Melatonin, sleep and circadian rhythms in critical care patients

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7 KINETICS OF ORAL MELATONIN IN CRITICAL CARE PATIENTS

Introduction

Drug dose selection is primarily based on two factors; safety and efficacy. The general aim is to use the minimum effective dose that provides the desired therapeutic effect, *i.e.* the best risk-benefit ratio. Pharmacokinetic data for a drug in a special population facilitates selection of an appropriate dose and improves treatment. Although there is a large number of published papers examining wide ranging aspects of oral melatonin therapy in humans, relatively little data exist concerning its pharmacokinetics. As discussed in Chapter 2, a wide range of oral melatonin doses has been used in various clinical studies of sleep and circadian rhythm disorders. Doses up to several grams per day have been used, even though physiological levels are produced by doses in the region of 0.3-0.5 mg [10]. The dose response curve for melatonin on sleep is relatively flat, which means that very large doses may increase the risk of toxicity [10]. For example, oral doses of 5 to 6 mg of melatonin had similar soporific effects to 10 to 15 mg of temazepam in healthy volunteers [283, 284]. Unlike conventional hypnotic agents, melatonin produces a chronohypnotic effect that is governed by a phase response curve [290]. Melatonin administered in the morning will phase delay, while evening administration will phase-advance individuals with a normal circadian rhythm. Therefore, the use of excessive doses risks confusing the circadian rhythm by producing supraphysiological daytime levels. Conversely, insufficient dosage risks lack of efficacy, especially since melatonin has a low and variable bioavailability [256, 422]. Free-running rhythms in blind people were entrained (resynchronised to an appropriate day-night cycle) by appropriately timed melatonin doses of 10 mg [287]. However, in Sack's study, [287] one of the seven subjects was resistant to entrainment. Increasing the dose to 20 mg did not produce a benefit, but entrainment

did occur when the dose was reduced to 0.5 mg [423]. To maximise the soporific and circadian effects of melatonin, a dose that provides a rapid peak exposure, physiological night-time concentrations and also low levels in the morning is desirable.

A summary of studies of melatonin that included the measurement of blood concentrations in adult patients is shown in Table 7-1. Doses used in these studies varied from 0.01 to 100 mg per day. Until recently, all studies have been conducted in relatively healthy individuals *i.e.* even though some studies included volunteers with chronic insomnia, blindness and older age, none were acutely unwell. This obviously limits any extrapolation of data, including appropriate dose to use in critical care patients. Oral dose selection is further complicated by the variation in release characteristics provided by the variety of preparations used. The lack of a licensed product means that for many clinical studies, extemporaneous formulations or even health food products are used, compounding the variability in melatonin bioavailability.

In the preliminary study described in Chapter 3, a 5 mg oral dose was used, although subsequently doses of 10 mg were used in patients deemed non-responders. A 10 mg dose was used in the randomised controlled trial (Chapter 6). This dose was selected based on its use in other clinical studies, and safety data demonstrating no obvious adverse effects compared to placebo after one months treatment [337].

The pharmacokinetics of many drugs are affected by critical illness. For example, oral bioavailability may be affected by changes in gastric emptying and gut membrane permeability as a result of sepsis, [424] and multi-organ failure can affect drug metabolism and excretion. This complex interrelationship makes dose planning difficult and the optimum oral dose for use in critical care patients is unknown.

Therefore, a pharmacokinetic analysis of plasma melatonin concentrations was undertaken to try to come to a conclusion regarding the best dosing strategy in critical illness.

Reference	Subjects (n; % male)	Oral dose [mg] (Preparation)	Plasma C_{max} [mean, pg/ml]	t_{max} [hours]	AUC [mean, pg.hr/ml] (Time period)	Clearance (D/AUC) [l/h]	Elimination $t_{1/2}$ [hours]	Assay	Comments
Aldhous (1985) [262]	Healthy volunteers (12; 50)	1. 2 (Capsule) 2. 2 (Solution–corn oil)	Not reported	1. Fed: 0.46 2. Fasting: Not reported 1. Fed: Not reported 2. Fasting: 0.95	1. Fed: 8,036 2. Fasting: 3,712 1. Fed: 5,826 2. Fasting: 3,953 (Not reported)	1. 249 2. 343	1. 0.54 2. 0.67	RIA	Significantly higher drug exposure in fed *versus* fasting subjects
Benes (1997) [425]	Healthy volunteers (12; 100)	0.76 (C/R Capsule)	82	1.3	894 (0-24)	850	Not reported	RIA	
Cagnacci (1992) [426]	Healthy volunteers (13; 0)	1, then 0.75 after 2 hours & 0.75 after 4 hours (Not reported)	1,989	1.5-2	Not reported	Not reported	Not reported	RIA	Serum samples. Initial dose of 1 mg, followed by two further doses of 0.75 mg at 2 hourly intervals

(Table 7-1 continued)

Cagnacci (1996) [427]	Healthy volunteers (7; 0)	2.5, then 0.75 after 2 hours & 0.75 after 4 hours (Not reported)	Not reported	Not reported	Follicular phase: 638 Luteal phase: 669 (0-24)	Follicular phase: 3,918 Luteal phase: 3,737	Not reported	RIA	Serum samples. Initial dose of 1 mg, followed by two further doses of 0.75 mg at 2 hourly intervals. Difference not significant
Dawson (1996) [428]	Healthy volunteers (32; 34)	1. 5 2. 1 3. 0.5 4. 0.1 (Not reported)	1. 5,571 2. 1,356 3. 709 4. 125	1. 0.97 2. 0.78 3. 0.88 4. 1.25	Not reported	Not reported	Not reported	RIA	
Deacon (1995) [429]	Healthy volunteers (6; 50)	1. 5 2. 0.5 3. 0.05 (Solution-corn oil)	1. 18,495 2. 1,327 3. 118	1. 0.5 2. 1.0 3. 0.5	Not reported	Not reported	1. 1.17 2. 0.71 3. 1.08	RIA	
DeMuro (2000) [256]	Healthy volunteers (12; Not reported)	1. 2 2. 4 (Not reported)	1. 2,175 2. 5,766	1. 0.87 *2.* 1.0	1. 3,963 2. 8,843 (0-infinity)	1. 505 2. 452	1. 1.01 2. 1.08	RIA	Serum samples. Mean bioavailability 15%
Di (1997) [254]	Healthy volunteers (4; 100)	0.5 (Not reported)	Not reported	Not reported	Not reported	Not reported	0.78	Not reported	Mean bioavailability 33%

(Table 7-1 continued)

Dollins (1993) [430]	Healthy volunteers (20; 100)	1. 10 2. 20 3. 40 4. 80 (Capsule)	Not reported	Not reported	1. 12,228 2. 27,186 3. 52,557 4. 106,223 (-2-6)	1. 818 2. 736 3. 761 4. 753	Not reported	RIA	Serum samples
Dollins (1994) [431]	Healthy volunteers (20; 100)	1. 10 2. 1 3. 0.3 4. 0.1 (Capsule)	Not reported	Not reported	1. 21,000 2. 1,599 3. 460 4. 213 (-2-6)	1. 476 2. 625 3. 652 4. 469	Not reported	RIA	Serum samples
Fourtillan (2000) [422]	Healthy volunteers (12; 50)	0.25 (Solution)	Male: 244 Female: 624	Male: 0.38 Female: 0.38	Male: 236 Female: 701 (0-Infinity)	Male: 1059 Female: 357	Male: 0.6 Female: 0.75	GC-MS	Significantly higher drug exposure in females *vs.* males. Bioavailability of 9 and 17% in males and females, respectively
Fourtillan (2001) [432]	Healthy older volunteers (11; 55)	0.25 (Solution)	Male: 527 Female: 686	Male: 0.54 Female: 0.4	Not reported	Not reported	Male: 1.09 Female: 0.91	GC-MS	No significant gender difference in C_{max}, T_{max} or $t_{1/2}$
Hartter (2000) [345]	Healthy volunteers (12; 100)	5 (Not reported)	2,180	1.0	6,200 (0-28)	806	9.4	RIA	Serum samples 4/5 patients *CYP2D6* extensive metabolisers

(Table 7-1 continued)

Hartter (2001a) [383]	Healthy volunteer (1; Not reported)	25 (Not reported)	19,200	1.5	Not reported	Not reported	Not reported	HPLC-MS	6-hydroxymelatonin concentrations 35 times melatonin concentrations
Hartter (2001b) [255]	Healthy volunteers (12; Not reported)	25 (Not reported)	18,973	1.5	32,708 (0-last measure)	764	0.9	HPLC-MS	$t_{1/2}$ from last quantifiable data points
Hartter (2003) [386]	Healthy volunteers (12; Not reported)	6 (Tablet)	Smokers: 3,360 Non-smokers: 5,610	Smokers: 1.0 Non-smokers: 1.0	Smokers: 5,500 Non-smokers: 9,650 (0-last measure)	Smokers: 1,091 Non-smokers: *622*	Smokers: 2.43 Non-smokers: 1.11	RIA	Serum samples
Hartter (2006) [433]	Healthy volunteers (12; 58)	6 (Tablet)	6,600	1.5	Not reported	Not reported	Not reported	HPLC-MS	Serum samples Sampled only at 1.5 hours as part of a study of the effects of *CYP1A2* polymorphism and caffeine

(Table 7-1 continued)

Hoffmann (1998) [434]	Healthy volunteers (15; 100)	1. 5 (Capsule) 2. 10 (M/R Capsule) 3. 10 (M/R Capsule)	1. 4,819 2. 3,819 3. 2,258	1. 0.5 2. 0.75 3. 0.5	1. 4,276 2. 8,455 3. 9,911 (0-Infinity)	1. 1,169 2. 1,183 3. 1,009	Not reported	RIA	Serum samples
Ibrahim (2006) [403]	Intensive Care patients (14; 57)	3 (Not reported)	3453	1.5	Not reported	Not reported	Not reported	Not reported	All melatonin administered via NG tube. Single predetermined blood sample taken 1.5 hours after dose. Type of blood sample not reported.
Kane (1994) [435]	Healthy volunteers (5; 60)	50 Administered 4 hourly (Capsule)	41,600	Not reported	Not reported	Not reported	Not reported	RIA	Serum samples
Kovacs (2000) [436]	Healthy volunteers (17; 71)	3 (Tablet)	4,701	1.0	9,514 (0-16)	315	Not reported	RIA	Serum samples

(Table 7-1 continued)

Lee (1997) [437]	Healthy volunteers (4; Not reported)	0.2 (S/R capsule)	Batch 1: 117 Batch 2: 108	Batch 1: 0.5 Batch 2: 1.0	Batch 1: 516 Batch 2: 557 (Not reported)	Batch 1: 388 Batch 2: 359	Not reported	RIA	
Lewy (1998) [438]	Healthy volunteers (6; 17)	0.5 Morning and evening dose on different days (Capsule)	Not reported	Not reported	Not reported	Not reported	Morning: 0.84 Evening: 1.06	RIA	No significant differences in elimination $t_{1/2}$ between morning and evening administration
MacFarlane (1991) [279]	Chronic insomniacs (2; Not reported)	1. 2 2. 75 (Capsule)	1. 2,630 2. 64,730	Not reported	Not reported	Not reported	Not reported	RIA	Serum samples
Markantonis (2008) [439]	Healthy volunteers (18; 0)	6 (Capsule)	Premen: 16,756 Postmen: 16,438	Premen: 0.5 Postmen: 0.88	Premen: 19,614 Postmen: 20,595 (0-12)	Premen: 506 Postmen: 593	Premen: 0.76 Postmen: 0.86	HPLC-F	No significant difference in any results between the groups
Rajaratnam (2003) [440]	Healthy volunteers (8; 100)	1.5 (Surge-S/R capsule)	626	3.0	Not reported	Not reported	Not reported	RIA	

(Table 7-1 continued)

Satoh (2001) [441]	Healthy volunteers (6; 100)	1. 9 2. 3 3. 0.5 (Capsule)	1. 5,499 2. 1,869 3. 378	1. 2.2 2. 1.5 3. 0.58	Not reported	Not reported	Not reported	RIA	Serum samples 9 mg dose produced supraphysiological plasma conc. the next day
Shah (1999) [442]	Healthy older volunteers (12; 50)	1. 0.11 2. 0.44 (C/R tablet)	1. 57 2. 179	1. 5.8 2. 5.5	1. 318 2. 1,234 (0-Infinity)	1. 346 2. 357	1. 1.8 2. 2.2	HPLC-MS	Serum samples Mean $t_{1/2}$ reported
Shirakawa (1998) [443]	Healthy volunteers (7; 100)	3 (Capsule)	3,561	0.33	Not reported	Not reported	Not reported	GC-MS	Serum samples
Shirakawa (2001) [444]	Healthy volunteers (7; 100)	3 (Capsule)	1,056	2.25	Not reported	Not reported	Not reported	Not reported	First blood sample taken 2.25 hours after dosing
Ursing (2005) [445]	Healthy volunteers (8; 13)	25 (Capsule)	1. Smoking: 640 2. Non-smoking: 1,855	1. 1.5 2. 1.5	1. 1,708 2. 4,905 (0-12)	1. 14,637 2. 5,096	Not reported	RIA	Serum samples
Vakkuri (1985) [261]	Healthy volunteers (5; 100)	100 (Capsule)	101,268	1.0	Not reported	Not reported	0.68	RIA	Serum samples
Waldhauser (1984) [381]	Healthy volunteers (5; 100)	80 (Capsule)	Not reported	Not reported	464,480 (0-3 times endogenous level)	172	0.8	RIA	Serum samples

(Table 7-1 continued)

Zhdanova (2001) [446]	Chronic insomniacs and Healthy volunteers (15+15; Not reported)	1. 3 2. 0.3 3. 0.1 (Capsule)	1. 1,370 2. 220 3. 84	Not reported	Not reported	Not reported	Not reported	RIA	3mg dose produced supraphysiological plasma concentrations the next day

Table 7-1 Summary of studies reporting blood melatonin concentrations after oral dosage

Studies in adults and published in English

AUC: Area under the plasma/ serum concentration-time curve; C_{max}: Maximum plasma/ serum concentration; C/R: Controlled release; D: Dose; HPLC-F: High performance liquid chromatography - fluorescence; HPLC-MS: High performance liquid chromatography-mass spectroscopy; GC-MS: Gas chromatography-mass spectroscopy; M/R: Modified release; Premen: Premenstrual; Postmen: Postmenstrual; RIA: Radio-Immunoassay; S/R: Sustained release; $t_{1/2}$: Plasma/ serum half-life; t_{max}: Time to maximum plasma/ serum concentration.

Methods

The blood sample collection, preparation, melatonin assay and kinetic analysis are described in detail in Chapter 5. In brief, intermittent blood samples were taken in the critical care subjects prior to, and after the first nights melatonin/ placebo therapy. Plasma samples were analysed for melatonin concentration using a radio-immunoassay. Non compartmental analysis was used to describe the melatonin kinetics.

Results

The pharmacokinetic data are summarised in Table 7-2. Plasma melatonin concentrations declined bi-exponentially (Figure 7-1). Both C_{max} and $AUC_{(0-24)}$ were correlated with plasma ALT concentrations (r = 0.70; 0.07 to 0.93; p = 0.04, and r = 0.62; -0.08 to 0.91; p = 0.07, respectively). No association was found with age, gender, weight, albumin, creatinine, bilirubin or administration of drugs affecting CYP1A2 activity (Table 7-3). No association was found between C_{max}, $AUC_{(0-24)}$ or $C_{(08)}$ and mean SEI or BIS AUC measurements of nocturnal sleep (Table 7-4). The associations between melatonin oral clearance and administration of CYP1A2 active drugs are shown in Table 7-5. The small sample size of the study contributed to the wide confidence intervals in the associations and limit definitive conclusions.

The majority (92%) of melatonin/ placebo oral solution doses were administered by feeding tubes (naso-gastric or naso-jejunal). None of the oral doses administered to patients in the melatonin group were given by the naso-jejunal route.

t_{max} (hours)	C_{max} (pg/ml)	$AUC_{(0-24)}$ (ng/l.hr)	$t_{1/2}$ (hours)	Oral Clearance (Cl/F) (l/hr)	$C_{(08)}$ (pg/ml)
0.5 (0)	14,974 (3,200)	29,979 (8,205)	1.47 (0.28)	351.0 (96.7)	84 (64)

Table 7-2 Summary of melatonin pharmacokinetic data after a 10 mg oral dose in critical care patients

Mean (SD)

$C_{(08)}$: Plasma concentration at 0800 hours; Cl/F: Clearance/ Bioavailability (oral dose/ area under the zero moment curve); $t_{1/2}$: Plasma half life; t_{max}: Time to maximum plasma concentration.

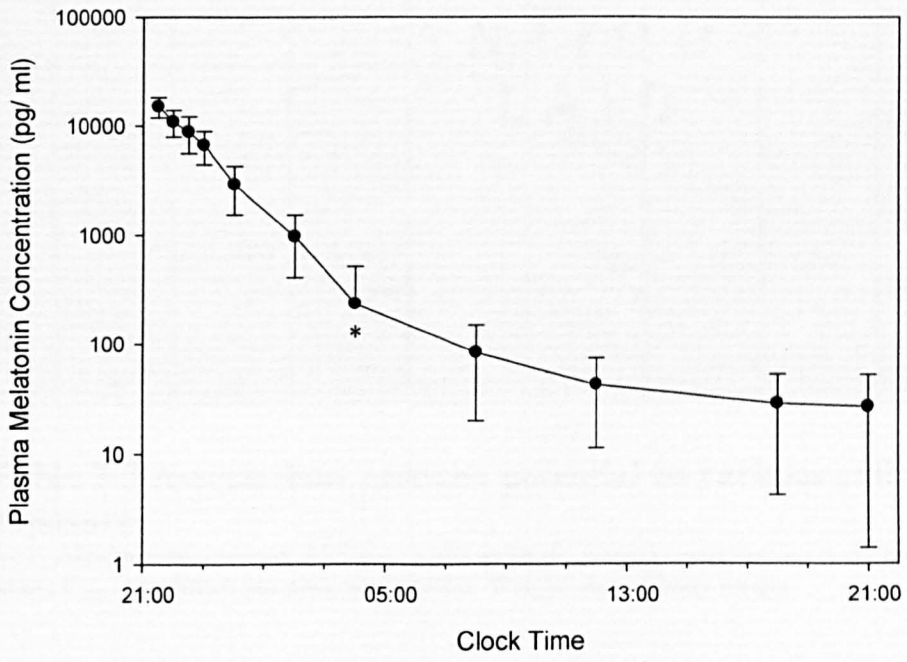


Figure 7-1 Plasma melatonin concentrations (mean ± SD) after oral administration of a 10 mg dose in solution at 2100 hours to critical care patients

* 04:00 data point. Mean concentration value minus SD is a negative number and cannot be represented on a logarithmic scale.

