

## REFERENCES

- Aarons L, Karlsson MO, Mentre F, Rombout F, Steimer JL and van Peer A (2001) Role of modelling and simulation in Phase I drug development. *Eur J Pharm Sci*, **13**:115-122.
- Abbrecht PH, O'Leary TJ and Behrendt DM (1982) Evaluation of a computer-assisted method for individualized anticoagulation: retrospective and prospective studies with a pharmacodynamic model. *Clin Pharmacol Ther*, **32**:129-136.
- Abdul Manap R, Wright CE, Gregory A, Rostami-Hodjegan A, Meller ST, Kelm GR, Lennard MS, Tucker GT and Morice AH (1999) The antitussive effect of dextromethorphan in relation to CYP2D6 activity. *Br J Clin Pharmacol*, **48**:382-387.
- Abelo A, Andersson TB, Antonsson M, Naudot AK, Skanberg I and Weidolf L (2000) Stereoselective metabolism of omeprazole by human cytochrome P450 enzymes. *Drug Metab Dispos*, **28**:966-972.
- Abernethy DR, Kaminsky LS and Dickinson TH (1991) Selective inhibition of warfarin metabolism by diltiazem in humans. *J Pharmacol Exp Ther*, **257**:411-415.
- Adachi K, Katsube T, Kawamura A, Takashima T, Yuki M, Amano K, Ishihara S, Fukuda R, Watanabe M and Kinoshita Y (2000) CYP2C19 genotype status and intragastric pH during dosing with lansoprazole or rabeprazole. *Aliment Pharmacol Ther*, **14**:1259-1266.
- Adcock DM and Duff S (2000) Enhanced standardization of the International Normalized Ratio through the use of plasma calibrants: a concise review. *Blood Coagul Fibrinolysis*, **11**:583-590.
- Adedoyin A, Prakash C, O'Shea D, Blair IA and Wilkinson GR (1994) Stereoselective disposition of hexobarbital and its metabolites: relationship to the S-mephenytoin polymorphism in Caucasian and Chinese subjects. *Pharmacogenetics*, **4**:27-38.
- Aithal GP, Day CP, Kesteven PJ and Daly AK (1999) Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. *Lancet*, **353**:717-719.
- Allabi AC, Gala JL and Horsmans Y (2005) CYP2C9, CYP2C19, ABCB1 (MDR1) genetic polymorphisms and phenytoin metabolism in a Black Beninese population. *Pharmacogenet Genomics*, **15**:779-786.
- Allabi AC, Gala JL, Horsmans Y, Babaoglu MO, Bozkurt A, Heusterspreute M and Yasar U (2004) Functional impact of CYP2C95, CYP2C96, CYP2C98, and CYP2C911 in vivo among black Africans. *Clin Pharmacol Ther*, **76**:113-118.
- Allonen H, Ziegler G and Klotz U (1981) Midazolam kinetics. *Clin Pharmacol Ther*, **30**:653-661.

Alvan G, Grind M, Graffner C and Sjoqvist F (1984) Relationship of N-demethylation of amiflamine and its metabolite to debrisoquine hydroxylation polymorphism. *Clin Pharmacol Ther*, **36**:515-519.

Andersson T, Andren K, Cederberg C, Lagerstrom PO, Lundborg P and Skanberg I (1990a) Pharmacokinetics and bioavailability of omeprazole after single and repeated oral administration in healthy subjects. *Br J Clin Pharmacol*, **29**:557-563.

Andersson T, Cederberg C, Regardh CG and Skanberg I (1990b) Pharmacokinetics of various single intravenous and oral doses of omeprazole. *Eur J Clin Pharmacol*, **39**:195-197.

Andersson T, Holmberg J, Rohss K and Walan A (1998) Pharmacokinetics and effect on caffeine metabolism of the proton pump inhibitors, omeprazole, lansoprazole, and pantoprazole. *Br J Clin Pharmacol*, **45**:369-375.

Anglicheau D, Le Corre D, Lechaton S, Laurent-Puig P, Kreis H, Beaune P, Legendre C and Thervet E (2005) Consequences of genetic polymorphisms for sirolimus requirements after renal transplant in patients on primary sirolimus therapy. *Am J Transplant*, **5**:595-603.

Anglicheau D, Thervet E, Etienne I, Hurault De Ligny B, Le Meur Y, Touchard G, Buchler M, Laurent-Puig P, Tregouet D, Beaune P, Daly A, Legendre C and Marquet P (2004) CYP3A5 and MDR1 genetic polymorphisms and cyclosporine pharmacokinetics after renal transplantation. *Clin Pharmacol Ther*, **75**:422-433.

Aquilante CL, Langae TY, Lopez LM, Yarandi HN, Tromberg JS, Mohuczy D, Gaston KL, Waddell CD, Chirico MJ and Johnson JA (2006) Influence of coagulation factor, vitamin K epoxide reductase complex subunit 1, and cytochrome P450 2C9 gene polymorphisms on warfarin dose requirements. *Clin Pharmacol Ther*, **79**:291-302.

Ariizumi K, Ohara S, Koike T, Inomata Y, Iijima K, Sekine H, Noguchi M, Sugiyama K, Eda Y, Kayaba S, Kawamura M and Shimosegawa T (2006) Therapeutic effects of 10 mg/day rabeprazole administration on reflux esophagitis was not influenced by the CYP2C19 polymorphism. *J Gastroenterol Hepatol*, **21**:1428-1434.

Austin RP, Barton P, Cockroft SL, Wenlock MC and Riley RJ (2002) The influence of nonspecific microsomal binding on apparent intrinsic clearance, and its prediction from physicochemical properties. *Drug Metab Dispos*, **30**:1497-1503.

Aylward M, Maddock J, Davies DE, Protheroe DA and Leideman T (1984) Dextromethorphan and codeine: comparison of plasma kinetics and antitussive effects. *Eur J Respir Dis*, **65**:283-291.

Aynacioglu AS, Brockmoller J, Bauer S, Sachse C, Guzelbey P, Ongen Z, Nacak M and Roots I (1999) Frequency of cytochrome P450 CYP2C9 variants in a Turkish population and functional relevance for phenytoin. *Br J Clin Pharmacol*, **48**:409-415.

Balimane PV, Chong S and Morrison RA (2000) Current methodologies used for evaluation of intestinal permeability and absorption. *J Pharmacol Toxicol Methods*, **44**:301-312.

Barger-Lux MJ and Heaney RP (2005) Calcium absorptive efficiency is positively related to body size. *J Clin Endocrinol Metab*, **90**:5118-5120.

Barnhart JW (1980) The urinary excretion of dextromethorphan and three metabolites in dogs and humans. *Toxicol Appl Pharmacol*, **55**:43-48.

Beil W, Sewing KF, Busche R and Wagner S (2001) Helicobacter pylori augments the acid inhibitory effect of omeprazole on parietal cells and gastric H(+)/K(+)-ATPase. *Gut*, **48**:157-162.

Beresford AP, Selick HE and Tarbit MH (2002) The emerging importance of predictive ADME simulation in drug discovery. *Drug Discov Today*, **7**:109-116.

Bertilsson L, Carrillo JA, Dahl ML, Llerena A, Alm C, Bondesson U, Lindstrom L, Rodriguez de la Rubia I, Ramos S and Benitez J (1994) Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. *Br J Clin Pharmacol*, **38**:471-473.

Bertilsson L, Henthorn TK, Sanz E, Tybring G, Sawe J and Villen T (1989) Importance of genetic factors in the regulation of diazepam metabolism: relationship to S-mephenytoin, but not debrisoquin, hydroxylation phenotype. *Clin Pharmacol Ther*, **45**:348-355.

Beutler E (1959) The hemolytic effect of primaquine and related compounds: a review. *Blood*, **14**:103-139.

Bezzina CR, Verkerk AO, Busjahn A, Jeron A, Erdmann J, Koopmann TT, Bhuiyan ZA, Wilders R, Mannens MM, Tan HL, Luft FC, Schunkert H and Wilde AA (2003) A common polymorphism in KCNH2 (HERG) hastens cardiac repolarization. *Cardiovasc Res*, **59**:27-36.

Bidstrup TB, Damkier P, Olsen AK, Ekblom M, Karlsson A and Brosten K (2006) The impact of CYP2C8 polymorphism and grapefruit juice on the pharmacokinetics of repaglinide. *Br J Clin Pharmacol*, **61**:49-57.

Blesch KS, Gieschke R, Tsukamoto Y, Reigner BG, Burger HU and Steimer JL (2003) Clinical pharmacokinetic/pharmacodynamic and physiologically based pharmacokinetic modeling in new drug development: the capecitabine experience. *Invest New Drugs*, **21**:195-223.

Bodin L, Verstuyft C, Tregouet DA, Robert A, Dubert L, Funck-Brentano C, Jaillon P, Beaune P, Laurent-Puig P, Becquemont L and Lloriot MA (2005) Cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase (VKORC1) genotypes as determinants of acenocoumarol sensitivity. *Blood*, **106**:135-140.

- Bonate PL (2000) Clinical trial simulation in drug development. *Pharm Res*, 17:252-256.
- Borges S, Desta Z, Li L, Skaar TC, Ward BA, Nguyen A, Jin Y, Storniolo AM, Nikoloff DM, Wu L, Hillman G, Hayes DF, Stearns V and Flockhart DA (2006) Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. *Clin Pharmacol Ther*, 80:61-74.
- Bouchez J, Dumur V, Lhermitte M and Goudemand M (1995) Genotypes of cytochrome P450 and clinical response to clomipramine in patients with major depression. *European Psychiatry*, 10:410-412.
- Breckenridge A, Orme M, Wesseling H, Lewis RJ and Gibbons R (1974) Pharmacokinetics and pharmacodynamics of the enantiomers of warfarin in man. *Clin Pharmacol Ther*, 15:424-430.
- Brenner SS, Herrlinger C, Dilger K, Murdter TE, Hofmann U, Marx C and Klotz U (2003) Influence of age and cytochrome P450 2C9 genotype on the steady-state disposition of diclofenac and celecoxib. *Clin Pharmacokinet*, 42:283-292.
- Brockmoller J, Kirchheiner J, Schmider J, Walter S, Sachse C, Muller-Oerlinghausen B and Roots I (2002) The impact of the CYP2D6 polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. *Clin Pharmacol Ther*, 72:438-452.
- Brosen K, Skjelbo E and Flachs H (1993) Proguanil metabolism is determined by the mephenytoin oxidation polymorphism in Vietnamese living in Denmark. *Br J Clin Pharmacol*, 36:105-108.
- Brynne N, Dalen P, Alvan G, Bertilsson L and Gabrielsson J (1998) Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamic of tolterodine. *Clin Pharmacol Ther*, 63:529-539.
- Bugrim A, Nikolskaya T and Nikolsky Y (2004) Early prediction of drug metabolism and toxicity: systems biology approach and modeling. *Drug Discov Today*, 9:127-135.
- Burger DM, Schwietert HR, Colbers EP and Becker M (2006) The effect of the CYP2C19\*2 heterozygote genotype on the pharmacokinetics of nelfinavir. *Br J Clin Pharmacol*, 62:250-252.
- Cai WM, Xu J, Chen B, Zhang FM, Huang YZ and Zhang YD (2002) Effect of CYP2D6\*10 genotype on propafenone pharmacodynamics in Chinese patients with ventricular arrhythmia. *Acta Pharmacol Sin*, 23:1040-1044.
- Capon DA, Bochner F, Kerry N, Mikus G, Danz C and Somogyi AA (1996) The influence of CYP2D6 polymorphism and quinidine on the disposition and antitussive effect of dextromethorphan in humans. *Clin Pharmacol Ther*, 60:295-307.

Caraco Y, Sheller J and Wood AJ (1999) Impact of ethnic origin and quinidine coadministration on codeine's disposition and pharmacodynamic effects. *J Pharmacol Exp Ther*, **290**:413-422.

Cascorbi I (2003) Pharmacogenetics of cytochrome P4502D6: genetic background and clinical implication. *Eur J Clin Invest*, **33** (S2):17-22.

Casner PR (2005) The effect of CYP2D6 polymorphisms on dextromethorphan metabolism in Mexican Americans. *J Clin Pharmacol*, **45**:1230-1235.

Cass LJ and Frederik WS (1953) Evaluation of a new antitussive agent. *N Engl J Med*, **249**:132-136.

Cass LJ and Frederik WS (1956) Quantitative comparison of cough-suppressing effects of romilar and other antitussives. *J Lab Clin Med*, **48**:879-885.

Chan E, McLachlan A, O'Reilly R and Rowland M (1994) Stereochemical aspects of warfarin drug interactions: use of a combined pharmacokinetic-pharmacodynamic model. *Clin Pharmacol Ther*, **56**:286-294.

Chang M, Tybring G, Dahl ML, Gotharson E, Sagar M, Seensalu R and Bertilsson L (1995) Interphenotype differences in disposition and effect on gastrin levels of omeprazole--suitability of omeprazole as a probe for CYP2C19. *Br J Clin Pharmacol*, **39**:511-518.

Chen G, Jiang S, Mao G, Zhang S, Hong X, Tang G, Li Z, Liu X, Zhang Y, Xing H, Wang B, Yu Y and Xu X (2006) CYP2C9 Ile359Leu polymorphism, plasma irbesartan concentration and acute blood pressure reductions in response to irbesartan treatment in Chinese hypertensive patients. *Methods Find Exp Clin Pharmacol*, **28**:19-24.

Chern HD, Ueng TH, Fu YP and Cheng CW (2006) CYP2C9 polymorphism and warfarin sensitivity in Taiwan Chinese. *Clin Chim Acta*, **367**:108-113.

Ching MS, Blake CL, Ghabrial H, Ellis SW, Lennard MS, Tucker GT and Smallwood RA (1995) Potent inhibition of yeast-expressed CYP2D6 by dihydroquinidine, quinidine, and its metabolites. *Biochem Pharmacol*, **50**:833-837.

Cleton A, Odman J, Van der Graaf PH, Ghijsen W, Voskuyl R and Danhof M (2000) Mechanism-based modeling of functional adaptation upon chronic treatment with midazolam. *Pharm Res*, **17**:321-327.

Cockcroft DW and Gault MH (1976) Prediction of creatinine clearance from serum creatinine. *Nephron*, **16**:31-41.

Coller JK, Krebsfaenger N, Klein K, Endrizzi K, Wolbold R, Lang T, Nussler A, Neuhaus P, Zanger UM, Eichelbaum M and Murdter TE (2002) The influence of CYP2B6, CYP2C9 and CYP2D6 genotypes on the formation of the potent antioestrogen Z-4-hydroxy-tamoxifen in human liver. *Br J Clin Pharmacol*, **54**:157-167.

