension and peripheral vasoconstriction.

The parasomnias are disorders that intrude into the sleep process and are not disorders of sleep and wakefulness, as such. They are disorders of arousal (or partial arousal) or sleep transition disturbances that occur during sleep. Parasomnias usually associated with REM sleep include nightmares and REM Sleep Behavioural Disorders. Patients recovering from critical illness are particularly susceptible to REM rebound when potent REM suppressing drugs such as opioids are discontinued acutely. REM rebound is characterised by hypertension, tachycardia, hypoxia, hypoventilation, hypopnea and nightmares.

Sleep disorders associated with mental, neurologic and other medical disorders are those where intercurrent illness disrupts the sleep-wake cycle. In critically ill patients, sleep disturbances are routinely listed as a precipitating factor for developing delirium. However, it may well be that in many patients, these sleep disturbances are actually an early symptom of delirium itself [19]. In particular, some patients may develop state dissociation disorders manifesting as hallucinations and, in the most extreme form, as REM Sleep Behavioural Disorders [20].

Of the proposed sleep disorders, terrifying hypnagogic hallucinations may pose the greatest problem to critical care patients. Hallucinations can also occur in the transition from wakefulness into NREM sleep (hypnagogic) and from NREM sleep to wakefulness (hypnopompic). Critical care patients may be particularly vulnerable to hypnagogic and hypnopompic hallucinations, [20] which present a form of state dissociation [21, 22]. Sleep disorders in the critically ill patient may therefore share some of the symptoms of delirium.

Excessive daytime sleepiness occurs in the form of narcolepsy, hypersomnia and sleep apnoea. In critically ill patients sleep apnoea is common. This is because many postoperative patients with sleep apnoea secondary to opioid-induced apnoea and hypoxia are referred to critical care areas. Additionally, critically ill patients with congestive heart failure or chronic obstructive pulmonary disease may develop Cheyne-Stokes respiration and sleep apnoeas during weaning from mechanical ventilation. Patients with sleep apnoeas may require prolonged continuous positive airway pressure ventilatory support.

Measurement of sleep

Sleep quantity has been measured by a variety of techniques, of which polysomnography is regarded as the gold standard.

Polysomnography

Polysomnography is the only method of sleep measurement that is capable of identifying individual sleep stages (sleep quality). It involves electroencephalogram (EEG), electro-oculogram (EOG) and electromyogram (EMG) recordings that are especially difficult to make in the critical care environment.

Because critically ill patients often become delirious, removal of one or more of the electrodes during recording is a significant risk. This and other issues relating to the cost of investing in the necessary equipment and skilled staff has led to the adaptation of other methods of assessing sleep in critical care. In a review of critical care sleep studies, only 25% used polysomnography continuously for 24 hours or more [23].

Actigraphy

An actigraph is a small wristwatch device that is capable of both sensing and storing information on movement. An accelerometer detects movement in two or three axes, translating this into digital counts during pre-defined epoch periods. The epoch length is the period of time over which the actigraphy data are averaged. The actigraph is capable of collecting data over extended periods before data is downloaded into a personal computer. Computer software based on validated algorithms translates the movement data into sleep-wake cycles, which can then be analysed further.

Actigraphy has advantages over polysomnography in the critical care setting relating to robustness, capability of monitoring continuously over extended periods and automated analysis. It has been shown to be very sensitive for the recording of Total Sleep Time (TST), Sleep Latency ((SL), time to fall asleep) and Sleep Efficiency ((SE) (total nocturnal sleep time expressed as a ratio/ percentage of time available for sleep), but tends to overestimate these parameters compared to polysomnography [24]. As actigraphy technology and algorithms have improved it has gained a greater acceptance. These improvements were reviewed [25] and led the American Academy of Sleep Medicine to outline practice parameters for the use of actigraphy [26]. In summary, the recommendation was that, while actigraphy should not be used routinely to evaluate sleep disorders, it may be used in the 'assessment of sleep variability, measurement of treatment effects, and detection of sleep phase alterations in insomnia secondary to circadian rhythm disturbance' [26].

However, in critical care patients, who are especially prone to neuromuscular problems, a measurement technique that relies on movement to interpret sleep-wake

patterns may be compromised. Indeed, actigraphy has never been validated against polysomnography in these patients.

Nurse assessment

It is usually the nursing staff from the night shift who identify patients who have not appeared to sleep. In local critical care practice they record whether the patient was asleep or awake on an hourly basis. Hypnotic therapy is often commenced on the basis of the sleep assessment record and the nursing staff recommendation. The accuracy of this form of sleep quantity assessment is questionable and it seems that TST is overestimated when compared to the findings of polysomnography [27]. On the other hand, according to Edwards, [28] nurses were able to assess a patient's sleep or wake state correctly 80% of the time compared to polysomnography . Over the course of a night shift, the nurse probably collects an impression of the patient's overall sleep during the period, which is not appropriate as a research method of sleep quantity, but is useful clinically.

Subjective assessment

The use of sleep diaries in critically ill patients is obviously limited by the mental and physical ability of the patient to record their experience, and their use in this context has never been widely developed.

The Richards-Campbell Sleep Questionnaire (RCSQ) comprises 5 visual analogue scales (VAS) covering the sleep domains of depth, latency, awakenings, percent time awake and quality of sleep [29]. A moderate correlation has been shown between the polysomnography sleep efficiency index (5 hours each night) in 70 critically ill men and the RCSQ.

The RCSQ has been used by nurses to assess the sleep of critically ill patients unable to report their own subjective sleep efficiency [30]. However, only about half of the patients studied were able to complete the questionnaire.

Bispectral index

The BIS is a processed EEG technique which digitises raw EEG data and rejects artefacts before translating it into a numerical range (0-100) based on a complex algorithm. A BIS score of zero reflects an isoelectric EEG and one of 100 a fully awake individual. BIS has been compared to polysomnography in 10 patients being investigated for sleep apnoea/ hypopnoea syndrome (SAHS) [31]. BIS scores fell during periods of sleep although there was considerable overlap between BIS values recorded for the various sleep stages. The BIS value increased during periods of patient arousal.

BIS has been used successfully to detect the loss of consciousness occurring at the onset of natural sleep in healthy volunteers [32]. None of the subjects were awake when BIS values were less than eighty and all were conscious at values greater than 92.

The ease of application of the BIS sensor and the simple scoring output are advantages that should be weighed against limitations in identifying sleep stages and a lack of validation against polysomnography in critical care patients.

Sleep in the critically ill

Sleep disturbances are common in critical care patients. The importance of this should not be underestimated as patients report sleep disturbance as one of the most stressful components of an intensive care admission [33].

Sleep architecture in critically ill patients

Recent reviews, [23, 34] have identified numerous studies of the effect of critical illness on sleep architecture. Of these studies, only seven used continuous polysomnography for more than 24 hours. There is conflicting evidence as to whether the patients suffer from sleep deprivation. Some studies show a reduced TST, [27, 35] while others found normal TST over the 24 hours. [36, 37] However, more than half of the TST may occur during the day [35, 36]. Therefore, patients have frequent sleep episodes throughout the 24 hour period that, at least according to some studies, accumulate to being equivalent to the normal nocturnal sleep TST. This constitutes an irregular sleep-wake rhythm sleep disorder [18]. In fact, the patients suffer from sleep fragmentation, in which they have frequent arousals and awakenings, [35, 36, 38] comparable to that observed in sleep apnoea patients [23]. It is, therefore, not unexpected that critically ill patients will experience a disrupted sleep-wake cycle as a direct result of the frequent arousals and awakenings. TST itself may be less important than the ability of the patient to achieve continuous, deeper and more restorative periods of sleep.

Critically ill patients demonstrate greatly reduced SWS and REM sleep percentages compared to healthy individuals [27, 35, 36]. The percentage of REM sleep has been reported to be approximately 5% of TST in critically ill patients compared to the normal 25% [23]. Importantly, patients with suppressed REM sleep are at risk of developing REM rebound at some stage during their recovery. There is an increase in

NREM Stage 1 sleep, although this is of no value in terms of restorative capability [27, 35, 36].

Both homeostatic and circadian processes of sleep regulation are required for optimum sleep to occur. Attempts to improve the sleep continuity of critically ill patients must also consider the effects on the sleep-wake cycle, which it is important to try to restore [39].

Consequences of disrupted sleep in the critically ill

Sleep disruption has adverse consequences that are especially important in critically ill patients. It is still debatable whether these patients actually suffer from sleep deprivation, as opposed to sleep fragmentation. Much more is known about the adverse effects of sleep deprivation. It remains unknown whether sleep continuity, or sleep quantity is more important with regard to the recuperative function of sleep [40].

Respiratory effects

Sleep fragmentation, similar to that exhibited by critically ill patients, has been shown to cause sleep related breathing abnormalities [41, 42]. Sleep fragmentation more than sleep deprivation produced upper airway collapse associated with a significant increase in the apnoea-hypopnoea index. This suggests that critically ill patients without a diagnosis of sleep-apnoea may show an increased tendency for apnoea as a direct result of sleep fragmentation. Obese patients or those known to be snorers, may be particularly at risk of the effects of sleep fragmentation when recovering from critical illness.

Human volunteers who were deprived of specific SWS or REM sleep stages showed a rebound increase in REM sleep on the subsequent night [43]. Average ventilation

was not altered during wakefulness in either group. However, the increased REM periods were associated with reduced ventilatory responses to both hypoxia and hypercapnia and an increase in the frequency of long episodes of decremented breaths. The latter may be particularly important in a high-risk group of known snorers and/ or obese critically ill patients who subsequently may develop apnoeas. REM sleep rebound may be caused by a variety of drugs and procedures, including anaesthesia [44]. Efforts to minimise REM sleep disruption and, therefore, to reduce the risk of REM rebound will minimise the risk of respiratory malfunction.

Further studies have reported that sleep deprivation reduces the ventilatory response to hypoxia and hypercapnia as a consequence of reduced chemoreceptor function [45-48]. Males appear to demonstrate a greater reduction in ventilatory response to hypercapnia during sleep stages than females [48]. However, a recent study found that sleep deprivation did not decrease the ventilatory response to hypercapnia [49]. Furthermore, all studies tested the response to sleep deprivation in healthy volunteers, [43, 45-49] and therefore, the effects of acute illness on ventilatory response remain unknown. Ultimately the type of sleep fragmentation, duration of deprivation and individual patient risk factors may determine the importance of sleep fragmentation in terms of hypercapnic response. This is an important issue, as critically ill patients who demonstrate a reduced chemoreceptor response are less capable of coping with withdrawal of mechanical ventilation [50].

Critical care patients discharged to the ward are still at risk of sleep related breathing disturbances. Patients who had received prolonged mechanical ventilation on an intensive care unit (ICU) were subsequently found to have significant nocturnal sleep-related breathing disorders on the ward [51]. Thirteen of the 15 patients studied had oxygen desaturation ($\text{SaO}_2 < 90\%$ for > 2 hours) and 11 had a raised apnoea-

hypopnoea index. The effect of sleep fragmentation on respiratory function may not only delay weaning from mechanical ventilation and hence length of ICU stay, it may also affect morbidity on discharge and increase the risk of readmission to ICU. This has important resource and cost implications with regard to the provision of ICU facilities.

Cardiovascular effects

Evidence that sleep disruption during critical illness is a direct cause of cardiovascular morbidity or mortality is lacking. The respiratory effects described above, are expected to increase demands on the cardiovascular system. Certainly critically ill patients who are aroused or awakened from sleep often have hypertensive episodes as a consequence of transiently increased sympathetic activity. Patients who have had suppression of their REM sleep may experience REM rebound as their acute illness resolves and/ or REM suppressing medication such as opioids are discontinued [52]. REM rebound augments the cardiovascular response that normally occurs during the REM sleep phase. This has the potential to cause tachycardia and hypertension in vulnerable patients. REM rebound also causes apnoeas and hypoxia, the cardio-respiratory consequences are important in this vulnerable patient group.

Neurological effects

Sleep disturbance is often considered to be a risk factor for 'ICU psychosis'. 'ICU psychosis' is one of the many misnomers for the acute confusional state that occurs in critically ill patients, and is more appropriately described as delirium [53]. The evidence that sleep disturbances are a cause of delirium in the intensive care unit is

limited and has recently been questioned [53]. Delirium itself is associated with a circadian rhythm abnormality which translates into an irregular sleep-wake rhythm. Delirium has many confirmed risk and precipitating factors such as high exposure to antimuscarinic drugs [54]. Tricyclic antidepressants and antihistamines, with significant antimuscarinic activity, are often used in critical care patients to aid sleep. Disruption of the sleep-wake cycle itself may be particularly important in the development/ pathophysiology of delirium. Nuttall *et al*, [55] reviewed the charts of intensive care patients to examine the relationship between the lack of circadian rhythm and the incidence of delirium. The nadirs of urine output and temperature were used as markers of circadian rhythm. However, no relationship was found between disrupted circadian rhythm and delirium. Some aspects of this study were questioned in an accompanying editorial [56]. In critically ill patients, urine output and temperature may be affected by numerous variables and may not be the most appropriate markers of circadian rhythm in this patient group. As discussed later, melatonin may be a more appropriate marker of the sleep-wake cycle, offering more information on the relationship with delirium. Also, in the study of Nutall *et al*, [55] the evaluation of delirium was based on clinical diagnosis alone and not on any of the recognised ICU screening tools. This may explain the low incidence of delirium (12% compared to 70% - 80% in other studies [57, 58]).

Outside of critical care, reinforcement of the sleep-wake rhythm has been shown to ameliorate behavioural disorders, including delirium, in elderly institutionalised patients [59].

The importance of delirium with regard to patient morbidity, length of stay and mortality, [58] is only now being realised. Factors predisposing to delirium need to be identified and methods to prevent them implemented [57, 58]. Also, delirium

should be taken into account when choosing pharmacological interventions to aid sleep. The treatment of underlying delirium with appropriate antipsychotic medication may improve sleep, whereas sedative hypnotics may aggravate delirium and hence sleep disturbance.

Immunological effects

On admission, critically ill patients often have disruption in their immune function as a consequence of disease, drug treatment or nutritional factors, compounded by SIRS or sepsis [60]. This may be further compromised by sleep deprivation [61, 62].

Sleep deprivation for 48 hours was shown to decrease cell-mediated immune reactions, as measured by lymphocyte production and adhesiveness in healthy subjects [63]. Return to baseline values after sleep deprivation was discontinued took 5 days. When immunised against influenza virus, mice allowed normal sleep achieved total viral clearance, whereas sleep deprivation ablated any effect of immunisation [64].

In volunteers deprived of sleep for 40 hours, IL-1 and IL-2 levels were increased [65]. Natural killer cell activity continued to decline even when normal sleep was re-established. Leucocytosis and increased natural killer cell activity have been reported in another group of volunteers deprived of sleep [61, 65]. The effect of sleep deprivation combined with intense physical activity on immune function has also been studied [66]. Overall there is a mixed picture; some elements of immune function are increased, such as neutrophil and monocyte activity, while eosinophil, lymphocyte and natural killer cell activity were decreased [66].

It appears that even relatively short periods of sleep disruption can impair immune function. In subjects deprived of sleep for only 5 hours during the first part of the night, natural killer cell and lymphokine killer cell activities were reduced, but

returned to baseline after one nights sleep [67]. Stimulated IL-2 levels were also reduced after sleep deprivation, but did not return to baseline after a recovery sleep [67].

The circadian rhythm of cortisol secretion does not appear to be adversely affected by short-term sleep deprivation [61, 65]. However, the effects of long term sleep disturbances on cortisol secretion remain unknown.

Recently, the effect on immune function of restricted sleep (6 hours sleep per night) over a prolonged period (1 week) was studied [68]. Pro-inflammatory cytokine secretion of IL-6 and tumour necrosis alfa (TNF α) (men only) was increased significantly. Prolonged sleep deprivation also reduced cortisol secretion [68]. The results of the study by Vgontzas *et al*, [68] may better represent the adverse immune effects of sleep disturbances in critical care patients compared to studies of short-term sleep restriction.

Long-term effects

The impact of a period of critical care on the long-term quality of life of patients is only now beginning to be appreciated [1]. Patients with acute respiratory distress syndrome (ARDS) receive prolonged mechanical ventilation necessitating sedation and sometimes paralysis. Sedated patients may appear to be sleeping, but do not achieve the restorative benefits of sleep [23]. Long term follow up (up to 41 months) of patients treated for ARDS has identified depression and post traumatic stress disorder (PTSD) associated with sedative and neuromuscular blocking drug use [69]. Although the incidence of psychological morbidity (anxiety and depression) is low three months after hospital discharge, [1] some patients may suffer significant problems related to their intensive care stay. Memory is adversely affected after intensive care admission, with one third of patients having no recall of their stay at 6

months post discharge [70]. Deep sedation increases the risk of memory loss and prolonged stay in intensive care increases the risks of delusional memory and hallucinations [71]. Delusional memories predispose to acute PTSD and preservation of factual, even unpleasant memories protects from later development of the symptoms of PTSD [72]. Attempts to recreate patient “memories” using diaries of patients intensive care stay have been suggested and are used by some intensive care units. However, preservation of memory by reducing the severity of illness, minimising depth of sedation, reducing the incidence and duration of delirium and reinforcing sleep-wake cycles are likely to be more beneficial in improving the memories of critical care patients.

Causes of sleep disruption

The causes of sleep disturbances in critically ill patients are multifactorial. This is important to understand as it emphasises that a single intervention (such as a medication) is unlikely to improve sleep quality and quantity.

Environment

Noise

Noise has long been acknowledged as a problem in intensive care [73-75].

“Standards for Intensive Care” acknowledges the problem and makes recommendations on how noise may it be reduced [76]. Investigations into noise levels in hospitals have shown that it is common to exceed 70 A-weighted decibels (dBA) during both day and night in the ICU [73]. Accordingly, the use of headphones has been studied in critical care staff, and found they improved subjective noise assessment [77]. The sources of high noise levels in intensive care

include monitor alarms, patient care activities, ventilators, audio-visual equipment, construction engineering and staff interaction.

Noise pollution in a coronary care unit was associated with cardiac arrhythmias and ischaemia [78]. Excessive noise has also been identified as a physical stress by intensive care patients [79] and noise levels are often regarded as one of the principal determinants of disrupted sleep in patients.

Early evidence for excessive noise as a cause of sleep disruption in critical care patients was based on sleep laboratory simulations. A correlation between reduced REM sleep and noise levels was observed in volunteers subjected to audiotapes of critical care unit night time sounds [80]. These subjects also reported a worsening of sleep quality compared to those in a quiet setting [81]. Sleep latency, total sleep time, number of awakenings but not dreams were reported to be worse. A small study of critical care patients monitored overnight, found a correlation between the number of arousals and the level of noise [82].

The results of a questionnaire given to over two hundred patients on the day of their discharge from a critical care environment indicated that they regarded noise as a cause of sleep disruption [83]. However, they also indicated that the monitoring of vital signs and phlebotomy was more disruptive to their sleep than noise [83].

Polysomnography recording of mechanically ventilated ICU patients suggested that environmental noise was responsible for 11.5% of sleep arousals and 17% of awakenings [37]. In mechanically ventilated patients noise was found to be responsible for 20.9% of total arousals and awakenings [35]. Only 35% of peak noise levels > 75 dBA resulted in an arousal or awakening. Recently, Cabello *et al* [84] reported that only 14% of the polysomnographic sleep fragmentation recorded in mechanically ventilated ICU patients was associated with an acute increase in noise.

It is clear from these studies that environmental noise is a cause of sleep disruption in critically ill patients. However, noise is only one factor and does not explain the majority of patient arousals and awakenings. It appears that talking amongst critical care staff is the single most disruptive source of noise [35, 73, 78, 85-88]. Therefore, it should be possible to reduce the magnitude of environmental noise and hence lessen its impact of on patients sleep [85, 87, 89-91], for example by the imposition of nurse led “quiet times” [87]. Similarly, attempts at promoting sleep at inappropriate times of the day should be discouraged in order not to diminish nocturnal sleep drive. Prolonged naps, particular late in the evening, reduce the homeostatic sleep drive and aggravate rather than reinforce the monophasic sleep-wake rhythm.

Light

Nocturnal light in the ICU is often regarded as a cause of sleep disruption. The timing and intensity of the environmental light-dark zeitgeber entrains animals and humans to a 24-hour sleep-wake cycle *via* the circadian pacemaker. Inappropriate light in the ICU has the potential to disrupt circadian rhythms, including the sleep-wake cycle. Factors specifically determining the disruptive effect of light on melatonin secretion are discussed later.

Walder *et al*, [90] found baseline nocturnal mean illuminance levels in an ICU to be 4.6 lux. These low levels would not be expected to disrupt melatonin secretion and should support maintenance of a normal sleep-wake cycle. However, attempts to control nocturnal light whilst reducing mean illuminance further to 1.6 lux, increased variability and maximum light intensities to a mean of 22.8 lux. Some patients would then have experienced illuminance levels sufficient to disrupt melatonin secretion.

Clearly, any attempts to switch lights off during the day could have confusing effects on the circadian sleep-wake cycle. Many ICU patients do not suffer from lack of total sleep throughout the 24-hour period, but demonstrate an irregular sleep-wake cycle. Attempts to promote nocturnal sleep are necessary as opposed to those that would encourage daytime napping. In fact, bright light during the daytime will help reinforce the light-dark zeitgeber and improve nocturnal sleep [92].

The United Kingdom ICU standards recommend that “The general lights should dim without flicker. There should be an independent control of light over each bed, with individual patient lighting independent of general background lighting. Good spotlighting and low level to illuminate drains and seals are needed at each bed” [76]. These recommendations acknowledge the potential for light disruption at night and attempt to minimise disruption to patients whilst maintaining their safe care. Unfortunately, these recommendations are not universally applied, especially in units built prior to their publication. Also, the standards do not stress the importance of a light-dark cycle sufficiently. Even units that do adopt these standards allow individual illuminance intensity and timing ultimately to be at the discretion of the staff.

Care activities

Patient care activities in a critical care unit occur throughout the 24-hour period. Unlike ward level 0 or 1 areas, level 2 and 3 areas are, by definition, more likely to undertake nursing activities at night including drug administration, blood sampling, turning of patients and recording of vital signs. A large study of patients from a mixture of medical, surgical and cardiac ICUs found that the taking of vital signs and blood samples were perceived to be the most sleep disruptive, while the administration of medication was less of a problem [83].

Another study of nocturnal nursing care reported that patients experienced hourly interruptions in 94% of 147 ICU patient nights studied [93]. The majority of patient baths were given during the night [93].

Acute illness

Cytokines have a role in the normal regulation of nocturnal sleep. During SIRS and sepsis, pro- and anti-inflammatory cytokines are released that may contribute to the sleep disturbance that occurs in acute illness [37]. Pro-inflammatory cytokines also augment blood brain barrier permeability, [94] which may potentiate sleep-wake regulation disturbances mediated through both endogenous and exogenous substances.

Injection of endotoxin in humans increases levels of TNF α and IL-6 followed by a reduction in REM sleep and increases in stage 2 NREM sleep [95, 96]. Direct injection of IL-6 in humans has the same effect, [14]. In rabbits, IL-4 has been shown to decrease REM sleep [97].

Clearly, complex changes in cytokine production during SIRS/ sepsis will have a disruptive effect on sleep, compounded by intensive drug therapy, environmental conditions and nursing interventions.

Respiratory considerations

One of the commonest reasons for admission to a critical care area is for advanced respiratory support, requiring either invasive or non-invasive mechanical ventilation. Mechanically ventilated patients experience sleep disruption, which is not primarily explained by noise and patient care activities [35].

Non-invasive positive pressure ventilation in patients with chronic obstructive pulmonary disease [98] and continuous positive airway pressure [99] or non-invasive

positive pressure ventilation [100] in Cheyne-Stokes respiration patients, can improve sleep quality acutely. Non-invasive mechanical ventilation maintains these sleep improvements when continued long term [101]. Air leakage through the mouth associated with nasal-continuous positive airway pressure ventilation causes sleep fragmentation due to patient arousal [102].

In the acutely ill patient, non-invasive mechanical ventilation is not always tolerated, due to fatigue, anxiety, delirium or discomfort (particularly with the masks). If clinically appropriate and the patient is in agreement, invasive ventilation is instigated. The mode of mechanical ventilation employed may be important with respect to sleep quality. Pressure support ventilation has been shown to increase sleep fragmentation compared to assisted control ventilation [38]. The most important cause of apnoea leading to arousal was similarity of the resting breath PCO_2 to the apnoea threshold. The addition of a dead space, thereby increasing resting PCO_2 above the apnoea threshold, reduced patient arousal and significantly increased sleep efficiency. The effect of dead space addition was only studied for 2-3 hours, [38] and so it is unknown how long it takes for the apnoea threshold to reset itself with the potential for central apnoeas to recur. Five of the six patients who developed apnoeas during pressure support had signs of cardiac failure [38]. This emphasises the fact that significant numbers of ICU patients may develop Cheyne-Stokes respiration as a consequence of their acute illness [103]. Differences between controlled and assist controlled mechanical ventilation have also been studied during NREM sleep in healthy volunteers [104]. Controlled mechanical ventilation reduced respiratory motor output when the frequency was increased even 1 breath per minute above eupnoea after mechanical ventilation. Increasing the tidal volume by 65% or more from baseline, in addition to increasing the frequency, totally blocked

respiratory motor output after mechanical ventilation. Assist controlled ventilation at tidal volumes of 165% of baseline or more prolonged expiratory time after mechanical ventilation. Controlled mechanical ventilation was associated with a significantly greater incidence of central apnoeas compared with assist-controlled ventilation. The duration of the apnoeas with controlled mechanical ventilation was proportional to the tidal volume. The authors proposed that the mechanism underlying the reduced respiratory function was diaphragmatic weakness.

Recently, two further studies of the effects of mechanical ventilation have emphasised the importance of patient-ventilator concordance on sleep quality.

Bosma randomised 13 patients to receive either pressure support or proportional assist ventilation in a cross over study conducted over two nights [105].

Polysomnographic recording of nocturnal sleep showed improvements in sleep quality (increased SWS and REM sleep) but not quantity during proportional assist ventilation. It was concluded that proportional assist ventilation reduces patient-ventilator discordance as a cause of sleep disruption. In 11 mechanically ventilated patients with good patient-ventilator synchrony during pressure support ventilation, there was no improvement in sleep quality when changed over to proportional assist ventilation [106].

Fluctuations in blood gases as a consequence of alteration in respiratory function may also affect sleep quality. Increased PCO_2 prior to airway occlusion potentiates the inspiratory effort response and provokes sleep arousal earlier than occlusion alone [107].