Parameter	C_{max} (95% CI)	p-Value	$AUC_{(0-24)}$ (95% CI)	p-Value
Age	-0.19 (-0.76; 0.54)	0.62	-0.23 (-0.78; 0.51)	0.55
Gender	-0.19 (-0.76; 0.54)	0.63	-0.26 (-0.79; 0.49)	0.51
Weight	0.50 (-0.25; 0.87)	0.17	0.39 (-0.37; 0.84)	0.31
Albumin	-0.30 (-0.80; 0.45)	0.43	-0.39 (-0.84; 0.37)	0.31
ALT	0.70 (0.07; 0.93)	0.04	0.62 (-0.08; 0.91)	0.07
Bilirubin	0.50 (-0.25; 0.87)	0.18	0.42 (-0.34; 0.85)	0.26
Creatinine	0.08 (-0.62; 0.71)	0.85	0.27 (-0.48; 0.79)	0.48
CYP1A2 Inducers	-0.21 (-0.77; 0.53)	0.59	-0.22 (-0.77; 0.52)	0.57
CYP1A2 Inhibitors	-0.34 (-0.82; 0.42)	0.38	0.09 (-0.61; 0.71)	0.81

Table 7-3 Associations between potential co-variates and melatonin exposure

ALT: Alanine transaminase; $AUC_{(0-24)}$: Area under the plasma concentration curve between 0 and 24 hours; C_{max}: Maximum plasma concentration; Weight: Actual body weight

Parameter	SEI (95% CI)	p-value	BIS AUC (95% CI)	p-value
C_{max}	-0.08 (-0.71; 0.62)	0.84	0.04 (-0.64; 0.69)	0.93
$AUC_{(0-24)}$	0.21 (-0.53; 0.77)	0.60	-0.19 (-0.76; 0.54)	0.63
$C_{(08)}$	0.50 (-0.25; 0.87)	0.17	-0.63 (-0.91; 0.06)	0.07

Table 7-4 Correlations between markers of melatonin exposure and BIS measures of sleep

$AUC_{(0-24)}$: Area under the plasma concentration curve between 0 and 24 hours; BIS AUC: Bispectral index area under the curve; $C_{(08)}$: Plasma concentration at 0800 hours; C_{max}: Maximum plasma concentration; SEI: Sleep efficiency index

Parameter	Oral Clearance (Cl/F) (95% CI)	p-value
CYP1A2 Inducers	0.21 (-0.53; 0.77)	0.59
CYP1A2 Inhibitors	-0.15 (-0.74; 0.57)	0.70

Table 7-5 Associations between melatonin oral clearance and administration of drugs affecting CYP1A2 activity

Cl: Clearance; F: Bioavailability

Discussion

This study is the first detailed report of the kinetics of melatonin after an oral dose in critical care patients. Melatonin appeared to be rapidly absorbed after administration in aqueous solution, and peak plasma concentrations were higher than most of those reported in studies with comparable doses in healthy subjects [255, 256, 386, 428, 433, 441]. Two other studies reported higher C_{max} values [429, 439]. However, direct quantitative comparison of the results of the current study with those of the studies in Table 7-1 is limited by methodological variations, including patient population, oral melatonin formulation, assay, feeding status, frequency of blood sampling, study period and kinetic parameters reported.

The data from the present study are consistent with those of Ibrahim *et al*, [403] who reported a single mean plasma melatonin concentration of 3,453 pg/ ml at 1.5 hours after a 3mg dose given *via* feeding tube to critical care patients. Ibrahim and colleagues [403] did not report any additional melatonin kinetic data which prevents further comparison with the results of the current study.

After oral dosing, C_{max} is affected by the solubility of melatonin in the formulation, alterations in bioavailability and clearance. Orally administered melatonin is subject to an extensive "first-pass effect", with bioavailability reported to vary between 9 – 33% [254, 256, 422]. As outlined in Chapter 2, this variability is due to factors such as CYP1A2 activity and co-administration of interacting drugs [345]. The acute inflammatory cascade related to sepsis may affect cytochrome P450 regulation, and hence CYP1A2 enzyme activity, [447, 448] and a prolonged reduction in enzyme function in patients recovering from critical illness may have contributed to the relatively high C_{max} values compared to reports in healthy volunteers. Conversely,

the C_{max} or $AUC_{(0-24)}$ results could not be accounted for by concurrent use of CYP1A2 inhibitors.

A RIA was used as it enabled measurement of plasma melatonin concentrations across the range of low endogenous levels and high exogenous concentrations (after dilution). Of the oral melatonin kinetic studies, the majority (22/ 30) that included the assay method in the report used a plasma/ serum RIA. Markantonis *et al*, [439] administered melatonin as a solid dose formulation (capsule) in their study, which would be anticipated to be associated with slower drug absorption compared to an oral solution. Examination of the post-menopause patient data in the Markantonis study, [439] (comparable age-group to the patients in the current study) the T_{max} was 0.88 compared to 0.5 hours. Deacon and colleagues [429] also reported a relatively higher C_{max} after administration of oral melatonin in healthy volunteers compared to the current study. Melatonin was formulated in an oral corn oil solution, which may have facilitated absorption and hence increased bioavailability [429].

Feeding status and gastric function are other factors which may explain differences between the studies. Patients in the current melatonin study were fed continually *via* enteral feeding tubes, while the patients in the Markantonis and Deacon studies, [429, 439] were fasted. The effect of food on absorption may explain differences in the results, however an earlier study reported increased melatonin exposure (AUC) when doses were administered with food compared to fasting [262]. Intensive care patients have slow gastric emptying, [449-451] reducing the rate but not extent of absorption of oral drugs such as paracetamol [451]. However, the delayed gastric emptying effects are most notable during the acute phase of a critical illness, when the combined actions of cytokines, opioids, sedatives, surgery and vasoconstrictors are greatest. Also, the patients in the current study were recovering from critical

illness and patients with high gastric aspirates, an indicator of reduced gastric motility, were excluded.

The kinetic studies identified measured total melatonin concentrations in plasma or serum. Melatonin is highly bound (approximately 80%) to plasma albumin [452]. Critical illness is associated with reduced plasma albumin levels, and as expected, the patients in the current study also demonstrated low albumin levels (mean approximately 17 g/l). Total plasma concentrations of hormones, such as cortisol, are poor indicators of their pharmacological activity [453]. Therefore, it is possible that total plasma melatonin concentrations may not accurately reflect free drug concentrations and activity. In the current study, the weak inverse correlation between albumin levels and markers of melatonin exposure (C_{max}, AUC_{0-24}) was not statistically significant. Melatonin also binds to α1-acid glycoprotein, an acute phase protein that has increased plasma levels in critical care patients. Plasma levels of α1-acid glycoprotein were not measured in the current melatonin study. Therefore, it is not possible to comment on the effect α1-acid glycoprotein level variability may have on total plasma melatonin concentrations. However, although melatonin is highly protein bound, its affinity for proteins is significantly less than that of hormones, such as cortisol [452]. Furthermore, melatonin readily crosses the blood brain barrier [454], thereby allowing distribution to the central nervous system, the primary site of melatonin pharmacological activity. Therefore, it can be anticipated that total plasma concentrations of melatonin provide a useful marker of drug activity in critical care patients.

In Table 7.1, D/AUC (dose divided by area under the concentration time curve) was calculated to provide an indication of oral clearance and allow some comparison between the studies. It was not possible to calculate oral clearance ($D/AUC_{(0\text{-infinity})}$)

for all studies, as $AUC_{(0\text{-infinity})}$ was not always reported. Overall, melatonin oral clearance in the critical care patients appeared reduced compared to healthy individuals [256, 422, 434, 439]. Oral clearance results from the current study were comparable to those of Shah *et al*, [442] who studied the kinetics of melatonin in older volunteers. The mean age of patients in the current study was 70 years *versus* 67 years, in the Shah study [442]. Older patients might be expected to show reduced clearance as a consequence of reduced CYP1A2 activity [455]. However, the use of very low melatonin doses (0.1-0.44mg) administered as a controlled release formulation in the Shah study, [442] limits direct comparison of results with the current study. Fourtillan *et al*, [422] reported reduced melatonin clearance in healthy female volunteers compared to males, although confidence intervals were not reported. In the current study there was no association between gender and markers of drug exposure, including oral clearance. The impact of CYP1A2 drug interactions on the clearance of melatonin has been demonstrated in studies of smokers (enzyme inducer), [386, 445] and individuals also receiving known inhibitors of CYP1A2, including fluvoxamine [345] and caffeine [386]. However, in the current study there was no association with administration of drugs known to affect CYP1A2 activity and oral clearance, although the power of the test for association was limited. Overall, the reduced clearance observed in the critical care patients is probably a result of older age and the residual effects of critical illness on the hepatic metabolism of melatonin.

Although conventional liver function tests are generally poor predictors of hepatic drug metabolism, there was a moderate correlation between plasma transaminase levels and measures of exogenous melatonin exposure. A previous study of endogenous plasma levels in cirrhotic patients reported a significant association

between melatonin and bilirubin levels ($r = 0.6$; $p < 0.01$) [260]. There was no association between plasma melatonin concentrations and total bilirubin levels in the current study, although, again, the power of the analysis was limited.

There was no association between markers of drug exposure and nocturnal sleep quantity in the current study. The soporific and entraining effects of melatonin have been shown to reach a plateau at lower plasma concentrations than described in the critical care patients [456]. Therefore, plasma melatonin concentrations in excess of this plateau would not be expected to further increase sleep efficiency. The ideal dosing schedule of melatonin would produce an appropriate rapid peak plasma concentration while maintaining "physiological" plasma levels over the nocturnal period. The decision to use a melatonin formulation suitable for administration *via* feeding tubes was supported by the need to administer the vast majority of doses by this route in the study. Therefore, a relatively large oral dose of an immediate release formulation was used to ensure continuous melatonin nocturnal exposure in the current study. However, the 10 mg dose resulted in some patients with relatively low clearance having potentially "nocturnal" plasma levels during the late morning, a finding in agreement with other reports [337, 441, 446, 457]. This may have negated some of the potential chronotherapeutic benefits of melatonin [265]. The presence of supraphysiological levels in the morning would be anticipated to have a phase delaying effect and, thereby, negate some of the benefits of the phase advancing effect of the 2100 h administration. However, an inverse correlation between nocturnal sleep markers and plasma melatonin concentration at 0800 h was not demonstrated. Conversely, there was a non-significant trend towards a moderate inverse correlation ($r = -0.63$; -0.91 to 0.06); $p = 0.07$)) with the average BIS AUC, suggesting "better" sleep with higher morning concentrations. There are several

possible explanations for the lack of association between higher morning melatonin concentrations and reduced nocturnal sleep quantity. Firstly, as melatonin has a weaker phase delaying than phase advancing effect, a significant phase delaying effect may not be demonstrable after acute melatonin administration [458]. Secondly, the protracted illness of the patients studied may have led to a DSPS. If the patients had a delayed sleep time of 6 hours, for example, higher morning plasma concentrations may have coincided with the patients "nocturnal" circadian time and hence facilitated sleep in the latter part of the night and early morning. A more prolonged sleep study, using a continuous measure of sleep to provide "daytime" sleep data is required to investigate this possibility further. Indeed half the patients in the placebo group did display a DSPS (see Chapter 9). Nevertheless, the kinetic data from the current study suggest that immediate release doses of 1-2 mg administered at 2100 h might provide suitable nocturnal plasma melatonin concentrations whilst minimising the risk of daytime over dose.

Conclusions

In critical care patients, melatonin appeared to be rapidly absorbed after nocturnal dosing of an oral solution, producing peak concentrations in excess of those reported in most studies of healthy volunteers. Oral clearance appeared to be reduced compared to other studies and resulted in supraphysiological morning plasma concentrations of melatonin in most patients. Therefore, a 10 mg nocturnal dose of melatonin may be excessive in these patients and doses of 1-2 mg might be more appropriate in future studies of chronotherapy with melatonin.

8 SLEEP MEASUREMENT IN CRITICAL CARE PATIENTS. RESEARCH AND CLINICAL IMPLICATIONS

Introduction

Polysomnography is the gold standard for monitoring the quantity and quality of sleep. However, polysomnography is technically difficult to perform, especially in critical care due to environmental and patient considerations. As a result polysomnography is not used in the daily clinical evaluation of patients sleep. Instead, clinical evaluation methods are used to assess sleep before deciding if interventions such as hypnotic therapy are warranted and subsequently to review their efficacy. The Society of Critical Care Medicine (SCCM) guidelines on sedation monitoring identify that sleep assessment should be undertaken [118]. The SCCM guidelines recommend patient self report, but if this is not possible, nurse observation may be used [118].

A range of objective and subjective sleep monitoring techniques is available for both research and clinical evaluation, each of which has advantages and limitations. An appreciation of the limitations is essential when choosing the most appropriate technique for interventional studies. Importantly, the technique nurses routinely use to assess the sleep of critical care patients will inevitably have consequences for patient treatment. Furthermore, the validity of patient assessment will also be affected by factors such as acuity of illness.

A comparison of the nocturnal sleep quantity data from the sleep measurement techniques used in the melatonin intervention trial (Chapter 6) was undertaken with the aim of assessing agreement between the techniques. This information will contribute to the design of future critical care sleep studies and the assessment of sleep in clinical practice.

Methods

Agreement between the sleep assessment techniques used in the randomised controlled trial of melatonin in critical care patients (Chapter 6) was investigated for a common measure, the SEI. Although the RCSQ comprises a 5 component VAS, the total score has been validated against polysomnography SEI [29]. The melatonin intervention study design and patient characteristics are described in Chapters 5 and 6, respectively. The limits of agreement method was used to evaluate agreement between the sleep measurement techniques and is documented in Chapter 5. To complement the test for agreement, a critical evaluation of all critical care sleep studies was undertaken with emphasis on the sleep measurement techniques used.

Literature review

MEDLINE (1966 to July 2008), EMBASE (1974 to July 2008) and CINAHL (1982 to July 2008) databases were searched using the following terms, both as MESH headings and text words: "sleep", "sleep disorders", "sleep deprivation", "actigraphy", "actimetry" and "polysomnography", in combination with "critical illness", "intensive care", "critical care" and "intensive care unit". Reference lists of all identified papers were also scanned for other relevant publications. Papers were restricted to those pertaining to sleep measurement in adult patients during their critical care admission and those published in English.

Results

Literature review

Both objective and subjective monitoring techniques have been used to study sleep in critical care patients. Objective techniques include polysomnography, processed EEGs and actigraphy; while subjective assessment generally relies on nurse observation or patient self report. Individual monitoring techniques are summarised in Table 8-1.

Thirty two studies in critical care patients were identified that used objective sleep measurement techniques. These were predominantly polysomnography studies [20, 27-29, 35-38, 82, 84, 105, 106, 193, 380, 408, 411, 459-470] (Table 8-2); the remainder used actigraphy [312, 313, 471] and the bispectral index [378] (Table 8-3). There were twelve subjective sleep measurement studies [30, 33, 83, 87, 121, 397, 403, 472-476] which used a variety of nurse and patient assessment techniques (Table 8-4).

Agreement between sleep measurement techniques in the melatonin intervention study

Data on 91 nights were available for evaluation. Missing data from the four sleep measurement methods are summarised in Table 8-5. Patient mean hand grip strength scores were 23.0% (95%CI: 10.1 to 35.9%) of age and sex matched controlled data [392].

Agreement between sleep measurement techniques was evaluated by scatter plots (Figure 8-1) and Bland-Altman plots (Figure 8-2).

Limits of agreement (upper limit and lower limit) for sleep efficiency index for selected sleep measurement techniques were:

Actigraphy versus BIS (Figure 8-2a): -0.12 (95% CI: -0.22 to -0.02) and 0.97 (95% CI: 0.87 to 1.06).

Patient assessment versus BIS (Figure 8-2b): -0.37 (95% CI: -0.46 to -0.28) and 0.65 (95% CI: 0.56 to 0.74).

Nurse assessment versus BIS (Figure 8-2c): -0.28 (95% CI: -0.36 to -0.21) and 0.57 (95% CI: 0.50 to 0.65).

Nurse assessment versus patient assessment (Figure 8-2d): -0.56 (95% CI: -0.66 to -0.46) and 0.57 (95% CI: 0.47 to 0.67).

Instrument	Validity and Reliability	Advantages	Disadvantages	Clinical application
Polysomnography	Gold standard Inter-rater reliability in critical care kappa = 0.79-0.83 [29, 193, 380, 466, 477]	Monitors sleep quantity and quality	Sleep technician needed continually during monitoring and to score results Significant set up time required Rater subjectivity especially when scoring Stage 1 sleep Potential for monitoring electrodes to adversely affect sleep in non sedated patients Few critical care studies over multiple days Cost – expensive set up and maintenance Prone to patient dislodgement Prone to electrical interference Critical illness *e.g.* delirium may affect EEG	Not practical for routine clinical use

(Table 8-1 continued)

Bispectral Index	BIS score < 80 all patients asleep in one study [32]	Can be used by non-specialists Sensor easily applied Continuous attendance of technician not required Low cost once monitor purchased Trend screen provides quick view of immediate sleep quantity	Prone to patient dislodgement Prone to electrical interference Some patients may find sensor intrusive EMG activity may raise BIS value Need to download into PC for complete evaluation Critical illness e.g. delirium may affect EEG	Not practical for routine clinical use. Validation and algorithm development required
Actigraphy	Correlation 0.72 to 0.98 versus polysomnography for total sleep time [478] Not validated versus polysomnography in critical care patients	Non-intrusive Can be used by non-specialists Low cost once device purchased Allows continuous measurement over days to weeks Some actigraphs have a facility to measure light exposure simultaneously Robust – unlikely to be removed by patient	Neuromuscular weakness increase risk of overestimating sleep quantity Nursing staff may remove and not replace watch during washing *etc* Periods of inactivity such as watching television scored as sleep	Yes – but only for circadian rhythm monitoring

(Table 8-1 continued)

Patient Assessment	1. Verran/Synder-Halpern (VSH) Sleep Scale Convergent validity (r = 0.39) only when polysomnography awakenings > 4 minutes scored [411] No significant difference in total sleep time results compared to Actigraphy [471] 2. HAD Scale (Sleep component) Not validated versus polysomnography [121] 3. Sleep in the Intensive Care Unit Questionnaire Not validated versus polysomnography [83] 4. Richards Campbell Sleep Questionnaire (RCSQ) Reliability (Cronbach's alpha = 0.90) Correlation = 0.58 with polysomnography sleep efficiency index in critical care patients [29]	1-4. If capable, patient can compare baseline quality with that currently experienced Relatively quick to complete	1-4. Cannot be used in cognitively impaired patients Memory problems may limit accuracy Patient perception of nocturnal sleep may be adversely affected by circadian rhythm abnormalities	1,2,4. Yes – but exclude patients with delirium/ dementia and beware of obvious patient sleep-state misperception

(Table 8-1 continued)

Nurse Assessment	1. Direct Observation Direct observation at 5 minute intervals. Observation significantly overestimated polysomnography total sleep time [27]. Direct Observation at 15 minute intervals. Nurses correct in 82% of sleep state assessments *versus* polysomnography [28] 2. Echols' Patient Sleep Behavioural Observation Tool Direct observation at 5 minute intervals. Moderate convergent validity demonstrated with polysomnography awakenings. Single trained observer [411] No significant difference in total sleep time results compared to Actigraphy [471] 3. Richards Campbell Sleep Questionnaire Reliability versus patients (Cronbach's alpha = 0.83-0.95) [30, 479]	1,3. Relatively easy to incorporate into routine nursing care 2. Attempts to qualify wake, NREM and REM sleep	1-3. Overestimates total sleep time Frequent assessment required Risk of data loss due to other direct and indirect nurse activities 3. Relies on nursing staff being able to make an accurate report of the patients total sleep quality	1. Yes – but even with frequent assessment likely to overestimate total sleep time. This may limit its practicality and a compromise between frequency and accuracy will be necessary 2. No - Extensive observation required of eyelid positioning, respiration, eye and body mobility and responses. 3. Yes – potentially the most useful sleep assessment tool currently available for clinical use

Table 8-1 Summary of methods used in critical care for sleep measurement

Reference	Number of patients	Critical Care Population	Duration	Sedation	Number Ventilated	Intervention monitored	Practical difficulties
Johns (1974) [459]	4	Surgical	Continuously for first few days	Opioids and nocturnal hypnotics	Not stated	No	None identified
Karacan (1974) [460]	4	Medical	Continuous x 24 to 108 hours	Majority nocturnal hypnotics	None	No	None identified
Hilton (1976) [461]	10	Medical	Continuous x 48 hours	Not stated	Not stated	No	Data incomplete for 3/ 10 patients
Orr (1977) [462]	9	Surgical	3 to 4 Nights	Majority nocturnal opioids and/ or benzodiazepines	Not stated	No	Considerable muscle artefact across all recording channels
Broughton (1978) [463]	12 (10 reported)	Medical	Majority 9 Nights but up to 13	Majority nocturnal benzodiazepines and/ or barbiturates	None	No	Two patients withdrew due to inconvenience of monitoring
Aurell (1985) [27]	9	Surgical	Continuous x approximately 72 hours	Opioid & local analgesia, some benzodiazepines	2/ 9	No	None identified
Richards# (1988) [380]	10	Medical	1-3 Nights	Not stated	None	No	One patient withdrew from study after EEG electrodes were positioned
Fontaine (1989) [411]	20	Trauma	1 Night	All received opioid and nocturnal benzodiazepine	1/ 20	No	None identified

(Table 8-2 continued)

Edwards (1993) [28]	21	Medical	1 Night	18/ 21 nocturnal benzodiazepine/ barbiturate	20/ 21	No	None identified
Gottschlich (1994) [464]	11	Burns	Continuous x 24 hours (repeated intervals)	Not stated	All	No	None identified
Aaron (1996) [82]	6	Medical	Continuous x 24 hours 2/6, x 48 hours 4/6	3/ 6 received hypnotics/ opioids	None	No – effect of environmental disturbances recorded	None identified
Richards# (1996) [465]	9	Medical	1 Night	3/ 9 received nocturnal benzodiazepines	None	No	None identified
Richards* (1998) [193]	69	Medical	1 Night	Minority received nocturnal hypnotics	None	Yes – Relaxation techniques	Standard sensitivity and paper speed settings for polygraph unavailable and were therefore altered 23/ 94 refused most commonly due to study/ polysomnography being an additional stressor. Only one patient could be studied per night.**
Cooper (2000) [36]	26 (20 reported)	Medical	Continuous x 24 hours	Majority received opioids, benzodiazepines or haloperidol	All	No	Six patient records unable to score due to technical difficulties - electrical artefact (4); respiratory artefact (2).