Cox EH, Kerbusch T, Van der Graaf PH and Danhof M (1998) Pharmacokinetic-pharmacodynamic modeling of the electroencephalogram effect of synthetic opioids in the rat: correlation with the interaction at the mu-opioid receptor. *J Pharmacol Exp Ther*, **284**:1095-1103.

Crettol S, Deglon JJ, Besson J, Croquette-Krokkar M, Gothuey I, Hammig R, Monnat M, Huttemann H, Baumann P and Eap CB (2005) Methadone enantiomer plasma levels, CYP2B6, CYP2C19, and CYP2C9 genotypes, and response to treatment. *Clin Pharmacol Ther*, **78**:593-604.

Crevoisier C, Ziegler WH, Eckert M and Heizmann P (1983) Relationship between plasma concentration and effect of midazolam after oral and intravenous administration. *Br J Clin Pharmacol*, **16** (S1):51S-61S.

D'Andrea G, D'Ambrosio RL, Di Perna P, Chetta M, Santacroce R, Brancaccio V, Grandone E and Margaglione M (2005) A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin. *Blood*, **105**:645-649.

Dahl ML, Tybring G, Elwin CE, Alm C, Andreasson K, Gyllenpalm M and Bertilsson L (1994) Stereoselective disposition of mianserin is related to debrisoquin hydroxylation polymorphism. *Clin Pharmacol Ther*, **56**:176-183.

Dalen P, Alvan G, Wakelkamp M and Olsen H (1996) Formation of meprobamate from carisoprodol is catalysed by CYP2C19. *Pharmacogenetics*, **6**:387-394.

Daly AK (2003) Pharmacogenetics of the major polymorphic metabolizing enzymes. *Fundam Clin Pharmacol*, **17**:27-41.

Danhof M and Mandema JW (1995) Modeling of Relationships between Pharmacokinetics and Pharmacodynamics, 139-174. In Welling PG and Tse FLS, *Pharmacokinetics: Regulatory, Industrial, Academic Perspectives*. Marcel Dekker, New York.

Davies BJ, Coller JK, James HM, Somogyi AA, Horowitz JD and Sallustio BC (2006) The influence of CYP2D6 genotype on trough plasma perhexiline and cis-OH-perhexiline concentrations following a standard loading regimen in patients with myocardial ischaemia. *Br J Clin Pharmacol*, **61**:321-325.

Delaporte E, Slaughter DE, Egan MA, Gatto GJ, Santos A, Shelley J, Price E, Howells L, Dean DC and Rodrigues AD (2001) The potential for CYP2D6 inhibition screening using a novel scintillation proximity assay-based approach. *J Biomol Screen*, **6**:225-231.

Desmeules J, Gascon MP, Dayer P and Magistris M (1991) Impact of environmental and genetic factors on codeine analgesia. *Eur J Clin Pharmacol*, **41**:23-26.

Desmeules JA, Oestreicher MK, Piguet V, Allaz AF and Dayer P (1999) Contribution of cytochrome P-4502D6 phenotype to the neuromodulatory effects of dextromethorphan. *J Pharmacol Exp Ther*, **288**:607-612.

Desta Z, Zhao X, Shin JG and Flockhart DA (2002) Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clin Pharmacokinet*, **41**:913-958.

Dickins M and Tucker GT (2001) Drug disposition: to phenotype or genotype. *International journal of pharmaceutical medicine*, **15**:70-73.

Dorado P, Berecz R, Caceres MC, Gonzalez I, Cobaleda J and Llerena A (2005) Determination of debrisoquine and 4-hydroxydebrisoquine by high-performance liquid chromatography: application to the evaluation of CYP2D6 genotype and debrisoquine metabolic ratio relationship. *Clin Chem Lab Med*, **43**:275-279.

Dorado P, Berecz R, Norberto MJ, Yasar U, Dahl ML and A LL (2003) CYP2C9 genotypes and diclofenac metabolism in Spanish healthy volunteers. *Eur J Clin Pharmacol*, **59**:221-225.

Du Bois D and Du Bois EF (1916) A formula to estimate the approximate surface area if height and weight are known. *Archives of Internal Medicine*, **17**:863-871.

Eap CB, Bender S, Jaquenoud SE, Cucchia G, Jonzier-Perey M, Baumann P, Allorge D and Broly F (2004a) Nonresponse to clozapine and ultrarapid CYP1A2 activity: clinical data and analysis of CYP1A2 gene. *J Clin Psychopharmacol*, **24**:214-219.

Eap CB, Buclin T, Hustert E, Bleiber G, Golay KP, Aubert AC, Baumann P, Telenti A and Kerb R (2004b) Pharmacokinetics of midazolam in CYP3A4- and CYP3A5-genotyped subjects. *Eur J Clin Pharmacol*, **60**:231-236.

Eble J, West B and Link K (1966) A comparison of isomers of warfarin. *Biochemical pharmacology*, **15**:1003.

Egan LJ, Myhre GM, Mays DC, Dierkhising RA, Kammer PP and Murray JA (2003) CYP2C19 pharmacogenetics in the clinical use of proton-pump inhibitors for gastro-oesophageal reflux disease: variant alleles predict gastric acid suppression, but not oesophageal acid exposure or reflux symptoms. *Aliment Pharmacol Ther*, **17**:1521-1528.

Eichelbaum M, Ingelman-Sundberg M and Evans WE (2006) Pharmacogenomics and individualized drug therapy. *Annu Rev Med*, **57**:119-137.

Eichelbaum M, Spannbrucker N, Steincke B and Dengler HJ (1979) Defective N-oxidation of sparteine in man: a new pharmacogenetic defect. *Eur J Clin Pharmacol*, **16**:183-187.

Evans WE and Relling MV (1991) Concordance of P450 2D6 (debrisoquine hydroxylase) phenotype and genotype: inability of dextromethorphan metabolic ratio to discriminate reliably heterozygous and homozygous extensive metabolizers. *Pharmacogenetics*, **1**:143-148.

Evans WE and McLeod HL (2003) Pharmacogenomics - drug disposition, drug targets, and side effects. *N Engl J Med*, **348**:538-549.

Fabre G, Rahmani R, Placidi M, Combalbert J, Covo J, Cano JP, Coulange C, Ducros M and Rampal M (1988) Characterization of midazolam metabolism using human hepatic microsomal fractions and hepatocytes in suspension obtained by perfusing whole human livers. *Biochem Pharmacol*, **37**:4389-4397.

FDA (2004) Innovation Stagnation: Challenge and opportunity on the critical path to new medical products. <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>, 5th August 2006.

FDA (October 1, 2004) Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling - PRELIMINARY CONCEPT PAPER. [http://www.fda.gov.lilac.une.edu/ohrms/dockets/ac/04/briefing/2004-4079B1\\_04\\_Topic2-TabA.doc](http://www.fda.gov/lilac.une.edu/ohrms/dockets/ac/04/briefing/2004-4079B1_04_Topic2-TabA.doc), 27 March 2006.

Fiegenbaum M, da Silveira FR, Van der Sand CR, Van der Sand LC, Ferreira ME, Pires RC and Hutz MH (2005) The role of common variants of ABCB1, CYP3A4, and CYP3A5 genes in lipid-lowering efficacy and safety of simvastatin treatment. *Clin Pharmacol Ther*, **78**:551-558.

Fletcher P, Hirji MR, Kuhn S, Alexander L and Mucklow JC (1986) The effects of diabetes mellitus, exercise, and single doses of biguanides upon lactate metabolism in man. *Br J Clin Pharmacol*, **21**:691-699.

Floyd MD, Gervasini G, Masica AL, Mayo G, George AL, Jr., Bhat K, Kim RB and Wilkinson GR (2003) Genotype-phenotype associations for common CYP3A4 and CYP3A5 variants in the basal and induced metabolism of midazolam in European- and African-American men and women. *Pharmacogenetics*, **13**:595-606.

Frohlich M, Hoffmann MM, Burhenne J, Mikus G, Weiss J and Haefeli WE (2004) Association of the CYP3A5 A6986G (CYP3A5\*3) polymorphism with saquinavir pharmacokinetics. *Br J Clin Pharmacol*, **58**:443-444.

Fu L-Q, Huang F, Wu D-Z and Guo J-H (2003) Pharmacokinetics of omeprazole and its metabolites in Chinese healthy subjects. *Chinese Journal of Pharmacology and Toxicology*, **17**:51-54.

Fu L-Q, Huang F, Wu D-Z and Liu Z-Y (2004) Pharmacokinetic comparison of omeprazole and its metabolites between Chinese CYP2C19 EMs and PM subjects. *Chinese Pharmaceutical Journal*, **39**:614-616.

Fukuda T, Yamamoto I, Nishida Y, Zhou Q, Ohno M, Takada K and Azuma J (1999) Effect of the CYP2D6\*10 genotype on venlafaxine pharmacokinetics in healthy adult volunteers. *Br J Clin Pharmacol*, **47**:450-453.

Furuta T, Ohashi K, Kobayashi K, Iida I, Yoshida H, Shirai N, Takashima M, Kosuge K, Hanai H, Chiba K, Ishizaki T and Kaneko E (1999a) Effects of clarithromycin on the metabolism of omeprazole in relation to CYP2C19 genotype status in humans. *Clin Pharmacol Ther*, **66**:265-274.



Furuta T, Ohashi K, Kosuge K, Zhao XJ, Takashima M, Kimura M, Nishimoto M, Hanai H, Kaneko E and Ishizaki T (1999b) CYP2C19 genotype status and effect of omeprazole on intragastric pH in humans. *Clin Pharmacol Ther*, **65**:552-561.

Furuta T, Sagehashi Y, Shirai N, Sugimoto M, Nakamura A, Kodaira M, Kenmotsu K, Nagano M, Egashira T, Ueda K, Yoneyama M, Ohashi K, Ishizaki T and Hishida A (2005) Influence of CYP2C19 polymorphism and Helicobacter pylori genotype determined from gastric tissue samples on response to triple therapy for H pylori infection. *Clin Gastroenterol Hepatol*, **3**:564-573.

Furuta T, Shirai N, Takashima M, Xiao F, Hanai H, Nakagawa K, Sugimura H, Ohashi K and Ishizaki T (2001) Effects of genotypic differences in CYP2C19 status on cure rates for Helicobacter pylori infection by dual therapy with rabeprazole plus amoxicillin. *Pharmacogenetics*, **11**:341-348.

Furuta T, Shirai N, Watanabe F, Honda S, Takeuchi K, Iida T, Sato Y, Kajimura M, Futami H, Takayanagi S, Yamada M, Ohashi K, Ishizaki T and Hanai H (2002) Effect of cytochrome P450C19 genotypic differences on cure rates for gastroesophageal reflux disease by lansoprazole. *Clin Pharmacol Ther*, **72**:453-460.

Fux R, Morike K, Prohmer AM, Delabar U, Schwab M, Schaeffeler E, Lorenz G, Gleiter CH, Eichelbaum M and Kivisto KT (2005) Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study. *Clin Pharmacol Ther*, **78**:378-387.

Gabrielsson J and Weiner D (2000) Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts & Applications, 3rd Edition. Swedish Pharmaceutical Press, Stockholm.

Galetin A, Brown C, Hallifax D, Ito K and Houston JB (2004) Utility of recombinant enzyme kinetics in prediction of human clearance: impact of variability, CYP3A5, and CYP2C19 on CYP3A4 probe substrates. *Drug Metab Dispos*, **32**:1411-1420.

Garcia-Martin E, Martinez C, Tabares B, Frias J and Agundez JA (2004) Interindividual variability in ibuprofen pharmacokinetics is related to interaction of cytochrome P450 2C8 and 2C9 amino acid polymorphisms. *Clin Pharmacol Ther*, **76**:119-127.

Gardner ER, Burger H, van Schaik RH, van Oosterom AT, de Bruijn EA, Guetens G, Prenen H, de Jong FA, Baker SD, Bates SE, Figg WD, Verweij J, Sparreboom A and Nooter K (2006) Association of enzyme and transporter genotypes with the pharmacokinetics of imatinib. *Clin Pharmacol Ther*, **80**:192-201.

Gascon MP and Dayer P (1991) In vitro forecasting of drugs which may interfere with the biotransformation of midazolam. *Eur J Clin Pharmacol*, **41**:573-578.

Gibbs MA and Hosea NA (2003) Factors affecting the clinical development of cytochrome p450 3A substrates. *Clin Pharmacokinet*, **42**:969-984.

- Gieschke R, Reigner BG and Steimer JL (1997) Exploring clinical study design by computer simulation based on pharmacokinetic/pharmacodynamic modelling. *Int J Clin Pharmacol Ther*, **35**:469-474.
- Goh BC, Lee SC, Wang LZ, Fan L, Guo JY, Lamba J, Schuetz E, Lim R, Lim HL, Ong AB and Lee HS (2002) Explaining interindividual variability of docetaxel pharmacokinetics and pharmacodynamics in Asians through phenotyping and genotyping strategies. *J Clin Oncol*, **20**:3683-3690.
- Gooley TA, Martin PJ, Fisher LD and Pettinger M (1994) Simulation as a design tool for phase I/II clinical trials: an example from bone marrow transplantation. *Control Clin Trials*, **15**:450-462.
- Gorski JC, Jones DR, Wrighton SA and Hall SD (1994) Characterization of dextromethorphan N-demethylation by human liver microsomes. Contribution of the cytochrome P450 3A (CYP3A) subfamily. *Biochem Pharmacol*, **48**:173-182.
- Grattan TJ, Marshall AE, Higgins KS and Morice AH (1995) The effect of inhaled and oral dextromethorphan on citric acid induced cough in man. *Br J Clin Pharmacol*, **39**:261-263.
- Greaves M (2005) Pharmacogenetics in the management of coumarin anticoagulant therapy: the way forward or an expensive diversion? *PLoS Med*, **2**:e342.
- Greco WR, Bravo G and Parsons JC (1995) The search for synergy: a critical review from a response surface perspective. *Pharmacol Rev*, **47**:331-385.
- Greenblatt D and Shader R (1986) Physiochemical and pharmacokinetic properties of midazolam in humans. *Anesthesiology*, **13**:7-12.
- Greenblatt DJ, Abernethy DR, Locniskar A, Harmatz JS, Limjuco RA and Shader RI (1984) Effect of age, gender, and obesity on midazolam kinetics. *Anesthesiology*, **61**:27-35.
- Guengerich FP (1995) Cytochromes P-450 of Human Liver. Classification and Activity Profiles of the Major Enzymes, 179-232. In Pacifici GM and Fracchia GN, *Advances in Drug Metabolism in Man*. European Commission, Luxembourg.
- Guidelines on oral anticoagulation: third edition (1998). *Br J Haematol*, **101**:374-387.
- Guo Y, Wang Y, Si D, Fawcett PJ, Zhong D and Zhou H (2005) Catalytic activities of human cytochrome P450 2C9\*1, 2C9\*3 and 2C9\*13. *Xenobiotica*, **35**:853-861.
- Gurwitz JH, Avorn J, Ross-Degnan D, Choodnovskiy I and Ansell J (1992) Aging and the anticoagulant response to warfarin therapy. *Ann Intern Med*, **116**:901-904.
- Hadama A, Ieiri I, Morita T, Kimura M, Urae A, Irie S, Kaneda T, Mamiya K, Tashiro N, Higuchi S and Otsubo K (2001) P-hydroxylation of phenobarbital: relationship to (S)-mephenytoin hydroxylation (CYP2C19) polymorphism. *Ther Drug Monit*, **23**:115-118.