Sleep arousal may be caused by not only hypercapnia, but also hypoxia and resistive load [108]. Sleep arousal due to all three stimuli may have a common mechanism of arousal. In healthy volunteers during NREM sleep, hypercapnia, hypoxia and

restrictive load all caused sleep arousal at similar peak-negative oesophageal pressure [108]. The authors concluded that, irrespective of the stimulus, increasing ventilatory effort (as measured by peak-negative oesophageal pressure) precipitated sleep arousal. The importance of a common alteration in respiratory mechanoreception as the unifying cause of sleep arousal has been questioned [109]. Hypercapnia induced sleep arousal in tetraplegic patients (spinal cord injury above C3 level) predicted to lack mechanoreceptor activity. Irrespective of the chemo or mechano-receptor mechanism(s) that ultimately causes sleep arousal, it is clear that respiratory causes of sleep disturbances occur in intensive care patients with or without mechanical ventilation.

Sleep deprivation reduces inspiratory muscle endurance in healthy volunteers [110]. Reduced inspiratory endurance may become clinically important in acutely ill patients weaning from mechanical ventilation who routinely have a chronic respiratory condition with minimal respiratory reserve [111]. However, ICU patients do not suffer sleep deprivation *per se*, but display sleep fragmentation [36]. It is unknown whether the effect of sleep deprivation on respiratory function can be extrapolated to patients suffering sleep fragmentation.

The timing of airway occlusion in the sleep cycle has an affect on the arousal response of the patient. Total nasal occlusion during REM sleep caused a quicker arousal response than during NREM sleep [112]. This has led some authors to speculate that the reduced REM sleep displayed in intensive care patients [36], is an adaptive response to reduce susceptibility to breathing abnormalities [23].

Drugs used in intensive care

Drugs frequently used in ICUs and their adverse effects on sleep architecture are listed in Table 2-3.

Sedative agents

The combination of a benzodiazepine and an opioid is often used to facilitate mechanical ventilation in patients requiring respiratory support. Benzodiazepines alter the normal sleep pattern by prolonging stage 2 sleep initially, with an increased TST but decreased duration of SWS and REM sleep [113, 114]. Tolerance to the stage 2 sleep effects occurs within days requiring dose escalation to maintain sedation. However, occasionally benzodiazepines can also have paradoxical effects including delirium manifesting as insomnia, hallucinations and nightmares. Propofol probably induces sedation by GABA_A activation [115, 116]. It has been postulated that the difference between GABA activation of endogenous sleep, and propofol induced sedation, is a result of different GABA_A beta subunit activity. [117]. Propofol has been considered to have similar disruptive effects on normal sleep architecture [118]. Short-term (12 hour) sedation with propofol in rats only reduced SWS and REM sleep during the first 4 hours compared to baseline [119]. Another study found that after 24 hours of sleep deprivation, rats subjected to a further 6 hours anaesthesia with propofol did not demonstrate a markedly different rebound in sleep characteristics compared to rats allowed to sleep *ad libitum* [120]. This study suggested that during propofol anaesthesia, some sleep homeostasis can occur and, therefore, it may be incorrect to classify all GABA-minergic drugs as having the same sleep disturbing potential. It is unknown whether this sleep restoration occurs in humans under prolonged sedation, and certainly patients report no differences between midazolam and propofol exposure with regard to sleep quality [121].

Opioids have been shown to decrease both REM and SWS phases in the postoperative period [122]. The sedation caused by the α_2 adrenoceptor agonist

clonidine has been reported to be associated with decreased REM sleep [123, 124]. A high affinity for α_2 receptors suggests that interruption of the normal sleep cycle may also occur with the new sedative agent dexmedetomidine. Whilst, there are no reports of dexmedetomidine affecting sleep characteristics in ICU patients, a study in rats found increased NREM and decreased REM sleep, and discontinuation led to a rebound increase in the latter [125]. Despite some theoretical advantages of dexmedetomidine as a sedative agent in critical care patients, one study found that patients rated dexmedetomidine worse than propofol in terms of sleep satisfaction [126].

Non-opioid analgesics

The use of non-steroidal anti-inflammatory drugs is often limited in critical care patients, but they may be useful as analgesics in appropriate patients who have sufficiently recovered from their acute illness. Non-steroidal anti-inflammatory drugs increase awakenings and decrease sleep efficiency, probably due to inhibition of prostaglandin synthesis [127], or possibly decreased melatonin secretion [127]. Additional sleep disturbance can be caused by direct gastric irritation.

Cardiovascular Drugs

Commonly used inotropic agents could affect sleep quality through their effects on adrenergic receptors. Normally, noradrenaline, adrenaline and dopamine do not appear to cross the blood brain barrier to a significant degree [128]. However, in ewes anaesthetised with propofol or isoflurane, dopamine, noradrenaline and adrenaline crossed the blood brain barrier sufficiently to increase cerebral blood flow [129]. Additionally, dopamine had a cerebrovascular effect in awake sheep and also increased cerebral vascular resistance and intracranial pressure in the anaesthetised

animals. Anaesthetic doses of propofol appear to increase blood brain barrier permeability [130]. However, it is not known whether this occurs in patients receiving sedative doses in the ICU. Nevertheless, the administration of adrenaline to patients sedated with propofol increased their sedation score and bispectral index values [131]. In rats, blood brain barrier permeability is increased by TNF α and IL-6, released as part of the sepsis cascade [94]. However, cytokines/ inflammatory mediators are not the only factors increasing blood brain permeability. There is increased permeability in the elderly and in association with hyperglycaemia and hypertension. It is possible that sedated, critically ill patients experience sleep disorders induced by sympathomimetic agents used for cardiovascular support which penetrate the blood brain barrier. In this patient group dopamine, *via* D₂ agonism, has the potential to decrease SWS and REM, whilst adrenaline and noradrenaline may decrease REM sleep.

Acute beta-blocker therapy is infrequently required in some critical care patients in response to a myocardial event or rhythm disturbance. This use can be associated with insomnia and nightmares (probably due to REM sleep suppression). The potential for β -blockers to cause these sleep disruptions is dependent on their lipid solubility [132]. Thus, atenolol and sotalol are less likely to cause sleep disturbances than more lipid soluble compounds such as propranolol and labetalol. Lack of intrinsic sympathomimetic activity may also reduce the risk of sleep disruption [133]. β -blocker induced sleep disturbances may be partly due to inhibition of nocturnal melatonin secretion [134]. In the critical care setting the choice of β -blocker is limited by the indication, desired duration of action and the route of administration.

Treatment of atrial fibrillation with amiodarone has been associated with sleep disturbances, primarily nightmares [135], probably as a result of covert antimuscarinic activity. Insomnia and nightmares can occur in patients with high plasma digoxin concentrations [136], possibly reflecting precipitation of delirium due to increased plasma antimuscarinic activity. The use of statins in the secondary prevention of myocardial infarction or cerebral vascular accident has been reported to lead to sleep disturbances and, as with β -blockers, this may be related to the lipophilicity of the individual drug [137]. However, tolerance may develop as another study found no difference in the incidence of sleep-related problems in patients receiving simvastatin *versus* placebo after therapy for over a year [138].

Gastric protectors and antiemetic agents

Ranitidine and other H_2 receptor antagonists can cause insomnia [139], although cimetidine may also increase SWS, [140] as it is the most likely drug in this group to cross the blood brain barrier. There have been a few reports of insomnia and hallucinations associated with omeprazole [141]. Additionally, dopamine antagonists such as domperidone and metoclopramide can cause sleep disturbances [142, 143]. Domperidone was associated with a higher incidence of sleep disturbances than metoclopramide, even though its central nervous system penetration is relatively low [142].

Anti-asthma therapy

Patients ventilated and sedated for *status asthmaticus* may also be at risk of sleep disorders due to the administration of high dose nebulised or intravenous β -adrenoceptor agonists. Aggressive corticosteroid therapy is an important adjunct to the control of acute exacerbation of asthma, including *status asthmaticus*.

Corticosteroids can cause sleep disturbances by decreasing SWS and REM sleep, [144] especially when high dose therapy is used [145].

Theophylline increases sleep latency, fragmentation and stage 1 sleep; SE and TST are decreased along with REM and SWS phases [146]. Nightmares have also been reported with this drug. Janson and co-workers [147] concluded that the sleep disrupting effects of theophylline were most pronounced in caffeine sensitive individuals. Theophylline and caffeine associated sleep disorders may be due to antagonism of central adenosine mediated central nervous system depression. However, Janson and colleagues [148] found no sleep advantage with enprofylline therapy, which produces little or no adenosine receptor antagonism, in patients who experienced sleep disturbances with theophylline. Insomnia is more likely to occur as a symptom of mild theophylline toxicity [149]. The use of ketamine in cases of intractable *status asthmaticus* is accompanied by the risk of emergence reactions including insomnia and nightmares. Hypnotic coverage with benzodiazepines or propofol will reduce this risk.

Antimicrobial agents

Multi-organ failure may result in the accumulation of beta-lactam antibiotics and increased concentrations in the central nervous system, causing sleep disturbances and agitation. Sleep disturbances often attributed to antimicrobial agents may have been due to host defence mechanisms and not the antibiotic [62]. However, quinolones, including ciprofloxacin, sparfloxacin, ofloxacin, grepafloxacin and levofloxacin have been reported to cause sleep disturbances possibly due to GABA_A receptor inhibition. *In vitro* data suggest that benzodiazepines can prevent the adverse central nervous system effects of quinolones [150]. If quinolone induced insomnia is suspected and the antibiotic dose has been reviewed, benzodiazepine

therapy could be considered. However, if an alternative antimicrobial agent can be utilised instead then this is a better option than merely adding another drug with delirium inducing potential. Sleep disturbances have rarely been reported with the new oxazolidinone antibiotic, linezolid, which weakly and reversibly inhibits type A monoamine oxidase [151].

Antidepressants

Because many of the common antidepressants have sedative effects, they may be used to treat insomnia. However, they primarily decrease REM sleep with a minimal effect on SWS, probably due to serotonergic effects, especially on 5HT_{1A} receptors [152]. Amitriptyline and other sedating tricyclic antidepressants decrease sleep latency and prolong SWS but also decrease REM sleep. Clomipramine almost completely blocks REM sleep [153]. Venlafaxine can cause nightmares due to suppression of REM sleep, possibly by indirect stimulation of 5HT₂ receptors [154]. Selective serotonin reuptake inhibitors increase wakefulness, decrease TST and SE and suppress REM sleep [155, 156]. Sleep disruption caused by fluoxetine was associated with eye movement during the NREM sleep phase and the occurrence of periodic limb movement in almost half the patients studied [157]. The sleep disturbing effects of selective serotonin reuptake inhibitors are usually restricted to early treatment and resolve over a period of weeks.

Anticonvulsants

Epilepsy is associated with sleep disruption, irrespective of seizure activity, and antiepileptic drugs may augment this effect. Phenobarbital decreases SL and increases SE, primarily by increasing stage 2 sleep at the expense of REM sleep [158]. Acute phenytoin and carbamazepine treatment affects sleep architecture, but

patients appear to become tolerant with prolonged therapy. Phenytoin therapy decreases SL and stage 1 and 2 sleep but increases SWS without affecting REM sleep [158]. Carbamazepine also increases both the number of sleep stage shifts and sleep fragmentation whilst reducing the percentage of REM [159]. The acute adverse effects on sleep induced by carbamazepine do not occur with chronic therapy [159]. There are conflicting data regarding the effects of valproate on sleep [160, 161]. However, it has been shown to reduce nocturnal melatonin blood levels [162]. In patients without a history of epilepsy, gabapentin increased the SWS percentage from baseline as compared to placebo, without reducing REM sleep [163]. Hence, gabapentin may be a better choice for treating neuropathic pain than carbamazepine or a tricyclic antidepressant in patients experiencing or at risk of sleep disturbances.

Miscellaneous Drugs

Transdermal nicotine has been reported to cause sleep disturbances and nightmares, but this is probably due to inadequate replacement leading to nicotine withdrawal [164]. ICU Patients with haematological disorders will often receive granulocyte colony-stimulating factor (G-CSF) during periods of neutropenia; filgrastim was reported to cause insomnia in 14% of patients in one study [165].

The immunosuppressants tacrolimus and ciclosporin are associated with neurotoxicity that can manifest as insomnia [166, 167]. In patients undergoing primary liver transplantation, sleep disorders occurred more frequently with tacrolimus (29.2 %) than with ciclosporin (20.2 %) and appeared to be dose independent [167].

Haloperidol is sometimes used to treat delirium in critical care patients [118].

Although it has been reported to cause sleep disturbances in 4% of patients receiving antipsychotic therapy, [168] by treating the delirium *per se*, there may be

improvements in patient's sleep-wake cycles. Newer atypical antipsychotics such as risperidone appear to increase SWS compared to haloperidol, probably due to 5HT₂-antagonist activity [169].

Drug Withdrawal Reactions

The most common withdrawal reactions occurring in critically ill patients are those related to sedative agents used to facilitate mechanical ventilation. A small study by Cammarano and colleagues [170] reported that nine out of 28 patients mechanically ventilated for more than seven days experienced withdrawal reactions including insomnia and sleep disturbances. The authors found a relationship between withdrawal syndromes and prolonged administration of high dose opioids and benzodiazepines. Another small retrospective study of burn patients in ICU observed withdrawal symptoms in all eleven of the patients evaluated [171]. The rate of opioid and benzodiazepine weaning was associated with duration of withdrawal symptoms. It has been recommended that patients at risk of withdrawal reactions should have their sedative dosage tapered systematically [118]. An alternative, sometimes used in ICUs, is to replace the opioid and benzodiazepine with longer acting agents such as methadone and diazepam, the dosage of which is then slowly tapered. However, the optimum method for withdrawing sedation remains unclear. Clonidine may be used to control the withdrawal symptoms of opioids, although it does not prevent the insomnia that occurs [172]. The use of validated sedation scoring systems will minimise the risk of excessive doses, [173] and other objective measures systems such as bispectral index may be of use in paralysed patients [174]. Kress and co-workers, [175] also proposed that sedation should be interrupted daily, allowing the patient to awake, thereby minimising excessive dosing. Clearly this is an adjunctive intervention and good titration of sedation is still required as a background otherwise

the potential benefits of daily wake up will not be realised. The same group showed that interruption of sedatives daily also tended to reduce PTSD on follow up [176]. All of these techniques, if used appropriately, can minimise the risk of withdrawal reactions. The degree of lorazepam exposure is an independent predictor of developing delirium in ICU patients [177]. The ultimate aim, therefore, is to balance the use of these sedative agents and to minimise the extent of over sedation. The short half-life of remifentanyl may increase the risk of withdrawal reactions when used for longer term sedation in ICU patients compared to longer acting agents. It is possible that the higher re-intubation rates found in the remifentanyl group in a study comparing analgesic based sedation with that produced by midazolam, [178] may have been due to intense REM rebound induced by acute remifentanyl withdrawal.

There is little evidence that clinically important withdrawal reactions occur with propofol in the ICU, although tolerance to propofol has been described [179]. Au and colleagues, [180] reported a case of severe grand mal convulsions attributed to propofol withdrawal. However, the interpretation of this observation was obscured by confounding factors [181, 182]. Valenete and colleagues [183] also described a case of propofol tolerance and then withdrawal leading to generalised tonic-clonic seizures. Compared to benzodiazepines, the potential for sleep disturbances after propofol withdrawal seems reduced, possibly due to subtle differences in GABA-minergic activity.

Administration of chronic medication is often discontinued in critical care patients during their acute illness. Chronic medication may be omitted intentionally because the critical illness makes the patient vulnerable to adverse effects of the medication; or unintentionally, when drug histories are unavailable, administration is not possible

(e.g. oral drugs), or simply forgotten. However, although continued therapy may not always be appropriate, medication histories should be complete, and a daily review made to consider recommencing therapy. Withdrawal effects that occur after long term treatment with tricyclic antidepressants, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors include insomnia, nightmares and excessive dreaming related to REM rebound [184]. Drugs with short half-lives are more likely to produce acute withdrawal reactions compared to those with longer half-lives or active metabolites. For example, paroxetine ($t_{1/2}$ 15 – 22 hours) use is associated with a much greater reporting rate of withdrawal reactions per prescription than fluoxetine ($t_{1/2}$ 4 – 6 days; norfluoxetine $t_{1/2}$ 4 – 16 days) [185]. However, there remains a difficulty in establishing whether the patient's delirium symptoms are in fact due to withdrawal or toxicity. Detection will depend on identifying high risk drugs, anticipating withdrawal problems and recommencing chronic therapy as soon as deemed appropriate. For example, drugs known to increase serotonin activity (e.g. selective serotonin reuptake inhibitors, tricyclic antidepressants) may be detrimental in patients with a SIRS or sepsis when serotonin over activity may contribute to delirium. Sometimes it will be necessary to recommence medication and to monitor improvement or worsening of symptoms in order to decide whether to continue or withdraw the medication.

Drugs that are known to suppress REM sleep, such as opioids, tricyclic antidepressants, monoamine oxidase inhibitors and selective serotonin reuptake inhibitors, will cause REM rebound when discontinued abruptly. REM rebound is associated with respiratory problems due to reduced accessory muscle function, which may adversely affect ventilation. Chronic obstructive pulmonary disease patients are particularly prone to hypoxia during REM sleep [186]. Abrupt

withdrawal of H₂ antagonists, cimetidine and ranitidine can cause neurological disorders including irritability, anxiety, headaches and insomnia [187].

Withdrawal from recreational drugs may also be a cause of disrupted sleep in the critical care unit. Alcohol withdrawal is a common problem encountered in critical care patients, requiring benzodiazepine therapy. The cannabis withdrawal syndrome is not dissimilar to that of alcohol and opioids and includes insomnia, which may be prolonged. Amphetamine withdrawal is characterised by a prolonged period of sleep disturbance with rebound REM sleep and nightmares. Rebound REM also occurs after abrupt discontinuation of cocaine [188]. Cocaine and amphetamine abusers often take other drugs such as opioids, benzodiazepines, alcohol and cannabis.

Nicotine withdrawal has been reported to cause delirium and insomnia in patients on a neurological ICU [189].

Drug Class or Individual Drug	Sleep Disorder Induced or Reported	Possible Mechanism
Benzodiazepines	↓ REM, ↓ SWS	GABA _A receptor stimulation
Opioids	↓ REM, ↓ SWS	μ receptor stimulation
Clonidine	↓ REM	α ₂ receptor stimulation
Non steroidal anti-inflammatory drugs	↓ TST, ↓ SE	Prostaglandin synthesis inhibition
Noradrenaline/ adrenaline	Insomnia, ↓ REM, ↓ SWS	α ₁ receptor stimulation
Dopamine	Insomnia, ↓ REM, ↓ SWS	D ₂ receptor stimulation / α ₁ receptor stimulation
β-Blockers	Insomnia, ↓ REM, Nightmares	Central nervous system β-blockade by lipophillic agents
Amiodarone	Nightmares	Antimuscarinic activity
Corticosteroids	Insomnia, ↓ REM, ↓ SWS	Reduced melatonin secretion
Aminophylline	Insomnia, ↓ REM, ↓ SWS, ↓ TST, ↓ SE	Adenosine receptor antagonism
Quinolones	Insomnia	GABA _A receptor inhibition
Tricyclic antidepressants	↓ REM	Antimuscarinic activity and α ₁ receptor stimulation
Selective Serotonin Reuptake Inhibitors	↓ REM, ↓ TST, ↓ SE	Increased serotonergic activity
Phenytoin	↑ Sleep Fragmentation	Inhibition of neuronal calcium influx
Phenobarbital	↓ REM	Increased GABA activity
Carbamazepine	↓ REM	Adenosine receptor stimulation and/ or serotonergic activity

Table 2-3 Drugs commonly used in ICU and their effects on sleep architecture

REM: rapid eye movement, SWS: slow wave sleep, TST: total sleep time, SE: sleep efficiency,

Treatment of Sleep Disorders in Critically Ill Patients

Treatment with drugs in isolation will not resolve or prevent the majority of sleep disorders experienced by critical care patients. Sometimes it is not possible or appropriate to make changes in drug treatment to minimise sleep related disturbances *e.g.* sympathomimetic agents in septic shock. Both non-pharmacological and pharmacological approaches are required. Consideration of the environment, ventilator synchrony and patient specific factors is also required.

Sleep *versus* Sedation

The terms sleep and sedation are often used interchangeably in critical care. For example, the original description of the Ramsay Sedation Scale refers to ‘asleep levels’. Pharmacological interventions are commonly referred to as ‘night sedation’, however, the ultimate aim is to improve the quality and quantity of sleep. It is important to acknowledge that sedation and sleep are two distinct states, although they share some important features [190].

Sleep deprivation potentiates the sedative effects of anaesthetic agents, [191] which emphasises the common neurotransmitter pathways involved in both sleep and sedation. Also, sleep and sedation share the same behavioural endpoints of hypnosis and amnesia. However, unlike sleep, sedation is not entirely reversible upon stimulation and lacks a temporal cycle. Furthermore, sedation does not produce the same biological functions as sleep.

Non-pharmacological treatment

Environmental controls on noise can be successfully implemented [90], and the use of ear plugs can reduce REM latency, increase REM and SE [89]. Non-invasive positive pressure ventilation in chronic obstructive pulmonary disease patients, [98]

and continuous positive airway pressure [99] or non-invasive positive pressure ventilation [100] in Cheyne-Stokes respiration patients can improve sleep quality acutely. In the ICU attempts to optimise patient-ventilator synchrony during pressure support ventilation will reduce arousals and awakenings, hence supporting sleep continuity [105, 106].

Cognitive behavioural therapy has been shown to be superior to pharmacological therapy in the treatment of chronic insomnia [192]. However, its value has not been investigated extensively in critical care. One study found that therapeutic massage increased sleep duration by approximately one hour compared to placebo [193]. The same study found no significant improvement in sleep in patients exposed to relaxing music or relaxation exercises [193].

Pharmacological treatment

The pharmacological treatment of sleep disorders in critical care patients should be prefaced by a review of all current medication with the aim to discontinue any unnecessary drugs. The possibility of withdrawal reactions to social or prescribed medication should be considered prior to commencing hypnotic therapy. Allowance for renal and hepatic dysfunction when prescribing drugs will minimise side effects, including sleep disorders, whilst maintaining effective treatment. Drugs started in critical care should be discontinued as soon as appropriate, *e.g.* H₂ antagonists for stress ulceration prophylaxis in patients no longer at high risk. Corticosteroid-related sleep disturbances may be minimised by using appropriate doses and duration of therapy. When possible, corticosteroids should be dosed in the morning, to minimise nocturnal cortisol exposure and adrenal suppression [194]. Theophylline related insomnia can be minimised by maintaining its plasma concentrations within the therapeutic range. Whilst the evidence that theophylline or aminophylline are

effective in acute asthma attacks is limited, these drugs may still have a role in intractable cases [195].

Drug therapy aimed at inducing sleep over a normal night time period has the potential to increase the TST but may not improve the quality of sleep. Critically ill patients do not suffer from lack of sleep, but have reduced restful sleep. Any drug prescription for acute sleep disturbances in the critical care unit should be for only a short course of therapy, as long-term prescription is not warranted without re-evaluation. Hypnotic therapy should be reviewed daily for efficacy and adverse effects, particularly cognitive defects in patients prone to delirium. This is emphasised by a meta-analysis of sedative use in elderly patients which found that the benefits were limited compared to the risk of adverse events [196]. A proposed approach to the drug treatment of sleep disorders in critically ill patients is shown in Figure 2-5.

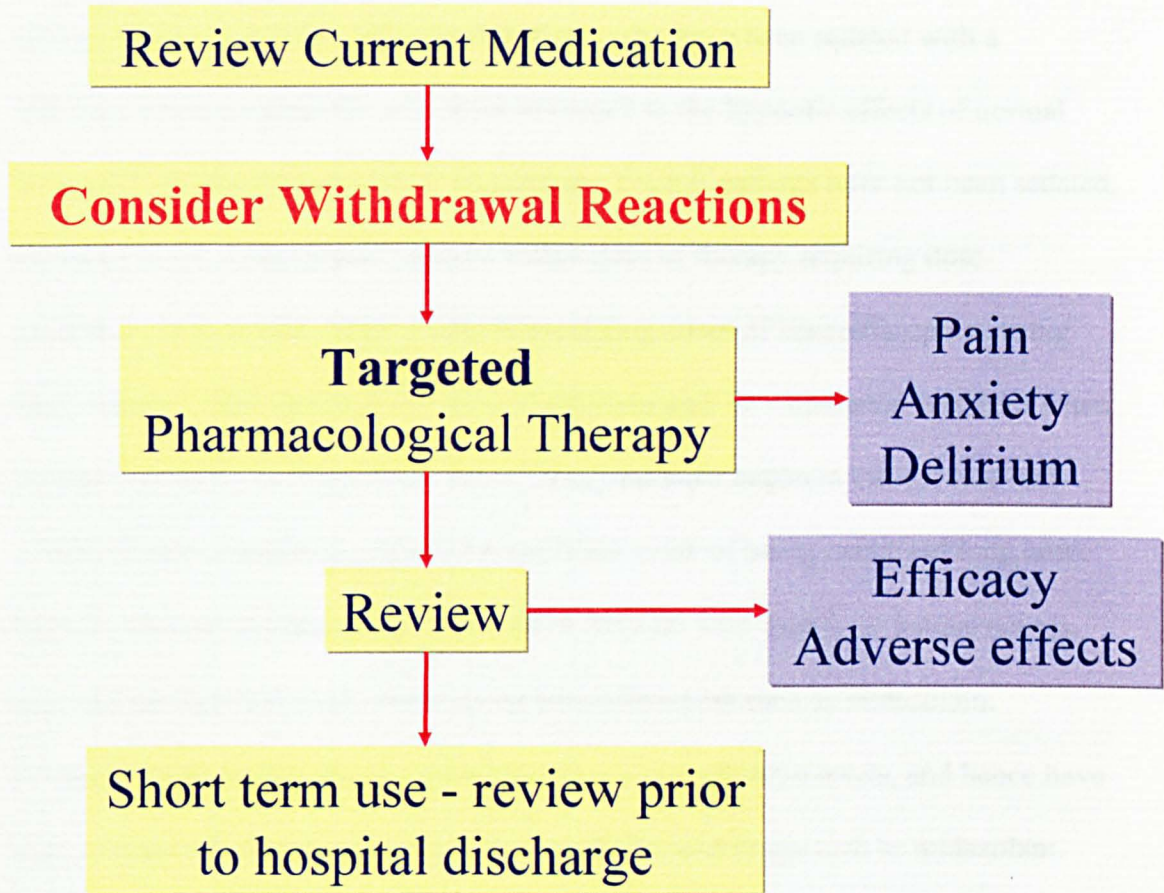


Figure 2-5 Proposed approach to the drug treatment of sleep disorders in critically ill patients

Benzodiazepines

Temazepam is often the first line hypnotic agent used in patients recovering from critical illness. However, critically ill patients who have been sedated with a benzodiazepine or propofol may show tolerance to the hypnotic effects of normal doses of benzodiazepines such as temazepam. Even if patients have not been sedated, tolerance to benzodiazepines appears within days of therapy requiring dose escalation. This in turn, often results in escalating doses of benzodiazepines being used, which in turn increases the risks of delirium and/ or withdrawal reactions when attempts are made to discontinue them. Drug treatment begun in critical care and continued after transfer to a general ward bears a risk of being continued long term. Patients who are not absorbing their feed or have no naso-gastric or jejunal access, may receive an intravenous short acting benzodiazepine such as midazolam. However, critical care patients often have low serum albumin levels, and hence have large volumes of distributions for highly protein bound drugs such as midazolam. Therefore, larger intravenous doses of midazolam are required to produce equivalent plasma concentrations to a non-critical care patient. Furthermore, any hepatic and/ or renal dysfunction predisposes these patients to a greater risk of prolonged sleep inertia (reduced arousal and performance after awakening from sleep) the next morning.