(Table 8-2 continued)

Richards* (2000) [29]	70	Medical	1 Night	Minority received nocturnal hypnotics	None	No – see above	**See above entry
Freedman (2001) [37]	22	Medical	Continuous x 24 hours 14/ 22, x 48 hours 8/ 22	8 of 22 intermittent benzodiazepine or opioid	20/ 22	No- effect of environmental disturbances recorded	Five patient records unable to be scored due to sepsis induced alterations to EEG pattern
Parathasarathy (2002) [38]	11	Medical	1 Night	All received sedatives	All	Yes – Mode of ventilation	None identified
Richards* (2002) [466]	64	Medical	1 Night	Minority received nocturnal hypnotics	None	No – see above	**See above entry
Valente (2002) [467]	24	Neuro-Trauma	Continuous x 24 hours	At least 24 hours post sedation discontinued	Not stated	No	None identified
Gabor (2003) [35]	7	Medical/ Trauma	Continuous x 24 hours	Majority opioids, benzodiazepines and/ or antipsychotics	All	No – effect of environmental disturbances recorded	None identified
Cochen (2005) [20]	17	Medical/ Trauma	1-2 Nights, some daytime	None	All	No	4/ 31 sleep recordings not scored due to electrical artefact

(Table 8-2 continued)

Hardin (2006) [408]	18	Medical	Continuous x 24 hours	6/ 18 received intermittent sedation only and were awake and alert, 12/ 18 received continuous sedation	All	No – group comparison between NMBA, CS & IS	Modified delta criteria used. Unknown quantity of epochs scored as non-classifiable. Recorder malfunctioned in 1 patient
Bosma (2007) [105]	13	Medical/ Surgical	2 Nights (Crossover study)	3/ 13 received opioids and 2 received haloperidol	All	Yes – Pressure support *versus* proportional assist controlled ventilation and patient-ventilator desynchrony	None identified
Toublanc (2007) [468]	20	Medical	1 Night	None	All	Yes – Assist controlled ventilation *versus* low pressure support ventilation	Study included 22 patients but 2 were not analysed, one because of excessive electrical artefacts on polysomnography records
Alexopoulou (2007) [106]	17	Medical/ Surgical	1 Night (sedated patients) 2 Nights (non-sedated patients)	11 sedated with propofol	All	Yes – Proportional assist *versus* pressure support controlled ventilation	None identified

(Table 8-2 continued)

Friese (2007) [469]	16	Surgical	Continuous for less than 24 hours	13 received opioids; of which 3 also received benzodiazepines	All	No	None identified
Cabello (2008) [84]	15	Medical	6 hour periods	None	All	Yes – Clinically adjusted *versus* automatically adjusted pressure support ventilation *versus* assist controlled ventilation	Recordings were reported to be well tolerated
Beecroft (2008) [470]	12	Medical/ Surgical	8-12 hours overnight	Patients were excluded if defined sedation limits were exceeded	All	No – compared polysomnography, actigraphy and nurse assessment of sleep quantity	None identified

Table 8-2 Polysomnography studies of sleep in critical care patients

*[#] Multiple reports refer to a single polysomnography study

Reference	Number of patients	Critical Care Population	Duration	Sedation	Number Ventilated	Intervention Monitored	Method/ Practical Difficulties
Shilo (1999) [312]	14	Medical	Continuous x 72 hours	Not stated, no opioids	Not stated	No	Actigraphy / None identified
Shilo (2000) [313]	8	Medical	Continuous x 72 hours	None	4/ 8	Yes – Exogenous melatonin	Actigraphy / None identified
Kroon (2000) [471]	13	Medical	1 Night	None	None	No	Actigraphy / None identified
Nicholson (2001) [378]	29 (27 reported)	Medical/ Surgical	1 Night	23/ 27 Received morphine and midazolam or propofol	17/ 27	No	Bispectral Index / 2 patients withdrew early in study

Table 8-3 Actigraphy and BIS studies of sleep in critical care patients

Reference	Number of patients	Critical Care Population	Duration	Sedation	Number Ventilated	Intervention monitored	Method/ Practical difficulties
Woods (1972) [472]	4	Surgical	8 Nights	Not Stated	Not Stated	No	Nurse Observation (10 minute intervals) / Not stated
Helton (1980) [397]	62	Medical/ Surgical	Continuous x 5 Days	Not stated	Not stated	No	Nurse Observation (15 minute intervals) – Interruptions recorded / Not stated
Williamson (1992) [473]	60	Surgical	3 Nights	Not stated	Not stated	Yes – Ocean sounds (white noise)	RCSQ / Not stated
Treggiari-Venzi (1996) [121]	40 (32 reported)	Trauma/ Surgical	3 Nights	Midazolam or propofol only	None	Yes – Midazolam versus propofol on sleep quality	Hospital Anxiety and Depression (HAD) Scale / Not stated
Freedman (1999) [83]	203	Medical/ Surgical	1 Night	Not stated	32/ 203	No – Assessed environmental aetiologies of sleep disturbances	Sleep in the ICU Questionnaire / Not stated
Olson (2001) [87]	239 (GCS $\geq$ 10)	Medical/ Surgical	Daily during monitoring periods (2 x 2 months)	Not stated	Not stated	Yes – Effect of environmental controls	Nurse Observation x 8 at predefined times / Not stated

(Table 8-4 continued)

Nelson (2001) [33]	100	Medical	Multiple days	Three quarters received sedatives	74/ 100	No – Assessed frequency of difficulty sleeping and related degree of stress	Edmonton Symptom Assessment Scale / Used verbal descriptions due to difficulties with visual analogue scale. Only 50% of patients were able to complete questionnaire
Frisk (2003) [30]	31	Medical/ Surgical/ Trauma	1-2 Nights	12/ 31 received hypnotics	Not stated	No – but RCSQ scores lower in patients on hypnotics	RCSQ / Half of eligible patients were unable to complete questionnaire
Richardson (2003) [474]	36	Medical/ Surgical	3 Nights	Not stated	Not stated	Yes – Combined relaxation and guided imagery	Verran/Synder-Halpern (VSH) Sleep Scale / Some patients required assistance with the VAS
Ibrahim (2006) [403]	32 (27 reported)	Not stated	Minimum 2 Nights	14 received extra sedation or haloperidol	All	Yes – Exogenous melatonin	Nurse Observation (Frequency not stated) / Not stated
Richardson (2007) [475]	64	Not stated	1 Night	None	None	Yes – Ear plugs and eye masks	Patient assessment using a simple visual analogue scale / Not stated
Nicolas (2008) [476]	104	Surgical	1 Night (18 patients 2 Nights)	None	None	No	RCSQ / No difficulties with use of RCSQ reported, although nurses recorded verbal response of patient on VAS

Table 8-4 Subjective studies of sleep in critical care patients

Method	Nights Missing data	Reasons
Bispectral Index	11 / 91 (12.1 %) Average 11.8 minutes lost per 9 hour night studied (2.2 %)	Patient removed sensor (4) Signal Quality Index Low (3) Hardware Failure (2) Patient refused (2)
Patient Assessment (Richards Campbell Sleep Questionnaire)	17 / 91 (18.7 %)	Delirium (16) Patient unable to complete (1)
Nurse Assessment	23 / 91 (25.3 %)	Unable to evaluate – Too busy, forgot or unsure of sleep status
Actigraphy	0/ 91 (0 %)	N/A

Table 8-5 Summary of missing data from the melatonin intervention study

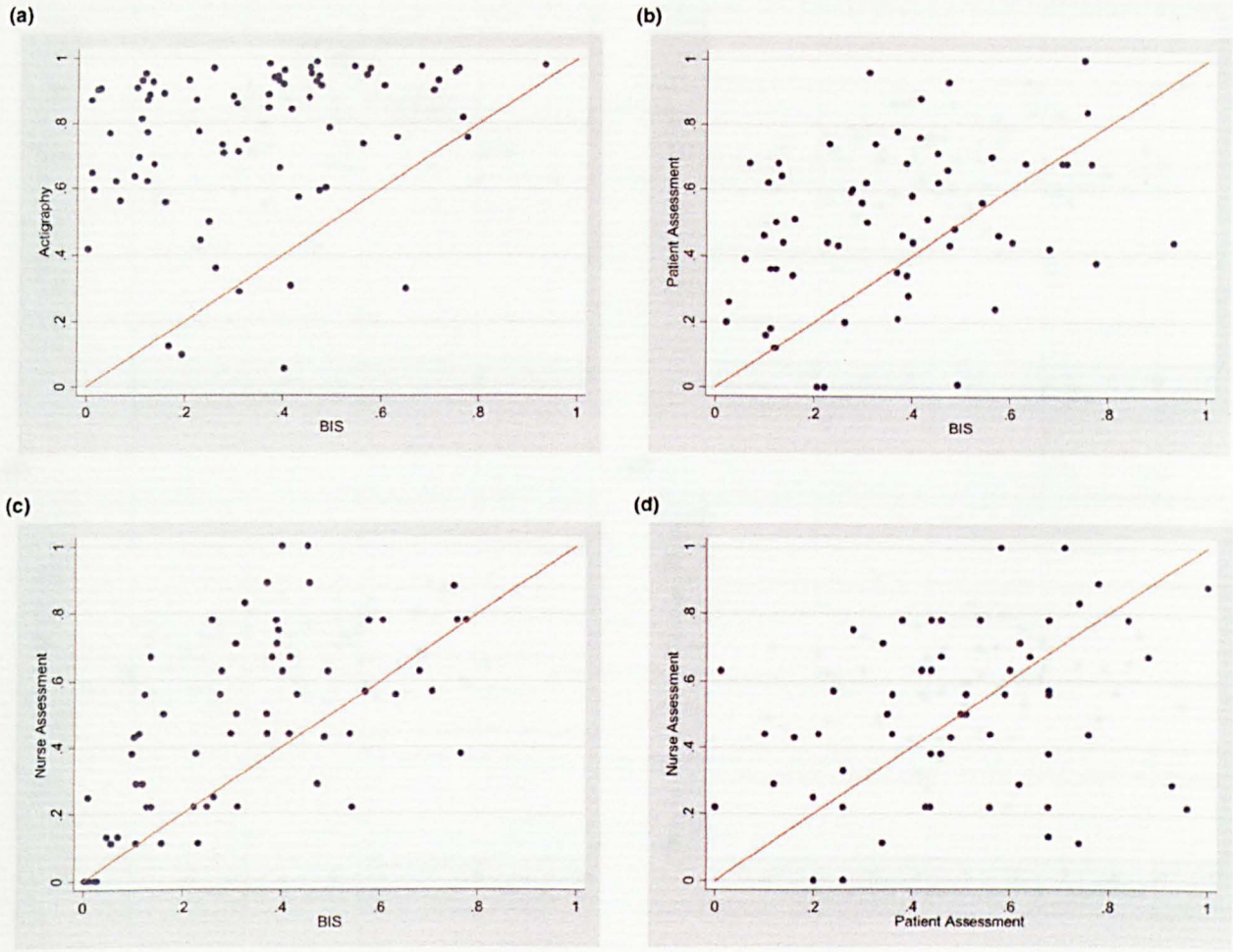


Figure 8-1 Scatter plots comparing the results from four different techniques used to measure nocturnal sleep efficiency in the melatonin intervention study

(a) BIS quantity *vs.* Actigraphy; (b) BIS quantity *vs.* Patient assessment (RCSQ); (c) BIS quantity *vs.* Nurse assessment; (d) Nurse assessment *vs.* Patient assessment.

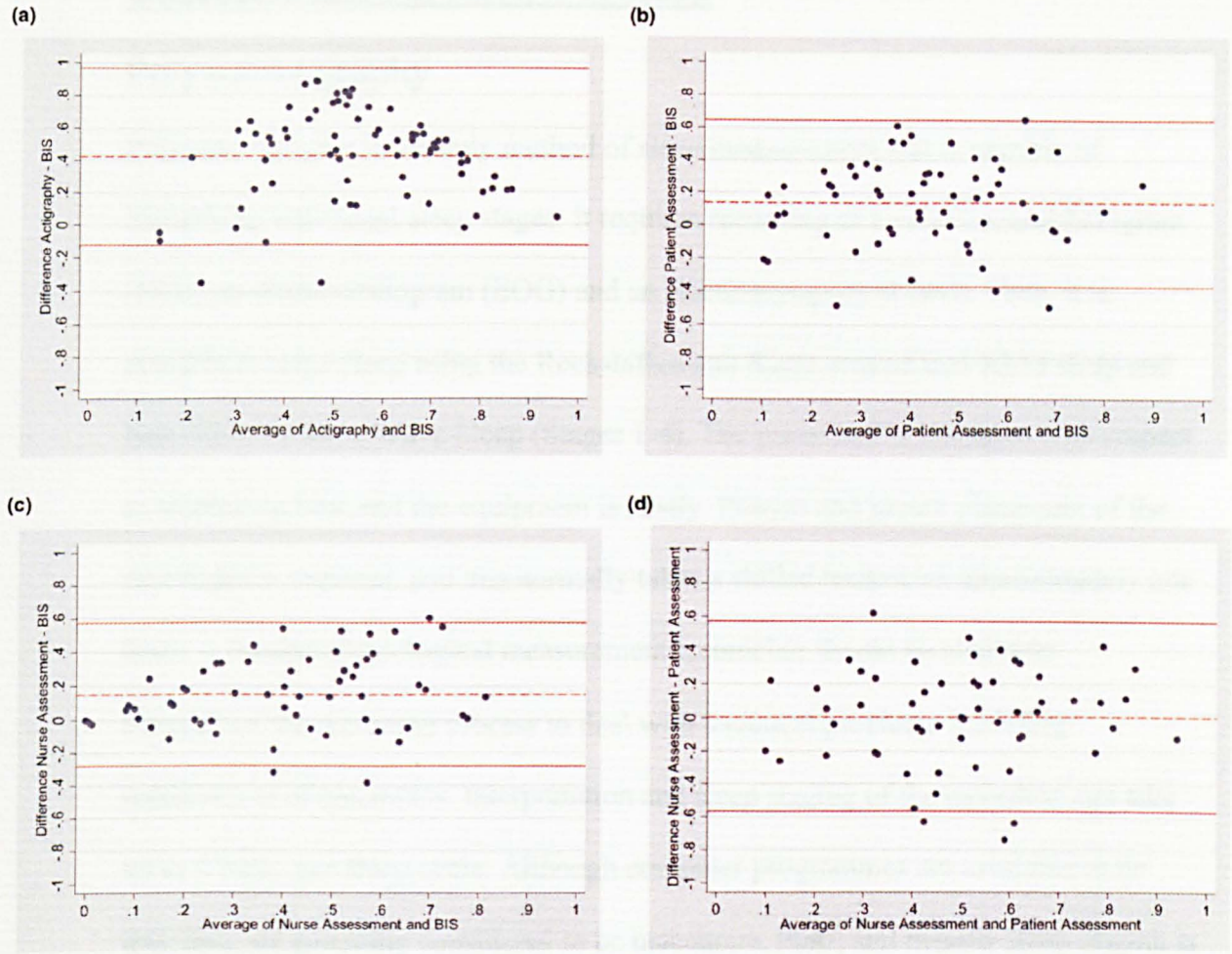


Figure 8-2 Bland-Altman plots for the four different techniques used to measure nocturnal sleep efficiency in the melatonin intervention study

Horizontal lines indicate the mean difference, and the mean difference plus and minus 1.96 times the standard deviation of the differences; (a) BIS quantity *vs.* Actigraphy; (b) BIS quantity *vs.* Patient assessment (RCSQ); (c) BIS quantity *vs.* Nurse assessment; (d) Nurse assessment *vs.* Patient assessment.

Objective measurements of sleep

Polysomnography

Polysomnography is the only method of sleep measurement that is capable of identifying individual sleep stages. It requires recording of an electroencephalogram (EEG) an electrooculogram (EOG) and an electromyogram (EMG). Thus, it is possible to stage sleep using the Rechstaffen and Kales criteria into REM sleep and Non-REM or Slow Wave Sleep (Stages 1-4). The procedure is intensive with respect to technician time and the equipment is costly. Precise and secure placement of the electrodes is required, and this normally takes a skilled technician approximately one hour. A trained physiological measurement technician should be available throughout the recording process to deal with technical problems including replacement of electrodes. Interpretation and sleep staging of the recording can take up to 4 hours per sleep cycle. Although computer programmes are available to do this, they are generally considered to be inaccurate, [480] and manual sleep staging is preferred. Nevertheless, there is a significant subjective element in manual analysis, particularly in identifying drowsiness and sleep onset in Stage 1.

All electrodes are glued to the skin with collodion, but the EMG electrodes, which are usually placed sub-mentally, are particularly prone to dislodgement.

The reliability of polysomnography recordings is compromised further by the hostile electrical environment of the critical care area. It can be difficult to eliminate 50Hz electrical artefact caused by various essential items of electrical equipment being used on the patient or other patients in the intensive care unit. Individuals subjected to polysomnography recording often find that the electrodes and recording equipment themselves have a disruptive effect on sleep [29]. This is overcome in sleep laboratories by having acclimatisation nights. The latter have not been used

routinely in critical care studies, and it could be argued that polysomnography equipment introduces yet another potential environmental disruption in non-sedated critical care patients. Additionally, they may impact on some nursing activities such as patient turning.