Hale MD, Nicholls AJ, Bullingham RE, Hene R, Hoitsma A, Squifflet JP, Weimar W, Vanrenterghem Y, Van de Woude FJ and Verpooten GA (1998) The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. *Clin Pharmacol Ther*, **64**:672-683.

Hallberg P, Karlsson J, Kurland L, Lind L, Kahan T, Malmqvist K, Ohman KP, Nystrom F and Melhus H (2002) The CYP2C9 genotype predicts the blood pressure response to irbesartan: results from the Swedish Irbesartan Left Ventricular Hypertrophy Investigation vs Atenolol (SILVHIA) trial. *J Hypertens*, **20**:2089-2093.

Hanatani T, Fukuda T, Onishi S, Funae Y and Azuma J (2003) No major difference in inhibitory susceptibility between CYP2C9.1 and CYP2C9.3. *Eur J Clin Pharmacol*, **59**:233-235.

Haufroid V, Mourad M, Van Kerckhove V, Wawrzyniak J, De Meyer M, Eddour DC, Malaise J, Lison D, Squifflet JP and Wallemacq P (2004) The effect of CYP3A5 and MDR1 (ABCB1) polymorphisms on cyclosporine and tacrolimus dose requirements and trough blood levels in stable renal transplant patients. *Pharmacogenetics*, **14**:147-154.

Hayhurst GP, Harlow J, Chowdry J, Gross E, Hilton E, Lennard MS, Tucker GT and Ellis SW (2001) Influence of phenylalanine-481 substitutions on the catalytic activity of cytochrome P450 2D6. *Biochem J*, **355**:373-379.

He P, Court MH, Greenblatt DJ and Von Moltke LL (2005) Genotype-phenotype associations of cytochrome P450 3A4 and 3A5 polymorphism with midazolam clearance in vivo. *Clin Pharmacol Ther*, **77**:373-387.

Heimark LD, Wienkers L, Kunze K, Gibaldi M, Eddy AC, Trager WF, O'Reilly RA and Goulart DA (1992) The mechanism of the interaction between amiodarone and warfarin in humans. *Clin Pharmacol Ther*, **51**:398-407.

Heinemann A, Wischhusen F, Puschel K and Rogiers X (1999) Standard liver volume in the Caucasian population. *Liver Transpl Surg*, **5**:366-368.

Heizmann P, Eckert M and Ziegler WH (1983) Pharmacokinetics and bioavailability of midazolam in man. *Br J Clin Pharmacol*, **16** (S1):43S-49S.

Henne KR, Gaedigk A, Gupta G, Leeder JS and Rettie AE (1998) Chiral phase analysis of warfarin enantiomers in patient plasma in relation to CYP2C9 genotype. *J Chromatogr B Biomed Sci Appl*, **710**:143-148.

Henningson A, Marsh S, Loos WJ, Karlsson MO, Garsa A, Mross K, Mielke S, Vigano L, Locatelli A, Verweij J, Sparreboom A and McLeod HL (2005) Association of CYP2C8, CYP3A4, CYP3A5, and ABCB1 polymorphisms with the pharmacokinetics of paclitaxel. *Clin Cancer Res*, **11**:8097-8104.

Herman D, Locatelli I, Grabnar I, Peternel P, Stegnar M, Mrhar A, Breskvar K and Dolzan V (2005) Influence of CYP2C9 polymorphisms, demographic factors and

concomitant drug therapy on warfarin metabolism and maintenance dose. *Pharmacogenomics J*, 5:193-202.

Hermida J, Zarza J, Alberca I, Montes R, Lopez ML, Molina E and Rocha E (2002) Differential effects of 2C9\*3 and 2C9\*2 variants of cytochrome P-450 CYP2C9 on sensitivity to acenocoumarol. *Blood*, 99:4237-4239.

Hesselink DA, van Gelder T, van Schaik RH, Balk AH, van der Heiden IP, van Dam T, van der Werf M, Weimar W and Mathot RA (2004) Population pharmacokinetics of cyclosporine in kidney and heart transplant recipients and the influence of ethnicity and genetic polymorphisms in the MDR-1, CYP3A4, and CYP3A5 genes. *Clin Pharmacol Ther*, 76:545-556.

Higashi MK, Veenstra DL, Kondo LM, Wittkowsky AK, Srinouanprachanh SL, Farin FM and Rettie AE (2002) Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. *Jama*, 287:1690-1698.

Hillman MA, Wilke RA, Caldwell MD, Berg RL, Glurich I and Burmester JK (2004) Relative impact of covariates in prescribing warfarin according to CYP2C9 genotype. *Pharmacogenetics*, 14:539-547.

Hokari K, Sugiyama T, Kato M, Saito M, Miyagishima T, Kudo M, Nishikawa K, Ishizuka J, Komatsu Y, Mizushima T, Kagaya H, Hige S, Takeda H and Asaka M (2001) Efficacy of triple therapy with rabeprazole for Helicobacter pylori infection and CYP2C19 genetic polymorphism. *Aliment Pharmacol Ther*, 15:1479-1484.

Holford NH (1986) Clinical pharmacokinetics and pharmacodynamics of warfarin. Understanding the dose-effect relationship. *Clin Pharmacokinet*, 11:483-504.

Hollt V (2002) A polymorphism (A118G) in the mu-opioid receptor gene affects the response to morphine-6-glucuronide in humans. *Pharmacogenetics*, 12:1-2.

Holstein A, Plaschke A, Ptak M, Egberts EH, El-Din J, Brockmoller J and Kirchheiner J (2005) Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. *Br J Clin Pharmacol*, 60:103-106.

Holtzman N (2001) Three views of genetics: The enthusiast, the visionary and the sceptic: The cautious view. *British Medical Journal*, 322:1016-1017.

Honda M, Nozawa T, Igarashi N, Inoue H, Arakawa R, Ogura Y, Okabe H, Taguchi M and Hashimoto Y (2005) Effect of CYP2D6\*10 on the pharmacokinetics of R- and S-carvedilol in healthy Japanese volunteers. *Biol Pharm Bull*, 28:1476-1479.

Horai Y, Kimura M, Furuie H, Matsuguma K, Irie S, Koga Y, Nagahama T, Murakami M, Matsui T, Yao T, Urae A and Ishizaki T (2001) Pharmacodynamic effects and kinetic disposition of rabeprazole in relation to CYP2C19 genotypes. *Aliment Pharmacol Ther*, 15:793-803.

Hoskins JM, Shenfield GM and Gross AS (1998) Relationship between proguanil metabolic ratio and CYP2C19 genotype in a Caucasian population. *Br J Clin Pharmacol*, **46**:499-504.

Howgate EM, Rowland Yeo K, Proctor NJ, Tucker GT and Rostami-Hodjegan A (2006) Prediction of in vivo drug clearance from in vitro data. I: impact of inter-individual variability. *Xenobiotica*, **36**:473-497.

Hu X-P, Xu J-M, Hu Y-M, Mei Q, Xu X-H and Xu S-Y (2005) Effects of CYP2C19 polymorphism on the pharmacokinetics and pharmacodynamics of omeprazole in Chinese volunteers. *Chinese Pharmacological Bulletin*, **21**:1210-1213.

Huang CW, Lai ML, Lin MS, Lee HL and Huang JD (2003) Dose-response relationships of propranolol in Chinese subjects with different CYP2D6 genotypes. *J Chin Med Assoc*, **66**:57-62.

Huang W, Lin YS, McConn DJ, 2nd, Calamia JC, Totah RA, Isoherranen N, Glodowski M and Thummel KE (2004) Evidence of significant contribution from CYP3A5 to hepatic drug metabolism. *Drug Metab Dispos*, **32**:1434-1445.

Ibrahim A, Karim A, Feldman J and Kharasch E (2002) The influence of parecoxib, a parenteral cyclooxygenase-2 specific inhibitor, on the pharmacokinetics and clinical effects of midazolam. *Anesth Analg*, **95**:667-673, table of contents.

Idle JR, Mahgoub A, Lancaster R and Smith RL (1978) Hypotensive response to debrisoquine and hydroxylation phenotype. *Life Sci*, **22**:979-983.

Ieiri I, Kimura M, Irie S, Urae A, Otsubo K and Ishizaki T (2005) Interaction magnitude, pharmacokinetics and pharmacodynamics of ticlopidine in relation to CYP2C19 genotypic status. *Pharmacogenet Genomics*, **15**:851-859.

Ieiri I, Kishimoto Y, Okochi H, Momiyama K, Morita T, Kitano M, Morisawa T, Fukushima Y, Nakagawa K, Hasegawa J, Otsubo K and Ishizaki T (2001) Comparison of the kinetic disposition of and serum gastrin change by lansoprazole versus rabeprazole during an 8-day dosing scheme in relation to CYP2C19 polymorphism. *Eur J Clin Pharmacol*, **57**:485-492.

Ieiri I, Mamiya K, Urae A, Wada Y, Kimura M, Irie S, Amamoto T, Kubota T, Yoshioka S, Nakamura K, Nakano S, Tashiro N and Higuchi S (1997) Stereoselective 4'-hydroxylation of phenytoin: relationship to (S)-mephenytoin polymorphism in Japanese. *Br J Clin Pharmacol*, **43**:441-445.

Ingelman-Sundberg M (2001) Pharmacogenetics: an opportunity for a safer and more efficient pharmacotherapy. *J Intern Med*, **250**:186-200.

Ingelman-Sundberg M, Oscarson M and McLellan RA (1999) Polymorphic human cytochrome P450 enzymes: an opportunity for individualized drug treatment. *Trends Pharmacol Sci*, **20**:342-349.

Inoue S, Howgate EM, Rowland-Yeo K, Shimada T, Yamazaki H, Tucker GT and Rostami-Hodjegan A (2006) Prediction of in vivo drug clearance from in vitro data. II: potential inter-ethnic differences. *Xenobiotica*, **36**:499-513.

Ito K and Houston JB (2004) Comparison of the use of liver models for predicting drug clearance using in vitro kinetic data from hepatic microsomes and isolated hepatocytes. *Pharm Res*, **21**:785-792.

Iwata H, Fujita K, Kushida H, Suzuki A, Konno Y, Nakamura K, Fujino A and Kamataki T (1998) High catalytic activity of human cytochrome P450 co-expressed with human NADPH-cytochrome P450 reductase in *Escherichia coli*. *Biochem Pharmacol*, **55**:1315-1325.

Iwatsubo T, Hirota N, Ooie T, Suzuki H and Sugiyama Y (1996) Prediction of in vivo drug disposition from in vitro data based on physiological pharmacokinetics. *Biopharm Drug Dispos*, **17**:273-310.

Jacqz-Aigrain E and Cresteil T (1992) Cytochrome P450-dependent metabolism of dextromethorphan: fetal and adult studies. *Dev Pharmacol Ther*, **18**:161-168.

Jacqz-Aigrain E, Funck-Brentano C and Cresteil T (1993) CYP2D6- and CYP3A-dependent metabolism of dextromethorphan in humans. *Pharmacogenetics*, **3**:197-204.

Jazwinska-Tarnawska E, Orzechowska-Juzwenko K, Niewinski P, Rzemislawska Z, Loboż-Grudzien K, Dmochowska-Perz M and Slawin J (2001) The influence of CYP2D6 polymorphism on the antiarrhythmic efficacy of propafenone in patients with paroxysmal atrial fibrillation during 3 months propafenone prophylactic treatment. *Int J Clin Pharmacol Ther*, **39**:288-292.

Jetter A, Kinzig-Schippers M, Skott A, Lazar A, Tomalik-Scharte D, Kirchheiner J, Walchner-Bonjean M, Hering U, Jakob V, Rodamer M, Jabrane W, Kasel D, Brockmoller J, Fuhr U and Sorgel F (2004) Cytochrome P450 2C9 phenotyping using low-dose tolbutamide. *Eur J Clin Pharmacol*, **60**:165-171.

Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, Day RO and McLachlan AJ (2005) Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br J Clin Pharmacol*, **59**:425-432.

Jiang ZP, Shu Y, Chen XP, Huang SL, Zhu RH, Wang W, He N and Zhou HH (2002) The role of CYP2C19 in amitriptyline N-demethylation in Chinese subjects. *Eur J Clin Pharmacol*, **58**:109-113.

Jin Y, Desta Z, Stearns V, Ward B, Ho H, Lee KH, Skaar T, Storniolo AM, Li L, Araba A, Blanchard R, Nguyen A, Ullmer L, Hayden J, Lemler S, Weinshilboum RM, Rae JM, Hayes DF and Flockhart DA (2005) CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst*, **97**:30-39.