The sedative effect of benzodiazepines is primarily due to increased stage 2 sleep with reduced SWS and REM [113, 114]. The reduced REM activity may be advantageous in some patients such as those with Cheyne-Stokes respiration, in whom arousal is reduced [197] and COPD patients [186]. However, again these patients' sleep and Cheyne-Stokes respiration might worsen upon benzodiazepine withdrawal. Temazepam and other short acting benzodiazepines have less potential

for producing sleep inertia than longer acting agents such as diazepam or nitrazepam. However, even temazepam can produce hangover effects, especially in patients with renal failure.

Temazepam was made a controlled drug (Schedule 3; CD no reg) in the UK in 1998. This means that it must be stored in a controlled drugs cupboard; thereby prolonging the nursing time required for preparing it for administration. This increased nurse workload, albeit minimal, has promoted the use of alternative benzodiazepine and non-benzodiazepine hypnotics in some critical care units.

Non-benzodiazepine GABA_A agonists

Newer non-benzodiazepine hypnotic agents such as zolpidem (imidazopyridine) and zopiclone (cyclopyrrolone) do not suppress SWS compared to benzodiazepines.

Zolpidem appears to have less adverse effects on REM sleep than benzodiazepines at normal doses; REM sleep is not reduced although REM latency is increased [198].

However, patients do not perceive increased sleep quality with these agents compared to benzodiazepines, [199] and these drugs are not without their own risks of dependence and toxicity (*e.g.* psychiatric reactions with zopiclone) [200].

Zopiclone has also been reported to cause nightmares and sleep disturbances [201, 202]. It is unknown whether these non-benzodiazepine agents will increase SWS in critical care patients and whether this translates into improvement in memory or a reduced incidence of PTSD.

In the National Health Service, the National Institute for Clinical Effectiveness (NICE) has published 'Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia' [203]. They concluded that there was no advantage in using these drugs as alternatives to conventional (shorter acting) benzodiazepines, and that the cheapest drug should be used.

Propofol

It has been suggested that propofol should be used to induce nocturnal sleep in critically ill patients being weaned from mechanical ventilation [204]. Propofol affects sleep by increasing NREM and TST and reduces SL [115, 116]. In short-term sleep models in rats, REM sleep did not seem to be adversely affected by propofol [115, 116]. Unfortunately, NREM sleep stages were not differentiated and, therefore, the effect of propofol in these studies on SWS is unknown. The effect of propofol anaesthesia on sleep homeostasis has also been studied in rats [120]. Animals deprived of sleep for 24 hours then subjected to 6 hours of propofol anaesthesia did not demonstrate significant rebound of SWS and REM when compared to rats allowed to sleep *ad libitum*. This suggests that with short term propofol anaesthesia some sleep debt is recovered. Propofol was reported to be effective in producing “diurnal” sedation in nine of 15 critically ill patients [205]. However, no attempt was made to distinguish sleep from sedation [205]. Propofol did not appear to offer any advantage over midazolam with regard to subjective sleep quality in non-intubated ICU patients [121].

Antidepressants

Tricyclics

Amitriptyline is the most commonly used sedating antidepressant used to aid sleep in intensive care patients. The antidepressant effect of amitriptyline is primarily due to inhibition of noradrenaline and serotonin reuptake. Whilst individual tricyclic antidepressants differ in the degrees of noradrenaline, serotonin and antimuscarinic inhibition, they all reduce REM sleep. Amitriptyline reduces SL and fragmentation and increases TST [206]. Amitriptyline significantly reduces REM activity, the

number of REM periods and the percentage REM sleep, even though on prolonged use there is partial tolerance to some aspects of REM sleep, REM rebound occurs on discontinuation [206].

Critical care patients recovering from acute illness often have cardiovascular instability which cautions against the use of drugs with marked antimuscarinic activity. In such cases doxepin is a more appropriate alternative to amitriptyline owing to its lower antimuscarinic activity. The total antimuscarinic burden may also predict the risk of delirium development in elderly patients and must be taken into account when choosing a hypnotic agent in critical care patients.

Miscellaneous antidepressants

There may be a strong temptation to commence antidepressant therapy in patients who appear depressed during a prolonged critical care stay. However, since it takes a few weeks for the full antidepressant effect to occur, there is a real risk of unwarranted prolonged therapy after discharge from the acute care unit. The fact that patients with hypoactive delirium are often misdiagnosed as depressed accentuates the inappropriateness of antidepressant therapy when antipsychotics are indicated. Selective serotonin reuptake inhibitors (SSRIs) are often prescribed as they are considered as effective as the older tricyclic antidepressants in the treatment of depression and have a better safety profile in overdose. However, they have no sleep promoting effects and are known to cause sleep disorders. They should be avoided unless alternatives are contraindicated.

Similar to cyproheptadine, nefazodone has 5HT₂ antagonist activity, which may be important in the treatment of nightmares [207]. Hicks *et al*, [156] compared nefazodone and paroxetine in the treatment of depression and concluded that nefazodone was associated with increased SE, TST and a subjective feeling of sleep

improvement after only three days of treatment. Unfortunately, nefazodone has now been withdrawn in Europe because of an association with severe liver failure.

Two other antidepressants share 5HT₂ antagonist activity – trazodone and mirtazapine with the added advantage of low antimuscarinic effects. Trazodone has been shown to have a minimal effect on REM sleep compared to amitriptyline [208]. Mirtazapine is beneficial in the treatment of sleep disturbances in patients with depression [209]. However there is no objective evidence of benefit in critical care patients.

Trazodone has been shown to aid sleep in patients experiencing sleep disturbances due to stimulant antidepressants (SSRIs) [210]. This activity is particularly relevant for critical care patients as the sleep disturbances (and delirium) they experience may be partly due to excess serotonin activity. Although case reports suggest that trazodone may be of benefit in the treatment of delirium [211], no randomised placebo controlled trials have been done. While a review recommended that trazodone should not be used as a hypnotic agent in patients without a mood disorder [212], the high incidence (up to 80%) of delirium in critical care patients does not preclude its use.

Chloral hydrate

Chloral hydrate decreases SL and nocturnal awakenings with minimal effect on REM sleep. However, it is less effective than benzodiazepines as a hypnotic, [213] and its use in high doses is associated with a high incidence of daytime hangover effects.

Alcohol

Patients with a prior history of social alcohol intake may benefit from a “nightcap”. Roehrs *et al*, [214] reported that acute ethanol administration in insomniacs increased

SWS, but reduced REM sleep. The dose of ethanol is critical as higher doses may cause sleep disruption. Ethanol will not be an appropriate choice in those patients with significant liver disease or previous excessive alcohol intake.

Antipsychotics

Schizophrenic patients have reduced SWS and REM latency compared to non-schizophrenics and may, therefore, respond differently to medications that affect sleep stages. Chlorpromazine increases TST and decreases patient arousal in psychiatric patients, although tolerance to this soporific effect develops within days [215]. Generally, chlorpromazine increases SWS while low doses increase, and high doses decrease REM sleep [216, 217]. However, the profound antimuscarinic activity of chlorpromazine and other phenothiazines makes their use in critically ill patients undesirable. Also, as a significant proportion of critically ill patients are elderly, the use of antimuscarinic drugs would increase both the incidence and severity of delirium [218-221].

High doses of haloperidol have sedative effects, although information on its effect on sleep architecture is inconsistent. Newer atypical antipsychotic agents, such as risperidone, antagonise 5HT₂ and D₂ receptors at low doses and increase deep sleep in rats [222]. A small study of schizophrenic patients found that, compared to haloperidol, risperidone improved SWS [169].

Antipsychotics are currently the drugs of choice in the treatment of delirium. Sleep disturbances that occur in delirious patients resolve as the delirium resolves. In critical care patients with sleep disturbances, their delirium status needs to be taken into account when selecting pharmacological therapy. In delirium positive patients an antipsychotic dosed regularly, with or without weighted nocturnal dosing, would

seem appropriate as sedative hypnotic drugs may worsen the sleep disturbances in these patients (Figure 2-5).

Alpha-2 agonists

The α_2 agonists clonidine and dexmedetomidine are sometimes used for their analgo-sedative effects in critically ill patients. In the USA, dexmedetomidine is licensed for short term sedation of intensive care unit patients to facilitate mechanical ventilation. Dexmedetomidine is reported to block noradrenaline activity within the locus coeruleus and, activate GABA activity within the VLPO [223]. This mechanism of action more closely mimics the normal sleep-promoting pathways and represents a novel action of these drugs. However, there is no supporting evidence to date that α_2 agonists produce a more restorative sleep than other sedative agents. Indeed, a study designed to evaluate patient perceptions of sleep quality after overnight sedation with dexmedetomidine or propofol concluded that those receiving dexmedetomidine found it more difficult to sleep [126]. Nevertheless, another advantage of α_2 agonists may be that they reduce the need for other opioids or sedatives thereby reducing the adverse effects of these drugs on sleep and delirium. More evidence supporting the role of these agents is required to substantiate their routine application in critical care patients.

Antihistamines

Promethazine is regarded as an “antihistamine” in adult patients. However, it is a phenothiazine and, as such, has a similar effect to chlorpromazine on sleep characteristics. Diphenhydramine and promethazine have both been shown to reduce REM sleep, possibly due to their antimuscarinic activity [224, 225]. Tolerance to the sedative effects of diphenhydramine develops after the first dose [226].

Diphenhydramine has also been reported to make volunteers sad and antagonistic (probably delirious) [226]. The significant antimuscarinic effect of these drugs does not support their routine use as hypnotics in patients recovering from critical illness.

Melatonin

Recently, some intensive care units have begun to use melatonin to aid sleep in their patients [227]. The rationale, efficacy and potential advantages of melatonin in the treatment of sleep disorders in critically ill patients will be discussed in detail in the following section.

Melatonin

Circadian rhythm

The circadian pacemaker within the SCN triggers the pineal gland to produce melatonin at night. It is set by the phase-shifting actions of light such that physiological plasma melatonin levels during the day are very low but begin to rise from around 2200 h, with a peak at approximately 0200 h returning to daytime values by 0900 h. Endogenous production of melatonin is approximately 30 micrograms per day, [228] associated with peak plasma levels of approximately 100 pg/ml [229]. The amplitude of plasma melatonin levels is lower in elderly subjects and there is phase delay (*i.e.* delayed peaking) [230].

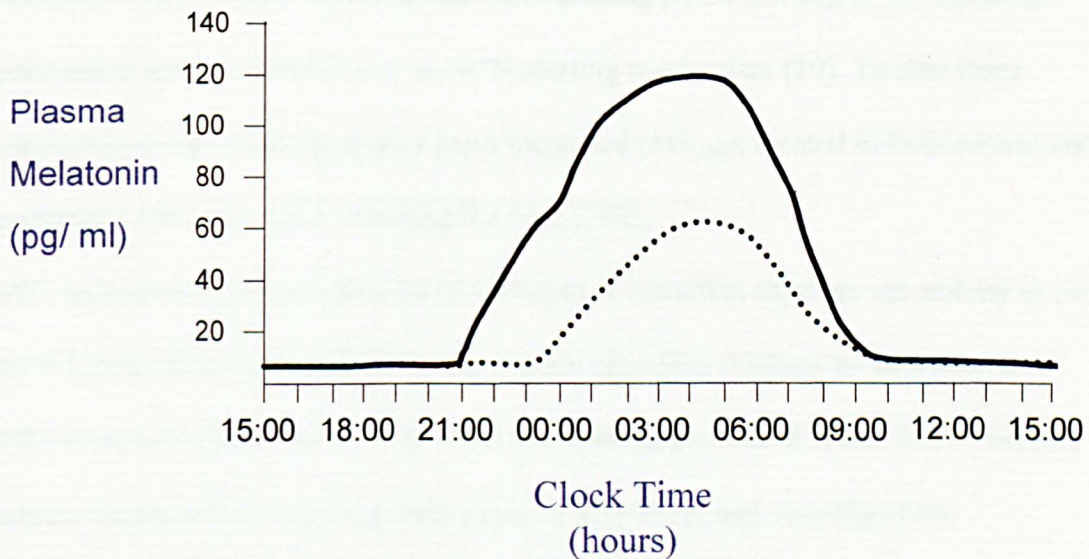


Figure 2-6 Effect of age on plasma melatonin versus time

19-25 years of age: — ; 66-75 years of age: ----
Representation adapted from [230]

The enterochromaffin cells within the gastrointestinal tract also synthesise melatonin. Melatonin secretion from the gastrointestinal tract probably accounts for the normal low daytime plasma concentrations and is not under the circadian control of the SCN (see Bubenik [231] for review).

Pharmacology

Darkness stimulates retinal photoreceptor release of noradrenaline, which activates α_1 and β_1 -adrenergic receptors in the pineal gland, increasing cyclic AMP, which then stimulates enzyme-catalysed synthesis of melatonin. The pineal gland converts tryptophan to melatonin *via* 5-hydroxytryptophan with serotonin, and N-acetylserotonin as intermediates. Serotonin is converted by N-acetyltransferase (NAT) to N-acetylserotonin which is then converted to melatonin by hydroxyindole-O-methyltransferase. NAT is the rate-limiting step in the pineal synthesis of melatonin (Figure 2-7). The precise mechanism of the sleep-promoting effects of melatonin is unknown. Possibilities include induced hypothermia, GABA receptor stimulation and a direct action on the SCN causing phase shifting of the circadian pacemaker and/ or inhibition of an SCN alerting mechanism [10]. To date three melatonin receptor subtypes have been identified (MT_{1-3}); located in both central and peripheral sites, the latter including the lung [232].

MT_1 receptors are responsible for modulation of circadian rhythms *via* activity in the SCN [233]. Melatonin appears to also entrain circadian rhythms by stimulation of MT_2 receptors within the SCN [234]. Melatonin agonism at MT_1 and MT_2 receptors within cardiac blood vessels results in vasoconstriction and vasodilatation, respectively [233]. Stimulation of MT_3 receptors appears to have effects on the regulation of intra-ocular pressure and can modifying inflammatory effects on the microvasculature [233]. The relationship between plasma melatonin level and receptor activity is complicated by the variation in receptor expression and function regulated by the light-dark cycle; the SCN; melatonin itself and possibly other hormones [233]. Developments in our understanding of the pharmacology of

melatonin have facilitated attempts to develop MT receptor agonists for therapeutic use.

In recent years synthetic melatonin agonists have been developed for clinical applications. Ramelteon and agomelatine are agonists at both MT₁ and MT₂ receptors [235, 236].

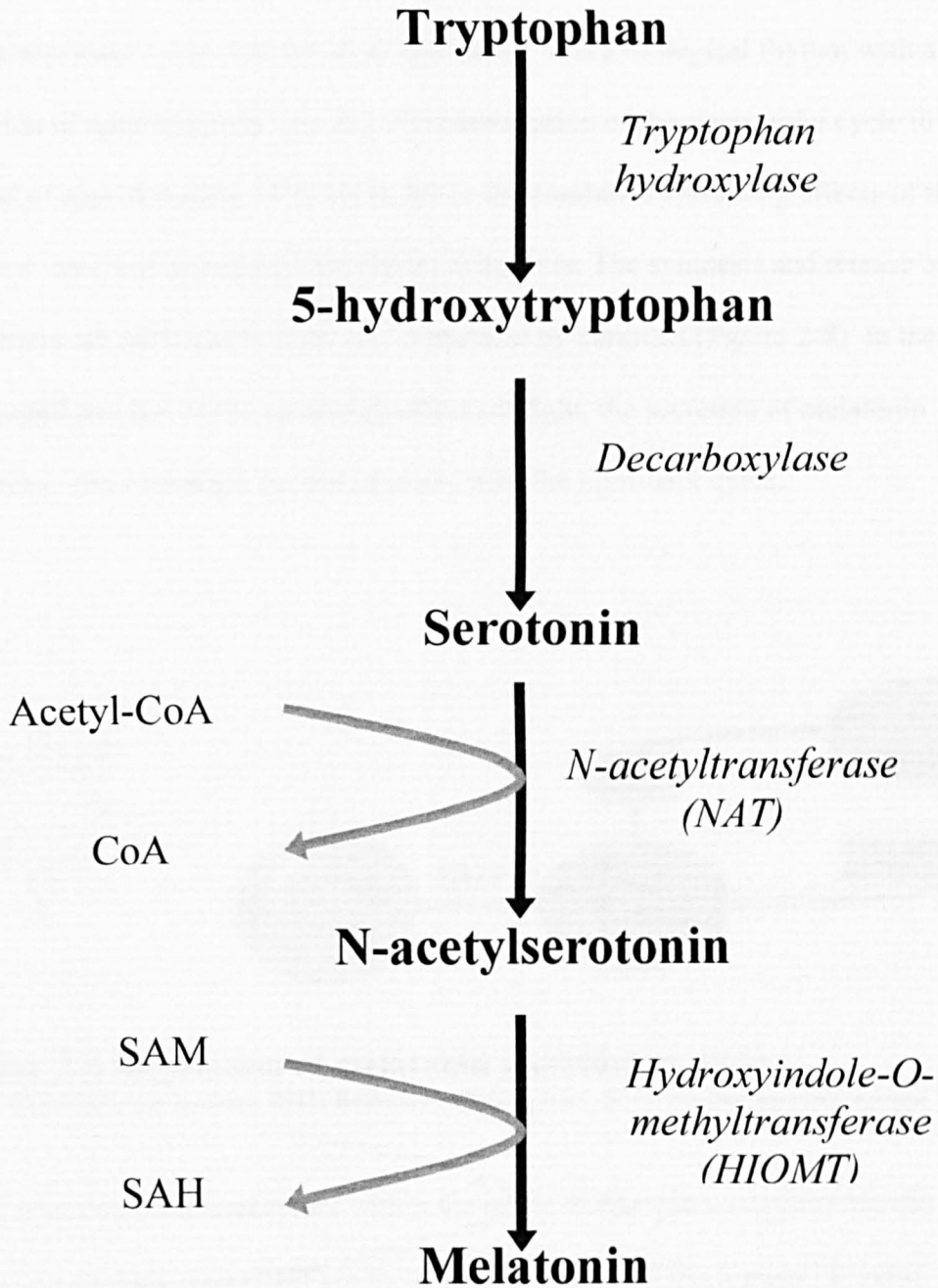


Figure 2-7 Synthesis of melatonin in the pineal gland

Acetyl-CoA: Acetyl Coenzyme A; CoA: Coenzyme A; SAM: S-adenosylmethionine; SAH: S-adenosylhomocysteine

Influence of light on melatonin secretion

The sleep-wake cycle is a circadian rhythm, *i.e.* it is a biological rhythm with a duration of approximately one day. Synchronisation of the sleep-wake cycle to a period of approximately 24 hours is due to the combined entraining effects of the internal (melatonin) and external (light) zeitgebers. The synthesis and release of melatonin are inhibited by light and stimulated by darkness (Figure 2-8). In the prolonged absence of the entraining effects of light, the secretion of melatonin becomes “free-running”, *i.e.* out of phase with the light-dark cycle.

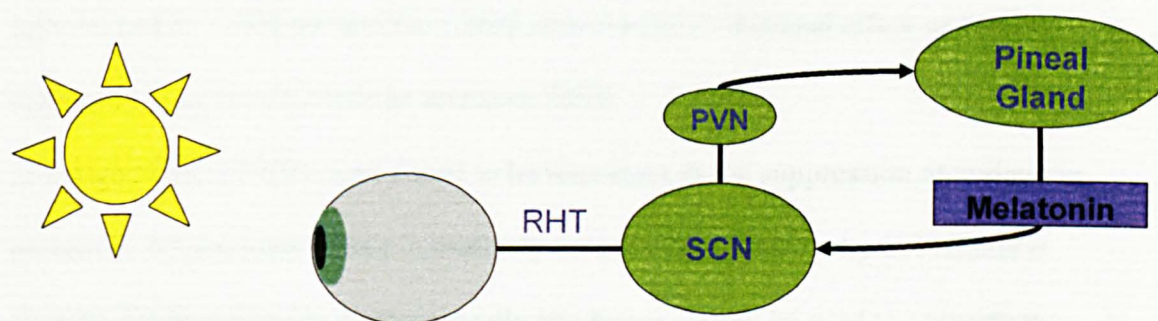


Figure 2-8 Regulation of melatonin secretion by light

PVN: Paraventricular nucleus; RHT; Retinohypothalamic tract; SCN: Suprachiasmatic nucleus

Light stimulates photoreceptors within the retina to transmit a response *via* the retinohypothalamic tract (RHT) to the hypothalamic SCN, the human circadian pacemaker. Neural signals then pass through the hypothalamic paraventricular nucleus (PVN), down the upper thoracic spinal cord and into the superior cervical ganglion before reaching the pineal gland [237].

Photoreception occurs only in the eyes, as bilateral enucleation results in the loss of the acute suppression of melatonin synthesis caused by light [238]. The effect of

light on the inhibition of melatonin is dependent on a number of factors including, irradiance, wavelength, duration of exposure, time of day and patient age.

The fact that blind subjects have a sleep wake cycle entrained by the light-dark cycle, [238] encouraged research to identify the specific photoreceptor(s) involved in the signalling of the SCN. This resulted in the study of light of various wavelengths on the secretion of melatonin in animals and then humans. A number of studies showed that light of short wavelength (420 – 520 nm) is potent in suppressing melatonin secretion [239-246]. An opsin-based photopigment has been identified as the SCN trigger for light induced melatonin suppression [243]. This is a non-rod, non-cone photoreceptor present in the human retina. Red fluorescent lamps emit light of approximately λ 600 nm and have been shown to have minimal effect on both the timing and extent of melatonin secretion [240].

Light intensity has also been found to be important in the suppression of melatonin secretion. Whilst illuminance is routinely measured by photometry in lux, this is specific for the photopic system; ideally irradiance should be used to quantify the effect of light in studies of melatonin secretion. Nevertheless, some studies have demonstrated that illuminance >80 lux reduces and delays melatonin secretion [247]. Doses of light greater than 200 lux are sufficient to produce maximal suppression of melatonin secretion, whilst delays require greater than 550 lux [247]. As light irradiance increases, (irrespective of λ) melatonin secretion decreases [241-243]. All short wavelength light intensities $\geq 5.5\mu\text{W}/\text{cm}^2$ significantly suppress melatonin [242].

There is a diurnal sensitivity in the response to light on melatonin secretion. This may result from either a change in retinal photoreceptor sensitivity and/ or alteration in the neural handling of the response. Higher light intensity is required in the

morning compared to the evening to suppress melatonin secretion [239]. The elderly have a thinner corneal lens than younger adults, which may increase their sensitivity to the effects of light on melatonin secretion [243]. This may explain why lower levels of endogenous melatonin occur in the elderly [248].

The acute effects of appropriate light therapy on the circadian rhythm are dependent on time of exposure according to a phase response curve (Figure 2-9). Intense light administered during the night will have a phase delaying activity, whilst exposure during the early morning will phase advance. Acute pulses of nocturnal light of appropriate wavelength and intensity will reduce melatonin secretion. It is believed that light exposure for more than 30 minutes is required for this acute affect [249]. Polarised light does not alter the photo effect on melatonin secretion [250].