Since critically ill patients frequently experience delirium, [379] removal of electrodes enhances this risk and their presence may increase the need for sedation or antipsychotic therapy. The significant resource needed to apply polysomnography, as well as associated practical difficulties has lead to investigators to adopt other techniques for assessing sleep in critical care patients. However, portable polysomnographic equipment capable of providing more limited data on sleep characteristics such as TST [481] may overcome some of the difficulties. Since the advent of digital polygraphic recording there is probably less variation in the performance of recording equipment and the instrumentation is less cumbersome. The technical difficulties of undertaking polysomnography in critical care patients are frequently emphasised [23, 36, 378, 403, 471]. However, fewer than half of the studies using polysomnography identified any practical difficulties or loss of data (Table 8-2), which may suggest that there is under reporting of these difficulties in research studies.

The majority of polysomnography studies have been conducted in non-sedated critical care patients. While there are some similarities between the states of sleep and sedation, *e.g.* neurotransmitter pathways involved, there are also significant differences such as the lack of temporal or circadian cycling during sedation [190]. Despite these differences, a review of polysomnography sleep studies in critical care patients found reports of similar sleep disturbances in sedated and non-sedated populations [23].

The limitations of conventional sleep staging have been identified as a particular problem in critical care patients, who demonstrate significantly disrupted sleep phases with complex electrophysiological changes [36, 378]. A preliminary report identified a number of difficulties of conventional sleep staging during continuous polysomnography in intensive care patients receiving mechanical ventilation [482]. Sedation induced low amplitude, high frequency EEG, recorded as wakefulness or NREM 1 sleep. Stage 1 sleep also was artificially increased due to the absence of k-complexes and stimulation increased delta activity, an arousal that would be incorrectly scored as SWS [482]. The rapid fluctuations between EEG patterns of wakefulness, NREM 1and 2 with rapid eye movements and REM sleep without atonia are characteristic of status dissociaticus [20, 483]. Status dissociaticus represents a significant breakdown in the clinical and polysomnographic markers of the three states of being *i.e.* REM sleep, Non-REM sleep and wakefulness [22]. It is possible that the combination of sleep disturbances and polypharmacy experienced by many critical care patients predisposes to this form of REM sleep behavioural disorder, which shares similar symptoms to delirium [484].

Studies published on the use of polysomnography in critical care patients tend to be very small (mostly 15 – 20 subjects). Only six polysomnography studies examined the effect of an intervention [38, 84, 105, 106, 193, 468]. A randomised controlled trial in 69 patients investigated back massage compared to standard nursing care, [193] and suggested increased sleep quantity in the intervention group. A randomised cross-over trial of eleven medical patients reported significant differences in the number of arousals and awakenings between pressure support and assist controlled ventilation modes within the same night [38]. Another randomised cross over study in thirteen patients found an increase in the number of nocturnal sleep arousals as a

consequence of patient-ventilator desynchrony [105]. Another recent study [468] found no difference in sleep quantity or quality in 20 non-sedated intensive care patients, when receiving assist controlled ventilation compared to low pressure support ventilation. When only the second part of the night was analysed, assist controlled ventilation was reported to increase SWS, but not REM sleep compared to pressure support ventilation. However, a study of 17 intensive care patients who had good patient-ventilator synchrony, reported that sleep quality was unaffected by the mode of mechanical ventilation [106]. Recently, a further critical care study investigating the effect of mode of mechanical ventilation on sleep fragmentation reported that when ventilation settings were optimised, the ventilation mode did not affect sleep quality [84]. Bosma *et al* [105] found that reduced ventilator desynchrony improved sleep quality, but had no effect on nocturnal sleep quantity. The ventilatory settings, *i.e.* minimising hyperventilation and patient-ventilator asynchrony, may be more important that the mode of mechanical ventilation used. Because of the marked inter and intra-patient variability in sleep, results of studies that crossed over interventions during a single night, [38, 84, 105, 468] may not fully represent the actual nocturnal sleep effects of the intervention. These studies [38, 84, 105, 468] also assume the absence of any normal circadian rhythm effect on the sleep quantity and quality results. While circadian rhythms are disturbed in intensive care patients receiving mechanical ventilation, [401, 402] it remains unknown how these disturbances affect nocturnal sleep quantity and quality. Ideally multiple nights would be studied. Fewer than half of the critical care studies collected data over several nights. Given the loss of the circadian rhythm of the sleep-wake cycle, continuous monitoring of sleep in critical care patients is important [460]. Critical care patients may not experience a decrease in total sleep time, when the full 24

hours is considered [23]. Five of the polysomnography studies [27, 37, 82, 460, 461] undertook continuous monitoring for 48 hours; only three studies [27, 459, 460] examined periods greater than this, totalling no more than 15 patients. Seven studies were undertaken in a single isolation room within the critical care unit [27-29, 193, 463, 464, 466] and may, therefore, be of limited applicability to general critical care practice, where most patients are still cared for in open bays.

Clearly, it is a significant challenge to design research studies examining the full effects of sleep interventions over multiple days and to identifying appropriate endpoints and in large numbers of patients.

Polysomnography is currently the definitive sleep monitoring technique, but it may not meet all the requirements for sleep research in critical care patients.

Bispectral Index

A number of processed EEG monitoring devices have been developed for monitoring sedation during anaesthesia and intensive care. Of these, the BIS is the most studied for the measurement of sleep. The BIS is calculated from multiple analysis of the raw EEG waveform including, power spectral analysis, bispectral analysis and time-based analysis for suppression/ non-suppression. Multivariate statistical modelling of these EEG factors is used in an algorithm that provides a scaled BIS value (Index), which has been shown to correlate with clinical depth of anaesthesia [485]. BIS values near 100 represent an "awake" clinical state, while a score of 0 represents EEG silence.

Studies of sleep using BIS indicate that the BIS index falls during physiological sleep and rises during arousal, but that there is significant overlap of values for a given sleep stage [31, 32, 486]. One group has used BIS to investigate sleep in critical care patients [378]. Nicholson *et al*, [378] classified critical care patient sleep depth using

banding derived from a study in healthy volunteers; [486] BIS >85 (awake), BIS 60-85 (light sleep), BIS < 60 (SWS) and BIS > 60 with reduced EMG (REM). The results of the BIS study of critical care patients sleep [378] showed that the intensive care patients had abnormal sleep. The sleep that did occur was low quality and approximately half of patients studied had abnormal cyclical sleep [378].

BIS has been shown to correlate with neurological status in non-sedated critically ill patients [413]. BIS values were higher in patients with higher neurological scores [413]. Therefore, neurological abnormalities *e.g.* traumatic brain injury, would be expected to reduce BIS values obscuring the evaluation of sleep. Also, studies of patients with dementia [414] and delirium, [415] indicate a decrease in fast wave activity in the EEG and BIS values. Cognitive dysfunction whether chronic or acute, may therefore affect BIS data, and potentially sleep interpretation. Residual effects of sedative agents in patients with renal and/ or hepatic failure would also potentially affect the interpretation of the results of any EEG based analysis technique.

An advantage of BIS quantification of sleep compared to polysomnography is that a technician does not need to be in attendance to ensure good recording. However, it is not without practical problems. As with conventional EEG measurement, BIS is subject to electrical interference and movement and particularly increased EMG activity adversely affects the signal quality index (SQI). Patient removal of the sensor is a risk, although compared to polysomnography electrodes, those required for BIS do not require a skilled technician for placement.

The missing data record the melatonin intervention study indicated that transient drops in the SQI below 15 resulted in loss of some, albeit minimal (2%), BIS data in most patients (Table 8-5). Three patients had insufficient SQIs, resulting in loss of

more than 2 hours of data, and were excluded from analysis. Patient removal, refusal and hardware failure also accounted for some data loss.

A recent review concluded that the BIS is capable of detecting sleep, but the spread of overlap of BIS values for a given sleep stage prevents its current use in monitoring depth of sleep [409]. A preliminary report of concomitant BIS and polysomnography assessment of sleep in 4 critical care patients found that mean BIS values correlated with depth of sleep [487]. Thus, BIS remains a potentially useful technique, as its continuous monitoring capabilities promise to capture the dynamics of sleep better than other methods [409]. It is important to stress that the algorithm for analysis of BIS data have been based primarily on depth of sedation in patients undergoing general anaesthesia. As noted previously, there are some similarities between sleep and sedation states, but also important differences [190]. Therefore, substantial algorithm development, specifically in sleep monitoring, is required before BIS can be used routinely in research studies in critical care patients.

Actigraphy

An actigraph is a small wristwatch device that is capable of both sensing and storing information on patient movement. An accelerometer detects movements in two or three planes, which are then translated 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 periods, which can then be analysed to provide data on various parameters such as the total sleep time, number and frequency of awakenings and sleep efficiency index. However, it does not provide any information related to the stage/ quality of a patient's sleep.

A variety of commercial products with associated algorithms are available. However, results from one actigraph/ algorithm are not necessarily translatable to another [488]. Developments in actigraph hardware and software led the American Academy of Sleep Medicine to acknowledge its merit in measuring sleep variability over multiple nights and the efficacy of various interventions in insomniacs [26]. In healthy individuals, actigraphy is more accurate in recording total sleep time compared to subjective sleep assessment [25]. However, actigraphy still overestimates TST compared to polysomnography as it has a high sensitivity for detecting sleep, but is less reliable in detecting wakefulness (*i.e.* reduced sleep specificity) [25]. That actigraphy overestimates TST is not unexpected as it commences at an earlier phase of the sleep-onset process compared to polysomnography [478].

Compared to polysomnography, there are relatively few studies of sleep in critical care patients using actigraphy. In common with polysomnography studies, one report found that sleep was fragmented and limited to short periods of naps throughout 24 hours [312]. Actigraphy has also been used to monitor the effects of a pharmacological intervention on the sleep characteristics of intensive care patients [313]. No studies have compared actigraphy against polysomnography in measuring sleep quantity in critical care patients. It seems reasonable to expect that technology that detects movement and uses a predefined algorithm to convert the data into various sleep parameters may be less accurate in critical care patients. This follows because abnormalities of the neuromuscular system are associated with sepsis, certain drugs such as steroids, [389] and neuromuscular blockers and severity of illness. Although these abnormalities may affect nerves, muscles or both, myopathy is probably the most important problem. The reported occurrence of neuromuscular

abnormality varies widely, from 33-82%, [390, 489-494] probably due to the variability in diagnostic methods. Clinical studies such as that of De Jonghe [389] evaluated muscle weakness when the patients were awake, using the MRC scale and found severe weakness in 25%. Similarly 26% of patients with two organ failure due to sepsis or SIRS developed severe weakness [495]. The incidence of mild or moderate weakness was far higher. Although limited, the grip strength data the melatonin intervention study provided an estimate of the degree of neuromuscular weakness. Therefore, there is a significant risk that actigraphy will overestimate sleep quantity in critical care patients. Actigraphy was found to overestimate the sleep efficiency index compared to BIS and nurse and patient assessment (data not shown). A recent study compared actigraphy to polysomnography assessment of sleep quantity in critical care patients also reported that actigraphy significantly overestimated sleep efficiency [470]. Therefore, actigraphy should not be used to measure sleep in critical care patients using currently available technology. However, actigraphy is particularly suited to patient rest-activity rhythm monitoring in the critical care environment over protracted periods of time; [25, 496] where the principle factor of interest is the timing of movement as opposed to amplitude of movement.

Subjective measurements of sleep

Compared to polysomnography studies, reports of sleep assessment in critical care patients utilising subjective methods have evaluated much larger patient numbers over more prolonged periods and have studied more interventions. In clinical practice, subjective measures currently offer the only real means of assessing the efficacy of interventions in attempting to improve individual patients sleep.

Patient assessment

Use of patient's own assessment of their sleep during their critical care stay is recommended, [118] based on the premise that the patient is best able to relate chronic sleep quality and quantity with acute illness. Sleep diaries, where the patient records their sleep quantity and quality each day, are an important measure of chronic sleep disturbances, and their use in combination with actigraphy provides an assessment of sleep comparable to polysomnography [25]. However, the use of sleep diaries in critically ill patients is limited by the cognitive and physical capabilities of the patient. For these reasons, sleep diaries have not been adopted for critical care assessment of sleep and other measures of subjective sleep have been developed such as those based on visual analogue scales.

Verran/Synder-Halpern Sleep Scale

Patients using the Verran/Synder-Halpern (VSH) Sleep Scale showed comparable assessment of TST when compared to actigraphy [471]. However, compared to polysomnography, patients were only able to reliably judge the frequency of awakenings when periods of wakefulness in excess of 4 minutes were evaluated [411].

Richards-Campbell Sleep Questionnaire

The Richards-Campbell Sleep Questionnaire (RCSQ) [29] comprises 5 visual analogue scales (VAS). These cover the sleep domains of depth, latency, awakenings, percent time awake and quality of sleep. A moderate correlation between RCSQ and polysomnography sleep efficiency index was found in one study of critical care patients [29].

Patient sleep perception has been used as the endpoint in four interventional studies in critical care patients [121, 473-475]. Patients in a critical care area who were exposed to nocturnal ocean sounds (white noise) rated their sleep by the RCSQ significantly better than those exposed to ambient sounds [473]. A comparison of overnight midazolam or propofol sedation reported no significant differences in sleep quality between the agents using the Hospital Anxiety and Depression Scale (HAD) [121]. Relaxation and guided imagery did not have a statistically significant benefit on the sleep quality of critical care patients [474]. A recent study which compared patient perception of sleep between those who used ear plugs and eye masks against no intervention was underpowered to detect a difference in sleep quantity [497].

A problem with RCSQ when used in a critical care setting is that patients might not be able to complete the questionnaire. Failure rates of up to 50% have been reported [30]. In the melatonin intervention study (Chapter 6), almost 20% of patients were unable to complete the RCSQ, primarily because of delirium. Also, some patients struggle to use visual analogue scales [498] and verbal descriptions have therefore been used in another study of patients sleep [33].

In the melatonin intervention study, patient perception of sleep differed greatly from SEI by any other measures even when patients deemed unable to complete the RCSQ were excluded. Compared with BIS, RCSQ tended to overestimate nocturnal SEI. Patient assessment of sleep did not agree well with direct nurse observations either, which is in agreement with the findings of a previous report [472]. Patient sleep misperception is encountered in chronic insomniacs and even non-delirious critical care patients may be particularly prone to perceptual difficulties due to memory problems. The complex pharmacokinetics and pharmacodynamics of the sedative drug regimes these patients receive, in tandem with multiple organ failure, have the

potential to adversely affect patient assessment. Critical care patients may have memory problems as a direct consequence of sedative exposure [71] and even in patients with good memory, these may be delusional [71, 72]. Memory processing appears to be sleep dependent [499] and, therefore, critical care patients with sleep disturbances may be particularly vulnerable to poor recall of their own sleep quality and quantity. Furthermore, patients may lack time cues for day and night and, therefore, will struggle to identify when they actually slept. Finally, the circadian rhythm abnormalities these patients exhibit may further compound difficulties in subjectively assessing their own nocturnal sleep.

While patient assessment of sleep has been recommended, [118] caution is required to exclude patients with acute cognitive dysfunction and obvious perceptual problems. This limits the application of tools such as the RCSQ in a significant number of critical care patients.

Nurse assessment

Nurse assessment of a patient's sleep is often the trigger used to identify patients with significant sleep disturbances in the clinical environment. Research studies in critical care have used direct nurse observation as well as a variety of scales and questionnaires. The frequency of sleep recording by direct observation has ranged from every 5 minutes to 8 times per day. Direct nurse observation has been used to assess sleep in two intervention studies [87, 403]. During periods of reduced environmental noise and disturbances, patients were reported to have increased sleep quantity [87]. In another study, exogenous melatonin was reported to have no effect on nocturnal or diurnal total sleep time [403]. One study found that even at five minute intervals, nursing staff observation significantly overestimated total sleep time compared to polysomnography [27]. In the melatonin intervention study, direct

nurse observation was found to overestimate SEI in patients compared to BIS. Therefore, it is possible that studies that purely rely on direct nurse observation may not be sensitive enough to detect some changes in sleep quantity due to a given intervention. As regards the comparison of nurse assessment with patient RCSQ, there was no evidence of a tendency towards either overestimation or underestimation, but the agreement was poor (Figure 8-1d and Figure 8-2d). Hourly sleep assessment by nurse observation forms part of the routine nocturnal observation procedure in the Critical Care Units of the Royal Hallamshire Hospital. However, the need for other direct and indirect nursing care activities will obviously affect the reliability of results. Due to frequent awakenings in critical care patients, particularly in those receiving mechanical ventilation, intensive observation is probably required for precise recording of sleep quantity [411]. Also, there are occasions when the nursing staff experience difficulties in judging the patient's sleep status as emphasised by missing data in the melatonin intervention study. Compared to polysomnography, nurses have been shown to correctly assess patients sleep status 82% of the time [28]. However, Edwards *et al*, [28] also reported that nurses were too busy, or were unable to differentiate sleep from wakefulness in almost 20% of the observations, even over the relatively short period of the study (4 hours). Richardson *et al* [497] reported only a weak association between nurse and patient assessment of sleep quantity using three simple rating scales in an intensive care setting. Recently, nurse observation of sleep in critical care patients was reported to underestimate the number of patient awakenings, and provide an inaccurate measure of sleep efficiency compared to polysomnography [470].

The use of a sleep assessment tool such as the RCSQ by the nursing staff may well give a better indication of sleep quality compared to direct observation of sleep

quantity. Frisk *et al*, [30] evaluated RCSQ use by both patients and nurses, and reported that nurses tended to rate the RCSQ slightly higher than those of patients, but the difference was not statistically significant, although comparison was made in only 13 patients. The coefficient for reliability (Cronbach's alpha) for nurses using the RCSQ has been reported to be between 0.83 and 0.95, [30, 479] which suggests a reasonable degree of inter-rater reliability when nurses use this subjective sleep measurement technique. Recently, Nicolas *et al* [476] compared patient and nurse ranking of the RCSQ in intensive care patients after surgery. The RCSQ results were ranked as "poor sleep" (0 - 33), "normal sleep" (34 - 66) and "good sleep" (> 66). Patient and nurse assessment of sleep quality disagreed on 56% of the nights studied [476]. When there was disagreement between nurse and patient sleep assessment, nurses generally overestimated patient's sleep quality [476]. Nurse use of the RCSQ may provide a useful clinical indication of critical care patients sleep quality, while avoiding reliance on patient assessment, and therefore patient variability to accurately complete the score. However further validation is necessary and nurses should receive further training on the subjective assessment of sleep.

Methodological problems of reviewed studies

A methodological pitfall common to almost all of the method comparison studies reviewed relates to the statistical approach used to compare different techniques and, in particular, the use of correlation coefficients. Although the correlation coefficient (r) between the results of two measurement methods is often used as a measure of agreement, this approach has been shown to be inappropriate for a number of reasons [394]. Firstly, r measures the strength of association between two variables and not their agreement. The hypothesis being tested is that there is no association, precisely no linear relationship ($r = 0$), between the measurements by the two methods, so that

a very small p-value indicates that indeed these measurements are related. However, as the measurement methods were designed to measure the same quantity, the statistical significance of their correlation is irrelevant to the question of agreement. Secondly, large values of r do not necessarily imply high agreement. As an extreme example, if a method tends to give values that are double those of another method, the correlation between the measurements by the two methods would be very high, but the agreement would not. A high correlation for any two methods designed to measure the same property is thus in itself just an indication that a wide spread sample was used, which has nothing to do with whether the true agreement is high or low.