- Joffe HV, Xu R, Johnson FB, Longtine J, Kucher N and Goldhaber SZ (2004) Warfarin dosing and cytochrome P450 2C9 polymorphisms. *Thromb Haemost*, 91:1123-1128.
- Johnson JA (2001) Drug target pharmacogenomics: an overview. *Am J Pharmacogenomics*, 1:271-281.
- Johnson JA and Lima JJ (2003) Drug receptor/effector polymorphisms and pharmacogenetics: current status and challenges. *Pharmacogenetics*, 13:525-534.
- Jones DR, Gorski JC, Haehner BD, O'Mara EM, Jr. and Hall SD (1996) Determination of cytochrome P450 3A4/5 activity in vivo with dextromethorphan N-demethylation. *Clin Pharmacol Ther*, 60:374-384.
- Jonker DM, Visser SA, van der Graaf PH, Voskuyl RA and Danhof M (2005) Towards a mechanism-based analysis of pharmacodynamic drug-drug interactions in vivo. *Pharmacol Ther*, 106:1-18.
- Jonsson EN and Sheiner LB (2002) More efficient clinical trials through use of scientific model-based statistical tests. *Clin Pharmacol Ther*, 72:603-614.
- Joseph PD, Guengerich FP and Miners JO (2005) "Phase I and phase II" Drug Metabolism: Terminology That we Should Phase out? *Drug Metabolism Reviews*, 37:575-580.
- Junghard O, Hassan-Alin M and Hasselgren G (2002) The effect of the area under the plasma concentration vs time curve and the maximum plasma concentration of esomeprazole on intragastric pH. *Eur J Clin Pharmacol*, 58:453-458.
- Kajinami K, Brousseau ME, Ordovas JM and Schaefer EJ (2004) CYP3A4 genotypes and plasma lipoprotein levels before and after treatment with atorvastatin in primary hypercholesterolemia. *Am J Cardiol*, 93:104-107.
- Kakihara S, Yoshimura R, Shinkai K, Matsumoto C, Goto M, Kaji K, Yamada Y, Ueda N, Ohmori O and Nakamura J (2005) Prediction of response to risperidone treatment with respect to plasma concentrations of risperidone, catecholamine metabolites, and polymorphism of cytochrome P450 2D6. *Int Clin Psychopharmacol*, 20:71-78.
- Kalow W (1986) Genetics of drug transformation. *Clin Biochem*, 19:76-82.
- Kalow W and Staron N (1957) On distribution and inheritance of atypical forms of human serum cholinesterase, as indicated by dibucaine numbers. *Can J Biochem Physiol*, 35:1305-1320.
- Kamali F, Edwards C, Butler TJ and Wynne HA (2000) The influence of (R)- and (S)-warfarin, vitamin K and vitamin K epoxide upon warfarin anticoagulation. *Thromb Haemost*, 84:39-42.
- Kamali F, Khan TI, King BP, Frearson R, Kesteven P, Wood P, Daly AK and Wynne H (2004) Contribution of age, body size, and CYP2C9 genotype to anticoagulant response to warfarin. *Clin Pharmacol Ther*, 75:204-212.

Kaneko A, Bergqvist Y, Taleo G, Kobayakawa T, Ishizaki T and Bjorkman A (1999a) Proguanil disposition and toxicity in malaria patients from Vanuatu with high frequencies of CYP2C19 mutations. *Pharmacogenetics*, 9:317-326.

Kaneko A, Lum JK, Yaviong L, Takahashi N, Ishizaki T, Bertilsson L, Kobayakawa T and Bjorkman A (1999b) High and variable frequencies of CYP2C19 mutations: medical consequences of poor drug metabolism in Vanuatu and other Pacific islands. *Pharmacogenetics*, 9:581-590.

Karam WG, Goldstein JA, Lasker JM and Ghanayem BI (1996) Human CYP2C19 is a major omeprazole 5-hydroxylase, as demonstrated with recombinant cytochrome P450 enzymes. *Drug Metab Dispos*, 24:1081-1087.

Kartunnen P, Tukiainen H, Silvasti M and Kolonen S (1987) Antitussive effect of dextromethorphan and dextromethorphan-salbutamol combination in healthy volunteers with artificially induced cough. *Respiration*, 52:49-53.

Katashima M, Yamamoto K, Tokuma Y, Hata T, Sawada Y and Iga T (1998) Comparative pharmacokinetic/pharmacodynamic analysis of proton pump inhibitors omeprazole, lansoprazole and pantoprazole, in humans. *Eur J Drug Metab Pharmacokinet*, 23:19-26.

Katsuki H, Nakamura C, Arimori K, Fujiyama S and Nakano M (1997) Genetic polymorphism of CYP2C19 and lansoprazole pharmacokinetics in Japanese subjects. *Eur J Clin Pharmacol*, 52:391-396.

Kendall MJ (2003) Review article: esomeprazole--the first proton pump inhibitor to be developed as an isomer. *Aliment Pharmacol Ther*, 17 (S1):1-4.

Kerry NL, Somogyi AA, Bochner F and Mikus G (1994) The role of CYP2D6 in primary and secondary oxidative metabolism of dextromethorphan: in vitro studies using human liver microsomes. *Br J Clin Pharmacol*, 38:243-248.

Khan T, Wynne H, Wood P, Torrance A, Hankey C, Avery P, Kesteven P and Kamali F (2004) Dietary vitamin K influences intra-individual variability in anticoagulant response to warfarin. *Br J Haematol*, 124:348-354.

Kim KA, Shon JH, Park JY, Yoon YR, Kim MJ, Yun DH, Kim MK, Cha IJ, Hyun MH and Shin JG (2002) Enantioselective disposition of lansoprazole in extensive and poor metabolizers of CYP2C19. *Clin Pharmacol Ther*, 72:90-99.

King BP, Khan TI, Aithal GP, Kamali F and Daly AK (2004) Upstream and coding region CYP2C9 polymorphisms: correlation with warfarin dose and metabolism. *Pharmacogenetics*, 14:813-822.

Kirchheiner J, Bauer S, Meineke I, Rohde W, Prang V, Meisel C, Roots I and Brockmoller J (2002a) Impact of CYP2C9 and CYP2C19 polymorphisms on



tolbutamide kinetics and the insulin and glucose response in healthy volunteers. *Pharmacogenetics*, 12:101-109.

Kirchheiner J, Brockmoller J, Meineke I, Bauer S, Rohde W, Meisel C and Roots I (2002b) Impact of CYP2C9 amino acid polymorphisms on glyburide kinetics and on the insulin and glucose response in healthy volunteers. *Clin Pharmacol Ther*, 71:286-296.

Kirchheiner J, Heesch C, Bauer S, Meisel C, Seringer A, Goldammer M, Tzvetkov M, Meineke I, Roots I and Brockmoller J (2004a) Impact of the ultrarapid metabolizer genotype of cytochrome P450 2D6 on metoprolol pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther*, 76:302-312.

Kirchheiner J, Klein C, Meineke I, Sasse J, Zanger UM, Murdter TE, Roots I and Brockmoller J (2003a) Bupropion and 4-OH-bupropion pharmacokinetics in relation to genetic polymorphisms in CYP2B6. *Pharmacogenetics*, 13:619-626.

Kirchheiner J, Kudlicz D, Meisel C, Bauer S, Meineke I, Roots I and Brockmoller J (2003b) Influence of CYP2C9 polymorphisms on the pharmacokinetics and cholesterol-lowering activity of (-)-3S,5R-fluvastatin and (+)-3R,5S-fluvastatin in healthy volunteers. *Clin Pharmacol Ther*, 74:186-194.

Kirchheiner J, Meineke I, Freytag G, Meisel C, Roots I and Brockmoller J (2002c) Enantiospecific effects of cytochrome P450 2C9 amino acid variants on ibuprofen pharmacokinetics and on the inhibition of cyclooxygenases 1 and 2. *Clin Pharmacol Ther*, 72:62-75.

Kirchheiner J, Meineke I, Muller G, Bauer S, Rohde W, Meisel C, Roots I and Brockmoller J (2004b) Influence of CYP2C9 and CYP2D6 polymorphisms on the pharmacokinetics of nateglinide in genotyped healthy volunteers. *Clin Pharmacokinet*, 43:267-278.

Kirchheiner J, Meineke I, Muller G, Roots I and Brockmoller J (2002d) Contributions of CYP2D6, CYP2C9 and CYP2C19 to the biotransformation of E- and Z-doxepin in healthy volunteers. *Pharmacogenetics*, 12:571-580.

Kirchheiner J, Meineke I, Steinbach N, Meisel C, Roots I and Brockmoller J (2003c) Pharmacokinetics of diclofenac and inhibition of cyclooxygenases 1 and 2: no relationship to the CYP2C9 genetic polymorphism in humans. *Br J Clin Pharmacol*, 55:51-61.

Kirchheiner J, Sasse J, Meineke I, Roots I and Brockmoller J (2003d) Trimipramine pharmacokinetics after intravenous and oral administration in carriers of CYP2D6 genotypes predicting poor, extensive and ultrahigh activity. *Pharmacogenetics*, 13:721-728.

Kirchheiner J, Stormer E, Meisel C, Steinbach N, Roots I and Brockmoller J (2003e) Influence of CYP2C9 genetic polymorphisms on pharmacokinetics of celecoxib and its metabolites. *Pharmacogenetics*, 13:473-480.

Kirchheiner J, Ufer M, Walter EC, Kammerer B, Kahlich R, Meisel C, Schwab M, Gleiter CH, Rane A, Roots I and Brockmoller J (2004c) Effects of CYP2C9 polymorphisms on the pharmacokinetics of R- and S-phenprocoumon in healthy volunteers. *Pharmacogenetics*, 14:19-26.

Kita T, Tanigawara Y, Aoyama N, Hohda T, Saijoh Y, Komada F, Sakaeda T, Okumura K, Sakai T and Kasuga M (2001) CYP2C19 genotype related effect of omeprazole on intragastric pH and antimicrobial stability. *Pharm Res*, 18:615-621.

Kivisto KT, Niemi M, Schaeffeler E, Pitkala K, Tilvis R, Fromm MF, Schwab M, Eichelbaum M and Strandberg T (2004) Lipid-lowering response to statins is affected by CYP3A5 polymorphism. *Pharmacogenetics*, 14:523-525.

Klotz U, Schwab M and Treiber G (2004) CYP2C19 polymorphism and proton pump inhibitors. *Basic Clin Pharmacol Toxicol*, 95:2-8.

Klotz U and Ziegler G (1982) Physiologic and temporal variation in hepatic elimination of midazolam. *Clin Pharmacol Ther*, 32:107-112.

Knodell RG, Dubey RK, Wilkinson GR and Guengerich FP (1988) Oxidative metabolism of hexobarbital in human liver: relationship to polymorphic S-mephenytoin 4-hydroxylation. *J Pharmacol Exp Ther*, 245:845-849.

Knoester PD, Jonker DM, Van Der Hoeven RT, Vermeij TA, Edelbroek PM, Brekelmans GJ and de Haan GJ (2002) Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. *Br J Clin Pharmacol*, 53:501-507.

Kobayashi K, Morita J, Chiba K, Wanibuchi A, Kimura M, Irie S, Urae A and Ishizaki T (2004) Pharmacogenetic roles of CYP2C19 and CYP2B6 in the metabolism of R- and S-mephobarbital in humans. *Pharmacogenetics*, 14:549-556.

Koopmans R, Dingemans J, Danhof M, Horsten GP and van Boxtel CJ (1988) Pharmacokinetic-pharmacodynamic modeling of midazolam effects on the human central nervous system. *Clin Pharmacol Ther*, 44:14-22.

Koyama E, Tanaka T, Chiba K, Kawakatsu S, Morinobu S, Totsuka S and Ishizaki T (1996) Steady-state plasma concentrations of imipramine and desipramine in relation to S-mephenytoin 4'-hydroxylation status in Japanese depressive patients. *J Clin Psychopharmacol*, 16:286-293.

Kuang T-Y, Lou Y-C and Tao P (1994) Pharmacokinetics of propafenone and its relationship with debrisoquin and mephenytoin metabolism polymorphisms in healthy Chinese volunteers. *Chinese Journal of Pharmacology and Toxicology*, 8:13.

Kuehl P, Zhang J, Lin Y, Lamba J, Assem M, Schuetz J, Watkins PB, Daly A, Wrighton SA, Hall SD, Maurel P, Relling M, Brimer C, Yasuda K, Venkataramanan R, Strom S, Thummel K, Boguski MS and Schuetz E (2001) Sequence diversity in CYP3A

promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat Genet*, **27**:383-391.

Kupfer A and Branch RA (1985) Stereoselective mephobarbital hydroxylation cosegregates with mephenytoin hydroxylation. *Clin Pharmacol Ther*, **38**:414-418.

Kvasz M, Allen IE, Gordon MJ, Ro EY, Estok R, Olkin I and Ross SD (2000) Adverse drug reactions in hospitalized patients: A critique of a meta-analysis. *MedGenMed*, **2**:E3.

Kvist EE, Al-Shurbaji A, Dahl ML, Nordin C, Alvan G and Stahle L (2001) Quantitative pharmacogenetics of nortriptyline: a novel approach. *Clin Pharmacokinet*, **40**:869-877.

Laine K, Anttila M, Nyman L, Wahlberg A and Bertilsson L (2001) CYP2C19 polymorphism is not important for the in vivo metabolism of selegiline. *Eur J Clin Pharmacol*, **57**:137-142.

Lane HY, Liu YC, Huang CL, Chang YC, Wu PL, Lu CT and Chang WH (2006) Risperidone-related weight gain: genetic and nongenetic predictors. *J Clin Psychopharmacol*, **26**:128-134.

Lasker JM, Wester MR, Aramsombatdee E and Raucy JL (1998) Characterization of CYP2C19 and CYP2C9 from human liver: respective roles in microsomal tolbutamide, S-mephenytoin, and omeprazole hydroxylations. *Arch Biochem Biophys*, **353**:16-28.

Lazarou J, Pomeranz BH and Corey PN (1998) Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *Jama*, **279**:1200-1205.

Le Meur Y, Djebli N, Szelag JC, Hoizey G, Toupance O, Rerolle JP and Marquet P (2006) CYP3A5\*3 influences sirolimus oral clearance in de novo and stable renal transplant recipients. *Clin Pharmacol Ther*, **80**:51-60.

Lee CR, Goldstein JA and Pieper JA (2002a) Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. *Pharmacogenetics*, **12**:251-263.

Lee CR, Pieper JA, Frye RF, Hinderliter AL, Blaisdell JA and Goldstein JA (2003) Tolbutamide, flurbiprofen, and losartan as probes of CYP2C9 activity in humans. *J Clin Pharmacol*, **43**:84-91.

Lee CR, Pieper JA, Hinderliter AL, Blaisdell JA and Goldstein JA (2002b) Evaluation of cytochrome P4502C9 metabolic activity with tolbutamide in CYP2C91 heterozygotes. *Clin Pharmacol Ther*, **72**:562-571.

Lee EJ and Williams KM (1990) Chirality. Clinical pharmacokinetic and pharmacodynamic considerations. *Clin Pharmacokinet*, **18**:339-345.

Lee JT, Kroemer HK, Silberstein DJ, Funck-Brentano C, Lineberry MD, Wood AJ, Roden DM and Woosley RL (1990) The role of genetically determined polymorphic drug metabolism in the beta-blockade produced by propafenone. *N Engl J Med*, **322**:1764-1768.