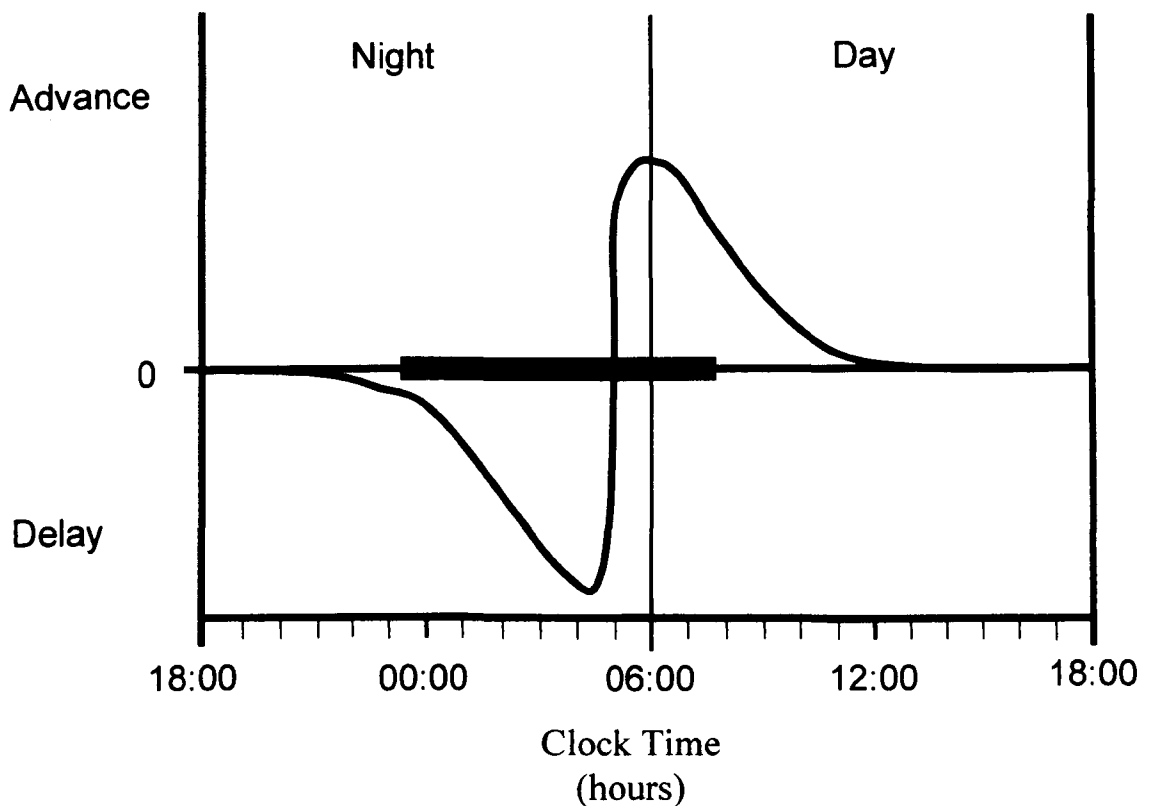


Figure 2-9 Light phase response curve

Note: Representation only; times will vary according to an individual's circadian rhythm

The ICU provides an interesting environment for considering the effect of light on melatonin secretion. Firstly, a significant percentage of the patients are elderly and, hence, particularly light sensitive. Secondly, the control of lighting is outside the control of the patient. Acute periods of high light intensity have resulted when specific guidelines to reduce overall light intensity in the ICU have been implemented [90]. Therefore, further methods to minimise light interruptions are required. The duration of normal illuminance is dictated in the morning by the arrival of the next nursing shift and at night by the night shift completing their patient care and observations. This may result in a delayed and shortened melatonin secretion with periods of interruption throughout the night. In the organisation of critical care services, lighting should be considered in respect to patient care. The current United Kingdom – “Standards for Intensive Care Units” makes no recommendations regarding the wavelength of light used on the ICU [76]. Red lighting causes minimal disruption to the melatonin circadian rhythm, [240] and its use may be sufficient for the majority of direct nursing care activities at night. Furthermore, high intensity white light in the morning will assist in the entrainment of the sleep-wake cycle. However, it is necessary to regard both the hormonal needs of the patients and those of the staff caring for them. The needs of medical and nursing staff should also be considered with regard to lighting arrangements. The rhythm and intensity of light exposure during shift work affects the sleep-wake cycle of staff [251]. Sleep disturbances in shift work staff can affect performance and have potential detrimental effects on patients care [252] In the future, lighting should be considered more carefully in the design of ICUs.

It may seem an easier option to apply eye masks to the patients, thereby minimising the effect of light during the night. However, as described in Chapter 6, ICU patients

are often unwilling to wear such masks, possibly as a result of their anxiety regarding their condition and environment. Staff in adult ICUs are becoming increasingly aware of the importance of the light-dark cycle and human circadian rhythms [56]. In contrast, those in neonatal units have long accepted that a regulated light-dark cycle is of benefit to their patients [253].

The pharmacokinetics of exogenous melatonin

Orally administered melatonin is subject to extensive first-pass metabolism involving conversion to inactive 6-sulfatoxymelatonin (6-SMT) [254]. A wide variability in the oral bioavailability of melatonin is due to the variable expression and activity of hepatic cytochrome P450 1A2 (CYP1A2), which is exclusively responsible for the metabolism of melatonin [255]. Absolute oral bioavailability is reported to be approximately 15% [254, 256]. Plasma melatonin concentrations have been reported to be dependent on a number of factors including; dose, time of administration and type of oral preparation used [257]. However, concomitant interacting drug administration and liver function are obviously also important determinants. The conjugated metabolites of melatonin are renally excreted and, in healthy subjects, changes in urine 6-SMT levels provide an indication of changes in plasma melatonin levels [258]. The elimination of melatonin from the blood is bi-exponential, with a clearance of approximately 950 ml/ min [259]. Melatonin has a steady state volume of distribution (V_{ss}) of approximately 35 L [259] and an elimination half-life ($t_{1/2}$) of 30 - 45 minutes [259-262]. In patients with cirrhosis, the metabolism of melatonin is impaired, and its average $t_{1/2}$ is extended to approximately 100 minutes [260].

Exogenous oral doses greater than 0.3 mg produce supraphysiological plasma levels in humans [263].

Melatonin therapy for sleep disorders

It is too simplistic (and probably incorrect) to regard exogenous melatonin as simply a soporific or hypnotic agent. Melatonin administered at the appropriate time in a patient's sleep-wake cycle will have sleep inducing effects. Similar to light, it has a phase response curve, although the phase delaying response is relatively weak compared to the phase advancing effect. Melatonin administered to healthy individuals during the nocturnal period when endogenous melatonin plasma levels are raised had no effect on sleep parameters; while administration during the day (low endogenous levels) had a soporific effect comparable to temazepam [264]. In fact, melatonin has been described as a "chronohypnotic" or "chronobiotic" agent *i.e.* it primarily acts to entrain circadian rhythms and, for this reason, it may have a beneficial effect on circadian rhythm sleep disorders [265, 266].

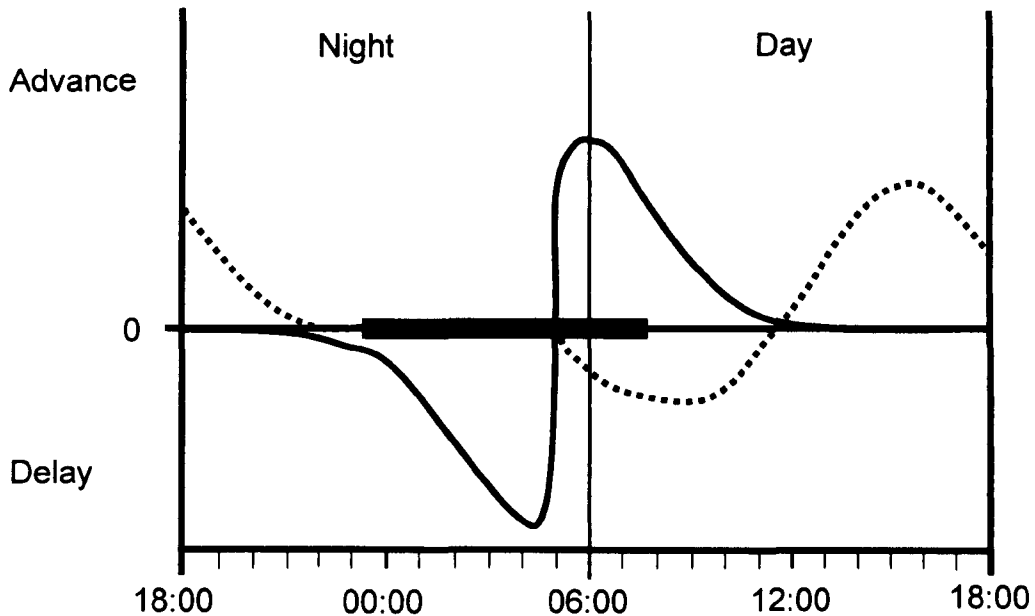


Figure 2-10 Melatonin phase response curve

Melatonin phase response curve: ----; Light phase response curve: —; Solid bar represent dark night-time period

Administration of melatonin or light will Advance or Delay the circadian rhythm depending on time of exposure according to the phase response curves. For example, appropriate melatonin administration at 1600 h will have a phase advancing effect; whereas administration at 0900 h will phase delay.

Note: Representation only; times will vary according to an individual's own circadian rhythm

Jet lag

Jet lag is the term used to describe the malaise experienced by a person who has travelled across several time zones. It is not due to a lack of circadian rhythm in the internal body clock, but reflects the resistance of the body clock to change in the new time zone. The symptoms of jet lag include fatigue, inability to sleep, loss of appetite, indigestion, feeling bloated, reduced concentration, reduced motivation, increased irritability and headache. The duration and severity of jet lag vary between individuals and with the direction of travel and number of time zones crossed.

Travelling east is associated with worse symptoms than crossing the same number of

time zones westwards. Potential treatment of jet lag includes adjustment of meal times, physical activity, bright light and exogenous melatonin. Melatonin has been shown to reduce fatigue and improve sleep [267, 268]. Whilst, not all trials have found melatonin to be of benefit in jet lag, [269] a recent Cochrane Review confirmed its value [270]. The timing of melatonin administration is important in order to effect entrainment optimally. A dose of 5 mg appears to be most effective [270].

The melatonin agonist LY156735 appears to be of some benefit in relieving the symptoms of jet lag, [271] although it may not be as effective as melatonin [270].

Night Shift

Night shift work is associated with a malaise that is similar to the symptoms of jet lag. The symptoms are again due to the individual's rest-activity being out of synchrony with their own internal biological clock. However, the continued presence of fixed time cues such as daytime light exposure, confuse the messages to the biological clock and therefore make transition to the new rest-activity pattern more difficult. Critical care patients are at risk not only due to the morbidity associated with the sleep disturbances they experience, but also because of sleep disturbance in the attending staff which may increase the likelihood of medical error [252]. It seems reasonable to suggest that changes to the working practices of junior doctors may have benefits for their patients in this regard.

Night workers often take a variety of stimulant drugs, such as caffeine or nicotine, to promote alertness and then use hypnotics during the day to promote sleep. The evidence for the efficacy of melatonin in the treatment of shift worker's malaise is limited. Volunteers subjected to a stimulated period of night shift work found that melatonin improved day time sleep without any beneficial effect on nocturnal

alertness [272]. Similarly, in a study of nurses working night shifts, morning administration of melatonin also increased total sleep time, but again did not have a significant effect on night-time alertness [273]. An earlier study reported no benefit of morning melatonin administration in doctors working night shifts [274]. A recent systematic review concluded that there was no evidence that melatonin therapy was effective in treating sleep disturbances related to shift work [275].

It is not surprising that administration of a single internal zeitgeber, such as melatonin, has limited efficacy in counteracting the continuous effects of light and other time cues on the biological clock during acute rest-activity rhythm changes, such as working night shifts.

Insomnia

Evidence for the efficacy of exogenous melatonin in inducing and improving sleep quality is conflicting [276, 277]. It is, therefore, important to identify differences in the design of reported studies in order to identify patient groups in which, and conditions under which the use of exogenous melatonin is most likely to be of benefit. Studies reporting a positive effect used a wide range of melatonin doses from 0.3 mg (physiological) to 75 mg [277]. Studies demonstrating no positive sleep effect used doses of 0.5 to 5 mg. Thus, the dose of melatonin required to induce sleep has not been defined [10]. However, there is a very obvious plateau effect that occurs at a dose of around 5 mg, above which there appears to be no advantage in increasing the dose further. Since the potential beneficial effect of exogenous melatonin on sleep disturbances is through a chronotherapeutic effect, [265, 266] it is desirable to use a dose sufficient to produce the phase advancing effect, but avoiding overdose. Excessive doses will risk supraphysiological plasma melatonin concentrations in the morning and therefore the potential for a phase delaying effect.

Rogers *et al*, [277] identified no differences between the results of sleep studies that used immediate release and sustained release melatonin products. In theory, a dosing regime that ensures raised melatonin levels throughout the night would be more effective than a regime that did not.

Another explanation of the different reported findings is variation in the timing of administration of melatonin. Stone and colleagues [264] administered melatonin to healthy volunteers at two different times to investigate the effect of melatonin administration time on sleep efficiency. When administered at 2330 h there was no significant effect on any sleep characteristics, while administration at 1800 h increased TST and SE. Melatonin therapy is more likely to be effective in improving sleep in those patients with poorer quality sleep associated with a disrupted circadian rhythm of melatonin secretion. Healthy volunteers exposed to experimental insomnia showed significantly reduced sleep latency, increased TST and SE when given melatonin compared to placebo [278].

Exogenous melatonin therapy for insomnia does appear to be more effective in elderly subjects [248, 279-281]. Nocturnal plasma levels of melatonin are lower and daytime levels are higher than in young subjects, indicating a disrupted circadian rhythm [282].

Melatonin should be administered such that raised plasma concentrations coincide with the normal melatonin increase in secretion at night (i.e. at approximately 2100 h). The hypnotic effects of exogenous melatonin therapy may not be manifest for 2-3 nights after start of dosing [279]. It is possible that this is due to a phase advancing effect as opposed to a direct hypnotic effect of melatonin.

One of the potential disadvantages of hypnotic agents for the treatment of insomnia is a hangover effect the next day. In elderly patients given long acting agents this has

been associated with an increase in falls and hospital admission. A systematic review of adverse effects related to hypnotic use in the elderly reported a number needed to harm (NNH) of only 6 patients [196]. It is also desirable in hospitalised patients to avoid hangover effects that reduce compliance with tasks such as physiotherapy that are required to speed their recovery and discharge. High dose melatonin (75 mg at night) over 14 days did not produce any subjective adverse effects on daytime alertness in 13 chronic insomniacs [279]. The effects of daytime administration of melatonin and temazepam on neurobehavioural tasks were compared in healthy volunteers [283]. Both drugs induced sleepiness, but melatonin produced a significantly reduced deficit in task performance. The effect of melatonin on post sleep psychomotor performance was compared to that of zaleplon, temazepam and zopiclone in military personnel [284]. All four agents induced sleep, but melatonin had the least impact on task performance [284].

It would appear from these studies that melatonin is advantageous in terms of reduced hangover effects compared to more conventional hypnotics. Additionally, unlike the majority of hypnotics, melatonin appears to cause minimal disruption to the normal sleep architecture [285].

Other circadian rhythm disorders

Blind persons often suffer from circadian rhythm disorders, due to the loss of entrainment by the light zeitgeber. Melatonin was administered, in a double blind placebo controlled trial to 5 totally blind individuals with free running (cycle > 24 hours duration) circadian rhythms [286]. Melatonin (5 mg), administered at 2200 h, phase advanced the circadian rhythm of melatonin in all subjects and that of cortisol in 3 cases. In another small placebo controlled trial in blind patients with a free running circadian rhythm, [287] melatonin (10 mg) administered one hour before

normal bedtime for 3 to 9 weeks resulted in entrainment of circadian rhythm to a 24-hour cycle in 6 of 7 subjects. This effect persisted on continued dosing of 0.5 mg over a 3-month period [287].

Melatonin may be particularly effective in resetting of circadian rhythms in blind individuals due to the absence of light as a more powerful zeitgeber.

Treatment of DSPS with melatonin was investigated in a small (n=8), placebo controlled trial [288]. Patients were administered 5 mg melatonin at 2200 h, approximately 5 hours in advance of their normal sleep onset time. Compared to placebo, melatonin significantly advanced sleep and wake times.

Older patients requiring long term institutionalised care for chronic cognitive impairment frequently experience sleep disturbances associated with circadian rhythm disorders. Mishima *et al* [289] reviewed the results of clinical studies of melatonin and bright light administration in elderly patients with dementia.

Melatonin and bright light administration corrected some of the circadian rhythm disturbances these patients experience [289]. Specific recommendations were made for further studies, including the optimal timing and dosage of the combined melatonin and bright light intervention [289].

The timing of melatonin administration is crucial with regard to its effect on circadian rhythms. A phase response curve for the effect of exogenous melatonin on the circadian rhythm has been described [290]. In healthy individuals with a normal circadian rhythm, melatonin administered at 1600 h for example, phase advances, while 0900 h administration phases delays (Figure 2-10). There appears to be some crossover of effect around noon and, therefore, dosing should be avoided during this period. The phase advancing efficacy of melatonin appears to be much more evident than its phase delaying capability [276].

Appropriately timed melatonin administration affects the timing of endogenous melatonin secretion without suppressing the quantity secreted. Administration of exogenous melatonin (0.5 to 50 mg) did not affect the amplitude of melatonin secretion measured pre and post treatment [291].

The potential effects of acute illness on melatonin

Patients exposed to extensive surgery and/ or with critical illness are subjected to physiological, pharmacological and environmental insults which may adversely affect the circadian rhythms of many systems, including the sleep-wake cycle.

Intra and post-operative disturbances in melatonin turnover

It is important to emphasise, that even though many of the papers cited refer to melatonin secretion, it is actually the plasma level that is measured, which reflects the net difference between secretion and elimination. Patient factors, anaesthetic factors and/ or the surgical procedure itself may have an impact on the balance between melatonin secretion and elimination. Therefore, depending on this balance, intraoperative plasma melatonin levels may be either increased or decreased in comparison to normal daytime physiological levels.

Patients undergoing laparoscopic gynaecological surgery have been reported to have significantly increased plasma melatonin levels during the procedure compared to pre-operative values [292]. Similarly, in a study of two groups of patients undergoing cardiac or oesophageal surgery, melatonin levels were raised compared to normal daytime levels during the surgical procedure [293]. However, plasma melatonin levels in the cardiac patient group were significantly higher than those in the oesophageal group throughout the perioperative period. Significantly older patients

and use of local anaesthetics, [293, 294] may explain the lower plasma melatonin levels reported in the oesophageal surgery group. Local anaesthetics inhibit protein kinase C, and thereby NAT activity, which may explain the reduced melatonin levels after local anaesthetic administration compared to placebo [293, 294]. Unlike local anaesthetics, opioid analgesics may increase melatonin plasma levels by increasing NAT activity and, therefore, melatonin synthesis. In bovine pineal extracts, morphine dose dependently increased the activity of NAT [295].

In contrast to findings in the cardiac patients in the study of Uchida *et al*, [293] plasma levels of melatonin were found to be below the sensitivity of the assay (12.1 pmol/l; 2.8 pg/ml) in patients during coronary artery bypass grafting [296]. Reasons for this difference may include differences in patient age, β -blocker administration and benzodiazepine premedication. Central nervous system (CNS) β_1 blockade reduced urinary 6-SMT excretion compared to placebo in studies of healthy volunteers [134, 297]. Nocturnal plasma melatonin levels are lower during benzodiazepine administration compared to placebo in healthy volunteers [298, 299]. Benzodiazepines have been reported to reduce melatonin synthesis by reducing NAT activity in the pineal gland [300].

The circadian rhythm of melatonin secretion is not affected by acute periods of daytime darkness. Therefore, intraoperative darkness is not a cause of the increases in plasma melatonin levels reported [292, 293]. Reuptake of noradrenaline by sympathetic nerve endings within the pineal gland prevents stress induced increases in melatonin secretion during surgery [301].

In the Guo *et al* study, [296] low postoperative melatonin levels were accompanied by raised cortisol concentrations. Corticosteroids decrease the activity of NAT in the pineal gland [302] and, hence raised cortisol levels, may negatively influence the

synthesis of melatonin. There is normally a reciprocal relationship between plasma melatonin and cortisol levels. The hormones are phase locked in that the peak plasma levels of melatonin occur as cortisol plasma levels are at their nadir. Melatonin appears to have a phasic inhibitory influence on the pituitary adrenal axis, possibly mediated by inhibition of corticotrophin releasing factor [303]. This activity may explain the low plasma melatonin levels and raised cortisol concentrations found in some postoperative patients [296].

Different anaesthetic agents may have varying effects on melatonin plasma levels during surgery. Reber *et al* [292] compared the effects of propofol and isoflurane on plasma melatonin levels during and after laparoscopic gynaecological surgery.

During surgery, plasma melatonin levels were significantly elevated from baseline in patients receiving propofol or isoflurane compared to controls (volunteers in a theatre environment who did not receive anaesthesia or surgery). In recovery, the levels were significantly higher in the isoflurane group compared to the propofol group.

There was no significant difference in levels between the propofol group in recovery and healthy controls. It was suggested that the difference between the anaesthetic groups might be due to differential effects of the two agents on hepatic blood flow. Indeed, melatonin has a high extraction ratio, [228] and therefore changes in hepatic flow may affect hepatic clearance. Furthermore, it is unknown what effect these anaesthetic agents may have on the distribution into the systemic circulation of gastrointestinal synthesised melatonin [304].

Postoperative patients have been shown to have decreased plasma melatonin levels during the first postoperative night [296, 305-310]. However, the majority of patients studied demonstrated a normal circadian rhythm of melatonin secretion by the second postoperative night [296, 305, 306].

The reduced melatonin plasma levels observed in the initial postoperative period may simply reflect the effect of melatonin depletion and clearance after the transient increase in levels during the intraoperative period. Other possible causes include premedication with intermediate or long acting benzodiazepines which suppress melatonin synthesis, [298, 299] although reduced melatonin levels on the first postoperative night have been seen even without benzodiazepine premedication [307, 308].

Saliva melatonin levels were found to be lower on the first postoperative night after orthopaedic surgery compared to preoperative levels, following both general and spinal anaesthesia [307]. However, the study groups were too small to demonstrate any significant difference in saliva melatonin levels due to differences in anaesthesia. The extent of the surgical procedure does not appear to influence the extent of disruption in the circadian rhythm of plasma melatonin, as indicated by studies in patients undergoing laparoscopic cholecystectomy [309] and major abdominal surgery [310]. A significant delay in the timing and amplitude of the rhythm of both plasma and urinary melatonin was demonstrated after both types of surgical procedure [309, 310]. A positive correlation between duration of surgery and the delay in time of dim light melatonin onset (DLMO, time of increase in melatonin plasma levels during dim light conditions) was found in the patients studied after major surgery [310].

In healthy volunteers, plasma melatonin levels are an excellent marker of circadian rhythm even when studied over extended periods [311]. The effects of surgical stress and anaesthesia on the timing of the melatonin rhythm may be more important for patient recovery than simply changes in amplitude of melatonin plasma levels. Prolonged disruption of the patient's circadian rhythm may have adverse effects on

mood, delirium risk, rest-activity and sleep-wake cycles and ultimately affect patient recovery. However, the implications circadian rhythm disorders have on patient recovery have not to date been investigated.

Melatonin and sleep disruption in the critically ill patient

High risk or critically ill surgical patients are often admitted to general medical/surgical ICUs for postoperative care. Therefore, it is possible that some of their sleep disturbance while in the ICU is a carry-over from the postoperative period. Shilo *et al* [312] assessed melatonin secretion and carried out actigraphic sleep analysis in fourteen conscious medical ICU patients. Actigraph results demonstrated the characteristic pattern of short, fragmented periods of sleep. Urine levels of 6-SMT were shown to be abnormal in all patients, with 12 not displaying the normal nocturnal rise. Control patients from general medical wards showed normal urine 6-SMT profiles and sleep patterns.

The same investigators also studied the effect of exogenous melatonin on the sleep of medical ICU patients [313]. In a double blind, placebo-controlled study eight COPD/pneumonia patients in a respiratory ICU, including four ventilated patients, were given 3 mg melatonin or placebo tablets at 2200 h on two consecutive nights.

Melatonin induced sleep in all of the patients, producing a mean duration of sleep of 6.3 (1.1) hours that was only slightly less than that experienced by the controls (general medical ward patients) (7.4 (2.1) hours). However, the duration of night time sleep while on placebo was not stated (only baseline data were provided).

Melatonin was reported to increase total sleep time and reduce sleep fragmentation after a single dose although, without the placebo data, this is difficult to conclude.

Previously, melatonin has been reported to require two to three days' dosage to improve subjective sleep duration in chronic insomniacs [279].

In contrast to the findings of Shilo, [312] Mundigler *et al* [314] reported a normal circadian rhythm of urine 6-SMT in seven non-septic patients. Possible reasons for the differences between the results of the two studies [312, 314] are differences in illness (COPD/ pneumonia *versus* post-anoxic coma), duration of illness (unknown), different medication and environmental influences (such as the wearing of eye masks in the latter study). Both studies measured urine 6-SMT levels as a surrogate marker of melatonin secretion [312, 314].

Melatonin in septic patients

Urine 6-SMT levels in septic patients were compared to those in outpatients undergoing rehabilitation for rheumatological conditions [314]. All 17 septic patients were ventilated, received continuous sedation with midazolam and sufentanil and required inotropic support with dopamine. Four also received adrenaline and 10 received noradrenaline. Sixteen patients demonstrated a high urinary excretion of 6-SMT, without any circadian rhythm during sepsis. A more normal day-night profile of urinary 6-SMT was noted in patients recovered from septic shock. Reasons for the high urinary excretion of 6-SMT in septic patients include hormone interactions, effects of cytokines and drugs, as well as alterations in hepatic enzyme activity. The absence of a circadian rhythm in melatonin secretion during sepsis may be related to that also seen with respect to cortisol. In primates, physiological doses of endogenous melatonin blocked the adrenocortrophic hormone (ACTH) stimulated rise in plasma cortisol [315]. It is possible that melatonin may contribute to the ACTH resistance that occurs in septic patients [316]. Some studies also support an inverse relationship between melatonin and cortisol production [317, 318], but others have found no role for melatonin in the regulation of adrenal function [319, 320].

Further work to investigate the relationship between melatonin and adrenocortical function in septic patients is indicated.

Physiological levels of melatonin increase vasopressin secretion whilst pharmacological doses impair it [319]. In critically ill septic patients, vasopressin levels are initially high then become inappropriately low [321]. However, it remains unknown if the vasopressin secretion pattern seen in septic shock is also associated with changes in melatonin secretion. Melatonin and its metabolites have significant antioxidant activity, [322] and elevated levels may be of benefit in septic patients [323]. However, significant antioxidant activity may require pharmacological doses of melatonin. Melatonin has also been reported to stimulate cellular release of granulocyte macrophage-colony stimulating factor (GM-CSF) [324]. Therefore, the potential immuno-stimulatory and suppressive actions of melatonin need to be considered in terms of current knowledge of the pathophysiology of sepsis [60]. During sepsis elevated levels of endogenous adrenaline and noradrenaline are often increased further by exogenous administration of these sympathomimetics for their inotropic effects. Increased CNS activity of noradrenaline would be predicted to increase melatonin secretion. The pineal gland is not situated within the blood brain barrier and, therefore, drugs without CNS activity may affect melatonin secretion. All of the septic patients studied by Mundigler *et al* [314] were ventilated and received IV infusions of sufentanil for sedation. It is unlikely that sufentanil increased melatonin secretion, because this did not occur in the single non-septic sedated patient and postoperative opioid analgesia does not increase melatonin levels. Alterations in cytochrome P450 1A2 activity, which is responsible for the metabolism of melatonin, would affect melatonin plasma levels. If CYP1A2 activity increased, plasma levels of melatonin would decrease, whilst increasing plasma 6-

SMT levels. However, in septic mice CYP1A2 activity is reduced [325] and in the presence of sepsis, parenteral feeding potentiates this effect [326, 327]. This again underlines the important information provided by measurements of the plasma levels of both the parent drug, as well as its metabolites.

The effect of cytokines released during sepsis, such as IL-6, on melatonin secretion is unknown. However, it is possible that there is a relationship as IL-6 is capable of disrupting sleep [14] and exogenous melatonin has been shown to reduce IL-6 and IL-10 levels in mice [328].