What is the appropriate approach which should be taken when analysing results from method comparison studies on sleep? The answer mainly depends on the nature of the comparison, which can be;

a) Comparison of two methods for measuring sleep, neither of which can be regarded as providing the true value, *i.e.* both methods provide an approximate measure of sleep. This is the case for the comparisons in the melatonin intervention study (Chapter 6) where all four techniques were approximate measures of sleep, and the best analytical approach is that based on limits of agreement method as described in Chapter 5. The calculation of the limits of agreement assumes an approximate normal distribution of the differences, which can be graphically assessed by drawing a histogram of the differences. More importantly, the limits of agreement calculation assumes that the mean and standard deviation of the differences are constant, *i.e.* they do not depend on the magnitude of the measurement. The limits of agreement are graphically assessed in the Bland-Altman plots. If a trend is present, then alternative methods have to be used [477];

b) Comparison of a simpler approximate method with a very precise one, with the aim of assessing whether the two methods agree sufficiently for the simpler method to replace the precise one. In this case, the nature of the question is calibration of the simpler method against the "exact" method rather than agreement. Standard regression analysis can be used to predict the measurement obtained by the reference method from the measurement obtained by the simpler method.

Conclusions

Polysomnography undoubtedly remains the gold standard for qualifying and quantifying sleep. However, the critical care environment provides many unique challenges and this has led to the utilisation of alterative sleep assessment methods in research studies. All of these techniques have limitations, and these should be anticipated in interventional study designs. Of the alternative objective techniques, the BIS has particular advantages over actigraphy in critical care patients. Further algorithm development of the BIS as a measure of sleep quantity may be a useful compromise to polysomnography, and should facilitate larger research studies over multiple days in critical care patients.

Clinically, patient self assessment is attractive, although potentially misleading and should be regarded with appropriate caution. Perhaps nurse assessment using a tool such as the RCSQ provides the most useful clinical technique currently available.

Clearly, there is room for further developments in the techniques for measuring sleep in the critical care patient. Concurrent assessment of sleep and delirium is particularly important if pharmacological and non-pharmacological therapies are to be appropriately guided.

The statistical evaluation of differences between results obtained using different methods of sleep measurement should be more rigorous, and the naive use of correlation coefficients should be discouraged.

9 MELATONIN, CORTISOL AND REST-ACTIVITY RHYTHMS IN CRITICALLY ILL PATIENTS

Introduction

Circadian rhythm disorders have important consequences for both sleep-wake and rest-activity cycles in humans. Jet lag is one of the most studied circadian rhythm disorders, in which the most common symptoms are fatigue, disorientation, insomnia, daytime sleepiness, irritability, lethargy, reduced daytime alertness and difficulty concentrating [500]. Post-operative patients experience disturbances in the circadian rhythms of hormone secretion, sleep-wake cycles and rest-activity cycles [296, 305-310, 336, 501]. Such circadian rhythm disturbances may contribute to the characteristic disturbances in sleep phase distribution [502] and delirium [308, 336] in postoperative patients. It is likely that the post-operative circadian rhythm changes are a consequence of the combined effects of the acute stress of the surgical procedure, anaesthesia and pain. However, in patients without post-operative complications, the circadian rhythms begin to return to normality from the second post-operative night [296, 305, 306, 310, 501].

Critical care patients experience prolonged and repeated stressful conditions, polypharmacy and environmental conditions that result in protracted circadian rhythm disorders [55]. Initial reports of circadian rhythm disturbances in critical care patients used heart rate, temperature and urine output as markers of rhythm [55, 503, 504]. However, such physiological parameters are very vulnerable to acute changes in the patient's illness and subsequent interventions and, therefore, are unreliable markers of circadian rhythm in critical care patients. Plasma melatonin and cortisol levels have been demonstrated to be reliable markers of human circadian rhythm in healthy individuals [311]. Furthermore, prolonged best rest (periods up to 11 days), does not affect the timing or quantity of melatonin and cortisol secretion [505].

Normally there is 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 lowest [440]. However, reports of plasma melatonin and cortisol levels in post-operative patients disagree regarding the maintenance of this association in the immediate postoperative period [292, 296, 501, 506].

Minimising the delayed restoration of these circadian rhythms may have benefits for critical care patients, such as improved sleep-wake cycles, reduced delirium and reduced length of stay.

The aims of this study were to investigate the acute effects of exogenous melatonin on the rest-activity rhythms of patients recovering from critical illness and, to describe the rhythms and relationship between plasma melatonin and cortisol levels in patients recovering from critical illness.

Methods

A detailed description of the methods is provided in Chapter 5. In brief, 24 critical care patients were randomised to receive placebo or 10 mg exogenous melatonin at 2100 h for four nights. Twelve plasma samples were taken periodically from the first eighteen of these patients over the first 24 hour period and assayed for melatonin and cortisol levels. Actigraphy was used to monitor patient activity in all 24 patients. Rhythm analysis of plasma hormone levels and activity data used single cosinor analysis and nonparametric parameters, respectively. Fits of single cosinor model regression analysis for non-equispaced data were calculated using Time Series Analysis Seriel Cosinor software according to cosinor methodology of Nelson *et al* [507] and Bingham *et al* [508].

Results

Patient enrolment and demographics are described in Chapter 6. Both groups were well matched, although patients were significantly older in the melatonin group. Circadian rhythm terminology is used to describe the results - acrophase is the time at which the peak of the rhythm occurs, mesor provides an estimate of the central tendency of the distribution of values of an oscillating variable, amplitude is the difference between the mesor and peak or nadir of the rhythm, M10 and L5 indicate activity during the 10 most active and 5 least active hours, respectively, M10 and L5 Onset indicate the start times of M10 and L5 activity periods, respectively, Relative Amplitude is the ratio of M10 to L5 activity, Intra-daily Variability represents rhythm fragmentation with values between 0 (perfect sine wave) and 2 (noise), Inter-daily Stability is the 'invariability' between days with values between 0 (noise) and 1 (perfect stability).

Corticosteroid exposure

Five of the 18 (28%) patients studied received corticosteroid therapy on study entry (Table 9-1). Two patients received hydrocortisone and three received prednisolone. Eleven patients (61%) had received corticosteroids therapy for greater than 24 hours at some time prior to study enrolment. One other patient had what was defined as an adequate response to a low dose (1 microgram) tetracosactide (Synacthen) test *i.e.* either a baseline or 30 minutes post test plasma cortisol greater than 700 nmol/l.

Patient Number	Group	Receiving Corticosteroids At Study Entry	Received Corticosteroids During Intensive Care Admission	Dose	Comments
1	Melatonin	Yes	Yes	Hydrocortisone 25 mg IV OD	Day 1 only
2	Placebo	No	No	-	-
3	Melatonin	Yes	Yes	Prednisolone 80mg PO OD	-
4	Placebo	Yes	Yes	Prednisolone 30 mg PO OD	-
5	Placebo	No	No	-	-
6	Placebo	No	No	-	-
7	Melatonin	Yes	Yes	Prednisolone 40 mg PO OD	-
8	Placebo	No	Yes	-	-
9	Placebo	No	No	-	-
10	Melatonin	No	Yes	-	-
11	Melatonin	No	Yes	Hydrocortisone 50 mg IV QDS	Stopped on day study commenced
12	Melatonin	No	No	-	-
13	Placebo	No	Yes	-	-
14	Placebo	No	Yes	-	-
15	Melatonin	Yes	Yes	Hydrocortisone 50 mg IV QDS	-
16	Placebo	No	Yes	-	-
17	Melatonin	No	No	-	SST
18	Melatonin	No	No	-	-

Table 9-1 Patient corticosteroid exposure

PO: Oral/ enteral; IV: Intravenous; OD: Once daily; QDS: Four times daily; SST: Short Synacthen Test.

Effect of melatonin on rest-activity rhythms

There were no significant differences between the groups in any of the rest-activity measures (Table 9-2). Overall, the critical care patients rest-activity rhythms were phase delayed, fragmented and suppressed (Table 9-3; Figure 9-1).

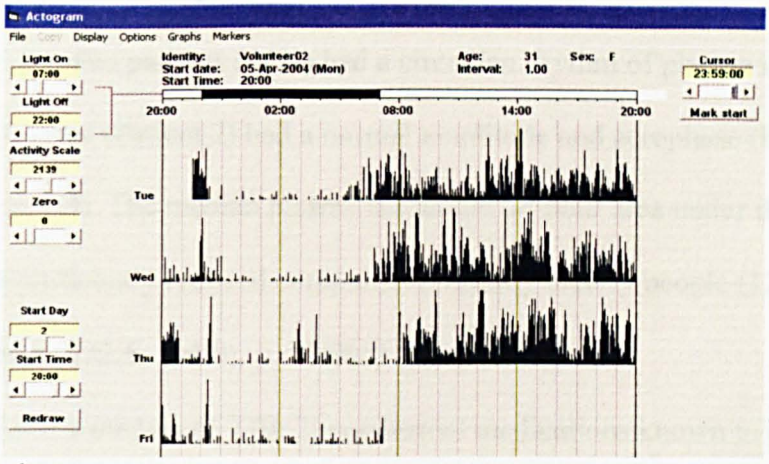
Parameter	Placebo Group	Melatonin Group	Difference (95% CI)	p-value of the difference
Relative Amplitude	0.43 (0.26; 0.63)	0.47 (0.35; 0.58)	0.04	0.931
Intra-daily Variability	1.35 (0.98; 1.74)	1.47 (0.87; 1.54)	0.12	0.312
Inter-daily Stability	0.38 (0.28; 0.60)	0.43 (0.29; 0.52)	0.05	0.840
M10 Onset	10:13 (07:02 to 13:24)	11:55 (09:26 to 14:24)	1:42 (-2:07 to 5:30)	0.367
L5 Onset	02:00 (22:55 to 05:05)	02:45 (01:00 to 04:30)	0:45 (-2:56 to 4:26)	0.678

Table 9-2 Rest-activity analysis by treatment allocation
Relative Amplitude: Ratio of M10 to L5 activity; Intra-daily variability: represents rhythm fragmentation with values between 0 (perfect sine wave) and 2 (noise); Inter-daily stability: represent 'invariability' between days with values between 0 (noise) and 1 (perfect stability); M10 and L5 Onset: represent commencement of the periods of most and least activity respectively.

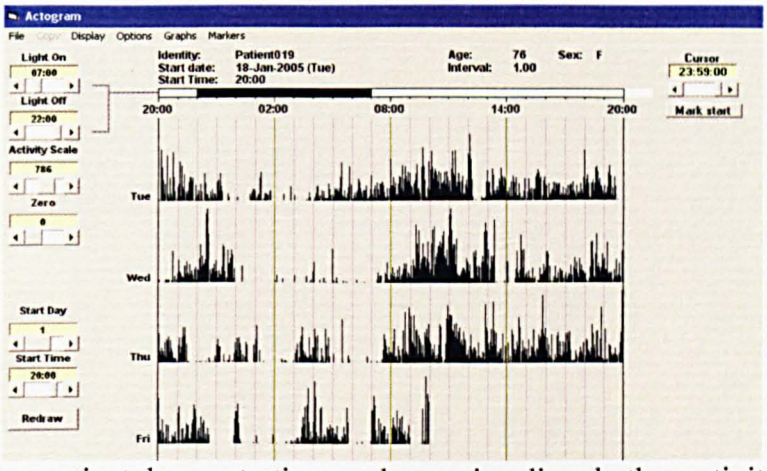
Parameter	All patients	95% Confidence Interval
Relative Amplitude	0.46	0.38 to 0.54
Intra-daily Variability	1.28	1.10 to 1.46
Inter-daily Stability	0.43	0.35 to 0.51
M10 Onset	11:04	09:10 to 12:58
L5 Onset	02:23	00:35 to 04:11

Table 9-3 Rest-activity analysis for all critical care patients

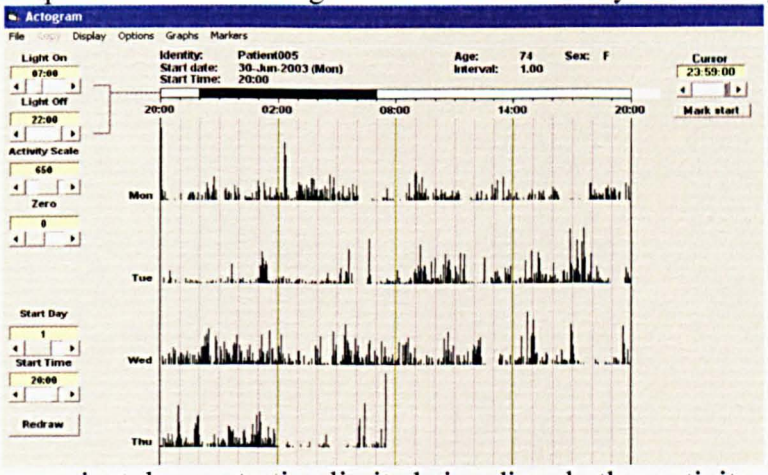
Relative Amplitude: Ratio of M10 to L5 activity; Intra-daily variability: represents rhythm fragmentation with values between 0 (perfect sine wave) and 2 (noise); Inter-daily stability: represent 'invariability' between days with values between 0 (noise) and 1 (perfect stability); M10 and L5 Onset: represent commencement of the periods of most and least activity respectively.



(a) Healthy volunteer



(b) Critical care patient demonstrating moderate circadian rhythm activity variation



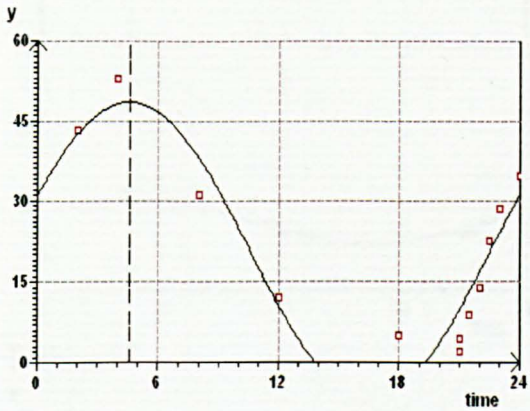
(c) Critical care patient demonstrating limited circadian rhythm activity variation

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

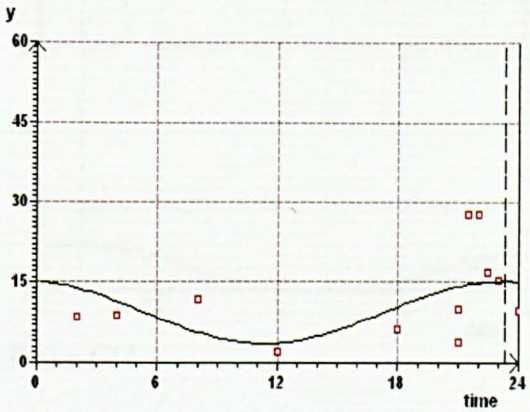
Plasma melatonin rhythm analysis

Four of the 9 placebo patients (44%) had a circadian rhythm of plasma melatonin levels, but only one (Patient 2) had a normal amplitude and acrophase (Figures 9-2 and 9-3; Table 9-4). The median plasma melatonin 24 hour area under the curve (AUC) was significantly reduced compared to healthy elderly people (128.4 (112.6; 217.0) *vs.* 464.5 (372.5; 594.0), $p < 0.001$) (Figure 9-4).

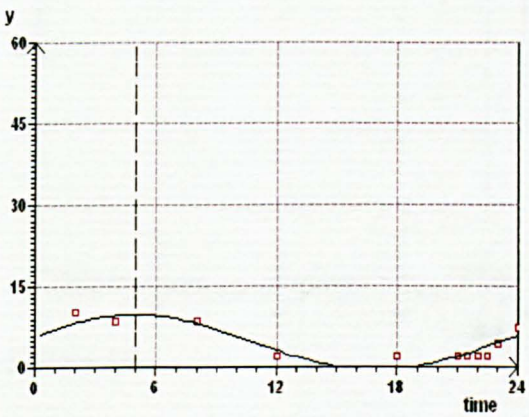
Patients received a median of 1 (0; 2) concurrent medications known to affect plasma melatonin levels (Table 2-5).



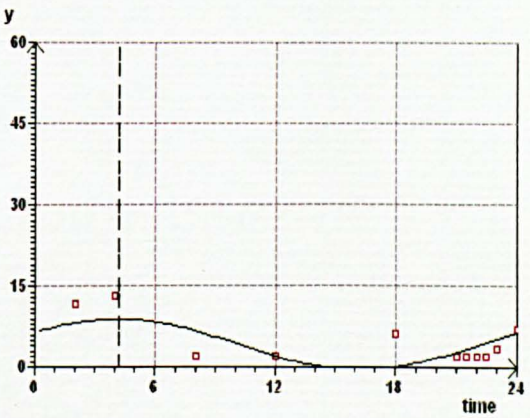
Patient 2



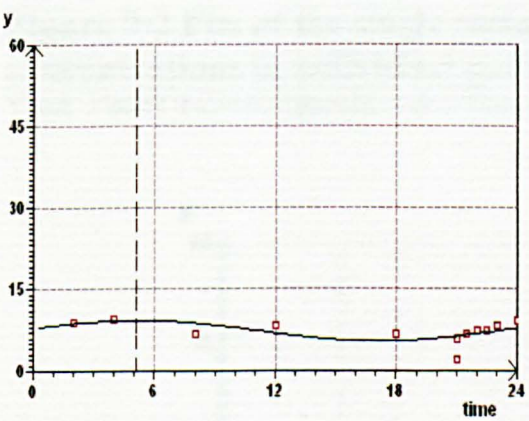
Patient 4



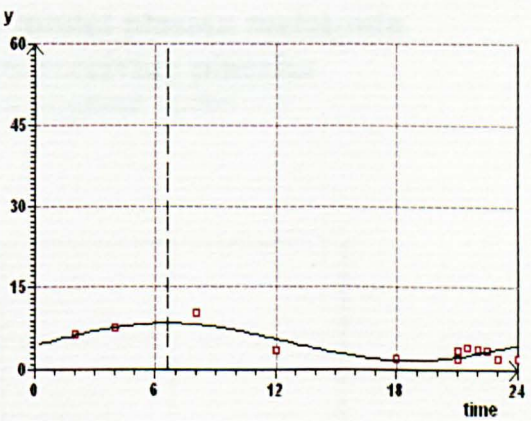
Patient 5



Patient 6



Patient 8



Patient 9

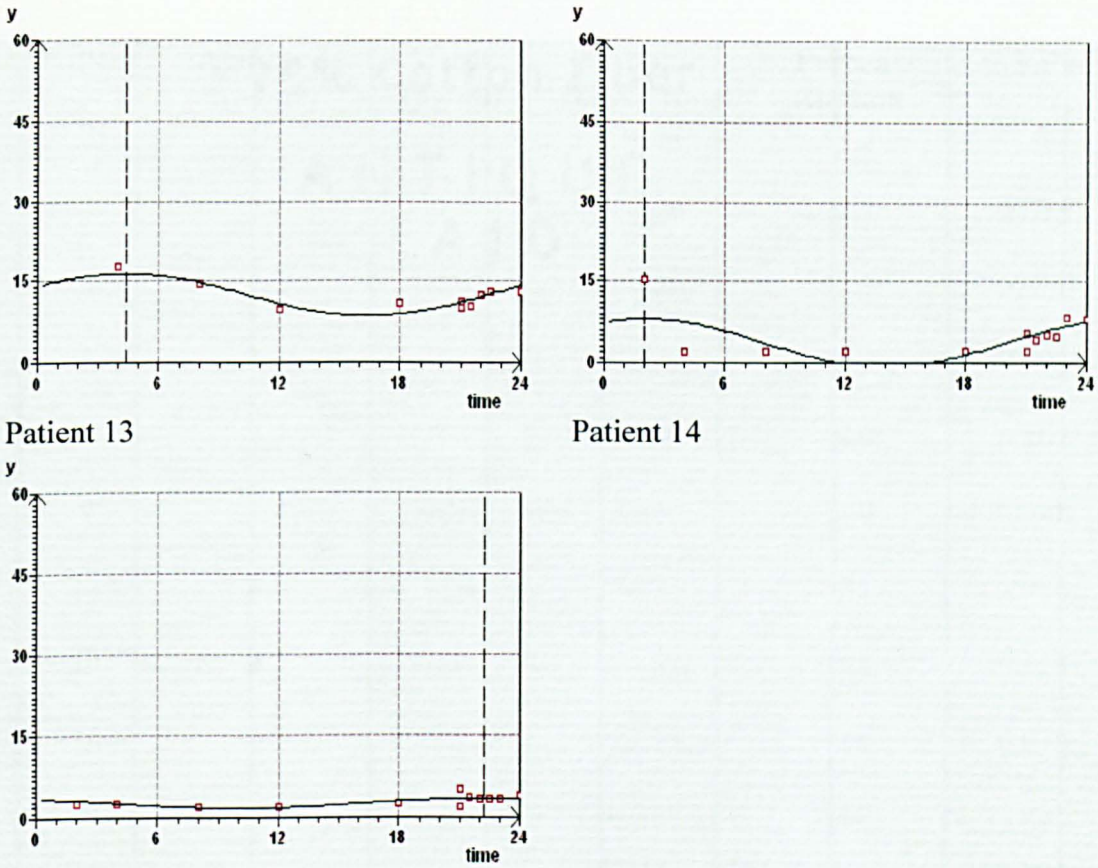


Figure 9-2 Fits of the single cosinor model plasma melatonin concentrations in individual patients receiving placebo
Y axis: Plasma melatonin (pg/ml); X axis: clock time; Acrophase: vertical -----.