Lennard MS, Tucker GT, Silas JH, Freestone S, Ramsay LE and Woods HF (1983) Differential stereoselective metabolism of metoprolol in extensive and poor debrisoquin metabolizers. *Clin Pharmacol Ther*, **34**:732-737.

Lepper ER, Baker SD, Permenter M, Ries N, van Schaik RH, Schenk PW, Price DK, Ahn D, Smith NF, Cusatis G, Ingersoll RG, Bates SE, Mathijssen RH, Verweij J, Figg WD and Sparreboom A (2005) Effect of common CYP3A4 and CYP3A5 variants on the pharmacokinetics of the cytochrome P450 3A phenotyping probe midazolam in cancer patients. *Clin Cancer Res*, **11**:7398-7404.

Li T, Lange LA, Li X, Susswein L, Bryant B, Malone R, Lange EM, Huang TY, Stafford DW and Evans JP (2006) Polymorphisms in the VKORC1 gene are strongly associated with warfarin dosage requirements in patients receiving anticoagulation. *J Med Genet*, **43**:740-744.

Liggett SB (2000) The pharmacogenetics of beta2-adrenergic receptors: relevance to asthma. *J Allergy Clin Immunol*, **105**:S487-492.

Lilja JJ, Backman JT and Neuvonen PJ (2005) Effect of gemfibrozil on the pharmacokinetics and pharmacodynamics of racemic warfarin in healthy subjects. *Br J Clin Pharmacol*, **59**:433-439.

Lin JH and Lu AY (1997) Role of pharmacokinetics and metabolism in drug discovery and development. *Pharmacol Rev*, **49**:403-449.

Lin YS, Dowling AL, Quigley SD, Farin FM, Zhang J, Lamba J, Schuetz EG and Thummel KE (2002) Co-regulation of CYP3A4 and CYP3A5 and contribution to hepatic and intestinal midazolam metabolism. *Mol Pharmacol*, **62**:162-172.

Lind T, Cederberg C, Ekenved G, Haglund U and Olbe L (1983) Effect of omeprazole--a gastric proton pump inhibitor--on pentagastrin stimulated acid secretion in man. *Gut*, **24**:270-276.

Lindh JD, Lundgren S, Holm L, Alfredsson L and Rane A (2005) Several-fold increase in risk of overanticoagulation by CYP2C9 mutations. *Clin Pharmacol Ther*, **78**:540-550.

Lipsky MS and Sharp LK (2001) From idea to market: the drug approval process. *J Am Board Fam Pract*, **14**:362-367.

Liu J, Liu ZQ, Tan ZR, Chen XP, Wang LS, Zhou G and Zhou HH (2003) Gly389Arg polymorphism of beta1-adrenergic receptor is associated with the cardiovascular response to metoprolol. *Clin Pharmacol Ther*, **74**:372-379.

Liu ZQ, Cheng ZN, Huang SL, Chen XP, Ou-Yang DS, Jiang CH and Zhou HH (2001) Effect of the CYP2C19 oxidation polymorphism on fluoxetine metabolism in Chinese healthy subjects. *Br J Clin Pharmacol*, **52**:96-99.

Loboz KK, Gross AS, Williams KM, Liauw WS, Day RO, Blievernicht JK, Zanger UM and McLachlan AJ (2006) Cytochrome P450 2B6 activity as measured by bupropion hydroxylation: effect of induction by rifampin and ethnicity. *Clin Pharmacol Ther*, **80**:75-84.

Loebstein R, Yonath H, Peleg D, Almog S, Rotenberg M, Lubetsky A, Roitelman J, Harats D, Halkin H and Ezra D (2001) Interindividual variability in sensitivity to warfarin--Nature or nurture? *Clin Pharmacol Ther*, **70**:159-164.

Lotsch J, Skarke C, Grosch S, Darimont J, Schmidt H and Geisslinger G (2002) The polymorphism A118G of the human mu-opioid receptor gene decreases the pupil constrictory effect of morphine-6-glucuronide but not that of morphine. *Pharmacogenetics*, **12**:3-9.

Lutz U, Volkel W, Lutz RW and Lutz WK (2004) LC-MS/MS analysis of dextromethorphan metabolism in human saliva and urine to determine CYP2D6 phenotype and individual variability in N-demethylation and glucuronidation. *J Chromatogr B Analyt Technol Biomed Life Sci*, **813**:217-225.

Macphee IA, Fredericks S, Mohamed M, Moreton M, Carter ND, Johnston A, Goldberg L and Holt DW (2005) Tacrolimus pharmacogenetics: the CYP3A5\*1 allele predicts low dose-normalized tacrolimus blood concentrations in whites and South Asians. *Transplantation*, **79**:499-502.

Mahgoub A, Idle JR, Dring LG, Lancaster R and Smith RL (1977) Polymorphic hydroxylation of Debrisoquine in man. *Lancet*, **2**:584-586.

Mamiya K, Hadama A, Yukawa E, Ieiri I, Otsubo K, Ninomiya H, Tashiro N and Higuchi S (2000) CYP2C19 polymorphism effect on phenobarbitone. Pharmacokinetics in Japanese patients with epilepsy: analysis by population pharmacokinetics. *Eur J Clin Pharmacol*, **55**:821-825.

Mamiya K, Ieiri I, Shimamoto J, Yukawa E, Imai J, Ninomiya H, Yamada H, Otsubo K, Higuchi S and Tashiro N (1998) The effects of genetic polymorphisms of CYP2C9 and CYP2C19 on phenytoin metabolism in Japanese adult patients with epilepsy: studies in stereoselective hydroxylation and population pharmacokinetics. *Epilepsia*, **39**:1317-1323.

Mandema JW, Tuk B, van Steveninck AL, Breimer DD, Cohen AF and Danhof M (1992) Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite alpha-hydroxymidazolam in healthy volunteers. *Clin Pharmacol Ther*, **51**:715-728.

Mankowski DC, Lawton MP and Ekins S (2000) Characterization of transgenic mouse strains using six human hepatic cytochrome P450 probe substrates. *Xenobiotica*, **30**:745-754.

- Margaglione M, Colaizzo D, D'Andrea G, Brancaccio V, Ciampa A, Grandone E and Di Minno G (2000) Genetic modulation of oral anticoagulation with warfarin. *Thromb Haemost*, **84**:775-778.
- Martinez C, Garcia-Martin E, Blanco G, Gamito FJ, Ladero JM and Agundez JA (2005) The effect of the cytochrome P450 CYP2C8 polymorphism on the disposition of (R)-ibuprofen enantiomer in healthy subjects. *Br J Clin Pharmacol*, **59**:62-69.
- Masica AL, Mayo G and Wilkinson GR (2004) In vivo comparisons of constitutive cytochrome P450 3A activity assessed by alprazolam, triazolam, and midazolam. *Clin Pharmacol Ther*, **76**:341-349.
- Mathijssen RH, Marsh S, Karlsson MO, Xie R, Baker SD, Verweij J, Sparreboom A and McLeod HL (2003) Irinotecan pathway genotype analysis to predict pharmacokinetics. *Clin Cancer Res*, **9**:3246-3253.
- Matthys H, Bleicher B and Bleicher U (1983) Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. *J Int Med Res*, **11**:92-100.
- McGinnity DF, Parker AJ, Soars M and Riley RJ (2000) Automated definition of the enzymology of drug oxidation by the major human drug metabolizing cytochrome P450s. *Drug Metab Dispos*, **28**:1327-1334.
- Meibohm B and Derendorf H (1997) Basic concepts of pharmacokinetic /pharmacodynamic (PK/PD) modelling. *Int J Clin Pharmacol Ther*, **35**:401-413.
- Meyer UA (1991) Genotype or Phenotype: the Definition of a Pharmacogenetic Polymorphism. *Pharmacogenetics*, **1**:66-67.
- Mihara K, Otani K, Tybring G, Dahl ML, Bertilsson L and Kaneko S (1997) The CYP2D6 genotype and plasma concentrations of mianserin enantiomers in relation to therapeutic response to mianserin in depressed Japanese patients. *J Clin Psychopharmacol*, **17**:467-471.
- Min DI, Ellingrod VL, Marsh S and McLeod H (2004) CYP3A5 polymorphism and the ethnic differences in cyclosporine pharmacokinetics in healthy subjects. *Ther Drug Monit*, **26**:524-528.
- Miura M, Tada H, Yasui-Furukori N, Uno T, Sugawara K, Tateishi T and Suzuki T (2004) Pharmacokinetic differences between the enantiomers of lansoprazole and its metabolite, 5-hydroxylansoprazole, in relation to CYP2C19 genotypes. *Eur J Clin Pharmacol*, **60**:623-628.
- Miyoshi M, Mizuno M, Ishiki K, Nagahara Y, Maga T, Torigoe T, Nasu J, Okada H, Yokota K, Oguma K and Tsuji T (2001) A randomized open trial for comparison of proton pump inhibitors, omeprazole versus rabeprazole, in dual therapy for Helicobacter pylori infection in relation to CYP2C19 genetic polymorphism. *J Gastroenterol Hepatol*, **16**:723-728.

Moghadamnia AA, Rostami-Hodjegan A, Abdul-Manap R, Wright CE, Morice AH and Tucker GT (2003) Physiologically based modelling of inhibition of metabolism and assessment of the relative potency of drug and metabolite: dextromethorphan vs. dextrorphan using quinidine inhibition. *Br J Clin Pharmacol*, **56**:57-67.

Molden E, Johansen PW, Boe GH, Bergan S, Christensen H, Rugstad HE, Rootwelt H, Reubsaet L and Lehne G (2002) Pharmacokinetics of diltiazem and its metabolites in relation to CYP2D6 genotype. *Clin Pharmacol Ther*, **72**:333-342.

Morin S, Bodin L, Lorient MA, Thijssen HH, Robert A, Strabach S, Verstuyft C, Tregouet DA, Dubert L, Laurent-Puig P, Funck-Brentano C, Jaillon P, Beaune PH and Becquemont L (2004) Pharmacogenetics of acenocoumarol pharmacodynamics. *Clin Pharmacol Ther*, **75**:403-414.

Morin S, Lorient MA, Poirier JM, Tenneze L, Beaune PH, Funck-Brentano C, Jaillon P and Becquemont L (2001) Is diclofenac a valuable CYP2C9 probe in humans? *Eur J Clin Pharmacol*, **56**:793-797.

Morinobu S, Tanaka T, Kawakatsu S, Totsuka S, Koyama E, Chiba K, Ishizaki T and Kubota T (1997) Effects of genetic defects in the CYP2C19 gene on the N-demethylation of imipramine, and clinical outcome of imipramine therapy. *Psychiatry Clin Neurosci*, **51**:253-257.

Moschitto LJ and Greenblatt DJ (1983) Concentration-independent plasma protein binding of benzodiazepines. *J Pharm Pharmacol*, **35**:179-180.

Mould DR, DeFeo TM, Reece S, Milla G, Limjuco R, Crews T, Choma N and Patel IH (1995) Simultaneous modeling of the pharmacokinetics and pharmacodynamics of midazolam and diazepam. *Clin Pharmacol Ther*, **58**:35-43.

Mouly SJ, Matheny C, Paine MF, Smith G, Lamba J, Lamba V, Pusek SN, Schuetz EG, Stewart PW and Watkins PB (2005) Variation in oral clearance of saquinavir is predicted by CYP3A5\*1 genotype but not by enterocyte content of cytochrome P450 3A5. *Clin Pharmacol Ther*, **78**:605-618.

Murphy GM, Jr., Kremer C, Rodrigues HE and Schatzberg AF (2003) Pharmacogenetics of antidepressant medication intolerance. *Am J Psychiatry*, **160**:1830-1835.

Naganuma M, Shiga T, Nishikata K, Tsuchiya T, Kasanuki H and Fujii E (2001) Role of desethylamiodarone in the anticoagulant effect of concurrent amiodarone and warfarin therapy. *J Cardiovasc Pharmacol Ther*, **6**:363-367.

Nagashima R, O'Reilly RA and Levy G (1969) Kinetics of pharmacologic effects in man: the anticoagulant action of warfarin. *Clin Pharmacol Ther*, **10**:22-35.

Nakajima M, Fujiki Y, Kyo S, Kanaya T, Nakamura M, Maida Y, Tanaka M, Inoue M and Yokoi T (2005) Pharmacokinetics of paclitaxel in ovarian cancer patients and

genetic polymorphisms of CYP2C8, CYP3A4, and MDR1. *J Clin Pharmacol*, 45:674-682.

Nakajima Y, Yoshitani T, Fukushima-Uesaka H, Saito Y, Kaniwa N, Kurose K, Ozawa S, Aoyagi N, Kamatani N, Yamamoto N, Kunitoh H, Ohe Y, Tamura T, Yoshida T, Minami H, Saijo N, Katori N and Sawada J (2006) Impact of the haplotype CYP3A4\*16B harboring the Thr185Ser substitution on paclitaxel metabolism in Japanese patients with cancer. *Clin Pharmacol Ther*, 80:179-191.

Nebert DW (1999) Pharmacogenetics and pharmacogenomics: why is this relevant to the clinical geneticist? *Clin Genet*, 56:247-258.

Neymour R (1993) Gastric pH and stomach contents. *Anesth Analg*, 76:906-907.

Nielsen F, Rosholm JU and Broesen K (1995) Lack of relationship between quinidine pharmacokinetics and the sparteine oxidation polymorphism. *Eur J Clin Pharmacol*, 48:501-504.

Niemi M, Cascorbi I, Timm R, Kroemer HK, Neuvonen PJ and Kivisto KT (2002) Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. *Clin Pharmacol Ther*, 72:326-332.

Niemi M, Leathart JB, Neuvonen M, Backman JT, Daly AK and Neuvonen PJ (2003) Polymorphism in CYP2C8 is associated with reduced plasma concentrations of repaglinide. *Clin Pharmacol Ther*, 74:380-387.

Nieminen T, Uusitalo H, Maenpaa J, Turjanmaa V, Rane A, Lundgren S, Ropo A, Rontu R, Lehtimaki T and Kahonen M (2005) Polymorphisms of genes CYP2D6, ADRB1 and GNAS1 in pharmacokinetics and systemic effects of ophthalmic timolol. A pilot study. *Eur J Clin Pharmacol*, 61:811-819.

Nishimura N, Naora K, Hirano H and Iwamoto K (1998) Effects of Sho-saiko-to on the pharmacokinetics and pharmacodynamics of tolbutamide in rats. *J Pharm Pharmacol*, 50:231-236.

Niu C, Luo J and Wang X (2004) Effects of cytochrome P450 2C19 genetic polymorphism on the acid-suppression of rabeprazole. *Chinese journal of gastroenterology*, 9:17-20.