Melatonin and delirium

The role of melatonin in psychiatric conditions has been an active area of interest for decades [329]. Although delirium and schizophrenia are distinct conditions, schizophrenic patients have decreased plasma melatonin levels, particularly in association with chronic disease [330]. Delirium predisposes to the development of dementia and there have been a number of studies that suggested an association with reduced plasma melatonin levels and, indeed, disrupted circadian rhythms and the symptoms of dementia [59, 331]. However, a systematic review of interventional trials of exogenous melatonin found no evidence of a beneficial effect of melatonin on cognitive function, although behavioural and affective symptoms may decrease [332].

Haloperidol, a commonly used antipsychotic that is recommended for treatment of acute delirium in the ICU [118], increases melatonin secretion in rats [333]. In a small study of seven post-oesophagogastratomy ICU patients, none experienced delirium even though three had disrupted melatonin levels [306]. Disrupted plasma melatonin levels have been reported in elderly postoperative patients [334]. In this study, patients experiencing delirium were divided into two groups, with or without

post-operative complications (pneumonia, haemorrhagic shock and cardiac failure) [334]. Patients with delirium, but no complications, had low melatonin levels, whilst patients experiencing complications had elevated melatonin levels, as seen in early sepsis [314].

Postoperative suppression of plasma melatonin levels may contribute to disrupted sleep and predispose to delirium. Prolonged surgery and anaesthesia might be expected to be associated with more severe decreases in nocturnal plasma melatonin levels. Indeed this has recently been demonstrated in patients undergoing major abdominal surgery [310].

It is anticipated that appropriately timed exogenous melatonin therapy would be most beneficial in patients undergoing major surgery. However, the evidence for this is limited to a case report, in which melatonin therapy was successful in treating postoperative delirium in one patient and preventing delirium in another who had previously experienced postoperative delirium [335].

There is conflicting evidence to suggest that an abnormal melatonin circadian rhythm may predispose to delirium. Recently, patients admitted to intensive care after oesophagogastrectomy were monitored for delirium and had serum melatonin levels measured [308]. Eleven patients (27%) developed delirium during the four days studied on the ICU. Delirium was associated with increased age and absence of a melatonin circadian rhythm, but not absolute serum melatonin concentrations. Seven of the patients who developed delirium demonstrated an irregular melatonin rhythm, the other four all had medical complications. After major surgery, half of the patients (18/ 36) developed delirium in another study [336]. Patients with delirium had significantly worse sleep quality, as would be expected [336]. However, there were

no significant differences between patients who did and did not develop delirium with respect to melatonin exposure or rhythm [336].

These studies do not allow any firm conclusions to be drawn regarding associations between melatonin and delirium. Delirium itself can be described as a type of circadian rhythm disorder, which is most markedly demonstrated by disturbances in the sleep-wake cycle. Patients who are slow to recover their circadian rhythm after an acute illness may be particularly vulnerable to developing delirium. However, it remains to be seen if circadian rhythm disturbances predispose to delirium or prolong its course. There is no doubt that multiple precipitating factors cause stress to the CNS and are important in the aetiology of delirium in critical care patients [53]. Strategies to minimise the acuity of illness will also reduce disruption of melatonin secretion postoperatively and in critical care, which, in turn, may be of benefit in reducing the occurrence of delirium. Whether specific interventions to reinforce a patient's circadian rhythm, such as exogenous melatonin, can also reduce the incidence, severity and duration of delirium requires further investigation.

Adverse effects

Some critical care units now administer nocturnal melatonin to their entire medium to long stay patients. However, no medication intervention is without the potential for adverse effects which need to be balanced against potential benefits on an individual patient basis.

Melatonin appears to be well tolerated and few adverse effects have been reported [337]. The latter include; sedation, drowsiness and a small decrease in temperature ($\approx 0.5^{\circ}\text{C}$). Headaches, dizziness, nausea and drowsiness are the most common adverse events reported with short term melatonin administration [275].

Melatonin has been reported to increase seizures in paediatric patients with pre-existing neurological disorders [338]. However, it is also claimed to potentiate the anticonvulsant activity of carbamazepine and phenobarbital [322]. Hyperglycaemia, headache, pruritis, depression, tachycardia, confusion and dysphoria have also been associated with melatonin therapy, as have autoimmune hepatitis [339] and psychosis [340] in single cases.

The safety and toxicity of long term (>28 days) melatonin has not been formally investigated. Until further data become available, it is reasonable to restrict melatonin use to the lowest effective dose and duration of therapy based on an individual patient basis.

Precautions

It would seem prudent not to use melatonin in patients with a history of convulsions until further information regarding pro or anti-convulsant activity is available.

Pregnant or lactating women should not be given pharmacological doses of the drug without evidence of lack of teratogenicity. Patients with ischaemic heart disease may be at risk from melatonin induced coronary artery vasoconstriction [341]. The immune stimulating effect of melatonin may contribute to exacerbations of autoimmune diseases such as, multiple sclerosis [342] and encephalomyelitis, [343] and exogenous administration should be avoided in these patients. There may be an association between peak serum melatonin levels and physiological impairment in nocturnal asthma [344]. The oral bioavailability of melatonin may be increased and its elimination impaired in patients with severe liver failure, requiring dose reduction.

Drug interactions

Any drug having an effect on CYP1A2 activity might affect the pharmacokinetics of melatonin (Table 2-4). Fluvoxamine increases its oral bioavailability dramatically as a consequence of CYP1A2 inhibition [345]. Melatonin may reduce calcium channel blocker antihypertensive activity [346].

Any concomitant medication exerting a central nervous (CNS) depressant effect would be expected to potentiate the effects of melatonin. Patients who receive drugs that increase serotonin levels, as well as melatonin, may therefore be at risk of adverse CNS effects. This is because melatonin levels may be further increased by pineal gland conversion of serotonin to melatonin. Fluvoxamine increases serum melatonin concentrations by an alternative mechanism. Metabolism is decreased, as a consequence of CYP1A2 inhibition rather than melatonin production being increased [347]. In practice, however, therapeutic doses of fluoxetine, paroxetine, citalopram, imipramine and desipramine have not been shown to increase serum melatonin concentrations [348] and acute psychosis has only been reported in a single patient receiving melatonin and fluoxetine [340].

There are two case reports of withdrawal effects after long-term melatonin therapy was abruptly discontinued [349, 350]. Administration of melatonin for 1 month in volunteers was not associated with any adverse effects on withdrawal after one week [337].

Drugs considered interfering with melatonin secretion or excretion are listed in Table 2-5.

Inhibitors	Inducers
Amiodarone	Carbamazepine
Cimetidine	Insulin [351]
Ciprofloxacin	Modafanil
Clarithromycin	Hydrocarbons in tobacco smoke
Enoxacin	Omeprazole
Erythromycin	Phenytoin
Fluvoxamine	Phenobarbital
Isoniazid	Rifampicin
Grepafloxacin	Ritonavir
Norfloxacin	Thiopentone
Oral contraceptives (containing oestrogen)	
Ticlopidine	

Table 2-4 Drugs with potential to affect melatonin metabolism by inhibition or induction of cytochrome P450 1A2

Adapted from references [352, 353]

Drug Group/ Drug	Proposed Mechanism	Effect on plasma melatonin level	Reference
Local anaesthetics	Inhibition of protein kinase C	↓	[293, 294]
Beta blockers	CNS β_1 -receptor blockade	↓	[134, 297]
Benzodiazepines	Decreased NAT activity	↓	[298, 300, 320]
Opioids	Opioid mediated increase in NAT	↑	[295]
Corticosteroids	Decreased NAT activity	↓	[302]
Calcium channel blockers (dihydropyridine)	Decreased NAT activity	↓	[354, 355]
Non-steroidal antiinflammatory drugs	Inhibition of prostaglandin synthesis	↓	[127]
<i>Clonidine</i>	α_2 receptor agonism	↓	[356]
<i>Sodium valproate</i>	Increased GABA levels	↓	[162]

Table 2-5 Drugs known to affect melatonin secretion or excretion

NAT: N-acetyltransferase; GABA: Gamma Amino Butyric Acid; CNS: Central Nervous System; ↑: Increased; ↓: Decreased

Dosage and administration

The large number of clinical trials using melatonin for a wide variety of indications have utilised a wide range of doses. Endogenous plasma levels similar to those seen in young adults are achieved with doses of approximately 0.5 mg at night. Doses greater than this are commonly used, and are regarded as producing a pharmacological effect. Physiological doses of melatonin reduce sleep latency (time to fall asleep), but do not increase total sleep time or adversely affect sleep architecture [285]. The sleep promoting effects of melatonin increase with dose, but appear to reach a plateau such that very large doses may not produce any additional benefit. Doses of 2 to 10 mg have been used successfully to improve sleep quality [248] and to reset irregular circadian rhythms [287].

Melatonin is available as immediate release or sustained release formulations. It may also be given sub-lingually, and attempts have been made to develop a transdermal delivery system, [357] which would bypass first-pass metabolism of the compound. Indeed a melatonin implant has been developed for animal use – specifically to accelerate the fur priming cycle in adult minks!

The study by Shilo *et al* [313] in ICU patients used a 3 mg controlled release formulation. This dosage form has the advantage of maintaining plasma melatonin levels throughout the night, mirroring the effect of normal secretion [358, 359].

However, controlled release formulations are not always suitable for ICU patients reliant on naso-gastric or jejunal feeding. An alternative approach would be to use a higher dose (10 mg), thereby overcoming the constraint on duration of effect imposed by the short elimination half-life of melatonin (\approx 40 minutes). The timing of administration is important and should be one hour before lights-out in the ICU. This is to reinforce both the effects of melatonin and light on the patient's body clock.

Patients most likely to respond to pharmacological melatonin are those with sleep deprivation and/or impaired melatonin secretion.

The majority of melatonin products are health foods, which cannot be relied on to meet pharmaceutical standards [360]. Pharmaceutical grade melatonin formulations are available, but may need to be imported and are unlicensed medicines. Although melatonin is normally produced by chemical synthesis, some products may contain material derived from animal sources.

If melatonin is to be used clinically for clearly defined indications, appropriate pharmaceutical products need to be available. There have been some pertinent developments in this regard over recent years. In April 2007, the European Medicines Agency (EMA) granted Neurim Pharmaceuticals orphan drug status for their melatonin product (Circadin), a 2mg prolonged release oral formulation, for the treatment of non-24-hour sleep-wake disorders in blind people with no light perception. Subsequently, the EMA licensed Circadin for the treatment of primary insomnia in patients 55 years and older. As of November 2007, phase III studies of a UK melatonin product are currently underway in the treatment of sleep disorders in blind people. Posidorm (Alliance Pharma) is a chemically synthesised 1.5 mg controlled release oral tablet formulation. Melatonin agonists have also gained licensing approval. Ramelteon (Rozerem) has been licensed by the US Federal Drug Administration (FDA) for insomnia characterised by sleep difficulty with sleep onset. Agomelatine (Valdoxan; Thymanax) has recently (July 2006) had a license application for the treatment of major depressive disorder rejected by the EMA, citing insufficient supporting evidence.

Conclusions

The states of sleep and wakefulness are controlled by a complex cascade of neurotransmitters involving numerous regions of the brain. Critical care patients commonly experience sleep fragmentation and an irregular sleep-wake rhythm. The causes of sleep disturbances in critical care patients are multifactorial, and include the effects of the environment, care activities, the acute illness, pain, delirium, circadian rhythm disturbances and ventilatory desynchrony.

Studies of sleep deprivation suggest that critical care patients experiencing sleep disturbances are predisposed to respiratory, cardiovascular, neurological and immunological morbidity. However, direct evidence of morbidity associated with sleep fragmentation in critical care patients including long term effects, are lacking.

Attempts to treat patient sleep disturbances with hypnotic agents are of limited patient benefit, and indeed, may have adverse consequences. Multicomponent interventions are likely to be required to treat sleep disturbances in critical care patients. The latter include re-enforcing the patient's circadian rhythm, and sleep-wake cycles.

Plasma melatonin levels are a robust marker of human circadian rhythm. There is evidence that critical care patients experience circadian rhythm disturbances and therefore, patients sleep may benefit from administration of exogenous melatonin. However, the effect of melatonin on critical care patients sleep quantity and quality has not been extensively studied. Furthermore, the kinetics of oral melatonin in critical care patients have not been investigated, and therefore dosing guidance are not available to optimise therapy.

3 PRELIMINARY EVALUATION OF MELATONIN THERAPY IN INTENSIVE CARE PATIENTS REFRACTORY TO CONVENTIONAL HYPNOTIC THERAPY

Introduction

The general medical-surgical intensive care unit at the Royal Hallamshire Hospital, Sheffield caters for patients requiring mechanical ventilation as part of advanced respiratory support for acute respiratory failure. In common with similar ICUs with a similar patient case mix, some patients require prolonged weaning from mechanical ventilation due to the severity of their acute illness and/ or chronic respiratory co-morbidities. It is relatively common for these patients to develop sleep disturbances during this weaning period.

It is usually the ICU nursing staff that identify patients as having sleep disturbances. This assessment is primarily based on a subjective assessment by the nurse caring for the patient during the night shift. Sometimes the patient themselves are able to communicate to the nursing or medical staff that sleep disturbances are a problem. Sedative or hypnotic therapy is frequently commenced based on these reports; ideally they are also used to direct therapy both in terms of efficacy (or potentially lack thereof) as well as possible adverse effects.

Historically, the intensive care unit has lacked formal guidance on the indications or selection of hypnotic agents. As such it was common for patients to receive multiple nocturnal sedative agents, often with limited success. At the time chloral hydrate, temazepam and lorazepam (*i.e.* GABAminergic drugs) were the most commonly prescribed hypnotic agents.

In late 1999 during discussion related to an individual ICU patient, one of the consultant medical staff questioned the potential benefit of melatonin administration in patients undergoing prolonged weaning from mechanical ventilation with sleep disturbances. Although the patient in question received conventional hypnotic therapy, a literature search was subsequently undertaken of MEDLINE and

EMBASE databases for studies pertaining to melatonin use in critical care or intensive care. This initial literature search was able to identify very limited supporting evidence for melatonin administration in critical care patients. However, it did stimulate the author's interest sufficiently to attempt to understand more about the regulation of sleep, pathophysiology of sleep disturbances, circadian rhythm disorders and specifically the potential role of exogenous melatonin in critical care patients. The most obvious question related to the potential efficacy regarding improvements in sleep quantity and quality, although other important questions co-existed. Which patients should receive melatonin? What dose should be used? What adverse effects could be expected? What precautions or contraindications were there?

Although classified as a medicine, no licensed melatonin products were identified in the UK. If the decision was to use melatonin in particular subgroups of patients, it would be necessary to identify an oral product that was suitable for clinical use. Although it would be unlicensed, the aim was to find a "pharmaceutical grade" product that was chemically synthesised. After a search of potential products, the most suitable oral dose identified was a 5 mg capsule preparation manufactured by Penn Pharmaceuticals. This product came supplied with a certificate of analysis which provided some reassurance regarding the quality of the dose form. The latter was a legitimate concern given the real potential for variation in content and contaminants in other melatonin products sold world-wide as health foods. At this time this product was used by a number of NHS hospitals, primarily for sleep disorders in paediatric patients with Attention Deficit Hyperactive Disorder (ADHD). In the era before Medicines Safety Committees requirement to approve the purchase and supply of all unlicensed medications and licensed medications for

unlicensed indications, specific criteria still had to be met before we could obtain a pharmacy supply. This included the requirement to have the support of the Clinical Director for the specialty, some guidance on its administration and an undertaking to evaluate an agreed clinical endpoint. Using the previously identified questions, draft guidance on the use of melatonin in critical care patients was compiled. In early 2000, the author formally presented a proposal to the Critical Care Directorate Clinical Management Group to consider exogenous melatonin therapy in ICU patients with sleep disturbances refractory to traditional hypnotic therapy. The Critical Care Directorate discussed the existing evidence base related to the potential application of exogenous melatonin therapy to improve sleep characteristics in intensive care patients. Evidence at the time suggested that intensive care patients lacked a nocturnal peak of urinary 6-SMT levels [312] and that exogenous supplementation may improve TST as measured by actigraphy [313]. Furthermore, an abstract reported that nocturnal administration of melatonin in mechanically ventilated patients decreased sedative requirements with a trend to reduced duration of ventilation [361]. The preliminary report by Lewis *et al* [361] had not appeared as a peer reviewed paper (and to date has not), but the Clinical Management Group agreed that there was sufficient evidence to consider melatonin in patients deemed unresponsive to conventional hypnotic therapy. Use would be on the authorisation of consultant medical staff only, to reduce the potential for indiscriminate use outside of the agreed criteria.

In November 2000 recommendations regarding dose, cautions, contraindications, drug interactions and prescribing authority were collated into guidance on melatonin use on the intensive care unit written (Appendix 1). To meet the pharmacy supply requirements for the use of an unlicensed medicine, a simple service evaluation was

designed to provide some objective measure of efficacy and safety in critical care patients (Appendix 2). Of particular concern was the potential hypothermic effect of melatonin and whether this would have consequences for infection surveillance.

Materials and Methods

Unblinded open label service evaluation of the effect of enteral melatonin administration on nocturnal sleep quantity in intensive care patients. The evaluation examined the use of melatonin therapy as part of the ICU procedure for treating refractory sleep disturbances. Analysis was based on data already routinely collected on the ICU, with the inclusion of a simple questionnaire for nursing staff. It was therefore classified as a service evaluation under the research governance procedures at the time. Ethics committee approval was not required or pursued.

The evaluation was undertaken on a single general medical-surgical intensive care unit. Melatonin 5 mg (Penn Pharmaceuticals, Gwent, UK) was administered orally or via enteral feeding tubes by the nursing staff at 2200 h for four nights. It was at the discretion of the medical consultant to increase the dose if they felt that an individual patient may benefit. Nocturnal total sleep time was estimated by nurse observation according to normal clinical practice. Each hour the nurse judged the patients as predominantly asleep or awake. Nocturnal sleep was considered as between 2200 and 0700 h and therefore there was a potential for 9 hours sleep to be recorded. The average sedation score for each night was ranked by the nursing staff using the Intensive Care Society definitions (Table 3-1). The lowest routine tympanic temperature between 2200 and 0700 h was also recorded during melatonin therapy and compared to the lowest previously recorded for each patient. Nursing staff were also asked to subjectively rank the quality of sleep of the patient during melatonin therapy compared to that when receiving traditional hypnotic medication. Quality of sleep was ranked as “worse”; “equivalent”; “better” each night compared to baseline sleep during conventional hypnotic therapy. Nursing staff also recorded if medical (non-nursing) interventions disturbed the patient during the night. Finally, nursing

staff were asked if they perceived sleep quality had benefited from melatonin administration compared to baseline hypnotic therapy.

Sedation Score	Description
3	Agitated and restless
2	Awake and uncomfortable
1	Awake but calm
0	Roused by voice
-1	Roused by touch
-2	Roused by painful stimuli
-3	Unarousable
A	Natural sleep
P	Paralysed

Table 3-1 Intensive Care Society Sedation Score

Baseline and historical data were collated from the intensive care unit clinical information system (MetaVision, IMD-Soft, Tel Aviv, Israel). Baseline nocturnal sleep time was the sleep duration observed and recorded by nursing staff for the patient on the last night of conventional hypnotic therapy immediately prior to the administration of melatonin.

Patients

Non-sedated intensive care patients that were identified by nursing staff observation to have severe sleep disturbances that were resistant to conventional hypnotic therapy. Patients with multiple sclerosis, encephalomyelitis and other severe autoimmune diseases were excluded. Sleep disturbances were defined as 4 hours or less observed sleep between 2200 and 0700 h each night.

Statistical Analysis

Data are described using descriptive statistics quoting mean and 95% confidence intervals (95% CI). Parametric analysis of continuous data undertaken with Student's *t* test displayed as mean (SD); non-parametric testing undertaken with Mann-Whitney Rank Sum Test displayed as median (IQR). Categorical data tested using Mann-Whitney Rank Sum Test displayed as median (IQR). Comparison of proportions of observations in groups was analysed by Fisher's Exact Test. The assessment of the relationship between continuous data lacking a normal distribution used Spearman Rank Order Correlation quoting correlation coefficient (*r*) and a *p*-value < 0.05 was regarded as statistically significant.

The primary endpoint was a difference in nurse observation of total sleep time between baseline and Nights 3 and 4 combined. Melatonin has a limited soporific effect when administered during the nocturnal period and probably has a predominantly chronohypnotic effect that may take up to three nights to demonstrate [279]. The secondary endpoint was a comparison between baseline and all four nights of melatonin administration.

Statistical analysis was undertaken using Sigmastat 3.1 (Systat Software Inc. California, USA) and SPSS 13.0 (SPSS Inc, Chicago, Illinois, USA).

Results

Fourteen patients received at least one nocturnal dose of melatonin. One patient received three courses of melatonin and only the first melatonin episode was analysed in this patient. A total of twelve patients received melatonin for at least three nights and were included for evaluation. Complete sleep quantity data were available for Nights 1-3; only seven of the 12 patients received melatonin on Night 4 for a variety of clinical reasons *e.g.* transfer out of intensive care unit. No patient received melatonin doses in excess of 5 mg during the courses evaluated.

Five different hypnotic agents were administered to the twelve patients prior to melatonin evaluation (Table 3-2). The patients received a median 1.0 (1.00; 1.50) hypnotics each, of which temazepam was the most commonly prescribed hypnotic agent administered to eight patients prior to melatonin.

Hypnotic drug	Number of patients
Chloral hydrate	2
Diazepam	1
Haloperidol	3
Lorazepam	2
Temazepam	8
Total	16

Table 3-2 Patient hypnotic administration prior to melatonin administration

Observed total sleep time at baseline and on subsequent nights after melatonin administration are shown in Table 3-3.

Nocturnal period	Nurse observation Total Sleep Time (hours)	95% Confidence Interval
Baseline	2.6	1.6 to 3.6
Night 1	3.2	1.3 to 5.1
Night 2	3.5	2.8 to 4.2
Night 3	5.2	4.4 to 6.0
Night 4	3.9	0.8 to 7.0

Table 3-3 Nurse observation of nocturnal total sleep time at baseline and after melatonin administration

Compared to baseline total sleep time, patients demonstrated a statistically significant increase in sleep duration on Nights 3&4 after commencing melatonin therapy. There was a trend to improved sleep quantity over the whole study period, but this did not reach statistical significance (Table 3-4).

	Total Sleep Time Coefficient	95% Confidence Interval	p-value
Nights 3&4	2.6	0.6 to 4.5	0.011
All Nights	1.4	-0.2 to 3.1	0.08

Table 3-4 Differences in observed Total Sleep Time means compared to baseline

Figure 3-1 shows the proportion of nights that patient's sleep were ranked subjectively by nursing staff as "better" than baseline conventional hypnotic treatment. There was a trend to increased perception of benefit by nursing staff when Nights 1 and 3 were compared, but this did not reach statistical significance (Table 3-5).

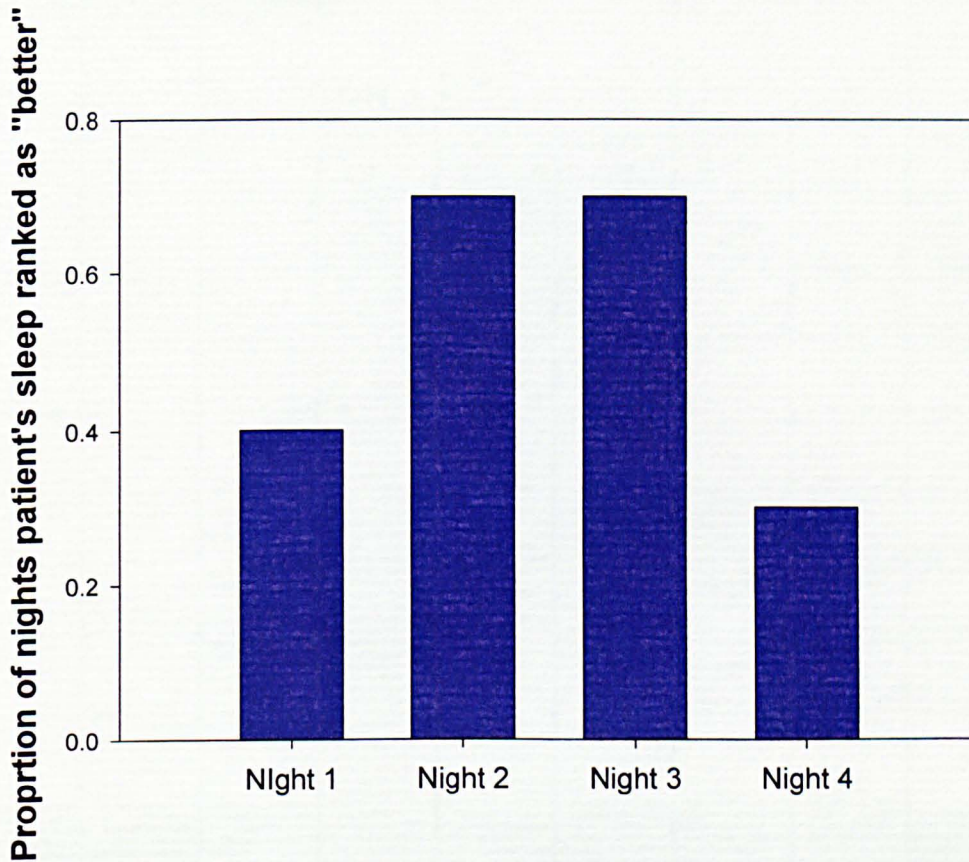


Figure 3-1 Proportion of nights in which nurse perception of observed sleep quality during melatonin administration was ranked as "better" than baseline hypnotic treatment

Nights Compared	p-value
Night 1 versus Night 2	0.179
Night 1 versus Night 3	0.070
Night 1 versus Night 4	1.000
Night 1 versus Nights 3 & 4	0.102

Table 3-5 Subjective nurse assessment of benefit Night 1 compared to subsequent nights

Medical interventions (non-nursing) disturbed patients on twenty of the 43 nights studied (47%). There was no significant relationship between nurse observation of total sleep time and medical interventions ($r = -0.05$ (-0.35 to 0.25); $p = 0.764$).

Average sedation score over the nocturnal period was recorded by the nursing staff each night. The median sedation score for each night is shown (Table 3-6). Sedation scores remained relatively constant during the study period, with patients all tending to be in the “awake” state. Those patients who were predominantly agitated on Night 1 remained so on the subsequent nights studied. There was no statistical difference in sedation score when Night 1 was compared to the other study nights (Table 3-7).