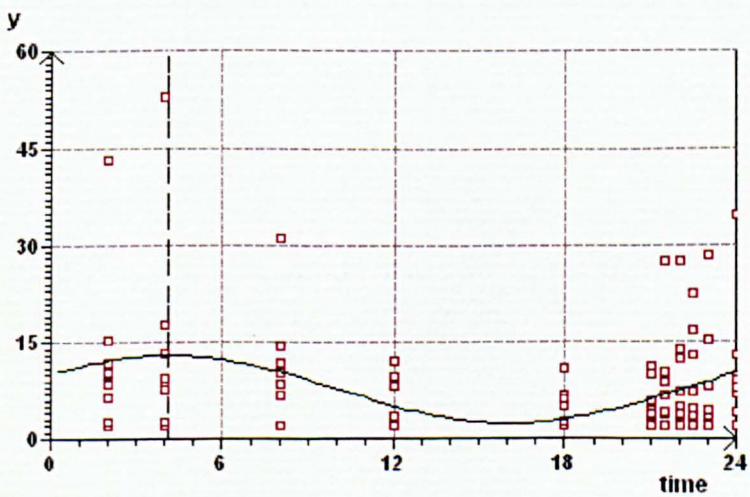


Figure 9-3 Fit of the single cosinor model to plasma melatonin concentrations in all patients receiving placebo
Y axis: Plasma melatonin (pg/ml); X axis: clock time; Acrophase: vertical -----.

Patient	Amplitude (pg/ml)	Mesor (pg/ml)	Acrophase (Clock time)	Percent Rhythm	p-Value
2	27.7	20.7	04:34	89.3	<0.001
4	5.8	9.4	23:20	22.7	0.315
5	5.2	4.6	04:58	83.1	<0.001
6	4.7	4.3	04:11	42.0	0.093
8	1.9	7.4	05:06	29.9	0.202
9	3.4	6.1	06:38	70.9	<0.001
13	4.0	12.4	04:23	79.1	0.004
14	4.2	3.6	01:59	38.4	0.113
16	0.9	2.7	22:13	43.6	0.076
All Placebo patients	**5.3 (2.3 to 8.3)**	**7.7 (5.7 to 9.7)**	**04:07 (02:11 to 06:03)**	**10.6**	**0.003**

Table 9-4 Cosinor analysis of plasma melatonin levels
Mesor: Midline estimating statistic of rhythm; Acrophase: Timing of curve peak.

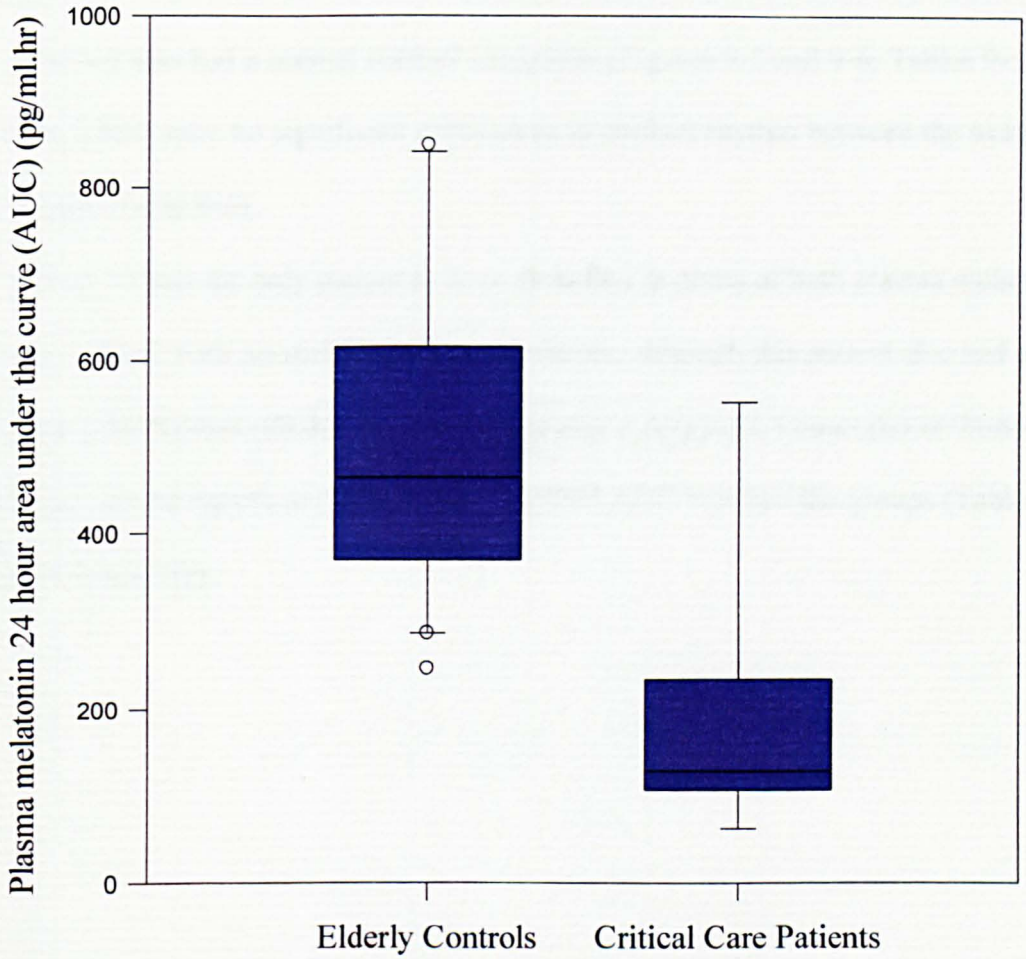
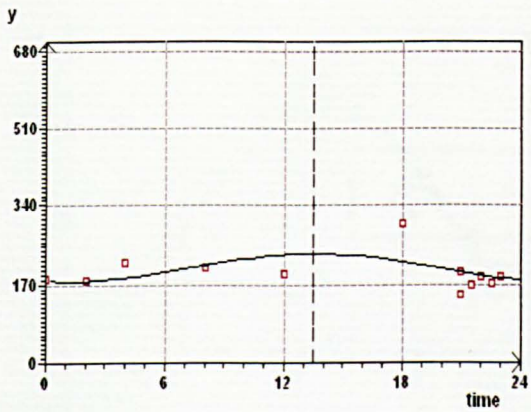


Figure 9-4 Plasma melatonin area under the curve for a 24 hour period in elderly controls [387] and critical care patients

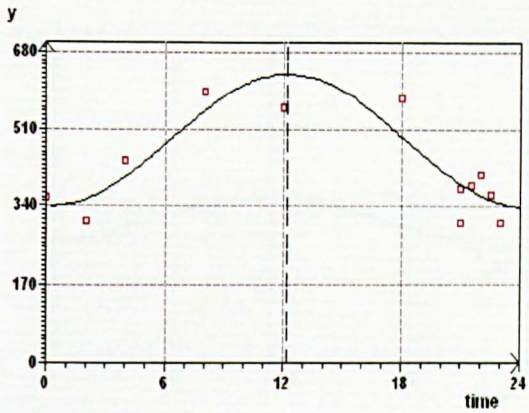
Plasma cortisol rhythm analysis

Seven of 18 patients (39%) had a circadian rhythm of plasma cortisol levels, while only two also had a normal cortisol acrophase (Figures 9-5 and 9-6; Tables 9-5 and 9-6). There were no significant differences in cortisol rhythm between the treatment groups (Table 9-6).

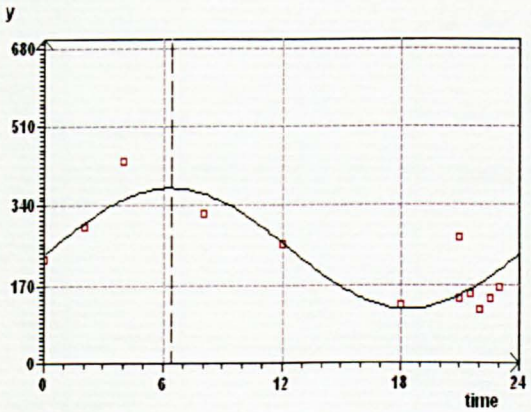
Patient 13 was the only patient to have circadian rhythms of both plasma melatonin and cortisol, with normal acrophases. However, although this patient also had a normal M10 onset (08.00), he still experienced a delayed L5 onset (03.00 hours). There was no significant difference in cortisol AUC between the groups (Table 9-7 and Figure 9-7).



Patient 1



Patient 2



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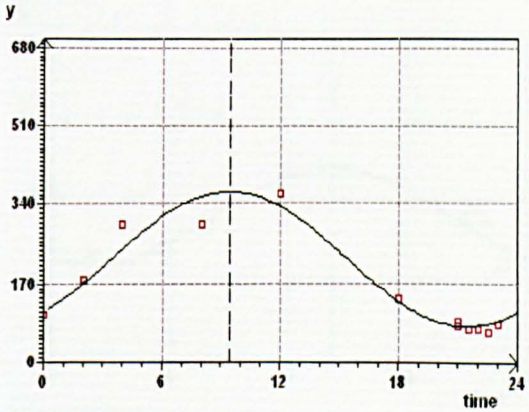

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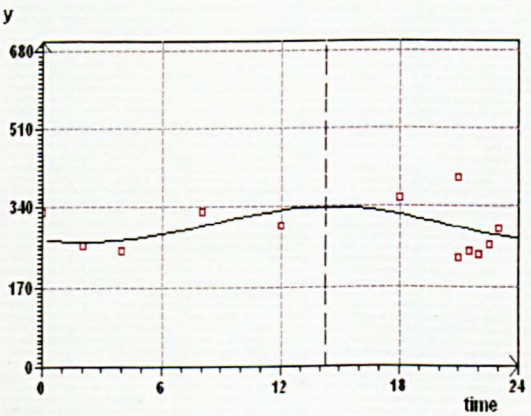

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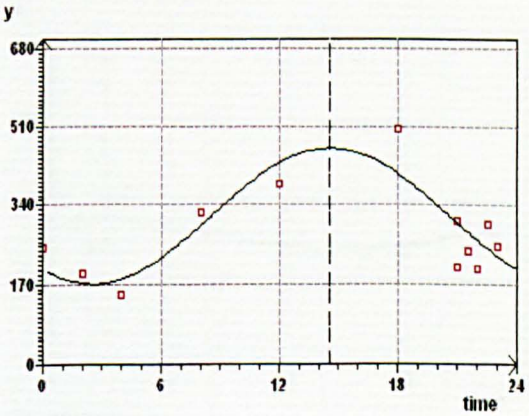

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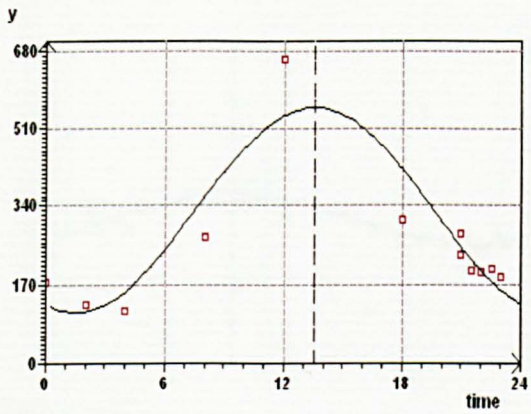

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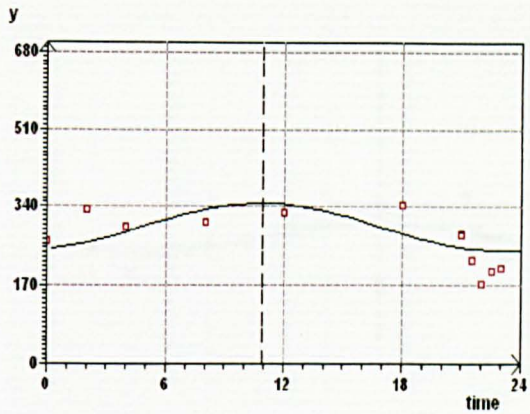

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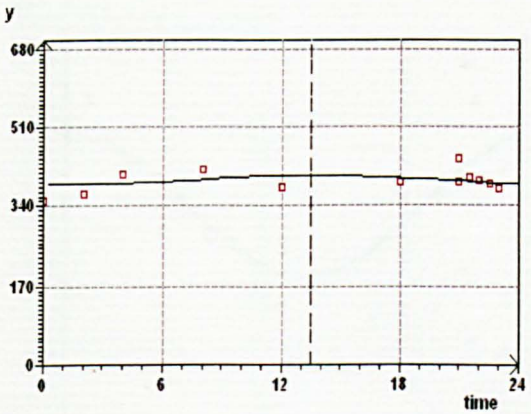

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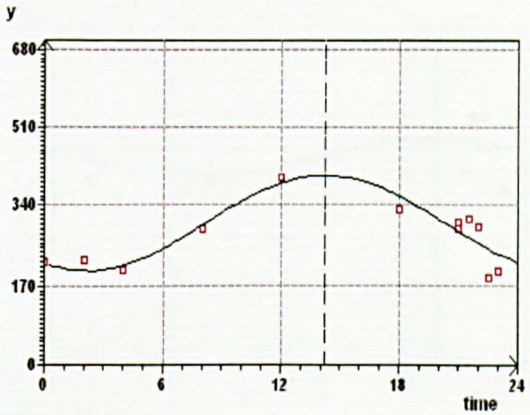

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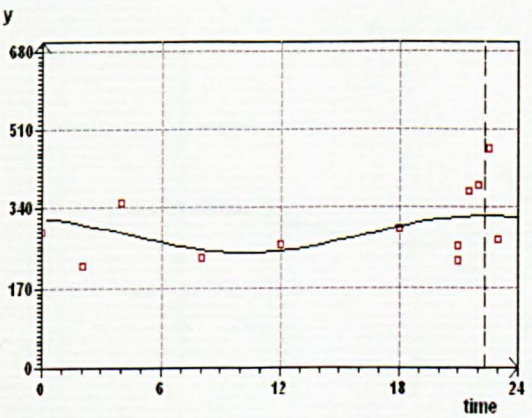

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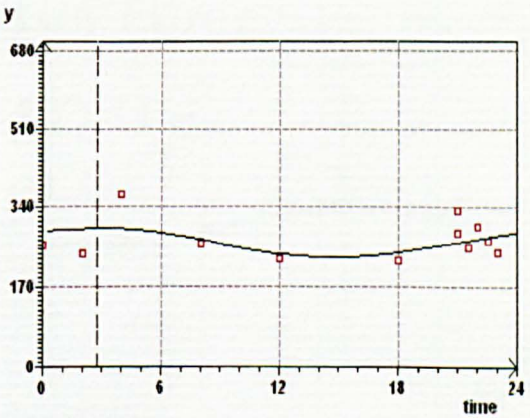


Patient 12

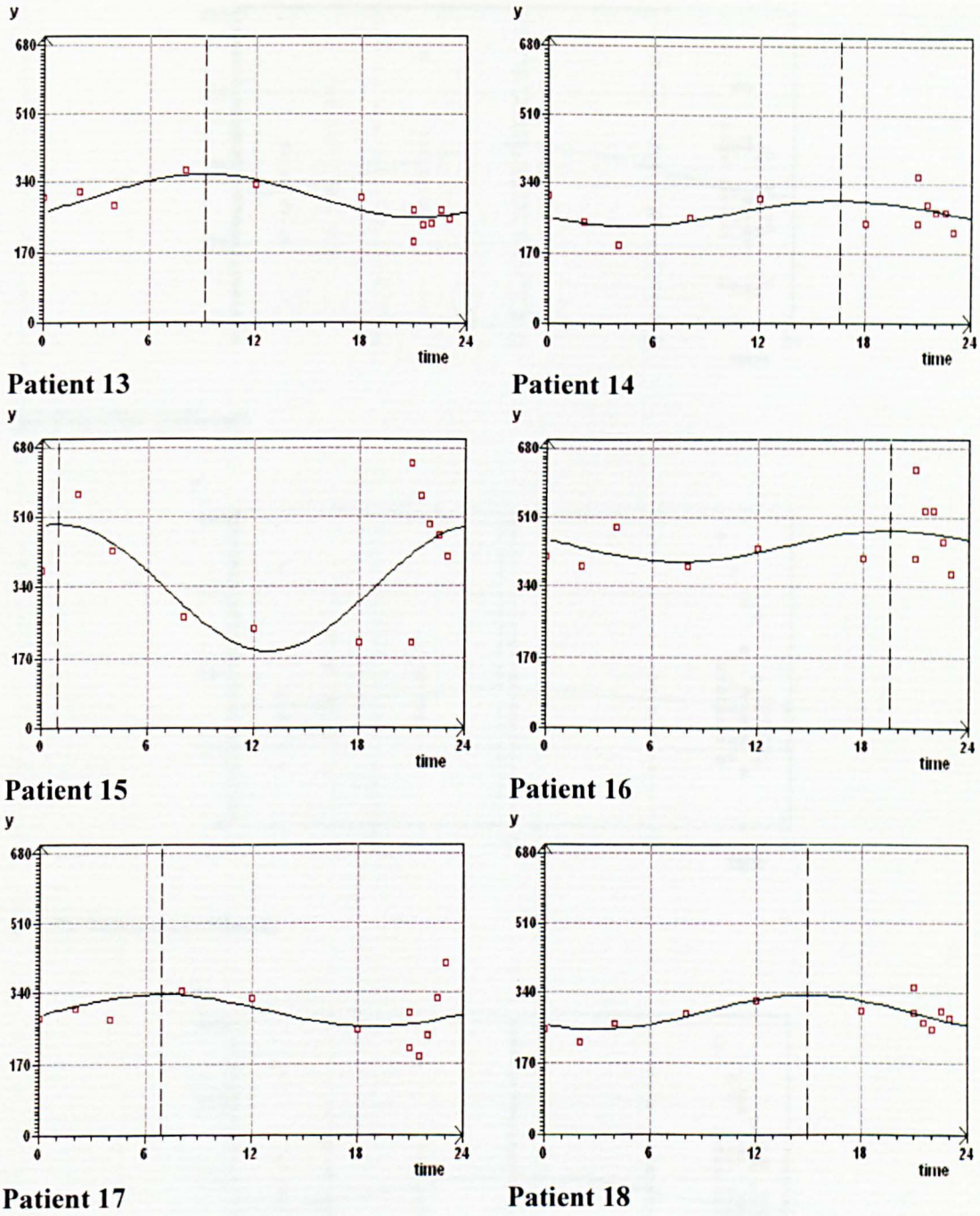
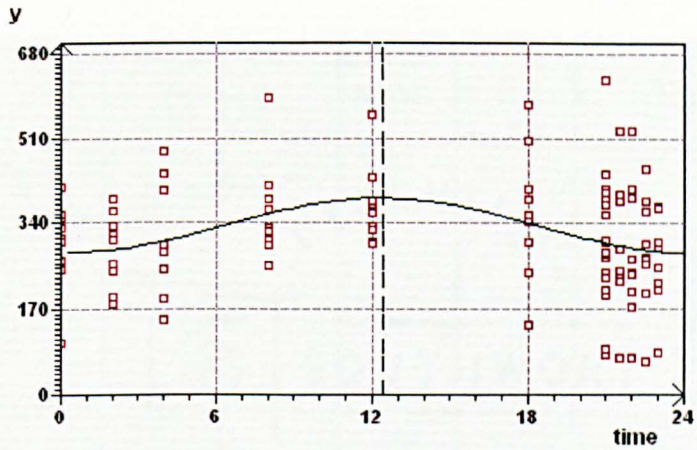
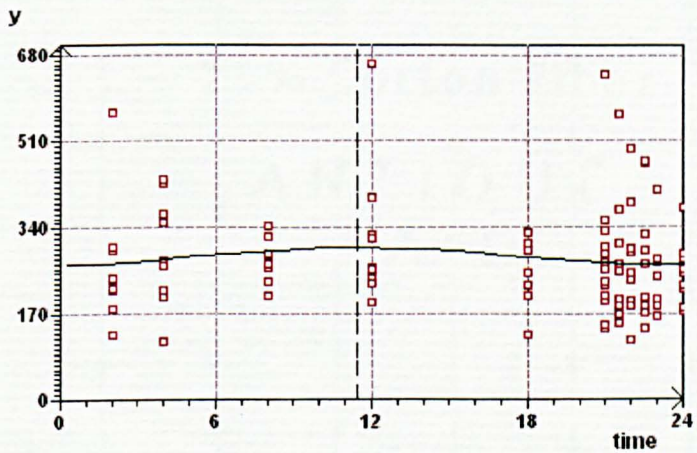