O'Reilly RA (1974) Studies on the optical enantiomorphs of warfarin in man. *Clin Pharmacol Ther*, 16:348-354.

Oates NS, Shah RR, Idle JR and Smith RL (1983) Influence of oxidation polymorphism on phenformin kinetics and dynamics. *Clin Pharmacol Ther*, 34:827-834.

Obach RS (1999) Prediction of human clearance of twenty-nine drugs from hepatic microsomal intrinsic clearance data: An examination of in vitro half-life approach and nonspecific binding to microsomes. *Drug Metab Dispos*, 27:1350-1359.



- Odani A, Hashimoto Y, Otsuki Y, Uwai Y, Hattori H, Furusho K and Inui K (1997) Genetic polymorphism of the CYP2C subfamily and its effect on the pharmacokinetics of phenytoin in Japanese patients with epilepsy. *Clin Pharmacol Ther*, **62**:287-292.
- Ohara K, Tanabu S, Ishibashi K, Ikemoto K, Yoshida K and Shibuya H (2003) CYP2D6\*10 alleles do not determine plasma fluvoxamine concentration/dose ratio in Japanese subjects. *Eur J Clin Pharmacol*, **58**:659-661.
- Ohkusa T, Maekawa T, Arakawa T, Nakajima M, Fujimoto K, Hoshino E, Mitachi Y, Hamada S, Mine T, Kawahara Y, Nagai T, Aoyama N, Yoshida N, Tadokoro K, Chida N, Konda Y, Seno H, Shimatani T, Inoue M and Sato N (2005) Effect of CYP2C19 polymorphism on the safety and efficacy of omeprazole in Japanese patients with recurrent reflux oesophagitis. *Aliment Pharmacol Ther*, **21**:1331-1339.
- Ohnishi A, Murakami S, Akizuki S, Mochizuki J, Echizen H and Takagi I (2005) In vivo metabolic activity of CYP2C19 and CYP3A in relation to CYP2C19 genetic polymorphism in chronic liver disease. *J Clin Pharmacol*, **45**:1221-1229.
- Otton SV, Schadel M, Cheung SW, Kaplan HL, Busto UE and Sellers EM (1993) CYP2D6 phenotype determines the metabolic conversion of hydrocodone to hydromorphone. *Clin Pharmacol Ther*, **54**:463-472.
- Ozdemir M, Crewe KH, Tucker GT and Rostami-Hodjegan A (2004) Assessment of in vivo CYP2D6 activity: differential sensitivity of commonly used probes to urine pH. *J Clin Pharmacol*, **44**:1398-1404.
- Paine MF, Hart HL, Ludington SS, Haining RL, Rettie AE and Zeldin DC (2006) The human intestinal cytochrome P450 "pie". *Drug Metab Dispos*, **34**:880-886.
- Paine MF, Khalighi M, Fisher JM, Shen DD, Kunze KL, Marsh CL, Perkins JD and Thummel KE (1997) Characterization of interintestinal and intrainestinal variations in human CYP3A-dependent metabolism. *J Pharmacol Exp Ther*, **283**:1552-1562.
- Palamanda J, Feng WW, Lin CC and Nomeir AA (2000) Stimulation of tolbutamide hydroxylation by acetone and acetonitrile in human liver microsomes and in a cytochrome P-450 2C9-reconstituted system. *Drug Metab Dispos*, **28**:38-43.
- Pan L, Vander Stichele R, Rosseel MT, Berlo JA, De Schepper N and Belpaire FM (1999) Effects of smoking, CYP2D6 genotype, and concomitant drug intake on the steady state plasma concentrations of haloperidol and reduced haloperidol in schizophrenic inpatients. *Ther Drug Monit*, **21**:489-497.
- Park JY, Kim KA, Park PW, Lee OJ, Kang DK, Shon JH, Liu KH and Shin JG (2006) Effect of CYP3A5\*3 genotype on the pharmacokinetics and pharmacodynamics of alprazolam in healthy subjects. *Clin Pharmacol Ther*, **79**:590-599.
- Peart GF, Boutagy J and Shenfield GM (1987) Lack of relationship between tolbutamide metabolism and debrisoquine oxidation phenotype. *Eur J Clin Pharmacol*, **33**:397-402.

Pedersen RS, Damkier P and Brosen K (2006) Enantioselective pharmacokinetics of tramadol in CYP2D6 extensive and poor metabolizers. *Eur J Clin Pharmacol*, **62**:513-521.

Perini JA, Vianna-Jorge R, Brogliato AR and Suarez-Kurtz G (2005) Influence of CYP2C9 genotypes on the pharmacokinetics and pharmacodynamics of piroxicam. *Clin Pharmacol Ther*, **78**:362-369.

Peyvandi F, Spreafico M, Siboni SM, Moia M and Mannucci PM (2004) CYP2C9 genotypes and dose requirements during the induction phase of oral anticoagulant therapy. *Clin Pharmacol Ther*, **75**:198-203.

Pieri L, Schaffner R, Scherschlicht R, Polc P, Sepinwall J, Davidson A, Mohler H, Cumin R, Da Prada M, Burkard WP, Keller HH, Muller RK, Gerold M, Pieri M, Cook L and Haefely W (1981) Pharmacology of midazolam. *Arzneimittelforschung*, **31**:2180-2201.

Polonsky KS, Licinio-Paixao J, Given BD, Pugh W, Rue P, Galloway J, Karrison T and Frank B (1986) Use of biosynthetic human C-peptide in the measurement of insulin secretion rates in normal volunteers and type I diabetic patients. *J Clin Invest*, **77**:98-105.

Pope LE, Khalil MH, Berg JE, Stiles M, Yakatan GJ and Sellers EM (2004) Pharmacokinetics of dextromethorphan after single or multiple dosing in combination with quinidine in extensive and poor metabolizers. *J Clin Pharmacol*, **44**:1132-1142.

Poulin P and Theil FP (2002) Prediction of pharmacokinetics prior to in vivo studies. II. Generic physiologically based pharmacokinetic models of drug disposition. *J Pharm Sci*, **91**:1358-1370.

Powers WF, Abbrecht PH and Covell DG (1980) Systems and microcomputer approach to anticoagulant therapy. *IEEE Trans Biomed Eng*, **27**:520-523.

Priskorn M, Sidhu JS, Larsen F, Davis JD, Khan AZ and Rolan PE (1997) Investigation of multiple dose citalopram on the pharmacokinetics and pharmacodynamics of racemic warfarin. *Br J Clin Pharmacol*, **44**:199-202.

Proctor NJ, Tucker GT and Rostami-Hodjegan A (2004) Predicting drug clearance from recombinantly expressed CYPs: intersystem extrapolation factors. *Xenobiotica*, **34**:151-178.

Qiao HL, Hu YR, Tian X, Jia LJ, Gao N, Zhang LR and Guo YZ (2006) Pharmacokinetics of three proton pump inhibitors in Chinese subjects in relation to the CYP2C19 genotype. *Eur J Clin Pharmacol*, **62**:107-112.

Qin XP, Xie HG, Wang W, He N, Huang SL, Xu ZH, Ou-Yang DS, Wang YJ and Zhou HH (1999) Effect of the gene dosage of CgammaP2C19 on diazepam metabolism in Chinese subjects. *Clin Pharmacol Ther*, **66**:642-646.

- Rane A, Wilkinson GR and Shand DG (1977) Prediction of hepatic extraction ratio from in vitro measurement of intrinsic clearance. *J Pharmacol Exp Ther*, **200**:420-424.
- Rau T, Heide R, Bergmann K, Wuttke H, Werner U, Feifel N and Eschenhagen T (2002) Effect of the CYP2D6 genotype on metoprolol metabolism persists during long-term treatment. *Pharmacogenetics*, **12**:465-472.
- Regardh CG, Andersson T, Lagerstrom PO, Lundborg P and Skanberg I (1990) The pharmacokinetics of omeprazole in humans--a study of single intravenous and oral doses. *Ther Drug Monit*, **12**:163-172.
- Rendell M (2004) Advances in diabetes for the millennium: drug therapy of type 2 diabetes. *MedGenMed*, **6**:9.
- Rendic S (2002) Summary of information on human CYP enzymes: human P450 metabolism data. *Drug Metab Rev*, **34**:83-448.
- Rettie AE, Korzekwa KR, Kunze KL, Lawrence RF, Eddy AC, Aoyama T, Gelboin HV, Gonzalez FJ and Trager WF (1992) Hydroxylation of warfarin by human cDNA-expressed cytochrome P-450: a role for P-450C9 in the etiology of (S)-warfarin-drug interactions. *Chem Res Toxicol*, **5**:54-59.
- Rettie AE, Wienkers LC, Gonzalez FJ, Trager WF and Korzekwa KR (1994) Impaired (S)-warfarin metabolism catalysed by the R144C allelic variant of CYP2C9. *Pharmacogenetics*, **4**:39-42.
- Riedel M, Schwarz MJ, Strassnig M, Spellmann I, Muller-Arends A, Weber K, Zach J, Muller N and Moller HJ (2005) Risperidone plasma levels, clinical response and side-effects. *Eur Arch Psychiatry Clin Neurosci*, **255**:261-268.
- Rolan P, Atkinson AJ, Jr. and Lesko LJ (2003) Use of biomarkers from drug discovery through clinical practice: report of the Ninth European Federation of Pharmaceutical Sciences Conference on Optimizing Drug Development. *Clin Pharmacol Ther*, **73**:284-291.
- Rooney KF, Snoeck E and Watson PH (2001) Modelling and simulation in clinical drug development. *Drug Discov Today*, **6**:802-806.
- Rosemary J, Surendiran A, Rajan S, Shashindran CH and Adithan C (2006) Influence of the CYP2C9 AND CYP2C19 polymorphisms on phenytoin hydroxylation in healthy individuals from south India. *Indian J Med Res*, **123**:665-670.
- Rostami-Hodjegan A, Abdul-Manap R, Wright CE, Tucker GT and Morice AH (2001) The placebo response to citric acid-induced cough: pharmacodynamics and gender differences. *Pulm Pharmacol Ther*, **14**:315-319.
- Rostami-Hodjegan A, Peacey SR, George E, Heller SR and Tucker GT (1998) Population-based modeling to demonstrate extrapancreatic effects of tolbutamide. *Am J Physiol*, **274**:E758-771.

- Rostami-Hodjegan A and Tucker G (2004) 'In silico' simulations to assess the 'in vivo' consequences of 'in vitro' metabolic drug-drug interactions. *Drug Discovery Today: Technologies*, **1**:441-448.
- Rostami-Hodjegan A and Tucker GT (2002) The effects of portal shunts on intestinal cytochrome P450 3A activity. *Hepatology*, **35**:1549-1550; author reply 1550-1541.
- Rowland M and Tozer TN (1995) *Clinical Pharmacokinetics: Concepts and Applications*, third edition. Lippincott Williams & Wilkins, Philadelphia.
- Rowland-Yeo K, Rostami-Hodjegan A and Tucker GT (2004) Abundance of cytochromes P450 in human liver: a meta-analysis. *Br J Clin Pharmacol*, **57**:687-688.
- Sachs G, Shin JM, Briving C, Wallmark B and Hersey S (1995) The pharmacology of the gastric acid pump: the H<sup>+</sup>,K<sup>+</sup> ATPase. *Annu Rev Pharmacol Toxicol*, **35**:277-305.
- Sachse C, Brockmoller J, Bauer S and Roots I (1997) Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. *Am J Hum Genet*, **60**:284-295.
- Sagar M, Seensalu R, Tybring G, Dahl ML and Bertilsson L (1998) CYP2C19 genotype and phenotype determined with omeprazole in patients with acid-related disorders with and without Helicobacter pylori infection. *Scand J Gastroenterol*, **33**:1034-1038.
- Sakai T, Aoyama N, Kita T, Sakaeda T, Nishiguchi K, Nishitora Y, Hohda T, Sirasaka D, Tamura T, Tanigawara Y, Kasuga M and Okumura K (2001) CYP2C19 genotype and pharmacokinetics of three proton pump inhibitors in healthy subjects. *Pharm Res*, **18**:721-727.
- Sandberg M, Johansson I, Christensen M, Rane A and Eliasson E (2004) The impact of CYP2C9 genetics and oral contraceptives on cytochrome P450 2C9 phenotype. *Drug Metab Dispos*, **32**:484-489.
- Schadel M, Wu D, Otton SV, Kalow W and Sellers EM (1995) Pharmacokinetics of dextromethorphan and metabolites in humans: influence of the CYP2D6 phenotype and quinidine inhibition. *J Clin Psychopharmacol*, **15**:263-269.
- Schalekamp T, Brasse BP, Roijers JF, Chahid Y, van Geest-Daalderop JH, de Vries-Goldschmeding H, van Wijk EM, Egberts AC and de Boer A (2006) VKORC1 and CYP2C9 genotypes and acenocoumarol anticoagulation status: interaction between both genotypes affects overanticoagulation. *Clin Pharmacol Ther*, **80**:13-22.
- Scheinin H, Anttila M, Dahl ML, Karnani H, Nyman L, Taavitsainen P, Pelkonen O and Bertilsson L (1998) CYP2D6 polymorphism is not crucial for the disposition of selegiline. *Clin Pharmacol Ther*, **64**:402-411.
- Schellens JH, van der Wart JH and Breimer DD (1990) Relationship between mephenytoin oxidation polymorphism and phenytoin, methylphenytoin and

phenobarbitone hydroxylation assessed in a phenotyped panel of healthy subjects. *Br J Clin Pharmacol*, 29:665-671.

Schmid E and Smith D (2005) Is declining innovation in the pharmaceutical industry a myth? *Drug Discovery Today*, 10:1031-1039.

Schmider J, Greenblatt DJ, Fogelman SM, von Moltke LL and Shader RI (1997) Metabolism of dextromethorphan in vitro: involvement of cytochromes P450 2D6 and 3A3/4, with a possible role of 2E1. *Biopharm Drug Dispos*, 18:227-240.

Schwab M, Schaeffeler E, Klotz U and Treiber G (2004) CYP2C19 polymorphism is a major predictor of treatment failure in white patients by use of lansoprazole-based quadruple therapy for eradication of *Helicobacter pylori*. *Clin Pharmacol Ther*, 76:201-209.

Schwabedissen CM, Mevissen V, Schmitz F, Woodruff S, Langebartels G, Rau T, Zerres K, Hoffmann R and Ortlepp JR (2006) Obesity is associated with a slower response to initial phenprocoumon therapy whereas CYP2C9 genotypes are not. *Eur J Clin Pharmacol*, 62:713-720.