Night	Median ICS Sedation Score	IQR
1	1.0	1.0 – 3.0
2	1.0	1.0 – 2.5
3	1.0	1.0 – 3.0
4	1.0	1.0 – 3.0

Table 3-6 Nocturnal Intensive Care Society sedation score over the study period

Nights Compared	p-value
Night 1 versus Night 2	0.931
Night 1 versus Night 3	0.931
Night 1 versus Night 4	0.766
Night 1 versus Nights 3 & 4	0.931

Table 3-7 Nocturnal sedation score Night 1 compared with subsequent nights

During the melatonin administration period, tympanic temperatures recorded were lower than or equal to the historical lowest temperature record in four of the twelve patients. However, the historical temperature nadir was significantly lower than that recorded during melatonin therapy. Mean lowest baseline temperature was 35.5°C (35.4°C to 35.6°C) compared to during melatonin administration 36.3°C (36.1°C to 36.5°C) ($p = < 0.001$).

Nursing staff assessment of Nights 3 and 4 reported that compared to baseline hypnotic therapy melatonin improved sleep in six of the twelve patients.

Comments were infrequently completed on the evaluation form and very highly variable as might be expected and were not analysed further. Examples include: “No difference compared to temazepam”; “Slept more near the end of night, not immediately after the drug was administered”; “Second dose worked very well but for a short time (3 hours)”; “Has not slept at all”; “Takes a long time to work!”.

Discussion

The results of the preliminary evaluation demonstrated an increased observed nocturnal sleep time with melatonin compared to baseline in a group of intensive care patients with severe sleep disturbances refractory to conventional hypnotics. A significant benefit of two and a half hours duration was seen after three night's therapy and whilst increased sleep was noted over the whole study period, this did not reach statistical significance. Similar to another study in elderly insomniacs, [279] melatonin did not appear to have an immediate soporific effect, instead compared to baseline subjective assessment by nursing staff, nocturnal sleep duration was significantly increased when Nights 3 and 4 were combined. There was also a trend to suggest nursing staff subjective rated melatonin therapy as better than the conventional hypnotic therapy by Night 3.

Some patients received multiple (range 1-3) hypnotic agents, on occasions at particularly large doses *e.g.* 2g chloral hydrate. This practice of using significant doses of multiple hypnotic agents is not uncommon in intensive care units as staff attempt to recreate a more normal sleep-wake cycle in patients who have and are vulnerable to repeated episodes of critical illness [205]. Previous, often prolonged exposure to GABAminergic medication as part of sedation regimes increases the risk of tolerance to benzodiazepine hypnotic medicines and predisposes to reduced nocturnal sleep efficacy. This probably manifests itself both as insomnia related to GABAminergic withdrawal and tachyphylaxis to nocturnal doses of hypnotic benzodiazepines. Increasing doses of hypnotic agents increases the potential for adverse events, including further disruption of sleep architecture, but also potential for respiratory depression and sleep inertia the next day and therefore delayed weaning from mechanical ventilation and increased intensive care length of stay. The

potential for adverse cognitive effects should not be underestimated. In attempting to obtain nocturnal sleep the hypnotics used may precipitate or aggravate delirium and result in increased sleep-wake disturbances.

The preliminary evaluation was initially designed to meet the Pharmacy and Critical Care requirements for the initial use of melatonin. The quantitative data provided some reassurance that vulnerable intensive care patients were not being subjected to an unlicensed medicine without some perception of benefit.

The evaluation had numerous obvious limitations. The evaluation was by definition unblinded and therefore there was potential for bias amongst the nursing staff recording sleep duration each night. At the time of the evaluation there had been significant local interest concerning the potential merits of melatonin therapy in this patient group and as such there was a degree of anticipation regarding actual clinical effects. This may have provided both positive and negative effects on the subjective evaluation by staff. The causes of sleep disturbances in intensive care patients are multifactorial, including the acute illness itself, environmental factors (e.g. noise, light), medication, pain, ventilator settings and patient factors (e.g. age, chronic sleep problems) [23]. Since the evaluation compared a pharmacological intervention of sleep in patients already identified as refractory to hypnotic medication, no attempt was made to take account of individual patient factors as they were considered to be relatively constant. However, this convenient approach did not acknowledge the acuity of illness, interventions or variability in environmental factors that characterise intensive care. The evaluation would have benefited from some demographic details which may have demonstrated an association with the sleep quantity data. Specifically, there was no measure of illness severity e.g. APACHE II score, and as such it was impossible to exclude patient recovery as a factor

contributing to the improved sleep duration recorded. Nocturnal sleep during melatonin was compared to a baseline night, *i.e.* the last night in which the patient received conventional hypnotic therapy prior to commencing melatonin. Sleep disturbances demonstrate significant intra and inter-night variability and it is possible that the use of the single baseline night that triggered a change in sleep intervention may have actually provided an artificially low quantification of sleep in which to compare subsequent nights to. Nursing staff were asked to subjectively rank the sleep quality during administration of melatonin compared to baseline hypnotic therapy, not all nurses experienced both periods for the same patient and therefore some nights relied on nursing kardex and discussions with colleagues, with compounded effects on subjectivity. There was no wash out period and therefore the results obtained on Night 1 are subject to the potential confounding hang over effects from the hypnotic administered on the previous night. Environmental factors such as noise and light disturbances are known to account for approximately 20% of arousals and awakenings in intensive care patients [35]. The only environmental factor recorded was medical disturbances. Patient care activities are a factor affecting sleep quality, [35]. There was no correlation between medical interventions and subjective nocturnal sleep duration; however these data were limited. Non-nursing disturbances were common, but there was no quantification of the degree of disturbance or frequency. Furthermore, there was no sample size calculation to inform the number of patients required to be evaluated and only twelve patients met the criteria of 3 or more nights of melatonin therapy. The small sample size obviously contributes to the caution required when drawing conclusions from this evaluation; however it was of a consistent sample size to other critical care reports on this subject at the time [313]. The evaluation relied entirely on nurse observation of nocturnal sleep duration as a

measure of sleep quantity and quality. Nurse observation has been demonstrated to correlate well with polysomnography in terms of a nurse's capability of recognising if a patient is asleep or awake [28]. However, in the study by Edwards *et al*, [28] nurses assessed sleep every 15 minutes, not hourly as was the local clinical practice. The validation period was also relatively short, at four hours compared with the four nights in the current evaluation. Although nurse observation is obviously a subjective measure of sleep, it provided some indication of sleep quality, which appeared to improve during the period of melatonin administration. The evaluation would have benefited from application of a validated objective measure of sleep quality in the intensive care patients studied. Generally patients are the best judges of the sleep quality. Patients would normally be anticipated to have insight into their baseline, pre illness sleep quality and in theory should be able to provide a useful subjective assessment of the impact of any intervention. A numeric rating or visual analogue scale used by the patients would also have added useful data; however this was inappropriate for a service evaluation. The potential adverse sleep effects of delirium were not accounted for. At the time "ICU psychosis" was a term commonly used to describe patients who were agitated and confused on the ICU. Beyond views that poor sleep was a risk factor, no attempt to screen for delirium was made and therefore it is not possible to comment on the possible effect delirium had on the sleep results. However, the fact that three patients had previously received haloperidol prior to melatonin administration does suggest that a degree of confusion or agitation had been previously identified in these individuals at least. Indeed the sedation score remained relatively constant during the study period in each patient, including those patients predominantly described as "agitated" (sedation score \approx 3).

Locally, there was no clinical experience with oral melatonin and therefore there was uncertainty regarding the degree of sedation or hypothermia a 5 mg dose of melatonin may have in patients recovering from critical illness. The literature at the time had studied a very wide range of doses, including those far in excess of 5 mg daily [10]. However, it was also unknown what affect critical illness would have on the pharmacokinetics [325, 326, 352] or pharmacodynamics of melatonin in these patients. For these reasons nurse assessment data for the average nocturnal sedation score for each patient night was recorded, to provide an indication of the depth of sleep or sedation related to melatonin administration. The median sedation score was 1 (“awake but calm”) and there was no significant difference between any of the melatonin nights. In fact no patient had a mean sedation score assessed by the nursing staff as sedated but “roused by voice” or “roused by touch” (0 to -1). This suggests that while melatonin may be sedation sparing, [361] it did not induce significant sedation in these patients. However, this is not totally unexpected as these patients represented a subgroup of patients recovering from critical illness who also appeared to be refractory to traditional hypnotic agents, possibly as a result of GABAminergic tachyphylaxis. GABAminergic activity remains a proposed pathway for the soporific effects of melatonin [10]. If melatonin had increased the depth of sleep as well as duration, it may be anticipated that a reduction of median sedation score at Night 3 would be reported. A patient demonstrating good quality sleep would be expected to have a median sedation score of zero (roused by voice), an overall nocturnal score none of the patients achieved on any of the nights evaluated. It remains that the Intensive Care Society sedation score is unvalidated as a subjective measure of sedation and certainly was not designed as a measure of depth of sleep.

Melatonin is known to have a hypothermic effect and indeed this may be one of its mechanisms of action in inducing sleep [10]. Although patients with a SIRS are normally pyrexial, some patients can be hypothermic ($< 36^{\circ}\text{C}$) and probably some degree of pyrexia is required to optimise host defence mechanisms targeting of infection. Therefore, routine nocturnal tympanic temperatures were also evaluated during melatonin administration and compared it to the lowest tympanic temperature the patient recorded during their intensive care stay. Four patients had temperatures as low as or lower than the historical data nadir. However, the historical tympanic temperature was statistically lower when compared to the lowest temperature recorded during melatonin administration. These data suggest that with a mean lowest tympanic temperature of 36.3°C there should be minimal concern concerned regarding the hypothermic effect of melatonin in these patients unless they have a severe infection. A continuous measure of temperature, such as provided by a rectal or bladder probe, would be needed to accurately determine nocturnal temperature variability. This was clearly beyond the remit of a service evaluation. The nocturnal temperature changes may simply reflect the normal variability in temperature that occurs during physiological sleep. The presence of better sleep continuity may therefore affect nocturnal sleep temperature and reflect a patient's circadian rhythm. It was not possible to comment on any chronobiotic (entraining) effect melatonin may have had on this marker of circadian rhythm. Although it remains that temperature is unlikely to be an accurate marker of rhythm in acutely ill patients [56]. Potential thermodynamic effects aside, melatonin may have desirable effects with regard to a patient's antioxidant capacity, which may ultimately prove to be of benefit during a septic insult [322].

The results of the preliminary evaluation of melatonin therapy provided the stimulus to undertake a larger, randomised placebo controlled study of the effects of melatonin on sleep in intensive care patients. Furthermore, the initial evaluation was useful in assisting with the design of a subsequent study, including sample size calculations. The duration of the study period had to be a minimum of three nights to ensure that the potential chronohypnotic effects of melatonin were evaluated. It was necessary to provide a subjective sleep assessment by nursing staff, patient assessment and objective sleep measurements. Ideally, a measure of sleep depth should be included to examine if melatonin increased deep stages (SWS and REM) of sleep rather than just increase total sleep time. To examine if melatonin's effect on the patient's sleep-wake rhythm it would be necessary to include an objective measure of sleep throughout the 24 hour period.

Appropriate baseline patient data would need to include an indicator of historical sleep quality, and also exclude patients with chronic sleep problems. A method of controlling for the environmental effects of noise, light and patient care activities needed to be accounted for. Similarly, potential for adverse effects of medicines and mode of ventilation had to be quantified.

It was also necessary to consider the administration method of oral melatonin *via* feeding tubes, to ensure dosing confidence and effective investigator blinding in the study. A pharmacokinetic study would be required to provide guidance on oral melatonin dosing in future studies of critical care patients. Finally, the results of the preliminary evaluation would also assist with obtaining ethics committee validation of both the study protocol and patient information sheets.

Conclusions

The open service evaluation found improved sleep quantity after 3 nights melatonin therapy when assessed by nurse observation. There was a trend to increased sleep quantity over all nights evaluated, although this did not reach statistical significance. Melatonin did not appear to have a sedative effect, demonstrating no change in the subjective sedation scores over the evaluation period. It may be that the benefits of melatonin are not related to a direct soporific, but a chronohypnotic effect which deserves further investigation in a randomised controlled trial.

4 **FORMULATION OF AN ORAL MELATONIN SOLUTION**

Introduction

A key issue identified when planning began for a randomised placebo-controlled study to investigate the efficacy of melatonin on sleep in intensive care patients, concerned the melatonin formulation to use. It was necessary to consider not only where to obtain a pharmaceutical grade product, but also the specific details of how the oral medication would be administered to critical care patients. Over half of all oral doses administered to critically ill patients in Sheffield high dependency and intensive care units are given through enteral feeding tubes. Patients with tracheostomies receive all their oral drugs by this route until either removal of the tracheostomy or deflation of the cuff and oral feeding has commenced with minimal gastro-intestinal aspirates. Therefore, it was not possible to use a proprietary modified release oral melatonin preparation such as done by other investigators [313] as this would require the tablet to be crushed by the nursing staff prior to naso-gastric or jejunal administration. This would result in, at best, an immediate release of the melatonin dose, or more likely a variable mixed immediate and delayed release pattern. This was undesirable in that it would add to the variability in plasma concentrations of melatonin.

Melatonin is an unlicensed medicine in the UK and, as such, authorisation from the Medicines Control Agency (MCA) was required to undertake a clinical trial with a named, pharmaceutical grade melatonin product. A request was made to use Melatonin 5 mg capsules (Penn Pharmaceuticals, Gwent, Wales) in the *Notification by a practitioner under the provisions of the medicines (exemptions from licenses) special cases and miscellaneous provisions order 1972 (SI 1972 No 1200)*, commonly referred to as a DDX. The DDX also required a brief overview of the planned study methods, setting and patients. Penn Pharmaceuticals, as the supplier,

were also required to complete an undertaking to the MCA certifying that they held a product licence for the melatonin capsules. Subsequently the DDX was granted for the study using the 5 mg capsules. As a pharmacist, the author was unable to be named as the lead investigator on the DDX application. Therefore, one of the medical consultants (Dr S P Hutchinson) assumed this responsibility.

In order to maintain the blinding of the nursing staff to the study, the melatonin and placebo presentations needed to be indistinguishable. Owing to the hygroscopic nature of melatonin it was necessary to find an inert placebo with similar characteristics when mixed with water. Initially, it was considered that the nursing staff would be able to mix the melatonin/ placebo powder with water for injection prior to administration. However, even with the assistance of the pharmacy manufacturing unit personnel, it was not possible to identify or formulate a placebo powder with sufficiently similar physiochemical characteristics to the powder content of the melatonin capsules. As an alternative to a powder formulation, it was decided to develop a liquid presentation. Although such liquids are available commercially under the classification of 'health foods', they were unsuitable because they do not have to meet pharmaceutical standards of active content and stability [360, 362, 363]. Consequently, it was necessary to formulate an oral melatonin solution for use in the study using pharmaceutical grade melatonin.

A "pharmaceutical grade" melatonin powder was sourced from BUFA (Uitgeest, Netherlands), and a new DDX was applied for with confirmation that the melatonin powder would be formulated into a pharmaceutical quality oral solution.

The oral solution was formulated to meet the immediate needs of the study. The majority of doses would be administered via naso-gastric or jejunal tubes and therefore the colouring, flavouring and texture of the oral liquid, were regarded of

limited importance. The aim was to formulate a simple aqueous solution that was stable, and contained a preservative to prevent microbiological contamination.

Materials and Methods

The oral melatonin solution was developed within the Extemporaneous Dispensing Unit of the Royal Hallamshire Hospital Pharmacy Department. Physiochemical stability testing was undertaken within the Quality Control Unit, also within the Pharmacy Department.

Materials

Since melatonin is hygroscopic it was necessary to add a small volume of ethanol to the formulation to ensure complete dissolution of the active ingredient in the final solution. The quantity of ethanol was minimised to ensure that any soporific effect was due to the melatonin and not the alcohol [214]. Sodium benzoate was used as the preservative, requiring pH adjustment to less than 5 to ensure optimal anti-microbiological activity [364]. A pH of about 4.5 would also increase the stability of the melatonin [365, 366]. Citric acid was used as the acidifying agent. The final solution was stored in amber bottles and refrigerated to reduce photodegradation of melatonin [365] and to increase microbiological stability.

Melatonin and glycerin BP were purchased from BUFA (Uitgeest, Netherlands), sodium benzoate and citric acid monohydrate from Courtin & Warner (London, UK), purified water BP from Baxter (Thetford, UK) and ethanol 90% BP from BDH (Poole, UK).

For HPLC analysis, purified water BP was purchased from Baxter (Thetford, UK) and ethanol 90% BP, potassium dihydrogen orthophosphate AR and methanol HPLC grade from BDH (Poole, UK). All HPLC assays were carried out using a Merck/Hitachi system with L5000 LC controller, a 655A-12 pump, a Jasco MD-910 diode array detector and a Jasco 851-AS autosampler. The reverse phase HPLC

column (HiQ sil, C18, 15cm, 5 micron and 4.6 mm internal diameter) was purchased from KYA Tech (Tokyo, Japan).

Methods

After several modifications, the formulation described in Table 4-1 was considered to be suitable.

Batch no.	Ingredients	Quantity	Measured by		Checked by	
02H20FN	Melatonin	0.05 g		CH		HB
101F16	Glycerin BP	10 ml		CH		HB
102F16	Ethanol 90%	5 ml		CH		HB
109D08	Sodium Benzoate	0.1 g		CH		HB
102F19	Citric Acid	Qs		CH		HB
101F12	Purified Water	To 100 ml		CH		HB
Sheet written by : HB			Checked by : HB			
Source of formula : N/A						
Method : Make a 2% citric acid solution (approx. 30ml). Weigh melatonin in 500ml beaker, add ethanol and dissolve (leave for 10 minutes). Dissolve sodium benzoate in 20 ml water before adding to beaker. Add glycerin and more water until nearly to volume then add citric acid solution until pH 4.5 (approximately 4 ml). Make to volume and pack.			Label : Label ref – N/A No. labels printed [____] Printed by [____] Checked by [____] Expiry : To Be Confirmed Store in a refrigerator. Shake well before use.			
Calculations :			Containers and closures : 1 x 100ml amber glass medical 1 x R3/22 black polycone cap or clic loc cap 1 x viskring			
Cautions :			Finished product approved By : Date :			

Table 4-1 Royal Hallamshire Hospital Pharmacy Production worksheet for a 0.5 mg/ml oral melatonin solution

pH testing

Single measurements of the pH of the solution were made with a Corning 250 ion-analyser and a Mettler-Toledo general-purpose combination electrode at preparation and then at 7, 14, 70 and 450 days after preparation.

Chemical stability

The stability of the melatonin the solution was assessed at preparation and then at 7, 14, 70 and 450 days by HPLC.

The mobile phase was 0.05M potassium dihydrogen orthophosphate, pH 4.5 - methanol 57:43 mixture delivered at a flow rate of 1 ml/min. Detection was by UV absorbance at 225nm. The components of the mobile phase were degassed ultrasonically under vacuum and filtered (0.45 microns) before mixing in the proportioning valve. Samples were diluted volumetrically in duplicate to give a concentration of approximately 0.002% w/v melatonin. Three aliquots of each dilution were injected onto the column three times. A fresh standard of melatonin was prepared on each day of analysis and triplicate injections made as for the sample dilutions.

A solution of 0.01% w/v melatonin in 0.1M hydrochloric acid was autoclaved at 121°C for 15 min to produce acid decomposition products.

Statistical analysis

The relationship between melatonin concentration and HPLC peak area was assessed by linear regression. The precision of the HPLC assay was expressed as relative standard deviation. Statistical analysis was done using SPSS 11.0 (SPSS Inc, Chicago, Illinois, USA).

Results

pH Stability

The pH of the solution was stable within the range 4.1 – 4.4 over 450 days (Table 4-2).

Time (days)	pH	
	4°C	25°C
0	4.34	4.36
7	4.34	4.32
14	4.37	4.34
70	4.34	4.33
450	4.19	4.30

Table 4-2 pH of 0.5 mg/ml oral melatonin solution over time

Chemical stability

The chromatogram shown in Figure 4-1 indicates baseline resolution of melatonin from products of acidic decomposition. At no time up to 450 days of storage were any decomposition peaks observed (Figure 4-2).

Plots of melatonin concentration (0.0008 to 0.004% w/v) against peak area were linear with a regression coefficient of 0.99997 and with a 95% CI of the Y-axis intercept including zero.

The relative standard deviation of the method was 0.43%. Duplicate measures of melatonin content of the solution stored at 4 and 25°C ranged from 98.6 – 101.5% over the period of the stability study (Table 4-3).

Time (days)	% of Original	
	4°C	25°C
0	100	100
7	98.6	99.1
14	100.6	99.6
70	101.5	101.3
450	99.9	99.1

Table 4-3 Stability of melatonin in the 0.5 mg/ml solutions

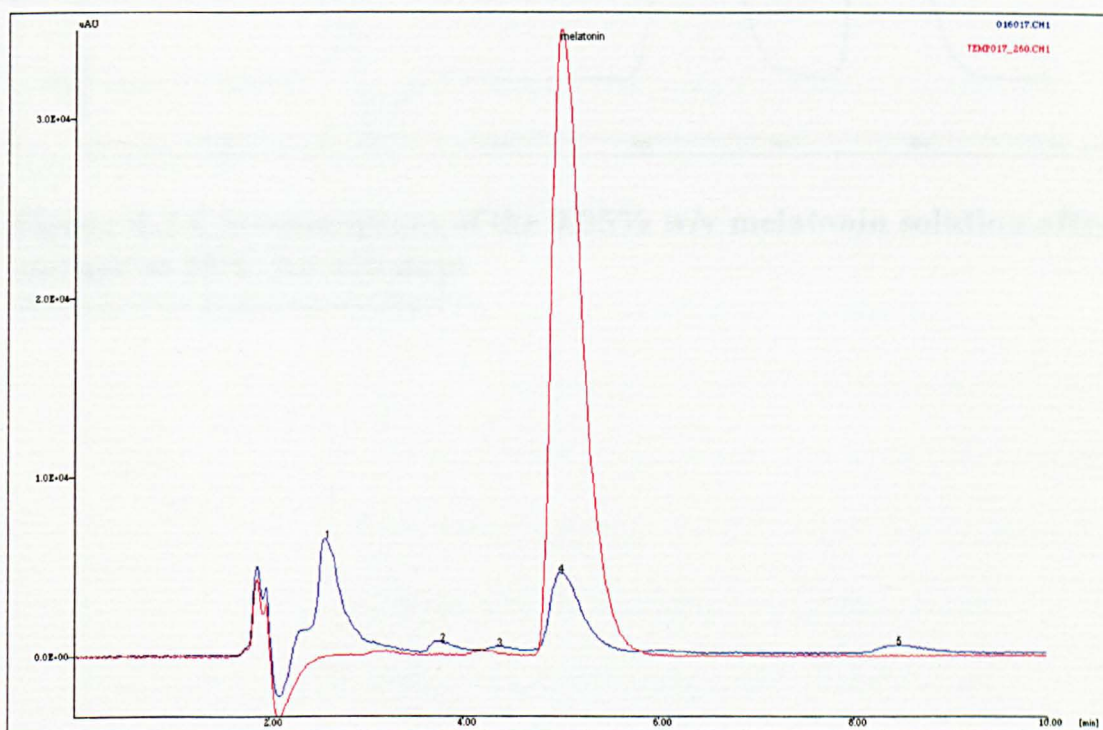


Figure 4-1 Chromatogram showing the separation of melatonin from acid decomposition products after autoclaving at 121-124°C for 15 min in 0.1M hydrochloric acid

Melatonin (Peak 4); Acid decomposition products (Peaks 1,2,3,5).

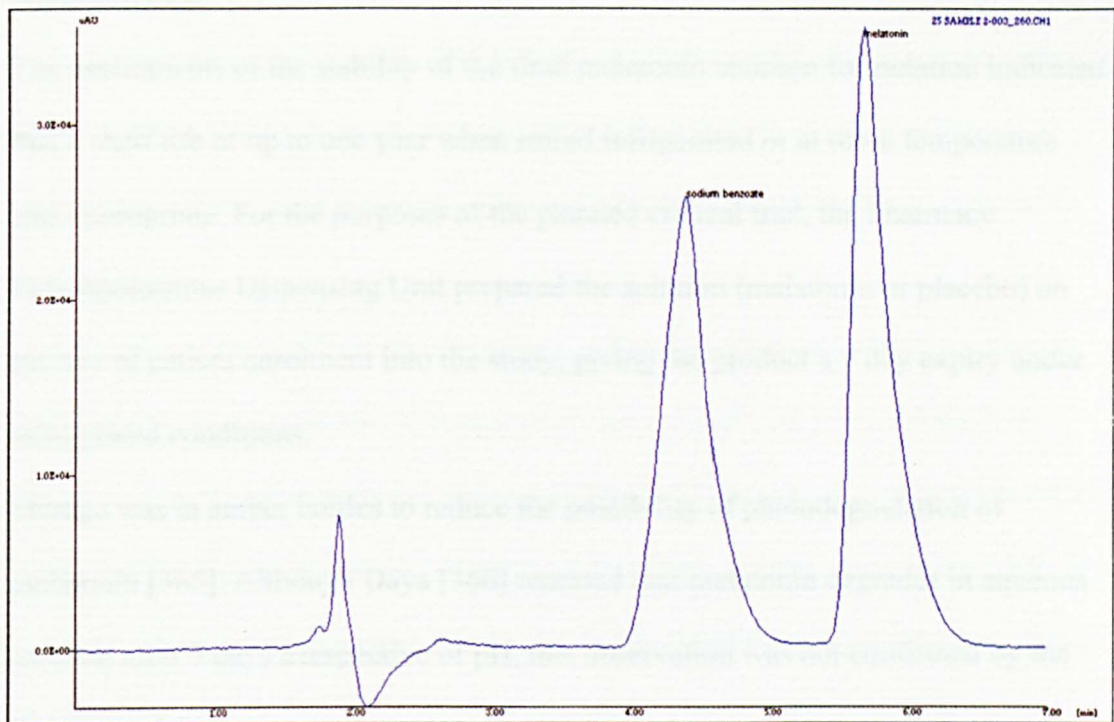


Figure 4-2 Chromatogram of the 0.05% w/v melatonin solution after storage at 25°C for 450 days
Melatonin (Peak 2); Benzoic acid (Peak 1).