Figure 9-5 Fits of the single cosinor model to plasma cortisol levels in individual patients

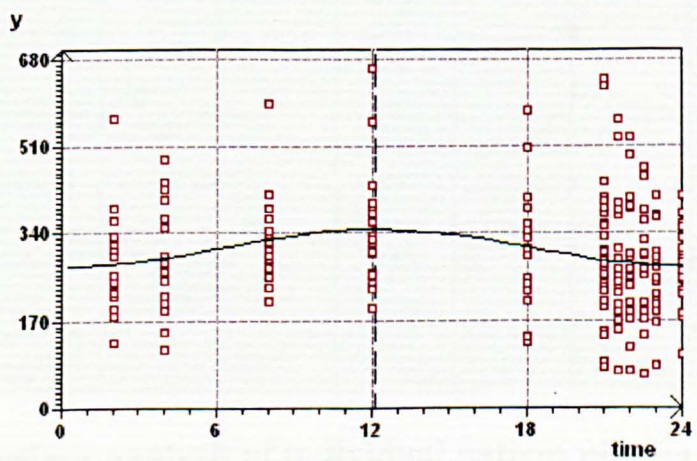
Y axis: Plasma cortisol (nmol/l); X axis: clock time; Acrophase: vertical -----.



(a) Placebo patients



(b) Melatonin patients



(c) All patients

Figure 9-6 Fits of the single cosinor model to plasma cortisol levels in (a) Placebo patients, (b) Melatonin patients and (c) All patients

Y axis: Plasma cortisol (nmol/l); X axis: clock time; Acrophase: -----.

Patient	Group	Amplitude (nmol/l)	Mesor (nmol/l)	Acrophase (Clock time)	Percent Rhythm	p-Value
1	Melatonin	29	206	13:30	20.2	0.363
2	Placebo	146	485	12:12	76.3	0.002
3	Melatonin	129	249	06:24	71.1	0.004
4	Placebo	144	222	09:27	93.8	<0.001
5	Placebo	37	302	14:18	14.2	0.502
6	Placebo	147	317	14:36	68.5	0.006
7	Melatonin	222	332	13:36	81.1	<0.001
8	Placebo	52	297	10:54	38.5	0.112
9	Placebo	9	395	13:30	4.8	0.800
10	Melatonin	102	303	14:12	78.1	0.001
11	Melatonin	39	284	22:18	12.6	0.546
12	Melatonin	31	265	02:46	15.6	0.465
13	Placebo	53	307	09:10	64.2	0.010
14	Placebo	33	267	16:36	17.3	0.425
15	Melatonin	153	339	00:57	39.3	0.106
16	Placebo	39	440	19:36	12.4	0.551
17	Melatonin	39	298	06:53	16.8	0.438
18	Melatonin	42	293	15:00	43.2	0.079

Table 9-5 Cosinor analysis of individual patient plasma cortisol levels

Amplitude: Difference between peak and nadir levels; Mesor: Midline estimating statistic of rhythm; Acrophase: Timing of curve peak

Group	Amplitude (nmol/l)	Mesor (nmol/l)	Acrophase (Clock time)	Percent Rhythm	p-Value
Placebo group	55 (19.7 to 91.1)	337 (310 to 363)	12:24 (09:43 to 15:05)	8.8	0.008
Melatonin group	18 (-13.5 to 49.5)	285 (261 to 310)	11:30 (07:57 to 15:03)	1.3	0.508
All patients	36.5 (12.2 to 60.7)	311 (293 to 329)	12:06 (09:22 to 14:50)	4.2	0.010

Table 9-6 Cosinor analysis of plasma cortisol levels
Amplitude: Difference between peak and nadir levels; Mesor: Midline estimating statistic of rhythm; Acrophase: Timing of curve peak

Effect of melatonin on plasma cortisol levels

Plasma cortisol AUC (nmol/l.hr) (95%CI)			
Melatonin group	**Placebo group**	**Difference**	**p-value of the difference**
6763.6 (6702.9 to 7369.3)	8064.6 (6544.4 to 9584.8)	-1300.9 (-2805.3 to 203.4)	0.085

Table 9-7 Effect of melatonin on plasma cortisol area under the concentration time curve for a 24 hour period

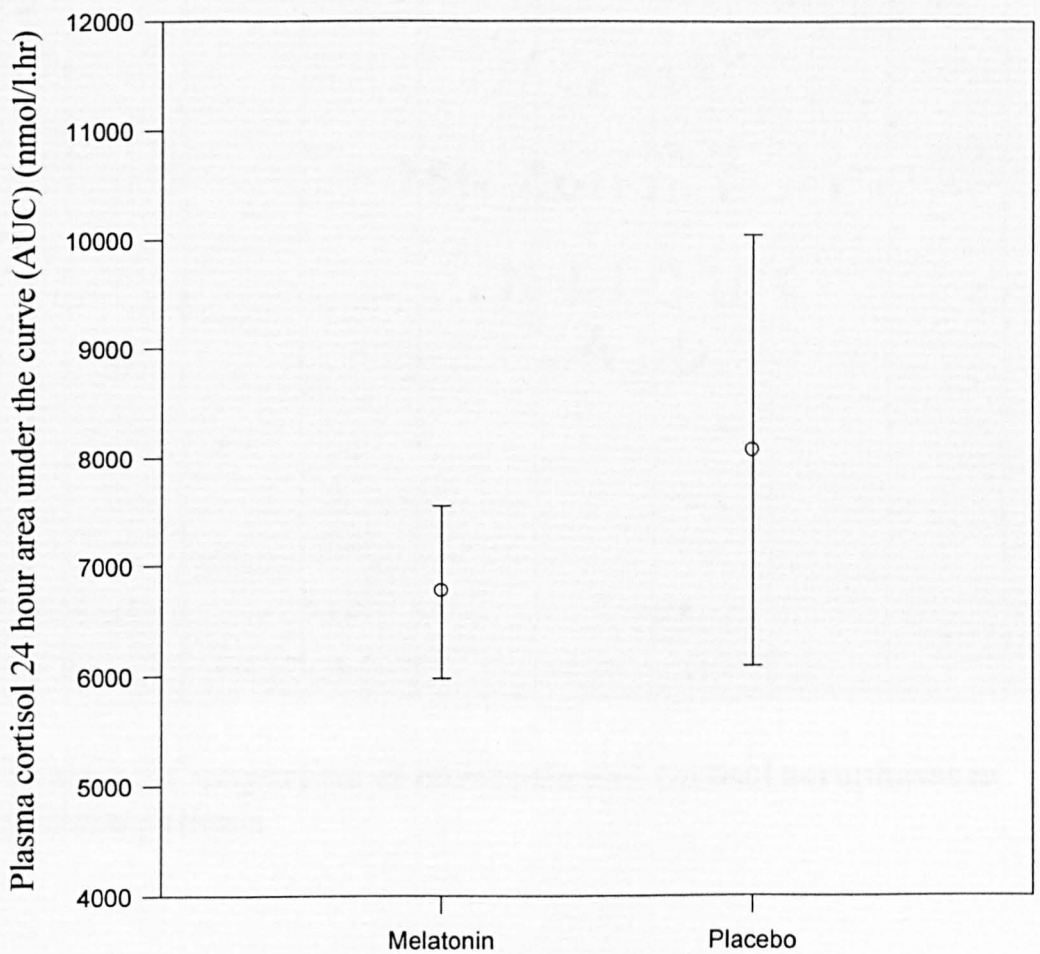


Figure 9-7 Plasma cortisol area under the curve for a 24 hour period in the Melatonin and Placebo groups
Mean and standard deviation

Relationship between plasma melatonin and cortisol levels

There was a weak inverse correlation between plasma melatonin and cortisol levels ($r = -0.22$ (-0.771 to 0.52), $p = 0.015$). However, there was no relationship between the timing of the acrophase of the hormones (Table 9-8).

Patient	Melatonin Acrophase (Clock time)	Cortisol Acrophase (Clock time)	Difference (hours)
2	04:34	12:12	7:38
4	23:20	09:27	10:07
5	04:58	14:18	9:20
6	04:11	14:36	10:25
8	05:06	10:54	5:48
9	06:38	13:30	6:52
13	04:23	09:10	4:37
14	01:59	16:36	14:37
16	22:13	19:36	21:23
All Placebo patients	**04:07 (02:11 to 06:03)**	**12:24 (09:43 to 15:05)**	**8:17**

Table 9-8 Comparison of melatonin and cortisol acrophases in placebo patients

Relationship between plasma melatonin and cortisol rhythms and rest-activity rhythms

There was a moderate inverse relationship between percent plasma cortisol rhythm and patient Intra-daily Variability (rhythm fragmentation) ($r = -0.70$ (-0.879 to -0.347), $p < 0.002$), but not with any other non-parametric rest-activity rhythm parameters. There was no association between plasma melatonin rhythm and any rest-activity results.

Discussion

Critical care patients treated with 10 mg of melatonin at 2100 h did not have significantly different rest-activity patterns compared to patients administered placebo. These results contrast with those from studies in healthy individuals with a normal circadian rhythm, in which evening administration of melatonin (0.5 to 5 mg) was effective in acutely advancing rhythms [429, 440, 509].

The timing of the rest-activity rhythm of patients recovering from critical illness was significantly delayed, with the periods of least and most activity commencing at approximately 0200 and 1100 h, respectively. Non-parametric circadian rhythm analysis also demonstrated reduced stability, increased fragmentation, and reduced differentiation between rest and activity, even when compared to patients with dementia [388], a patient group also known to experience circadian rhythm disturbances. Vinzio *et al* [496] used actigraphy to assess the circadian rest-activity rhythm of 8 elderly critical care patients. Non-parametric parameters of activity were analysed for two-5 day periods, representing the patient's acute admission and the period prior to discharge from the critical care unit [496]. Overall, the rest-activity disturbances of the patients in the current melatonin study were representative of a mid-point between the two periods studied by Vinzio *et al* [496]. Intra-daily Variability, Inter-daily Stability and Relative Amplitude results were comparable to patients in the recovery phase, while the timings of L5 and M10 onset were more representative of the acutely ill patients in the Vinzio study [496]. The variability in results may be partly explained by differences in severity of illness (patients in the current melatonin study had multiple rather than single organ failure) and timing of monitoring (only one patient was preparing for discharge from a critical care area during recording in the current melatonin study). The results of the current melatonin

study show that critical care patients staying in ICU for more than a median of 2 weeks had significant disturbances in their rest-activity rhythms.

Rest-activity data are highly non-sinusoidal and irregular and, therefore, non-parametric analysis is recommended as it is more sensitive in detecting changes in rhythm [388]. However, critical care patients show considerable inactivity as a consequence of illness, neuromuscular weakness, intermittent sedation, prolonged bed rest and lack of stimulation, and consequently have relatively low activity counts [510, 511]. Therefore, direct nursing care, turning, range of motion exercises and physiotherapy will have significant potential for confounding patient activity data [512]. Although it is not possible to quantify the potential effects of staff interventions on the results of the current rest-activity study, it does highlight clinical and educational issues. In some critical care units, inappropriate nursing care activities, such as patient washing, are still conducted during the night, [93] when conditions that facilitate rest should be re-enforced. Furthermore, the timing of physiotherapy and range of motion exercises employed in critical care patients should be reviewed and, ideally, commenced earlier in the day to advance the onset of patient activity.

Less than half of the placebo patients had a circadian rhythm in plasma melatonin levels. Furthermore, in all but one of the critical care patients in the placebo group, the plasma melatonin rhythm mesor and amplitude (rhythm strength), were significantly reduced compared to those in healthy older individuals [505]. The critical care patients also had a lower plasma melatonin 24 hour AUC values compared to those in older controls described in the literature [387]. As people age, the timing of the melatonin acrophase becomes more delayed and plasma melatonin levels are reduced [229].

Plasma melatonin levels can be increased or decreased by co-administration of some drugs (Table 2-5). Seven of the 9 patients in the placebo group received medication known to interact with plasma melatonin secretion. However, the small patient sample size and heterogeneity of drug exposure, direction of interaction and effects of endogenous cortisol, preclude any further analysis of specific drug effects. Other studies were also unable to distinguish an effect of drug exposure on plasma melatonin levels, [513] or 6-SMT excretion [514] in ICU patients. Paul and Lemmer [511] concluded that the effect of co-administered medication was difficult to assess in a study of plasma melatonin levels in 24 ICU patients.

Previous studies have also identified changes in the circadian rhythm of melatonin (or the urinary metabolite) in ICU patients. Shilo and colleagues [312] reported that only two of 14 ICU patients maintained a normal circadian rhythm of 6-SMT excretion. Mundigler *et al* [314] reported that only one of 17 septic ICU patients, but six out of 7 non-septic, recovering patients, had a rhythmic urinary 6-SMT excretion. Girotti and co-workers [514] measured urinary excretion of 6-SMT in 33 ICU patients with congestive heart failure. Compared to healthy controls the renal excretion of 6-SMT was significantly reduced in the ICU patients [514]. Olofsson *et al* [401] measured serum melatonin levels in 8 critically ill patients every 4 hours over a 3 day period. Only one of the 8 patients was reported to have maintained a circadian rhythm of serum melatonin levels with a normal acrophase. However, single cosinor analysis was not undertaken, instead the ratio of mean day/ night time serum melatonin levels was used as a proxy for rhythm analysis. Urinary excretion of 6-SMT was reported to be reduced in a study of 16 ICU patients receiving mechanical ventilation, when compared to data from healthy individuals [402]. The ratio of day to night time excretion of urinary 6-SMT was used as a surrogate marker

of rhythm. Circadian rhythms of melatonin and cortisol were reported to be maintained in only 4 and 6 patients, respectively [402]. Perras and colleagues [515] measured serum melatonin concentrations at 0200 h in 302 consecutive critically ill patients on admission to a medical ICU. In patients diagnosed with severe sepsis there was an inverse relationship between severity of illness and nocturnal serum melatonin level [515]. The authors suggested that in patients with a severe systemic inflammatory response, melatonin secretion was suppressed [515]. However, as serum melatonin levels were only measured at a single time point, the results do not allow direct comparison between patients with known variability in circadian rhythm disturbances. Furthermore, the serum melatonin level is determined by the net effects of secretion, metabolism and elimination and, therefore, a single serum measurement cannot provide a clear marker of melatonin turnover. A recent study reported the changes in urinary 6-SMT excretion in 32 patients requiring admission to a surgical ICU [516]. Again, the circadian rhythm was analysed from the ratio of day to night-time urinary 6-SMT excretion. By post-operative Day 3, patients were reported to have lost the circadian rhythm in urinary 6-SMT ratio compared to baseline, pre-operative data [516]. Although urinary 6-SMT excretion has been shown to be a reliable surrogate marker of plasma melatonin secretion in healthy individuals, [387] the relationship has not been verified in critical care patients in whom renal and hepatic dysfunction is relatively common.

In addition to the current melatonin study, only one other study has recently examined the circadian rhythm of plasma melatonin in ICU patients using cosinor analysis [511]. Paul and Lemmer [511] studied the circadian rhythm of melatonin in 24 sedated ICU patients, with and without brain injury. In all patients the normal 24 hour pattern of plasma melatonin was reported to be severely disturbed, suppressed

and desynchronised [511]. However, patients with brain injury had lower plasma melatonin levels and greater rhythm disturbance compared to ICU patients without brain injury [511].

Cosinor analysis of plasma cortisol levels also showed marked rhythm disturbances in the current melatonin study. Overall, the cortisol acrophase was delayed and there were no significant differences between the groups. Compared to data from healthy individuals, [440, 505] the cortisol mesor was increased, while the amplitude was reduced. This plasma cortisol pattern would be anticipated in patients exposed to stressful conditions. The potential consequences of the increased mesor of the cortisol rhythm may include promoting wakefulness and, thereby, delayed rest onset. However, the co-administration of corticosteroids in 5 of the 18 patients complicates any analysis. There was no obvious relationship between corticosteroid administration and individual plasma cortisol level profiles. Evaluation of this relationship is further complicated in the three patients that received prednisolone as a consequence of potential cross-reactivity with the cortisol assay. Furthermore, reduced levels of cortisol binding globulin would be anticipated in critical care patients with reduced albumin levels (Chapter 7), and hence the total cortisol levels measure may not be a definitive measure of free cortisol activity [316]. However, the patients in the melatonin group had a reduced cortisol AUC compared to placebo ($p = 0.085$), even though more patients in the melatonin group received cortisol replacement during the study period. In sedated ICU patients, Paul and Lemmer [511] recently reported a lack of any distinguishable circadian rhythm in plasma cortisol levels in critical care patients. Forty percent of the patients in the current melatonin study demonstrated a plasma cortisol rhythm. The ongoing recovery of critical care patients in the current melatonin study, compared to the sedated and

acutely ill patients studied by Paul and Lemmer [511] appears the most likely explanation for the differences in plasma cortisol rhythm results.