Sconce EA, Khan TI, Wynne HA, Avery P, Monkhouse L, King BP, Wood P, Kesteven P, Daly AK and Kamali F (2005) The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. *Blood*, 106:2329-2333.

Scordo MG, Pengo V, Spina E, Dahl ML, Gusella M and Padrini R (2002) Influence of CYP2C9 and CYP2C19 genetic polymorphisms on warfarin maintenance dose and metabolic clearance. *Clin Pharmacol Ther*, 72:702-710.

Sekino K, Kubota T, Okada Y, Yamada Y, Yamamoto K, Horiuchi R, Kimura K and Iga T (2003) Effect of the single CYP2C9\*3 allele on pharmacokinetics and pharmacodynamics of losartan in healthy Japanese subjects. *Eur J Clin Pharmacol*, 59:589-592.

Seo JS, Lee SY, Won KJ, Kim DJ, Sohn DS, Yang KM, Cho SH, Park JD, Lee KH and Kim HD (2000) Relationship between normal heart size and body indices in Korean. *J Korean Med Sci*, 15:641-646.

Shams ME, Arneith B, Hiemke C, Dragicevic A, Muller MJ, Kaiser R, Lackner K and Hartter S (2006) CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. *J Clin Pharm Ther*, 31:493-502.

Shargel L and Yu ABC (1999) *Applied Biopharmaceutics and Pharmacokinetics*, Fourth. Appleton and Lange, Stamford.

Sheiner LB (1969) Computer-aided long term anticoagulation therapy. *Computers and Biomedical Research*, 2:519-536.

- Shih PS and Huang JD (2002) Pharmacokinetics of midazolam and 1'-hydroxymidazolam in Chinese with different CYP3A5 genotypes. *Drug Metab Dispos*, **30**:1491-1496.
- Shimamoto J, Ieiri I, Urae A, Kimura M, Irie S, Kubota T, Chiba K, Ishizaki T, Otsubo K and Higuchi S (2000) Lack of differences in diclofenac (a substrate for CYP2C9) pharmacokinetics in healthy volunteers with respect to the single CYP2C9\*3 allele. *Eur J Clin Pharmacol*, **56**:65-68.
- Shimatani T, Inoue M, Kuroiwa T, Horikawa Y, Mieno H and Nakamura M (2003) Effect of omeprazole 10 mg on intragastric pH in three different CYP2C19 genotypes, compared with omeprazole 20 mg and lafutidine 20 mg, a new H2-receptor antagonist. *Aliment Pharmacol Ther*, **18**:1149-1157.
- Shimoda K, Someya T, Yokono A, Morita S, Hirokane G, Takahashi S and Okawa M (2002) The impact of CYP2C19 and CYP2D6 genotypes on metabolism of amitriptyline in Japanese psychiatric patients. *J Clin Psychopharmacol*, **22**:371-378.
- Shirai N, Furuta T, Moriyama Y, Okochi H, Kobayashi K, Takashima M, Xiao F, Kosuge K, Nakagawa K, Hanai H, Chiba K, Ohashi K and Ishizaki T (2001) Effects of CYP2C19 genotypic differences in the metabolism of omeprazole and rabeprazole on intragastric pH. *Aliment Pharmacol Ther*, **15**:1929-1937.
- Shon JH, Yoon YR, Kim KA, Lim YC, Lee KJ, Park JY, Cha IJ, Flockhart DA and Shin JG (2002) Effects of CYP2C19 and CYP2C9 genetic polymorphisms on the disposition of and blood glucose lowering response to tolbutamide in humans. *Pharmacogenetics*, **12**:111-119.
- Siguret V, Gouin I, Golmard JL, Geoffroy S, Andreux JP and Pautas E (2004) [Cytochrome P450 2C9 polymorphisms (CYP2C9) and warfarin maintenance dose in elderly patients]. *Rev Med Interne*, **25**:271-274.
- Sim SC, Risinger C, Dahl ML, Aklillu E, Christensen M, Bertilsson L and Ingelman-Sundberg M (2006) A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther*, **79**:103-113.
- Simonson SG, Martin PD, Mitchell PD, Lasseter K, Gibson G and Schneck DW (2005) Effect of rosuvastatin on warfarin pharmacodynamics and pharmacokinetics. *J Clin Pharmacol*, **45**:927-934.
- Sindrup SH, Broesen K, Hansen MG, Aaes-Jorgensen T, Overo KF and Gram LF (1993) Pharmacokinetics of citalopram in relation to the sparteine and the mephenytoin oxidation polymorphisms. *Ther Drug Monit*, **15**:11-17.
- Skjelbo E, Mutabingwa TK, Bygbjerg I, Nielsen KK, Gram LF and Broosen K (1996) Chloroguanide metabolism in relation to the efficacy in malaria prophylaxis and the S-mephenytoin oxidation in Tanzanians. *Clin Pharmacol Ther*, **59**:304-311.

Smith DA (2002) Hello Drug Discovery, I am from *insilico*, take me to your president. *Drug Discov Today*, 7:1080-1081.

Soga Y, Nishimura F, Ohtsuka Y, Araki H, Iwamoto Y, Naruishi H, Shiomi N, Kobayashi Y, Takashiba S, Shimizu K, Gomita Y and Oka E (2004) CYP2C polymorphisms, phenytoin metabolism and gingival overgrowth in epileptic subjects. *Life Sci*, 74:827-834.

Sohn DR, Kusaka M, Ishizaki T, Shin SG, Jang IJ, Shin JG and Chiba K (1992) Incidence of S-mephenytoin hydroxylation deficiency in a Korean population and the interphenotypic differences in diazepam pharmacokinetics. *Clin Pharmacol Ther*, 52:160-169.

Sohn DR, Kwon JT, Kim HK and Ishizaki T (1997) Metabolic disposition of lansoprazole in relation to the S-mephenytoin 4'-hydroxylation phenotype status. *Clin Pharmacol Ther*, 61:574-582.

Spigset O, Granberg K, Hagg S, Norstrom A and Dahlqvist R (1997) Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms. *Eur J Clin Pharmacol*, 52:129-133.

Steimer W, Zopf K, von Amelunxen S, Pfeiffer H, Bachofer J, Popp J, Messner B, Kissling W and Leucht S (2004) Allele-specific change of concentration and functional gene dose for the prediction of steady-state serum concentrations of amitriptyline and nortriptyline in CYP2C19 and CYP2D6 extensive and intermediate metabolizers. *Clin Chem*, 50:1623-1633.

Streetman DS, Bleakley JF, Kim JS, Nafziger AN, Leeder JS, Gaedigk A, Gotschall R, Kearns GL and Bertino JS, Jr. (2000) Combined phenotypic assessment of CYP1A2, CYP2C19, CYP2D6, CYP3A, N-acetyltransferase-2, and xanthine oxidase with the "Cooperstown cocktail". *Clin Pharmacol Ther*, 68:375-383.

Sullivan-Klose TH, Ghanayem BI, Bell DA, Zhang ZY, Kaminsky LS, Shenfield GM, Miners JO, Birkett DJ and Goldstein JA (1996) The role of the CYP2C9-Leu359 allelic variant in the tolbutamide polymorphism. *Pharmacogenetics*, 6:341-349.

Suzuki K, Yanagawa T, Shibasaki T, Kaniwa N, Hasegawa R and Tohkin M (2006) Effect of CYP2C9 genetic polymorphisms on the efficacy and pharmacokinetics of glimepiride in subjects with type 2 diabetes. *Diabetes Res Clin Pract*, 72:148-154.

Svec JM, Coleman RW, Mungall DR and Ludden TM (1985) Bayesian pharmacokinetic/pharmacodynamic forecasting of prothrombin response to warfarin therapy: preliminary evaluation. *Ther Drug Monit*, 7:174-180.

Swaisland HC, Cantarini MV, Fuhr R and Holt A (2006) Exploring the relationship between expression of cytochrome P450 enzymes and gefitinib pharmacokinetics. *Clin Pharmacokinet*, 45:633-644.

Tabrizi AR, Zehnbaauer BA, Borecki IB, McGrath SD, Buchman TG and Freeman BD (2002) The frequency and effects of cytochrome P450 (CYP) 2C9 polymorphisms in patients receiving warfarin. *J Am Coll Surg*, 194:267-273.

Tada H, Tsuchiya N, Satoh S, Kagaya H, Li Z, Sato K, Miura M, Suzuki T, Kato T and Habuchi T (2005) Impact of CYP3A5 and MDR1(ABCB1) C3435T polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients. *Transplant Proc*, 37:1730-1732.

Taguchi M, Nozawa T, Mizumaki K, Inoue H, Tahara K, Takesono C and Hashimoto Y (2004) Nonlinear mixed effects model analysis of the pharmacokinetics of metoprolol in routinely treated Japanese patients. *Biol Pharm Bull*, 27:1642-1648.

Takada K, Arefayene M, Desta Z, Yarboro CH, Boumpas DT, Balow JE, Flockhart DA and Illei GG (2004) Cytochrome P450 pharmacogenetics as a predictor of toxicity and clinical response to pulse cyclophosphamide in lupus nephritis. *Arthritis Rheum*, 50:2202-2210.

Takahashi H, Kashima T, Kimura S, Murata N, Takaba T, Iwade K, Abe T, Tainaka H, Yasumori T and Echizen H (1999) Pharmacokinetic interaction between warfarin and a uricosuric agent, bucolome: application of In vitro approaches to predicting In vivo reduction of (S)-warfarin clearance. *Drug Metab Dispos*, 27:1179-1186.

Takahashi H, Kashima T, Nomoto S, Iwade K, Tainaka H, Shimizu T, Nomizo Y, Muramoto N, Kimura S and Echizen H (1998) Comparisons between in-vitro and in-vivo metabolism of (S)-warfarin: catalytic activities of cDNA-expressed CYP2C9, its Leu359 variant and their mixture versus unbound clearance in patients with the corresponding CYP2C9 genotypes. *Pharmacogenetics*, 8:365-373.

Takahashi H, Wilkinson GR, Caraco Y, Muszkat M, Kim RB, Kashima T, Kimura S and Echizen H (2003) Population differences in S-warfarin metabolism between CYP2C9 genotype-matched Caucasian and Japanese patients. *Clin Pharmacol Ther*, 73:253-263.

Takanashi K, Tainaka H, Kobayashi K, Yasumori T, Hosakawa M and Chiba K (2000) CYP2C9 Ile359 and Leu359 variants: enzyme kinetic study with seven substrates. *Pharmacogenetics*, 10:95-104.

Takekuma Y, Takenaka T, Kiyokawa M, Yamazaki K, Okamoto H, Kitabatake A, Tsutsui H and Sugawara M (2006) Contribution of polymorphisms in UDP-glucuronosyltransferase and CYP2D6 to the individual variation in disposition of carvedilol. *J Pharm Pharm Sci*, 9:101-112.

Tang C, Shou M, Rushmore TH, Mei Q, Sandhu P, Woolf EJ, Rose MJ, Gelmann A, Greenberg HE, De Lepeleire I, Van Hecken A, De Schepper PJ, Ebel DL, Schwartz JI and Rodrigues AD (2001) In-vitro metabolism of celecoxib, a cyclooxygenase-2 inhibitor, by allelic variant forms of human liver microsomal cytochrome P450 2C9: correlation with CYP2C9 genotype and in-vivo pharmacokinetics. *Pharmacogenetics*, 11:223-235.



- Tanigawara Y, Aoyama N, Kita T, Shirakawa K, Komada F, Kasuga M and Okumura K (1999) CYP2C19 genotype-related efficacy of omeprazole for the treatment of infection caused by *Helicobacter pylori*. *Clin Pharmacol Ther*, **66**:528-534.
- Tassies D, Freire C, Pijoan J, Maragall S, Monteagudo J, Ordinas A and Reverter JC (2002) Pharmacogenetics of acenocoumarol: cytochrome P450 CYP2C9 polymorphisms influence dose requirements and stability of anticoagulation. *Haematologica*, **87**:1185-1191.
- Tate SK, Depondt C, Sisodiya SM, Cavalleri GL, Schorge S, Soranzo N, Thom M, Sen A, Shorvon SD, Sander JW, Wood NW and Goldstein DB (2005) Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin. *Proc Natl Acad Sci U S A*, **102**:5507-5512.
- Tateishi T, Watanabe M, Nakura H, Asoh M, Shirai H, Mizorogi Y, Kobayashi S, Thummel KE and Wilkinson GR (2001) CYP3A activity in European American and Japanese men using midazolam as an in vivo probe. *Clin Pharmacol Ther*, **69**:333-339.
- Taube J, Halsall D and Baglin T (2000) Influence of cytochrome P-450 CYP2C9 polymorphisms on warfarin sensitivity and risk of over-anticoagulation in patients on long-term treatment. *Blood*, **96**:1816-1819.
- Tenneze L, Tarral E, Ducloux N and Funck-Brentano C (2002) Pharmacokinetics and electrocardiographic effects of a new controlled-release form of flecainide acetate: comparison with the standard form and influence of the CYP2D6 polymorphism. *Clin Pharmacol Ther*, **72**:112-122.
- Tenneze L, Verstuyft C, Becquemont L, Poirier JM, Wilkinson GR and Funck-Brentano C (1999) Assessment of CYP2D6 and CYP2C19 activity in vivo in humans: a cocktail study with dextromethorphan and chloroguanide alone and in combination. *Clin Pharmacol Ther*, **66**:582-588.
- Thakor NV and Tong S (2004) Advances in quantitative electroencephalogram analysis methods. *Annu Rev Biomed Eng*, **6**:453-495.
- Tham LS, Goh BC, Nafziger A, Guo JY, Wang LZ, Soong R and Lee SC (2006) A warfarin-dosing model in Asians that uses single-nucleotide polymorphisms in vitamin K epoxide reductase complex and cytochrome P450 2C9. *Clin Pharmacol Ther*, **80**:346-355.
- Theofanous TG and Barile RG (1973) Multiple-dose kinetics of oral anticoagulants: methods of analysis and optimized dosing. *J Pharm Sci*, **62**:261-266.
- Thervet E, Anglicheau D, King B, Schlageter MH, Cassinat B, Beaune P, Legendre C and Daly AK (2003) Impact of cytochrome p450 3A5 genetic polymorphism on tacrolimus doses and concentration-to-dose ratio in renal transplant recipients. *Transplantation*, **76**:1233-1235.