Discussion

The assessments of the stability of the final melatonin solution formulation indicated that a shelf life of up to one year when stored refrigerated or at room temperature was appropriate. For the purposes of the planned clinical trial, the Pharmacy Extemporaneous Dispensing Unit prepared the solution (melatonin or placebo) on the day of patient enrolment into the study, giving the product a 7 day expiry under refrigerated conditions.

Storage was in amber bottles to reduce the possibility of photodegradation of melatonin [365]. Although Daya [366] reported that melatonin degrades in aqueous solution after 3 days irrespective of pH, this observation was not confirmed by the present study.

The results of the stability study were in agreement with the findings of Cavallo [367] who reported stability at 4°C in aqueous solution up to 6 months.

A supply of “pharmaceutical grade”, chemically synthesised melatonin was used to ensure confidence that the product was free from contaminants that have been found in some melatonin health food products. Analogues of impurities similar to those in L-tryptophan, and associated with the development of eosinophilia-myalgia syndrome, have been identified in such products [360, 368]. As there is no monograph on melatonin in the British Pharmacopoeia (BP), by definition there is no official pharmaceutical grade of melatonin. The US Pharmacopoeia (USP) includes a reference standard for melatonin, but currently there is no monograph to compare against. Nevertheless, the term “pharmaceutical grade” has been applied to the BUFA product as it meets the criteria for 99% purity and contains no binders, fillers, dyes or unknown substances.

In the initial attempts at formulation, there was some difficulty in getting the preservative, sodium benzoate, into solution. A concentration of 1% w/v was used, which was excessive for the antimicrobial activity required. Therefore, the concentration of sodium benzoate used in subsequent formulations was reduced to 0.1% w/v.

Ethanol has sedating effects that are often used by insomniacs to aid sleep onset at bedtime. The final melatonin solution contained 0.9g ethanol per 20ml dose of melatonin. This compares to the 14-16g of ethanol in a small glass (125ml) of white wine, and the 35g used in a typical study of the effects of ethanol on sleep [214]. The sedating effects of ethanol are also affected by the baseline alertness or sleepiness of the individual [369]. ICU patients with demonstrated sleep fragmentation (if not deprivation) may, therefore, be expected to demonstrate increased sensitivity to the sedating effects of ethanol. This relationship is further complicated by an individual's previous tolerance to alcohol as well as their more recent exposure to GABAergic drugs. In a dose ranging study of the sedating effects of ethanol, the starting dose of ethanol used was approximately 23g [370]. The dose of ethanol provided by administration of melatonin in the oral solution formulation would appear insignificant with respect to evaluating the sedative effects of melatonin. In any event, the placebo solution contained the same amount of ethanol as the active. The optimum use of melatonin as a chronohypnotic agent relies on the administration of an appropriate dose at an appropriate time. Ideally, there should be a peak effect soon after administration followed by exposure comparable to "normal nocturnal plasma levels", which then return to daytime levels by the morning. Given the relatively short plasma elimination half-life in healthy individuals, this could be best achieved with an oral dosage form with a two phase release profile. An initial

immediate release of melatonin should be followed by a modified release to provide the continuous nocturnal plasma concentrations. Such solid dosage forms have been manufactured, [359] and, in the case of Posidorm (Alliance Pharmaceuticals), are undergoing Phase III studies in preparation for clinical use. An oral product providing only a sustained release of melatonin would require that the lag time to reach a physiological nocturnal plasma melatonin concentration be allowed for in dosing. However, any solid formulation is impractical in patients undergoing feeding by a naso-gastric tube, and a liquid formulation for oral administration is necessary. Parenteral administration would not be acceptable in patients recovering from critical illness because of the need to limit multiple vascular access. Transdermal delivery of melatonin would be attractive if a dependable delivery system could be formulated to provide the desirable surge-sustained dosing described. An obvious advantage of such transdermal administration is of course that it can be used independent of a functioning gastric-intestinal tract, a common limitation in this patient group. Like any transdermal delivery system variation in blood supply to the skin as a consequence of sepsis, vasoconstrictors and pyrexia may adversely affect the release characteristics of the drug with the potential to adversely affect the entrainment signal achieved. As with all transdermal delivery systems they have the ability to be found in the patient's bed after becoming dislodged at an unknown point in the preceding day; something that even the best designed product cannot circumvent. Nevertheless, transdermal delivery systems for melatonin continue to be developed using novel vehicles such as elastic liposomes, [371] in an attempt to overcome the relatively short half life of melatonin. Sublingual delivery of melatonin would also bypass the "first pass effect" and improve bioavailability, irrespective of gastric-intestinal function. Lower doses would be required but modified release would be

difficult to achieve. The labelling of some of the available melatonin health food products advocate sublingual dosing without appropriate dose modification (*e.g.* BioTonin, EuroHealth Inc. Perkasi, Pennsylvania, USA). Sublingual dosing of melatonin has also been used in the clinical environment to provide sedative pre-medication prior to surgical procedures [372-374]. However, sublingual dosing may be haphazard in critical care patients with xerostomia as a consequence of factors such as dehydration, endotracheal tube *in situ* or the anticholinergic effects of drugs. Intranasal administration of melatonin as a liquid spray formulation again allows bypass of the liver to produce plasma concentrations comparable to IV doses [375]. A preliminary report suggests that work is ongoing with intranasal melatonin administration in ICU patients [376]. This is an attractive approach for clinical application in ICU patients, although development of an effective dosing strategy with this immediate release route is necessary.

Conclusions

This stability study found that melatonin could be formulated in an oral solution that remained stable for up to a year. The availability of a pharmaceutical grade oral solution of melatonin met the regulatory requirements of the MCA and ensured dosing confidence in the planned randomised controlled trial.

5 METHODS

Methodological Development

Study Design

Initially it was intended to carry out a cross over study thereby allowing better control of individual patient factors. However, this design necessitated the enrolment of patients for a long period (7-10 days), and there was a risk of carry over of the effects of melatonin into the placebo phase if the washout period was insufficient. Therefore, it was decided to adopt a parallel group design, despite the associated requirement for a greater number of patients.

Patient Selection

Non-sedated critical care patients were selected for recruitment who could be studied continuously over a period of 5 nights and who had a tracheostomy to assist weaning from mechanical ventilation. Such patients generally require a prolonged period of respiratory support as a consequence of cardiovascular or respiratory co-morbidities and/ or a severe acute lung injury and, therefore, are likely to require an extended ICU admission with vulnerability to acute sleep disturbances. It was necessary to exclude patients with sleep disturbances prior to admission, with co-morbidities predictive of sleep disturbances and low levels of consciousness.

Study Endpoints

The planned primary endpoint was patient nocturnal sleep efficiency index (SEI) over nights 3 to 5 (total nocturnal sleep quantity expressed as a ratio of time available for nocturnal sleep). Analyses would be limited to nights 3 to 5, since the potential chronohypnotic benefits of melatonin are not immediate and may take three days to be realised [279, 377]. All five nights would be considered in a secondary analysis.

Polysomnography, [36] actigraphy [312] and the bispectral index (BIS) [378] have all been used as objective studies of sleep in previous critical care studies. Initially, it was proposed to use actigraphy as a continuous objective measure of sleep quantity, *i.e.* it would provide data on sleep quantity during the diurnal and nocturnal sleep periods. The latter was important as critical care patients' sleep traverses the day-night period and as much as half of total sleep time can occur during the day [23]. While the primary interest was in using interventions such as medication to consolidate the quantity and quality of nocturnal sleep, daytime sleep, particularly later in the afternoon can have adverse effects on nocturnal sleep efficiency. Although this technique had been used previously to study the effects of melatonin in ICU patients, [313] it was thought that it would not provide all the information required. It was, therefore, planned to also use the BIS as another objective measure of sleep. It was decided to use the Richards Campbell Sleep Questionnaire to quantify patient assessment of sleep, as this tool has been validated in a critical care population versus polysomnography [29]. Nurse assessment of nocturnal sleep quantity would also be used. The frequency of nurse assessment of sleep in other critical care studies has ranged from 5 minutes, [27] to 8 times [87] per day. It was initially planned to adopt 15 minute intervals [28]. However, nursing staff felt that this may impinge on direct patient care. Therefore, it was agreed to limit nurse observation of sleep to hourly epochs during the night, according to the clinical practice at the time.

The sleep measurement techniques were, therefore, finalised as BIS (Aspect Medical Systems, USA), actigraphy (Actiwatch Plus, Cambridge Neurotechnology, UK); nurse assessment (direct nurse observation using hourly epochs) and patient assessment (Richards Campbell Sleep Questionnaire, RCSQ). Although the RCSQ

provides a five component rating of nocturnal sleep, a total score can be calculated from the mean of total scores in the 5 domains. This total score has been used as a measure of sleep efficiency index and has been validated against polysomnography [29].

Although the possibility of using polysomnography as measure of sleep quality was explored, this was not possible on grounds of both availability and cost. However, it was decided to evaluate the relationship between the BIS and EMG scores of the Bispectral index and polysomnography in a study with normal subjects.

Thus, the primary endpoint was planned to be nocturnal sleep efficiency as measured by actigraphy. Secondary endpoints would include nocturnal sleep efficiency measured by BIS, nurse assessment and patient assessment. Furthermore, diurnal sleep quantity as measured by actigraphy would also be investigated as a secondary analysis.

Delirium screening was also planned as part of the study for two reasons. Firstly, delirium symptoms include sleep disturbances and, as such, knowledge of delirium status at baseline has implications for between group comparisons. Secondly, a significant disadvantage of traditional hypnotic agents is the potential for delirium, and information regarding the incidence of delirium in patients commencing melatonin *versus* placebo would be beneficial. Diagnosis of delirium is difficult in intensive care patients primarily because of their limited ability to communicate. A number of delirium screening techniques have been developed for use in this patient population. It was decided to use the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) as it is both validated, [379] and accompanied by a substantial training package. Between group differences in delirium incidence, as measured by the CAM-ICU, was planned as a secondary endpoint.

Study Size

Based on data from two studies in critical care patients by Shilo *et al* [312, 313] (SD = 0.11), it was estimated that a minimum of 12 patients would be needed to detect a difference in SEI of 0.20 by actigraphy ($\alpha=0.05$; power=0.8). Using nurse observation the results from the preliminary melatonin evaluation provided a larger variation (SD = 0.26), indicating that a minimum of 56 patients would be required (Chapter 3). Data from several polysomnography studies reported SD values of 0.1 - 0.24 [29, 36, 193, 380]. Therefore, it was decided to use a SD of 0.20 which resulted in a desired sample size of 34 patients for the randomised controlled trial.

A review of the MetaVision clinical information system (iMDSOft, Tel Aviv, Israel) audit data over the period 2000-2002, identified 108 patients admitted to the Royal Hallamshire Hospital ICU with a tracheostomy requiring an ICU stay of at least 10 days. Thus a single site study seemed feasible with regard to patient recruitment and would serve to support the Ethics Committee application.

Melatonin Dose

The development of an oral solution of melatonin is described in Chapter 4. A 5 mg dose administered at 2200 h was used in the preliminary evaluation (Chapter 3), although subsequently other patients had received doses up to 10 mg. The latter dose was reported to entrain the circadian rhythm of melatonin secretion by Sack [287]. Therefore, it was decided to use a 10 mg dose administered at 2100 h hours to coincide with the normal phase response curve of melatonin [266].

Measurement of plasma melatonin

An assay was required to measure both endogenous plasma levels of melatonin and concentrations after oral administration. Radioimmunoassay (RIA) kits are commercially available that can be used to measure concentrations of the order of 10 pg/ ml, [259, 348, 381] while gas chromatography-mass spectrometry (GC-MS) has been used down to 1 pg/ ml [382] and high performance liquid chromatography-mass spectroscopy (HPLC-MS) has a lower detection limit of 2 ng/ ml [383]. Because of the low sensitivity of published HPLC-MS methods and a lack of access to GC-MS, it was decided to use a RIA (Immuno Biological Laboratories, Hamburg, Germany), despite its inherent lower precision. A particular concern with RIA is lack of specificity due to cross-reaction of the antibodies with drug metabolites. Plasma concentrations of 6-hydroxymelatonin are much higher (35 fold) than those of the parent compound [255]. However, preliminary studies with a source of this metabolite (BUFA, Uitgeest, Netherlands) indicated only 0.004% cross-reactivity with the kit that was used (Immuno Biological Laboratories, Hamburg, Germany). The suppliers of the kit claim cross-reactivities of 0.8, 0.7 and 0.08% with N-acetylserotonin, 5-methoxytryptophol and 5-methoxytryptamine, respectively. The latter are not important metabolites of exogenous melatonin, but are present endogenously in plasma as a result of indoleamine biosynthesis and metabolism [384]. 6-hydroxymelatonin is metabolised to 6-sulphamethoxymelatonin [385]. Although it was not possible to source an authentic sample of this compound to check cross-reactivity, Hartter *et al* [386] reported no cross reaction with any melatonin metabolites with the RIA kit that they used.

Melatonin RIA procedure

The RIA was undertaken according to the manufacturers' instructions (Melatonin direct RIA (Plasma), Immuno Biological Laboratories, Hamburg, Germany). Quality control samples were included and confirmed to be within the acceptable ranges. Plasma samples were defrosted immediately prior to testing and centrifuged before assaying in duplicate. Samples suspected to contain concentrations higher than the linear range of the assay (30 – 200 pg/ ml) were diluted with buffered bovine albumin solution prior to testing. The limit of detection was 3.5 pg/ ml. The intra-assay precision (% CV) of the assay at plasma concentrations of approximately 10 and 150 pg/ ml was 13.6 and 6.8%, respectively. The inter-assay coefficient of variation was 25%.

Pharmacokinetic analysis

A formal evaluation of the kinetics of melatonin was carried out on data from the first 9 patients on active treatment recruited to the study. Baseline levels (2100 h) of plasma melatonin in each subject receiving active treatment were subtracted from the data obtained after oral administration of melatonin. Values of the area under the corrected plasma concentration-time curves (AUC) were determined using the linear and log linear trapezoidal rules implemented in PKSolution 2.0 (Summit Research Services, Montrose, USA). Extrapolation of these values to infinity was done from the ratio of the last measured concentration divided by the terminal elimination rate constant (k) determined by the linear regression from the final data points (7 to 24 hours after melatonin administration). Mean Residence Time (MRT) was calculated using trapezoid area calculations extrapolated to infinity. Hence, oral clearance was calculated from $\text{dose}/\text{AUC}_{(0-\infty)}$ and reported together with C_{\max} (maximum

plasma concentration), t_{\max} (time to C_{\max}) and overall elimination life (from $\ln 2 \times$ MRT).

Circadian rhythm analysis

Plasma melatonin levels provide a robust marker of an individual's circadian rhythm [311]. It was planned to measure plasma melatonin and cortisol levels to provide both information on the patients' rhythm, and to describe the timing and concentration relationships between the hormones. Plasma samples in the first 9 placebo patients would also be assayed for melatonin levels to provide circadian rhythm data. Plasma melatonin $AUC_{(0-24)}$ was calculated in placebo patients using the trapezoidal rule to allow comparison of melatonin secretion over a 24 hour period with data from healthy elderly volunteers [387].

A chemiluminescent enzyme immunoassay was chosen to measure plasma cortisol levels. Rhythm analyses of plasma hormone levels would use single cosinor analysis (Time Series Analysis Serial Cosinor 6.3, Expert Soft Technologie, France).

In addition to providing sleep quantity data, actigraphy would also provide information on the patients' rest-activity rhythm [26]. Cosinor analysis is not suitable to describe the rest activity data, since it lacks sensitivity when analysing data that is irregular and/ or has a non-sinusoidal appearance [388]. Instead, non-parametric parameters analysis was used [388].

Cortisol assay procedure

Plasma samples were defrosted and centrifuged before cortisol assay in duplicate using a competitive chemiluminescent enzyme immunoassay (Immulite 1000, Diagnostic Process Corporation, Los Angeles, USA). The intra and inter-assay precisions (%CV) were 8.8 and 10%, respectively. Cross reactivity of cortisol with prednisolone was reported to be 62%.

Neuromuscular strength assessment

There were substantial concerns regarding the potential for significant neuromuscular weakness in patients recovering from a critical illness. Intensive care acquired abnormalities of the neuromuscular system are associated with sepsis, the use of drugs such as steroids [389] and neuromuscular blockers and severity of illness [390]. The pathology may affect nerves, muscles or both, although myopathy is probably the most common or predominant problem. Studies using electrophysiological testing suggest an incidence in the region of 50% in patients ventilated for 7 days or more [391]. Such patients would be anticipated to have reduced movement, which could be misinterpreted by the actigraphy algorithm as a sleep period, with consequent overestimation of sleep time. Diagnosis requires the use of nerve conduction studies or electromyography. However, it was not practical or feasible to undertake such monitoring in this study. Instead, it was decided to use grip strength testing and compare results to normal values from age and sex matched controls, [392] to provide a measure of neuromuscular weakness.

Environmental control

Environmental disturbances are a risk factor for sleep disturbances in critical care patients [35]. Therefore, it was necessary to control for potential differences in

nocturnal disturbances between groups. Ideally, continuous noise and light monitoring would have been undertaken during the study periods. After meetings with estates management concerning the equipment required and costs, this was regarded as unfeasible. Light levels at the head of each bed, when all non-emergency lighting was switched off, were measured prior to the start of the study (Luxmeter PU150, Eagle International, Wembley, UK). This would enable comment regarding illuminance level and any potential for suppression of dim light melatonin onset (DLMO), a circadian rhythm marker.

Meetings with nursing staff and environmental posters were used to raise awareness of the potential consequences for nocturnal sleep disturbances. Nursing staff were also encouraged to switch off all main lights at 2200 h and to minimise non-clinical light interruptions. The aim was to reduce noise and patient disruption during the night. A record of important environmental disturbances was developed to allow between group comparison of disturbances as well as the opportunity for subjective ranking of noise levels each night by nursing staff. The provision of ear plugs and eye masks was also deemed a useful patient option to minimise noise and light disturbances.

Peer support

To facilitate the implementation of the study, support was obtained from the Critical Care Directorate Clinical Management Team. A series of meetings were held with nursing staff to explain the trial rationale, the theoretical benefits of melatonin and its possible mechanism of action, the logistics of the study and how the nursing staff could assist with patient enrolment and data collection (demographics, delirium screening, patient sleep assessment) and blood sampling. Posters containing

information about melatonin in relation to critical care patients were also placed on notice boards.

Funding

Two internal hospital grants and one external project grant were applied for. The latter, from the Anaesthesia Research Society was short listed but not granted.

Funding (£15,000) was secured from the Sheffield Teaching Hospitals Department of Pharmacy and Medicines Management and Small Grants Schemes.

Ethics Committee Approval

The study protocol was submitted to the South Sheffield Research Ethics Committee (SSREC) in June 2002. As with other intensive care studies submitted at that time, the SSREC expressed reservations about the general intrusiveness of the study in a vulnerable group of patients, and requested a resubmission after modification. Issues were raised regarding the planned consenting options. In patients unable to provide consent, it was recommended to obtain retrospective consent from the patient in addition to the prospective consent from relatives. The SSREC also felt that a study over 5 nights was excessive and that delirium screening should not be undertaken daily. They also sought clarification on patient inclusion (restriction to patients with tracheostomies only), more details on exclusion criteria, time to study entry following discontinuation of sedation regimes and further supporting evidence for the choice of melatonin dose.

Thus ethics committee approval had several implications for the planned study.

Firstly, that the study would be conducted over 4 nights and, therefore, the primary sleep endpoint would now be sleep quantity over nights 3 and 4. Secondly, that delirium screening would only provide data to allow baseline group comparison, and

not incident delirium monitoring. Finally, the risk of including a patient in the study and subsequently an inability to use the data without retrospective consent was substantial. Therefore, it was decided to seek patients capable of providing informed consent, even though this would have an impact on patient recruitment.

A revised protocol was submitted in October 2002, which also included the addition of documentation of daily APACHE II (Acute Physiology and Chronic Health Evaluation) scores and current drug therapy. This was agreed in December 2002 and the study commenced in April 2003.

After commencing the study a COREC (Central Office for Research Ethics Committees) amendment application was submitted to change the primary sleep measurement technique to the BIS. This followed concerns about the validity of actigraphy sleep measurement in the presence of extreme neuromuscular weakness.

A measure of grip strength was also included in the protocol.

Final Study Protocol

Schema

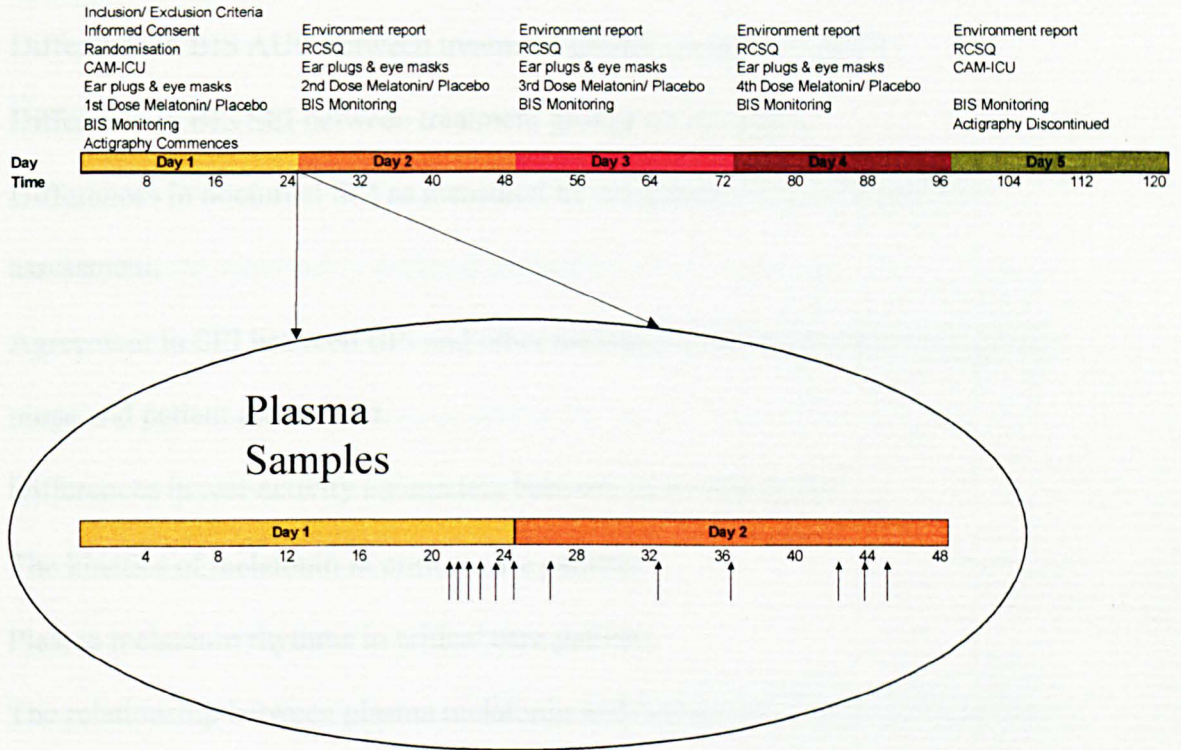


Figure 5-1 Final study protocol

CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; BIS: Bispectral Index; RCSQ: Richards Campbell Sleep Questionnaire

Study objectives

Primary end point

Difference in BIS SEI between treatment groups on nights 3 and 4.

Secondary end points

Difference in BIS AUC between treatment groups on nights 3 and 4.

Difference in BIS SEI between treatment groups on all nights.

Differences in nocturnal SEI as measured by actigraphy, nurse and patient assessment.

Agreement in SEI between BIS and other measures of sleep quantity; actigraphy; nurse and patient assessment.

Differences in rest-activity parameters between treatment groups.

The kinetics of melatonin in critical care patients

Plasma melatonin rhythms in critical care patients

The relationship between plasma melatonin and cortisol rhythms in critical care patients.

Patient eligibility criteria

Patients admitted to an adult general intensive care unit (ICU) with acute respiratory failure requiring mechanical ventilation and tracheostomy to assist weaning.

Exclusion criteria were: expected ICU length of stay <5 days; pre-admission treatment of sleep disturbances; contraindications to enteral feeding; previous history of convulsions; psychiatric or neurological disease; alcohol consumption ≥ 50 units per week or drug use; sleep apnoea; severe heart failure (NYHA III/IV); low levels of consciousness, defined as values < 4 on the Sedation Agitation Scale (SAS) [393].

Patient randomisation

Patients were included who met the inclusion/ exclusion criteria and who were deemed capable by the ICU consultant to provide informed consent. Patients were allocated to either active treatment or placebo by the Pharmacy, using randomisation in blocks of four.

Treatment schedule

Melatonin (10 mg) oral solution or matching placebo was administered enterally at 2100 h for four consecutive nights (Chapter 4). No other hypnotics were allowed during the study. Haloperidol was allowed in very agitated patients ($SAS \geq 6$). Ear plugs and eye masks were made available for use at the patients' discretion.

Environmental disturbances were documented on the locally derived scale composed of light interruptions and clinical activities (Appendix 3). Nursing staff subjectively ranked the noise level each night (Appendix 3).

Drug records were compiled daily for drugs known to adversely affect sleep (Table 2-3) or melatonin kinetics (Table 2-4).

Delirium was screened for at baseline upon study entry and after completion of the study using the CAM-ICU. Dynamometric measurements of patient grip strength (Jamar hydraulic hand dynamometer, Asimov Engineering Co. California, USA) were undertaken on study completion.

Sleep measurement

Nocturnal sleep was evaluated using the Bispectral Index (BIS; BIS XP, Quattro sensor) commenced prior to administration of melatonin/ placebo, BIS data was recorded in 5-second intervals and downloaded into a personal computer. Two outcome measures were calculated from the BIS data; sleep efficiency index (SEI)

and area under the curve (AUC). SEI was defined as the ratio of patient's total sleep time over time available for "nocturnal" sleep (9 hours, from 2200 to 0700 h, corresponding to nursing staff shift patterns). Sleep was defined as BIS < 80 [32]. AUC was calculated using the trapezoidal rule. For each night, SEI and AUC values were set to missing if recordings were not made for more than 2 hours.

Actigraphy was recorded continuously over the whole study period from the non-dominant hand in 30 second epochs. Delirium positive patients determined using the CAM-ICU [379] were excluded from RCSQ evaluation. Nurse assessment of nocturnal sleep was by direct observation using hourly epochs according to the critical care units routine sleep monitoring.

Results of the four techniques for nocturnal sleep were expressed as a common measure, the SEI, in order for comparison.