Ideally, patients that received corticosteroids should have been excluded from an analysis of plasma cortisol rhythms. However, this was impractical as the study was conducted in critically ill patients, the majority of whom were admitted with a diagnosis of severe sepsis and who, therefore, would be highly likely to receive corticosteroid therapy [517]. Recently, the potential benefits of corticosteroids therapy in patient with severe sepsis has been questioned [518]. The potential detrimental effects of continuous corticosteroid dosing may have on the circadian rhythm of critical care patients provides another reason to attempt to minimise indiscriminate use.

The rhythms of melatonin and cortisol are normally phase locked so that the increase in plasma melatonin level coincides with the decrease in plasma cortisol. Even though night workers demonstrate alterations in the timing of both melatonin and cortisol acrophases, the secretion patterns of these hormones maintain an inverse relationship [317]. Corticosteroids and Corticotrophin Releasing Hormone (CRH) have been demonstrated to reduce melatonin secretion *in vitro* and in healthy volunteers, respectively [302, 519]. It has also been suggested that melatonin may be the pineal factor that suppresses CRH secretion [303]. Exogenous melatonin has been shown to successfully advance cortisol secretion in humans in a number of studies [265, 440, 520]. However, not all studies have reported an acute chronobiotic effect of melatonin on plasma cortisol secretion [319, 521].

Previous studies have disagreed regarding the maintenance of an inverse relationship between melatonin and cortisol in the immediate post-operative period [292, 501, 506]. Only one of these studies, [501] examined the actual timing of the respective

rhythms, as opposed to purely examining an inverse correlation. There was no consistent relationship between the timing of the urinary cortisol nadir and the onset of the urinary 6-SMT surge in post-operative patients [501]. Although there was a weak inverse association between plasma melatonin and cortisol levels in the current melatonin study, the normal relationship in timing of the acrophases, [317, 522] was maintained in only one patient (Patient 13). Therefore, changes in total cortisol levels do not fully explain the disturbances in the circadian rhythm of melatonin.

A single patient maintained circadian rhythms and timing of plasma melatonin and cortisol acrophases. Although the patient also maintained an appropriate morning M10 onset, the nocturnal L5 onset was delayed. It is possible that nocturnal environmental factors such as care activities, patient admissions and noise disturbed nocturnal rest and hence delayed L5 onset. Therefore, even if circadian rhythms could be re-enforced in critical care patients, changes to the environmental and care activities are still necessary to enable normal rest-activity patterns. There was a moderate inverse relationship between percent plasma cortisol rhythm and Intra-daily Variability. However, the limited power of the study prevents any further discussion regarding the relationships between plasma hormone rhythms and rest-activity rhythms.

The direct consequences of the circadian rhythm disturbances critical care patients experience remain largely unknown. Symptoms related to relatively transient circadian rhythm disorders, such a jet lag, provide some information regarding acute mood and sleep-wake disturbances that critical care patients may experience. However, it remains unknown whether the circadian rhythm disturbances critical care patients experience are primarily a result of acute endogenous and exogenous factors, such as the stress response or ICU environment, or are reflective of acute

brain dysfunction related to critical illness. It has been suggested that the reduction in plasma melatonin levels is indicative of brain aging [229, 230]. Delirium, an acute brain dysfunction, is characterised as a circadian rhythm disorder and predisposes patients to significant long term cognitive dysfunction after discharge [58]. In patients requiring ICU care after cardiac surgery, there was an association between disruption in the ratio of day to night-time urinary 6-SMT excretion and worsening psychological score [516]. After minor traumatic brain injury, 36% (15 of 42) of patients studied had circadian related sleep and melatonin secretion disorders [396]. Post-traumatic brain injury, patient maintenance of a normal sleep-wake rhythm was a more predictive marker of patient survival and functional recovery, than the Glasgow Coma Scale [467]. The consequences of circadian rhythm disturbances on the long term mortality of critical care patients are also unknown. However, it is known that individuals exposed to long term nocturnal shift work are at increased risk of cardiovascular morbidity and mortality [523]. Furthermore, in institutionalised older patients, prolonged disturbances in sleep-wake rhythms are associated with increased mortality [524].

There are several possible explanations for the apparent lack of efficacy of melatonin therapy on the rest-activity rhythms of critical care patients. These include some notable limitations to the current melatonin study. Firstly, the size of the current melatonin study was underpowered to detect a difference between the groups (the current melatonin study had a power to detect a difference between the groups (α = 0.05) of 0.05 in Inter-daily Stability, which predicts that approximately 75 patients would be required per group to have an 80% power to detect a difference in mean Inter-daily Stability of 0.2. The melatonin dose and administration time are important determinants of the phase advancing effect of melatonin [509]. The melatonin dose

was excessive, being associated with supraphysiological melatonin concentrations during the day, which may have negated the phase advancing effects (Chapters 6 and 7). The rest-activity rhythm in critical care patients is very disturbed and may not be a sensitive measure of a given interventions effect on the circadian rhythm. Furthermore, another melatonin study [440] undertaken in 8 healthy individuals, which reported a phase advancing effect of exogenous melatonin on plasma melatonin and cortisol secretion, was unable to detect a difference in daytime and night-time activity compared to placebo. A longer duration of melatonin treatment may have been more effective, and a preliminary report of a study in critically ill patients administered melatonin for 10 days, suggested an earlier M10 onset time compared to placebo [410]. Although staff were encouraged to turn lights off at night and turn on in the morning, the levels of night and day-time light were not measured. When all lights were off, mean illuminance were less than 10 lux (Chapter 6), which is appropriate for allowing the onset of melatonin secretion [421]. A recent study [513] reported that in critically ill patients, the physiological regulation of melatonin secretion by light and darkness was abolished. Although, the change from ambient light (approximately 10 lux) to complete darkness (< 1 lux) between midnight and 0100 h in the study by Perras *et al*, [513] would not be expected to phase advance the normal rise in plasma melatonin level. The absence of an increase in melatonin plasma levels during the period of darkness suggests a delayed rhythm, as opposed to lack of effect of darkness [513]. Perrras *et al* [513] administered bright light at 0200 h for one hour in critical care patients, which would normally be expected to phase delay a normal circadian rhythm and reduce melatonin plasma levels. However, these critical care patients may already have been phase delayed and, therefore, the timing

of the light therapy may have been during the quiescent period of the light phase response curve in these patients (Chapter 2).

The rest-activity, plasma melatonin and cortisol rhythm analysis results in the current melatonin study confirm that critical care patients experience a delayed and irregular circadian rhythm. Therefore, further attempts to re-enforce circadian rhythms in patients recovering from critical illness may have benefits for sleep-wake cycles and recovery. There is an obvious need for co-ordinated research into the causes of circadian rhythm disturbances, acute and long term consequences, which include cognitive function. The efficacy of interventions that re-enforce rhythms, or prophylaxis measures that minimise the disruption of circadian rhythms are required in post-operative and critical care patients. Bright light therapy applied in the morning is a potentially useful intervention to re-enforce circadian rhythms in patients [289]. Further larger studies in critical care patients that combine the administration of low doses of melatonin administered in the evening, with morning bright light therapy, are indicated.

Conclusions

Acute administration of exogenous melatonin did not result in significant differences in rest-activity rhythms between the groups. Critical care patients demonstrated rest-activity rhythms that were phase delayed, fragmented and suppressed. Most patients lacked circadian rhythms of plasma melatonin and cortisol levels which were no longer phase locked. The amplitude of plasma melatonin levels is significantly suppressed when compared to that in normal elderly subjects.

10 CONCLUSIONS AND SUGGESTIONS FOR FURTHER RESEARCH

The preliminary evaluation of the effects of melatonin on sleep in critical care patients suggested potential benefits in sleep quantity. However, the improvements were not immediate, but became apparent after 3 or more nights therapy. This was important as it emphasised the chronobiotic *versus* hypnotic application of melatonin to aid sleep in critical care patients. The evaluation also provided useful experience that assisted with the design and sample size calculation for the randomised controlled trial.

One of the important aspects derived from the preliminary evaluation concerned the dose and formulation of melatonin to use in subsequent studies. Since the majority of melatonin doses were required to be administered by enteral feeding tubes, it was necessary to use a melatonin formulation and matching placebo that ensured dosing confidence by this route. As no commercial pharmaceutical grade liquid product existed, it was necessary to formulate a simple melatonin oral solution with confirmed stability over the dosing period of the planned study. The stability data was extended further to allow clinical application in other centres.

After completion of the preliminary evaluation, extensive literature reviews were undertaken which provided new perspectives on pharmacological aspects of sleep disturbances, circadian rhythms and melatonin in critical care patients. This literature base also contributed to the design of the randomised controlled trial.

No dose ranging guidance was available for oral melatonin in critical care patients and, therefore, a pharmacokinetic analysis was undertaken. The 10 mg nocturnal dose of melatonin administered as an oral solution provided rapid absorption, with higher peak plasma melatonin concentrations than those reported in most studies in healthy subjects. Furthermore, clearance was reduced compared to results in healthy individuals, and resulted in supraphysiological exposure the next morning. Future

studies should, therefore, use oral melatonin doses in the range of 1-2 mg. Indeed, this is consistent with the 2 mg dose of a newly licensed oral controlled release melatonin product in the UK (Circadin). However, an immediate, then sustained release melatonin oral formulation would allow both a predictably timed signal to the SCN, and also provide sustained, physiological nocturnal plasma levels. Such a product is currently undergoing Phase III trials in the UK, and if it could be made suitable for enteral feeding tube administration, this may be an appropriate formulation to use in future studies. Confirmation of the release characteristics and melatonin kinetics of such a product should be confirmed in critical care patients by HPLC assay. Furthermore, the use of a licensed melatonin product, or indeed a melatonin agonist such a ramelteon, would greatly assist with obtaining a Clinical Trial Authorisation (CTA) by avoiding the need for a full Investigational Medicinal Product Dossier (IMPD) for such a study.

The randomised controlled study showed that administration of melatonin appeared to increase the nocturnal sleep quantity of critical care patients weaning from mechanical ventilation. However, it was not possible to comment on how sleep quality was affected as originally planned. Although the BIS AUC data provided a measure of "sleep depth", without accurate actigraphy data, it was not possible to comment on aspects of sleep quality, such as sleep fragmentation index. Furthermore, in the absence of polysomnography, it was also not possible to investigate the effects of melatonin on REM sleep.

Agreement between the four measures of sleep used in the melatonin study emphasised the difficulty in quantifying sleep in critical care patients. Nurses tended to overestimate sleep quantity, whereas patients often were incapable of quantifying their sleep quantity compared to an objective technique. The validity of actigraphy as

a measure of sleep was highly questionable, while the BIS has potential for use in future critical care studies with further validation.

It was originally planned to undertake further validation of the BIS as a measure of REM sleep compared to polysomnography. Although the author underwent simultaneous BIS and polysomnography sleep monitoring, REM sleep could not be identified. It was, therefore, decided to test other volunteers who were sleep deprived after a night-shift on the basis that they would be more likely to experience REM sleep, despite the invasiveness of the monitoring. However, this proved not to be possible because of equipment and staffing limitations within the Neurophysiology Department at the time. A recent preliminary report found that the BIS score did indeed correlate with the polysomnography sleep stage in mechanically ventilated patients [487]. Critical care patients suffer primarily from sleep fragmentation as opposed to sleep deprivation. Sleep quality is poor as a result of frequent fluctuations between sleep stages or sleep and wakefulness [525]. Traditional polysomnography sleep staging techniques may not adequately reflect sleep fragmentation, and alternative EEG measures of "sleep stability" may have advantages in future critical care sleep studies [525].

Acute administration of exogenous melatonin did not result in significant differences in rest-activity rhythms between the groups. Critical care patients demonstrated rest-activity rhythms that were phase delayed, fragmented and suppressed. Most patients lacked circadian rhythms of plasma melatonin and cortisol levels which were no longer phase locked. Even in patients who did maintain a circadian rhythm in plasma melatonin levels, the strength of the rhythm (amplitude) was relatively weak and exposure was reduced compared to that in healthy elderly subjects. A study of longer

duration, or a prophylactic study with a reduced dose of melatonin, in conjunction with morning bright light therapy should be undertaken.

The studies described in this thesis had a number of limitations. In particular, there were limitations with respect to sample size and statistical power. Although the patient numbers enrolled were comparable to those in other ICU studies, the study only managed to recruit 25 of the planned 48 participants. There are a number of explanations for this: The local ethics committee constraints made it necessary for informed consent to be obtained from all patients. In patients recovering from critical illness, the ability to provide informed consent will vary subject to acute changes in cognitive function (delirium). The availability of informed consent from "a legal representative" [526] would have increased the number of patient participants. Although the PAC-Main trial studied more acutely ill ICU patients, analysis of patient recruitment showed that informed patient consent accounted for less than 3% of patient recruitment [527]. There was also a relatively high refusal rate from patients approached to enter the study (ultimately 1 in every 3 declined to participate in the study). Even though specific approaches to secure nursing staff support of the studies such as educational meetings and identification of a link nurse, some nurses remained unsupportive of the study. The latter may have inadvertently affected patient recruitment. Perhaps the use of a simplified informed consent form may also have improved patient recruitment, [528] assuming this would also gain local ethic committee approval. A multi-site study would have increased the number of potential patient participants. However, the Trusts' other general ICU, did not have a history of support for clinical research, and without the assistance of a research nurse, the data collection would not have been possible. Moreover, design differences between the two units would have added another confounding variable. Finally, it was not

uncommon for patients to meet the inclusion criteria of the study, but to then have excessive residual feeding tube aspirates which excluded them from a study involving oral drug administration.

The Critical Care Directorate has recently re-acquired the services of a dedicated research nurse, which should assist with implementation and data collection of future critical care studies in Sheffield. Furthermore, developments within the Neurophysiology and Sleep Medicine Departments in Sheffield have now made polysomnography available for future critical care sleep studies.

The potential inter-relationships between sleep and circadian rhythm disturbances and delirium are key areas that require further study in critical care patients. It remains unknown whether attempts to prevent sleep fragmentation will reduce the incidence and severity of delirium; or whether by reducing the incidence of delirium, sleep and circadian rhythm disturbances may be minimised. Given the high incidence of delirium in ICU patients, [379] prophylactic measures are an attractive area for investigation. It may be that prevention of circadian rhythm disturbances with appropriately dosed melatonin and light therapy are more effective than attempts to treat these problems once identified during a patient's recovery. Delirium also predisposes patients to early onset dementia, [58] and both critical care and dementia patients demonstrate similar circadian rhythm disturbances. Future critical care studies of sleep and circadian rhythms must include evaluation of long term cognitive outcomes.

Sleep regulation is governed by homeostatic and circadian processes. If sleep disturbances are to be improved in critical care patients, multi-component interventions are required that address environmental, sleep hygiene, medication, ventilator synchrony and circadian factors. Routine delirium screening should be

undertaken and, if positive, precipitants identified and corrected and appropriate supportive measures implemented. Simply relying on the administration of oral melatonin without due consideration of these other factors will not improve sleep quality.

Critical care units should explore the use of light sources in which blue light has been filtered out for clinical use during the night. It may be that such "orange" light allows the majority of routine direct nursing care to be undertaken, and would demonstrate whether critical care patients are capable of maintaining an appropriate melatonin secretion response to darkness [513]. A parallel study of nursing staff sleep and circadian rhythms during night-shifts before and after blue light has been filtered would also be important. Such a study should include a detailed record of clinical incidents and medications errors, as these may be increased or decreased [252]. Alternatively, at night, patients could be supplied with glasses capable of filtering out blue light, and a study examining their efficacy in maintaining nocturnal melatonin secretion should include patient tolerability endpoints.

There clearly remains a challenge in putting aspects of sleep and circadian rhythm research into critical care practice. A new critical care unit was opened this year in Sheffield, which included designs to maximise natural day-light, with large windows in most rooms. However, by late morning it is common that window blinds are still closed and internal lights are dimmed. Without addressing these important environmental aspects of sleep homeostasis and sleep hygiene, medication, including melatonin, will fail to improve sleep-wake and circadian rhythms in patients recovering from critical illness.

Future studies should specifically examine sub-populations of patients in relation to gender, age, severe sepsis and delirium; as different critical care patient groups may

demonstrate variable susceptibilities to circadian rhythm disturbances and treatment response rates.

In recent years there has been a significant increase in original research and review articles related to the subject of sleep in critical care patients. These serve to acknowledge the growing importance patient sleep has in critical care therapeutics as it affects the quality of patient recovery and long term outcome. This thesis has contributed to an understanding of melatonin, sleep and circadian rhythm disturbances in critical care patients [529, 530] and provides guidance on future research.

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Appendices

Appendix 1 Guidelines on melatonin use in intensive care

Introduction

Causes of sleep disturbances in intensive care patients are multifactorial, it should be remembered that environmental factors such as background noise and lighting are as important interventions as hypnotic agents.

Nocturnal administration of melatonin should only be used after inadequate sleep has resulted from appropriate doses of benzodiazepines or chloral hydrate.

Melatonin has been shown to improve some sleep characteristics in intensive care patients.[1-3]

Due to the limited experience of melatonin in intensive care patients, all patients receiving melatonin will be evaluated for its safety and efficacy.

Melatonin is an unlicensed medicinal product.

Dosage

Prescription is by Consultant Intensivist only.

The dose is 5 mg daily given at 22:00 hours.

Cautions

Melatonin therapy may reduce body temperature by up to 0.5°C which should be considered when evaluating results.

Melatonin should not be used in multiple sclerosis or other autoimmune conditions due to reports of aggravation of the disease in some patients.

Drug Interactions

Melatonin may potentiate the effects of benzodiazepines, opioids and neuromuscular blocking drugs.

References

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RS Bourne

November 2000

Appendix 2 Preliminary melatonin therapy evaluation form

Previous nocturnal sedatives:

☐ Temazepam	mg
☐ Chloral Hydrate	g
☐ Haloperidol	mg
☐ Midazolam	mg
☐ Lorazepam	mg
☐ Propofol	mg/kg/hr
☐ Other:	Dose:

Time melatonin administered: : Hours

Melatonin dose given: ☐ 5 mg ☐ Other (mg)

Lowest recorded body/ blood temperature 22:00 – 07:00 °C

Previous lowest recorded temperature (before melatonin therapy) °C

Average estimated sedation score between 22:00 – 07:00 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Approximate number of hours patient asleep 22:00 – 07:00 / 9 hours

Did medical interventions disturb patient? ☐ Yes ☐ No

How did quality of sleep compare to previous sedatives?

☐ Better	☐ Worse
☐ About the same	☐ Unknown

In your opinion was melatonin therapy successful in aiding sleep? ☐ Yes ☐ No

Comments

Appendix 3 Environmental disturbances log

Study Patient No: Nurse Initials:
Day No: Bed No:

Please circle any of the following environmental disturbances occurring between 22:00 and 07:00

1. **Were any of the ITU lights identified as >100 lux (marked with red sticker on switch) switched on between 22:00 and 07:00?**

   YES NO[0]

2. **If YES, how frequently did this occur?**

   1-3[1] 4-7[2] >7[3]

3. **Was the study patient disturbed for clinical reasons by medical or nursing staff?**

   YES[1] NO[0]

4. **Was the patient adjacent to the study patient disturbed for clinical reasons by medical or nursing staff during the study period?**

   YES[1] NO[0]

5. **Did any of the following occur on the ICU during the study period?**

   Patient Death[1] Resuscitation[1]

   Patient Admission[1] Patient Transfer Out/ Bed change[1]

Total Environmental Score = ☐

How would you rank the noise level last night (compared to 'normal')?

Quieter than normal Average Noisier than normal