Plasma samples

Twelve blood samples were collected from each patient at appropriately spaced intervals after the first oral dose. Sample times post 2100 h administration were 0, 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 5 h, 7 h, 11 h, 15 h, 21 h and 24 h. All blood samples were taken from the arterial line, immediately centrifuged, providing two plasma samples to be labelled and stored at -20°C until assay.

Statistical analysis

Sleep and Circadian Rhythm analysis

Differences between treatment groups in mean values of BIS SEI and AUC, averaged over nights 3 and 4, were analysed using the *t* test with equal variances (95% confidence intervals). The secondary analysis including all four nights used a multilevel model, namely Prais regression, which accounts for the within-patient

correlation between measurements on successive nights. Mean and standard deviation or median and interquartile range were used for descriptive statistics. The Pearson Correlation and Spearman Rank Order Correlation were used for tests of association as appropriate. Simple linear regression was used to test the relationship between administration of drugs with CYP1A2 activity and measures of melatonin exposure. Mean and standard deviation or median and interquartile range were used as appropriate for descriptive statistics.

Differences between treatment groups in non-parametric rhythm parameters were analysed by *t* test with equal variances. Cosinor analysis was used to describe the rhythms of plasma hormone levels.

Dynamometric testing of grip strength was based on the mean of three recordings and results were expressed as percentage of normal values for age and sex matched controls [392].

Agreement

Agreement between techniques was evaluated using the limits of agreement method [394]. This approach compares two techniques at a time and consists of; 1) drawing a simple scatter plot of the results of the two techniques for each patient with the line of equality ($y=x$). If the techniques have perfect agreement, then all points should fall along this line; 2) drawing a graph of the differences between the results of the two techniques plotted against the average measurement value (Bland-Altman plot).

From this plot it is possible to not only evaluate the magnitude of the differences and, thus, decide on its clinical acceptability, but also to see whether the magnitude of the differences varies with the magnitude of the measurements (e.g. increase in the differences with increase in the average values); 3) from the mean and standard deviation (SD) of these differences, calculating the 95% limits of agreement, *i.e.* the

range within which 95% of the differences should lie (mean - 1.96 * SD; mean + 1.96 * SD).

6 MELATONIN THERAPY TO IMPROVE NOCTURNAL SLEEP IN CRITICALLY ILL PATIENTS

Introduction

The sleep disturbances commonly experienced by critically ill patients are characterised by sleep fragmentation, with loss of monophasic nocturnal sleep combined and frequent diurnal naps. This sleep pattern is a circadian rhythm sleep disorder sub-type, classified as an Irregular Sleep-Wake Pattern, [18] most often seen in patients with neurological conditions such as dementia or brain injury [395, 396]. Compared to that in healthy individuals, the sleep that does occur in critical care patients has less of the deeper, more restorative sleep phases such as SWS and REM sleep [36]. Although the consequences of such prolonged sleep fragmentation are unknown, they may be comparable to the significant morbidity associated with prolonged sleep deprivation [23]. For example, such sleep loss may reduce inspiratory muscle endurance in mechanically ventilated patients, [110] hence prolonging weaning from mechanical ventilation and increasing associated risks, such as healthcare associated infections. Sleep disturbances may also predispose to delirium, either as a direct predisposing factor, [397] or as a consequence of attempts to correct sleep disorders with sedative medication [398]. Furthermore, patients themselves perceive sleep disturbances to be one of the most stressful components of their intensive care stay [33]. Therefore, interventions that reduce sleep disturbances in critical care patients are warranted. Conventional hypnotic agents are often of limited efficacy in treating sleep disorders in critical care patients, and may paradoxically worsen sleep quality, [398] or have adverse cognitive effects [196]. Nocturnal secretion of melatonin synchronises the sleep-wake and dark-light cycles, [276] and disruption to the normal timing and amplitude of the circadian rhythm of melatonin secretion is associated with reduced sleep efficiency [399, 400]. Compared to healthy individuals, critical care patients undergoing mechanical ventilation have

reduced plasma melatonin levels and lack of circadian rhythm [312, 401-403]. The pattern of critical care patients sleep disorders and the disruption in melatonin secretion suggest that specific circadian sleep disorder therapies may be beneficial. Exogenous melatonin has been demonstrated to be safe and effective in the treatment of other circadian rhythm sleep disorders [265, 404]. The current study aimed to examine further the effect of exogenous melatonin on nocturnal sleep in patients weaning from mechanical ventilation.

Methods

A detailed description of the study design, patient inclusion/ exclusion criteria, patient recruitment, randomisation, medication administration, sleep monitoring, data collection and data analysis is given in Chapter 5. In summary, the study was a randomised double-blind placebo controlled trial in patients admitted to an adult general ICU with acute respiratory failure requiring mechanical ventilation and a tracheostomy to assist weaning. Melatonin 10 mg or matching placebo were administered enterally at 2100 h for four consecutive nights.

Nocturnal sleep was evaluated primarily using BIS, with actigraphy, nurse and patient assessment as secondary measures. Analyses were limited to nights 3 and 4, since the potential chronohypnotic benefits of melatonin are not immediate and may take three days to be realised [279, 377, 405]. All four nights were considered in a secondary analysis.

Results

Figure 6-1 summarises patient inclusion in the study. Due to slow recruitment, it was only possible to recruit 24 patients. There were 4 patients (3 in the placebo and 1 in the melatonin group) with missing BIS data for nights 3 and 4, the reasons being; discharged/re-sedated (4 nights), patient removed sensor (2 nights); signal quality index low (1 night); patient refused (1 night).

Table 6-1 shows patients' baseline characteristics in the two treatment groups. An imbalance of known risk factors for sleep disturbances was present due to small sample size, potentially leading to more sleep disturbance in the melatonin group. The risk factors for sleep disturbances included older age, [406] delirium [19] and ventilation with pressure support ventilation (because of the possibility of desynchrony) [105]. No differences between the melatonin and control group were observed with regard to either patient use of ear plugs or eye masks (9% and 2% of nights, respectively), or nocturnal environmental disturbances score. Mean (SD) baseline illuminance at the head of each bed when all lights were turned off was 9.6 (2.6) lux.

There was no disparity between the groups in their exposure to potentially sleep disruptive medication. In patients that received morphine and midazolam, sufficient time elapsed between discontinuation of sedation and study enrolment to limit distortion of results due to accumulation of these agents. None of the patients received haloperidol on nights 3 or 4. Nocturnal sleep time did not seem to correlate with severity of illness, as measured by the daily APACHE II score, although a wide confidence interval does not allow for definitive conclusions ($r = 0.10$; -0.36 to 0.52; $p = 0.68$).

Results of the effect of melatonin on primary and secondary sleep measurements are shown (Table 6-2). Nocturnal sleep time was two and a half hours in the placebo group and it was one hour longer in the melatonin group, although the difference was not statistically significant (Table 6-2). BIS AUC showed a statistically significant 7% decrease in the melatonin group, with a lower AUC indicating “better” sleep (AUC difference = -54.23; -104.47 to -3.98; $p = 0.04$). In order to account for the imbalance in baseline characteristics, the analyses were adjusted using linear regression. The small sample size limited the number of covariates that could be adjusted for, [407] and therefore a single variable was created that provided an indication of the overall baseline risk of sleep disturbances. High risk was defined as the presence of any two of the following: age ≥ 70 years; delirium positive; ventilation with BIPAP or CPAP/ASB. The results of the adjusted analysis did not vary substantially, apart from an expected loss in precision of the estimates; SEI difference: 0.12 (-0.04 to 0.28; $p = 0.12$); AUC difference: -48.76 (-103.06 to 5.54; $p = 0.07$).

Any evidence of a treatment effect nearly disappeared when considering all four nights; SEI difference: 0.05 (-0.07 to 0.17); AUC difference: -26.62 (-70.51 to 17.28).

Results from the additional sleep measurement methods did not support those obtained with BIS, and indeed they were all inconclusive (Table 6-2).

As regards possible side effects of melatonin, one patient in the melatonin group reported a headache on a single night, which responded to acetaminophen administration.

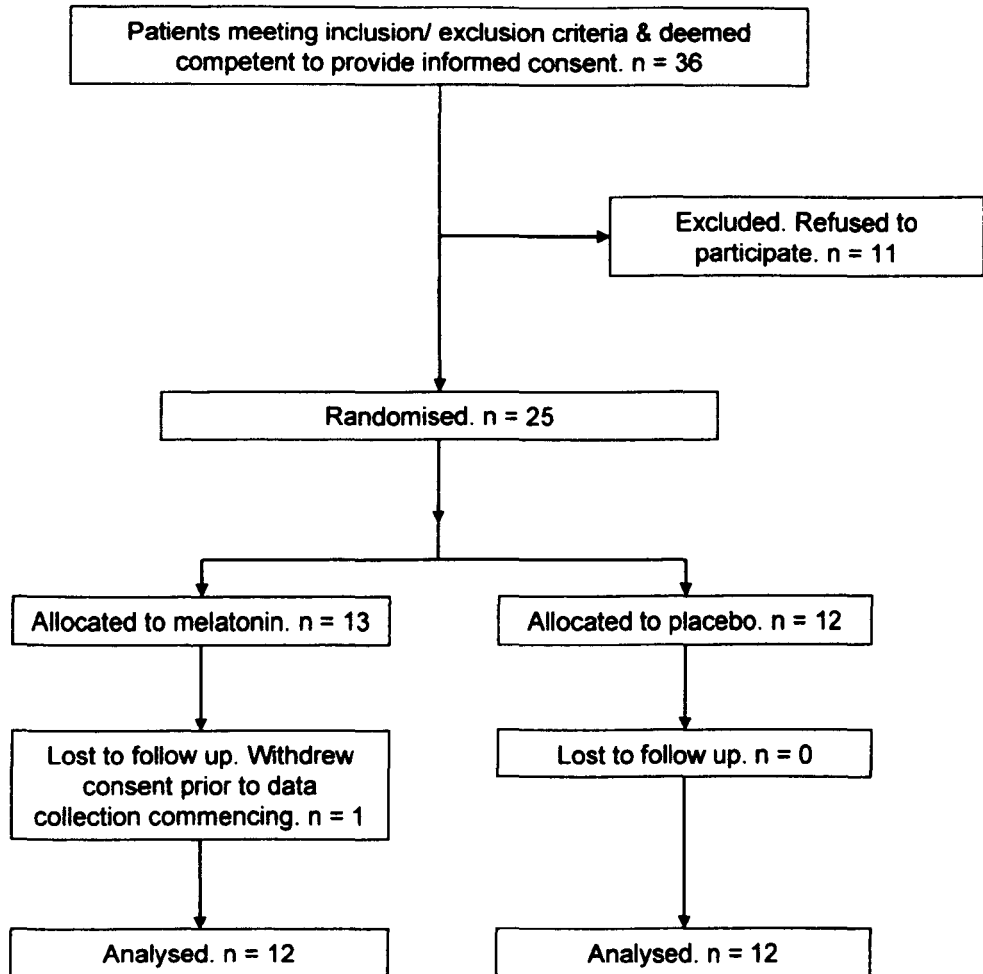


Figure 6-1 Patients recruitment analysis

	Placebo (n=12)	Melatonin (n=12)
Male [n (%)]	7 (58.3)	4 (33.3)
Reason for ICU admission [n (%)]		
Severe sepsis	8 (66.7)	10 (83.3)
Postoperative respiratory failure	2 (16.7)	1 (8.3)
Pneumonia	2 (16.7)	1 (8.3)
Age [mean (SD)]	58.7 (12.5)	69.9 (12.0)
APACHE II on study entry [mean (SD)]	16.8 (3.4)	17.3 (3.8)
ABW (kg) [median (IQR)]	69.0 (57.4; 77.5)	65.0 (63.5; 70.0)
IBW (kg) [mean (SD)]	60.0 (6.9)	57.2 (6.5)
BMI [mean (SD)]	24.6 (4.7)	25.0 (3.1)
Patients' usual sleep quantity (hours) ¹ [mean (SD)]	6.5 (1.57)	6.2 (2.07)
ICU length of stay prior to study (days) [median (IQR)]	16.5 (13.0; 20.5)	16.5 (11.0; 19.0)
Time of ventilation prior to study (days) [mean (SD)]	20.0 (14.3)	13.6 (6.5)
Sedation (morphine/midazolam) prior to study [n (%)]	2 (16.7)	2 (16.7)
Time since sedation stopped prior to study (days) [mean (SD)]	6.6 (2.9)	7.5 (4.7)
Delirium during study period [n (%)]	1 (8.3)	4 (33.3)
Ventilation mode on Nights 3 and 4 [n (%)]		
BIPAP/ CPAP-ASB	7 (70.0)	7 (58.3)
External CPAP/ High Flow Oxygen	3 (30.0)	5 (41.7)

Table 6-1 Baseline patient characteristics

ABW - Actual body weight; IBW - Ideal body weight; BMI - Body mass index

¹ Usual sleep time at home, reported by the patient.

Sleep measurement method	BIS SEI (95%CI)			<i>p</i> -value of the difference
	Placebo group	Melatonin group	Difference	
Primary Analysis				
BIS	0.26 (0.17 to 0.36)	0.39 (0.27 to 0.51)	0.12 (-0.02 to 0.27)	0.09
Secondary Analysis				
Actigraphy	0.75 (0.67 to 0.83)	0.73 (0.53 to 0.93)	-0.02 (-0.24 to 0.20)	0.84
Nurse Assessment	0.51 (0.35 to 0.68)	0.45 (0.26 to 0.64)	-0.06 (-0.29 to 0.17)	0.58
Patient Assessment (RCSQ)	0.50 (0.43 to 0.58)	0.41 (0.24 to 0.59)	-0.09 (-0.28 to 0.09)	0.32

Table 6-2 Effect of melatonin on nocturnal sleep efficiency on nights 3 & 4, determined using different outcome measures

BIS: Bispectral Index; RCSQ: Richards Campbell Sleep Questionnaire; SEI: Sleep efficiency index

Discussion

The results of the study are in agreement with previous reports [378, 408] that show nocturnal sleep in patients weaning from mechanical ventilation is highly compromised, with an average of only two and a half hours in the placebo group. Melatonin therapy was associated with a one-hour increase in nocturnal sleep compared with placebo, corresponding to an increase of 47%, although the SEI difference did not reach statistical significance. There was a statistically significant reduction of 7% in BIS AUC with melatonin administration, suggesting sleep improvement. The use of AUC has some advantages compared to SEI. Apart from providing greater statistical power, BIS AUC measures both sleep quantity and quality, [378] which might be more informative than sleep quantity data alone. However, the clinical significance and interpretation of a reduced AUC remains unclear [409].

Two other small trials investigated the effect of melatonin on nocturnal sleep in critically ill patients, [313, 403], but comparison is limited due to the use of different sleep measurement methods. In fact, although polysomnography is the gold standard for quantifying and qualifying sleep, the challenges of the critical care environment have led to the utilisation of a number of alternative methods. The potential for significant differences in sleep measurement results reported using the various sleep measurement techniques was the reason for the use of four different techniques in the current study with the additional aim of measuring agreement between them. The implications of sleep measurement technique selection for research and clinical applications in critical care patients are discussed in detail in Chapter 8. Shilo *et al* [313] examined the effects of melatonin on sleep in eight respiratory patients in a cross-over trial, and showed positive sleep quantity results as measured by

actigraphy. Baseline sleep was reported to increase from approximately three to six hours with melatonin administration, although results of the comparison between melatonin and placebo were not reported. A second study used nurse observation to evaluate 32 tracheostomised patients and showed negative results [403]. Placebo patients slept for about four hours, but only for 15 minutes more in the melatonin group. Alexander *et al*, [410] gave a preliminary report of an unpublished study of melatonin administration in critical care patients. Twenty three patients recovering from critical illness were randomised to receive 6 mg melatonin (n=11) or placebo for 10 nights [410]. Sleep was measured by actigraphy, nurse assessment (15 minute epochs) and patient assessment using a 10 point visual analogue scale (VAS) [410]. Conventional night sedation was allowed throughout the study according to a local ICU guideline. There were no differences between the groups in nocturnal sleep quantity, daytime sleep quantity or number of nocturnal sleep bouts [410]. Although melatonin was reported to have a “sedative-sparing affect”, differences in mean requirement for night sedation per night was not statistically significant (0.27 *versus* 0.6, $p = 0.13$). The primary sleep measure used was actigraphy, and no details regarding other measures of sleep quantity were provided [410]. The combined use of a conventional hypnotic with melatonin is representative of clinical practice in some UK ICUs [227]. This combined use is based on the premise that melatonin may facilitate the conditions for sleep, but that some patients require a further stimulus for sleep to commence. The latter is an attempt to create a “pseudo sleep homeostasis” or drive for sleep, in combination with the circadian drive created by the administration of nocturnal melatonin. However, there is no evidence that this combined approach increases efficacy, and indeed it may only increase adverse effects. A study in healthy volunteers reported no increase in daytime sleep quantity after combined

administration of melatonin 5 mg and zolpidem 20 mg, when compared to administration of the individual agents [405]. Individual melatonin administration maintained memory and cognitive performance, which was impaired when combined with zolpidem [405].

Actigraphy has important limitations when used as a measure of sleep in critically ill patients, being influenced by abnormalities of the neuromuscular system which are common in these patients [389]. As regards nurse observation, intensive observation of sleep (5 minute intervals) is probably necessary to allow differentiation between interventions in critical care studies [411] and even then it suffers from being a subjective measure which may overestimate sleep quantity [27]. Patient assessment has been used in critical care sleep studies of other interventions, but its applicability is limited by patient acute cognitive and perceptual problems [412]. BIS was chosen as the primary outcome measure in the current study since it is an objective measure of sleep that is not adversely affected by the presence of neuromuscular weakness. However, the BIS, as with other EEG based techniques, can be adversely affected by conditions such as traumatic brain injury, [413] dementia [414] or delirium [415] which result in electroencephalographic (EEG) slowing [413]. Although BIS XP technology was used, a degree of susceptibility to increased BIS values as a consequence of electromyographic (EMG) artefact remains [416]. The results from the secondary outcome measures, actigraphy, nurse observation and patient assessment, were all inconclusive. Differences between the BIS SEI results in the current study and those of the secondary measures may be explained in part by residual neuromuscular weakness in patients recovering from sepsis (actigraphy); the use of hourly epochs (nurse assessment) and limitations of patients' ability to

complete the RCSQ (patient assessment). All of these factors may contribute to overestimation of sleep quantity and SEI.

The effects of melatonin on sleep have also been studied in non-critical care hospitalised patients. A randomised placebo controlled study of nocturnal melatonin in 33 hospitalised medical patients reported improvements in nocturnal sleep parameters after administration of oral melatonin [417]. Melatonin was administered in a flexible dose regime, with a mean daily dose of approximately 5 mg administered to each patient over the 16 day study period. Patients who had received melatonin reported reduced sleep latency and increased night time sleep duration compared to patients who had received placebo [417]. Patient assessment was based on a simple 3 point VAS, which only allowed patients to indicate whether they subjectively rated their own sleep parameters at the end of the study as no different, better or worse than baseline. A small double-blind cross over study (n = 7), [418] compared the effects of melatonin and amitriptyline on sleep quality in patients with sleep disorders after traumatic brain injury. Patients assessed their own sleep based on sleep latency, sleep quantity, sleep quality and daytime alertness. Compared to baseline data, no significant improvements in any sleep variable were reported for either melatonin or amitriptyline. Given the small sample size, this is not unexpected and the authors went on to calculate effect sizes compared to baseline, which suggested small to medium beneficial effect sizes on the sleep variables for both drugs [418].

Rajaratnam *et al* [419] conducted a study of melatonin on sleep in 8 healthy individuals using an extended sleep opportunity model. Although undertaken in healthy individuals, the extended sleep opportunity protocol resembled some of the sleep conditions patients recovering from critical illness are exposed to [419].

Participants were confined to their beds for 9 days, with no interaction or recreational facilities provided; hence extended sleep periods were available. Volunteers were randomised to receive melatonin (1.5 mg immediate-sustained release) or placebo at 1600 h daily for 8 days, before repeating the study in the other treatment allocation after a 14 day washout period. Sleep was monitored in private research rooms using polysomnography for 16 hours each day. The results of the study showed that melatonin advanced the timing of sleep without affecting TST [419]. Comparison of results from the post treatment night and sleep parameters during melatonin administration allowed separation of the hypnotic and circadian phase-shifting effects of melatonin. Melatonin was reported to have direct sleep-promoting effects [419]. Melatonin both phase-advanced, and directly facilitated sleep for approximately 3 hours after administration [419]. Melatonin increased TST over the first 8 hours post dose, but when the full 16 hours were analysed, there was no change in TST. Therefore, melatonin changed the timing of sleep, *i.e.* it facilitated, rather than induced sleep, which contrasts with conventional hypnotic agents. Also, melatonin administration did not reduce the quantity of SWS or REM sleep [419].

When melatonin (5 mg) is administered during the nocturnal period in healthy patients with a normal melatonin circadian rhythm, it has no effects on sleep [264]. However, when administered during the day, when endogenous plasma melatonin levels are low, it has a soporific effect similar to temazepam 20 mg [264]. In critical care patients with a disrupted circadian rhythm of melatonin, appropriate melatonin dosing would be anticipated to re-enforce the timing and consolidate nocturnal sleep, without adversely affecting sleep quality. Furthermore, the absence of significant sleep inertia (morning hangover) and detrimental cognitive effects the next day after

drug administration, [264, 284, 405] are further advantages of melatonin over conventional hypnotic agents in critical care patients [196].

Melatonin appears to have a favourable adverse effect profile; headaches, dizziness, nausea and drowsiness are the most common adverse events reported with short term administration [275]. Melatonin treatment appeared to be well tolerated by the patients in the current study, with only one patient reporting a single episode of headache.

The sleep results of the current study are clinically significant as they suggest that administration of melatonin may form part of interventions to improve sleep in critical care patients. Sleep is regulated by two processes; circadian and homeostatic (sleep drive). Re-enforcing the circadian rhythm, for example, by the administration of exogenous melatonin may improve the circadian process, but sleep drive is still required. Therefore, correcting the circadian rhythm disorder alone will not result in maximum sleep quality without also encouraging sleep homeostasis. Furthermore, sleep disturbances in critical care patients are multi-factorial and, therefore, a single intervention, such a melatonin administration, cannot be expected to result in complete resolution of symptoms. Sleep hygiene, is a term used to describe an approach to ensuring lifestyle and environmental conditions are conducive to sleep. Sleep hygiene is used as a basis for the treatment of most sleep disorders and, in summary, is focused on maintaining a suitable environment for sleep to occur, re-enforcing circadian rhythms and avoiding sleep disturbing medications. In treating sleep disturbances in critical care patients, administration of melatonin may assist with re-enforcing the circadian rhythm, but other improvements in the environment and appropriate drug review must also be made. Unfortunately, this is frequently not

the case, and it is often regarded as easier to administer another drug than to embrace the significant practical changes that are required.

There are a number of obvious limitations to the current study that should be reviewed when considering the methodology of future studies.

The current study was smaller than planned, with only 71% of the target sample size being reached, mainly due to problems in obtaining consent in the most acutely ill patients. Statistical power was further decreased by the presence of missing data.

Both these problems should be taken into account when designing a study, particularly in deciding on inclusion criteria and the complexity of the study protocol. The small sample size also meant that there were imbalances in baseline characteristics between the groups, although the attempt to adjust for important sleep related factors (age, delirium and ventilator status) did not materially alter the results. Furthermore, the inclusion of ventilator status as a risk factor for sleep disturbances assumes that patient-ventilator desynchrony occurred [105]. Mode of mechanical ventilation has not been demonstrated to be an important factor affecting sleep in critical care patients when ventilatory settings are optimised [84].

The use of alternative sleep measurement techniques to polysomnography also limited the scope of the current results. Sleep stage data were not available and, therefore, it was not possible to comment on the effect of melatonin on SWS or REM sleep phases. The ultimate aim of sleep interventions in critical care patients is to attempt to consolidate nocturnal sleep and increase both SWS and REM sleep phases. At low doses melatonin has a sleep promoting effect without a significant adverse effect on normal sleep architecture, [419, 420] a potential advantage over conventional hypnotic agents. Indeed it could be suggested that the improvements in sleep quantity observed may have been achieved with a conventional hypnotic agent

e.g. zopiclone. The significant potential for adverse cognitive effects of these agents, particularly in older patients, [196] still makes melatonin (or melatonin agonists such as ramelteon) worth continued investigation.

Ideally polysomnography should be used as a continuous measure of sleep in further studies. However, this would present significant logistical and technical challenges, and is associated with specific difficulties, including patient tolerability and sleep stage interpretation in patients experiencing complex electrophysiological changes [378].

A useful measure of daytime sleep was not available because the actigraphy data appeared to significantly overestimate nocturnal and diurnal sleep quantity, (see Chapter 8) and the BIS recording was restricted to the nocturnal period due to patient tolerability. Therefore, it is also not possible to comment on the effect of melatonin on daytime sleep. While the primary aim of a sleep intervention is to optimise nocturnal sleep quality and quantity, the potential impact diurnal sleep periods have on nocturnal sleep efficiency should not be forgotten. Approximately half of total sleep time of critical care patients may occur during the diurnal period, with significant inter and intra-patient variability as to whether sleep deprivation is present over 24 hours [23].

A 10 mg oral melatonin dose was used in the current study. Although a similar melatonin dose has been used in other studies, [287] it may have been excessive and complicated the entraining effect of melatonin on the sleep rhythm (see Chapter 7 for discussion).

The environmental score only provided a guide to nocturnal patient disturbances. Noise, light and patient disturbances have been shown to account for approximately 30% of nocturnal arousals and awakenings [35]. Although the ambient nocturnal

illuminations were at an appropriate level to allow normal melatonin secretion, [421] an accurate measure of light interruptions was not used. The absence of continuous light and noise measurements and lack of quantification of patient disturbances by staff are, therefore, further potential limitations. Ear plugs can improve sleep quality in healthy volunteers exposed to simulated intensive care noise [89]. However, in the current study, patient willingness to use eye masks and/or ear plugs was very low, which limits their routine clinical application.

Finally, future studies should consider extending the sleep intervention to a coordinated bright light and exogenous melatonin therapy. The sleep-wake process relies on a combination of homeostatic and circadian factors for its optimum function, [266] and the full activity of melatonin on the sleep-wake cycle in humans requires the coordination of other time cues such as light [265].

Conclusions

Melatonin administration appeared to increase the sleep quantity of critical care patients weaning from mechanical ventilation. Although suggesting a possible future role of melatonin in the routine care of critically ill patients, the findings of the current study need to be confirmed by a larger, possibly multicentre, randomised controlled trial, ideally using polysomnography as a continuous measure of sleep quantity and quality.