- Thijssen HH, Drittij MJ, Vervoort LM and de Vries-Hanje JC (2001) Altered pharmacokinetics of R- and S-acenocoumarol in a subject heterozygous for CYP2C9\*3. *Clin Pharmacol Ther*, 70:292-298.
- Thummel KE, O'Shea D, Paine MF, Shen DD, Kunze KL, Perkins JD and Wilkinson GR (1996) Oral first-pass elimination of midazolam involves both gastrointestinal and hepatic CYP3A-mediated metabolism. *Clin Pharmacol Ther*, 59:491-502.
- Timm R, Kaiser R, Lotsch J, Heider U, Sezer O, Weisz K, Montemurro M, Roots I and Cascorbi I (2005) Association of cyclophosphamide pharmacokinetics to polymorphic cytochrome P450 2C19. *Pharmacogenomics J*, 5:365-373.
- Tsuchiya N, Satoh S, Tada H, Li Z, Ohyama C, Sato K, Suzuki T, Habuchi T and Kato T (2004) Influence of CYP3A5 and MDR1 (ABCB1) polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients. *Transplantation*, 78:1182-1187.
- Tucker GT (2004) Pharmacogenetics - expectations and reality. *British Medical Journal*, 329:4-6.
- Tucker GT, Houston JB and Huang SM (2001) Optimizing drug development: strategies to assess drug metabolism/transporter interaction potential--toward a consensus. *Pharm Res*, 18:1071-1080.
- Tucker GT, Silas JH, Iyun AO, Lennard MS and Smith AJ (1977) Polymorphic hydroxylation of debrisoquine. *Lancet*, 2:718.
- Tybring G, Bottiger Y, Widen J and Bertilsson L (1997) Enantioselective hydroxylation of omeprazole catalyzed by CYP2C19 in Swedish white subjects. *Clin Pharmacol Ther*, 62:129-137.
- Ufer M, Kammerer B, Kahlich R, Kirchheiner J, Yasar U, Brockmoller J and Rane A (2004) Genetic polymorphisms of cytochrome P450 2C9 causing reduced phenprocoumon (S)-7-hydroxylation in vitro and in vivo. *Xenobiotica*, 34:847-859.
- Vadher B, Patterson DL and Leaning M (1999) Prediction of the international normalized ratio and maintenance dose during the initiation of warfarin therapy. *Br J Clin Pharmacol*, 48:63-70.
- Valetin J (2002) Basic anatomical and physiological data for use in radiological protection: Reference values. A report of age- and gender-related differences in the anatomical and physiological characteristics of reference individuals. *Annals of the ICRP, Publication 89*, 32:5-265.
- van der Weide J, Steijns LS and van Weelden MJ (2003) The effect of smoking and cytochrome P450 CYP1A2 genetic polymorphism on clozapine clearance and dose requirement. *Pharmacogenetics*, 13:169-172.

van der Weide J, Steijns LS, van Weelden MJ and de Haan K (2001) The effect of genetic polymorphism of cytochrome P450 CYP2C9 on phenytoin dose requirement. *Pharmacogenetics*, 11:287-291.

Varsaldi F, Miglio G, Scordo MG, Dahl ML, Villa LM, Biolcati A and Lombardi G (2006) Impact of the CYP2D6 polymorphism on steady-state plasma concentrations and clinical outcome of donepezil in Alzheimer's disease patients. *Eur J Clin Pharmacol*, 62:721-726.

Vecsler M, Loebstein R, Almog S, Kurnik D, Goldman B, Halkin H and Gak E (2006) Combined genetic profiles of components and regulators of the vitamin K-dependent gamma-carboxylation system affect individual sensitivity to warfarin. *Thromb Haemost*, 95:205-211.

Venkatakrishnan K, von Moltke LL, Obach RS and Greenblatt DJ (2003) Drug metabolism and drug interactions: application and clinical value of in vitro models. *Curr Drug Metab*, 4:423-459.

Veronese ME, Doecke CJ, Mackenzie PI, McManus ME, Miners JO, Rees DL, Gasser R, Meyer UA and Birkett DJ (1993) Site-directed mutation studies of human liver cytochrome P-450 isoenzymes in the CYP2C subfamily. *Biochem J*, 289 (Pt 2):533-538.

Verstuyft C, Morin S, Robert A, Lorient MA, Beaune P, Jaillon P and Becquemont L (2001) Early acenocoumarol overanticoagulation among cytochrome P450 2C9 poor metabolizers. *Pharmacogenetics*, 11:735-737.

Veyrat-Follet C, Bruno R, Olivares R, Rhodes GR and Chaikin P (2000) Clinical trial simulation of docetaxel in patients with cancer as a tool for dosage optimization. *Clin Pharmacol Ther*, 68:677-687.

Visser LE, van Vliet M, van Schaik RH, Kasbergen AA, De Smet PA, Vulto AG, Hofman A, van Duijn CM and Stricker BH (2004) The risk of overanticoagulation in patients with cytochrome P450 CYP2C9\*2 or CYP2C9\*3 alleles on acenocoumarol or phenprocoumon. *Pharmacogenetics*, 14:27-33.

Visser SA, Wolters FL, Gubbens-Stibbe JM, Tukker E, Van Der Graaf PH, Peletier LA and Danhof M (2003) Mechanism-based pharmacokinetic/pharmacodynamic modeling of the electroencephalogram effects of GABAA receptor modulators: in vitro-in vivo correlations. *J Pharmacol Exp Ther*, 304:88-101.

Von Moltke L, Greenblatt D, Grassi J and al e (1998a) Reevaluation of the specificity of dextromethorphan as an index substrate. *Clinical pharmacology and therapeutics*, 63:227.

Von Moltke LL, Greenblatt DJ, Grassi JM, Granda BW, Venkatakrishnan K, Schmider J, Harmatz JS and Shader RI (1998b) Multiple human cytochromes contribute to biotransformation of dextromethorphan in vitro: role of CYP2C9, CYP2C19, CYP2D6, and CYP 3A. *Journal of Pharmacy and Pharmacology*, 50:997-1004.

von Moltke LL, Greenblatt DJ, Schmider J, Duan SX, Wright CE, Harmatz JS and Shader RI (1996) Midazolam hydroxylation by human liver microsomes in vitro: inhibition by fluoxetine, norfluoxetine, and by azole antifungal agents. *J Clin Pharmacol*, **36**:783-791.

Vormfelde SV, Engelhardt S, Zirk A, Meineke I, Tuchen F, Kirchheiner J and Brockmoller J (2004) CYP2C9 polymorphisms and the interindividual variability in pharmacokinetics and pharmacodynamics of the loop diuretic drug torsemide. *Clin Pharmacol Ther*, **76**:557-566.

Wan J, Xia H, He N, Lu YQ and Zhou HH (1996) The elimination of diazepam in Chinese subjects is dependent on the mephenytoin oxidation phenotype. *Br J Clin Pharmacol*, **42**:471-474.

Wandel C, Witte JS, Hall JM, Stein CM, Wood AJ and Wilkinson GR (2000) CYP3A activity in African American and European American men: population differences and functional effect of the CYP3A4\*1B5'-promoter region polymorphism. *Clin Pharmacol Ther*, **68**:82-91.

Wang JH, Liu ZQ, Wang W, Chen XP, Shu Y, He N and Zhou HH (2001) Pharmacokinetics of sertraline in relation to genetic polymorphism of CYP2C19. *Clin Pharmacol Ther*, **70**:42-47.

Wang R, Chen K, Wen S, Li J and Wang S (2005a) Relationship of the P450 2C9 genetic polymorphisms in Chinese healthy volunteers and the pharmacokinetic of tolbutamide. *Chinese Journal of Clinical Pharmacology*, **21**:255-259.

Wang R, Chen K, Wen SY, Li J and Wang SQ (2005b) Pharmacokinetics of glimepiride and cytochrome P450 2C9 genetic polymorphisms. *Clin Pharmacol Ther*, **78**:90-92.

Wang Y and Unadkat JD (1999) Enzymes in addition to CYP3A4 and 3A5 mediate N-demethylation of dextromethorphan in human liver microsomes. *Biopharm Drug Dispos*, **20**:341-346.

Watanabe M, Iwahashi K, Kugoh T and Suwaki H (1998) The relationship between phenytoin pharmacokinetics and the CYP2C19 genotype in Japanese epileptic patients. *Clin Neuropharmacol*, **21**:122-126.

Wedlund PJ (2000) The CYP2C19 enzyme polymorphism. *Pharmacology*, **61**:174-183.

Wedlund PJ and Wilkinson GR (1996) In vivo and in vitro measurement of CYP2C19 activity. *Methods Enzymol*, **272**:105-114.

Wiegman H and Vossepoel AM (1977) A computer program for long term anticoagulation control. *Comput Programs Biomed*, **7**:71-84.

Wilkinson GR and Shand DG (1975) Commentary: a physiological approach to hepatic drug clearance. *Clin Pharmacol Ther*, **18**:377-390.

- Williams JA, Hyland R, Jones BC, Smith DA, Hurst S, Goosen TC, Peterkin V, Koup JR and Ball SE (2004) Drug-drug interactions for UDP-glucuronosyltransferase substrates: a pharmacokinetic explanation for typically observed low exposure (AUC<sub>i</sub>/AUC) ratios. *Drug Metab Dispos*, **32**:1201-1208.
- Williams JA, Johnson K, Paulauskis J and Cook J (2006) So many studies, too few subjects: establishing functional relevance of genetic polymorphisms on pharmacokinetics. *J Clin Pharmacol*, **46**:258-264.
- Williams JA, Ring BJ, Cantrell VE, Jones DR, Eckstein J, Ruterbories K, Hamman MA, Hall SD and Wrighton SA (2002) Comparative metabolic capabilities of CYP3A4, CYP3A5, and CYP3A7. *Drug Metab Dispos*, **30**:883-891.
- Williams PJ and Ette EI (2000) The role of population pharmacokinetics in drug development in light of the Food and Drug Administration's 'Guidance for Industry: population pharmacokinetics'. *Clin Pharmacokinet*, **39**:385-395.
- Wilson ZE, Rostami-Hodjegan A, Burn JL, Tooley A, Boyle J, Ellis SW and Tucker GT (2003) Inter-individual variability in levels of human microsomal protein and hepatocellularity per gram of liver. *Br J Clin Pharmacol*, **56**:433-440.
- Wong M, Balleine RL, Collins M, Liddle C, Clarke CL and Gurney H (2004) CYP3A5 genotype and midazolam clearance in Australian patients receiving chemotherapy. *Clin Pharmacol Ther*, **75**:529-538.
- Wrighton SA, Brian WR, Sari MA, Iwasaki M, Guengerich FP, Raucy JL, Molowa DT and Vandenberg M (1990) Studies on the expression and metabolic capabilities of human liver cytochrome P450III<sub>A</sub>5 (HLP3). *Mol Pharmacol*, **38**:207-213.
- Wu XP, Liao EY, Liu SP, Zhang H, Shan PF, Cao XZ and Jiang Y (2004) Relationship of body surface area with bone density and its risk of osteoporosis at various skeletal regions in women of mainland China. *Osteoporos Int*, **15**:751-759.
- Wuttke H, Rau T, Heide R, Bergmann K, Bohm M, Weil J, Werner D and Eschenhagen T (2002) Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. *Clin Pharmacol Ther*, **72**:429-437.
- Xie HG, Prasad HC, Kim RB and Stein CM (2002) CYP2C9 allelic variants: ethnic distribution and functional significance. *Adv Drug Deliv Rev*, **54**:1257-1270.
- Xie HG, Xu ZH, Huang SL, Liu JH, Wu JX, Jiang CH and Zhou HH (1997) No correlation between side-chain of propranolol oxidation and S-mephenytoin 4'-hydroxylase activity. *Zhongguo Yao Li Xue Bao*, **18**:216-218.
- Yacobi A, Lampman T and Levy G (1977) Frequency distribution of free warfarin and free phenytoin fraction values in serum of healthy human adults. *Clin Pharmacol Ther*, **21**:283-286.

Yamashiro W, Maeda K, Hirouchi M, Adachi Y, Hu Z and Sugiyama Y (2006) Involvement of transporters in the hepatic uptake and biliary excretion of valsartan, a selective antagonist of the angiotensin II AT1-receptor, in humans. *Drug Metab Dispos*, **34**:1247-1254.

Yamazaki H, Inoue K, Chiba K, Ozawa N, Kawai T, Suzuki Y, Goldstein JA, Guengerich FP and Shimada T (1998) Comparative studies on the catalytic roles of cytochrome P450 2C9 and its Cys- and Leu-variants in the oxidation of warfarin, flurbiprofen, and diclofenac by human liver microsomes. *Biochem Pharmacol*, **56**:243-251.

Yamazaki H, Inoue K, Shaw PM, Checovich WJ, Guengerich FP and Shimada T (1997) Different contributions of cytochrome P450 2C19 and 3A4 in the oxidation of omeprazole by human liver microsomes: effects of contents of these two forms in individual human samples. *J Pharmacol Exp Ther*, **283**:434-442.

Yang J, Tucker GT and Rostami-Hodjegan A (2004) Cytochrome P450 3A expression and activity in the human small intestine. *Clin Pharmacol Ther*, **76**:391.

Yasar U, Eliasson E, Forslund-Bergengren C, Tybring G, Gadd M, Sjoqvist F and Dahl ML (2001) The role of CYP2C9 genotype in the metabolism of diclofenac in vivo and in vitro. *Eur J Clin Pharmacol*, **57**:729-735.

Yasar U, Forslund-Bergengren C, Tybring G, Dorado P, Llerena A, Sjoqvist F, Eliasson E and Dahl ML (2002) Pharmacokinetics of losartan and its metabolite E-3174 in relation to the CYP2C9 genotype. *Clin Pharmacol Ther*, **71**:89-98.

Yasuda S, Horai Y, Tomono Y, Nakai H, Yamato C, Manabe K, Kobayashi K, Chiba K and Ishizaki T (1995) Comparison of the kinetic disposition and metabolism of E3810, a new proton pump inhibitor, and omeprazole in relation to S-mephenytoin 4'-hydroxylation status. *Clin Pharmacol Ther*, **58**:143-154.

Yasui-Furukori N, Mihara K, Kondo T, Kubota T, Iga T, Takarada Y, De Vries R, Kaneko S and Tateishi T (2003) Effects of CYP2D6 genotypes on plasma concentrations of risperidone and enantiomers of 9-hydroxyrisperidone in Japanese patients with schizophrenia. *J Clin Pharmacol*, **43**:122-127.

Yin OQ, Shi XJ, Tomlinson B and Chow MS (2005a) Effect of cyp2d6\*10 allele on the pharmacokinetics of loratadine in chinese subjects. *Drug Metab Dispos*, **33**:1283-1287.

Yin OQ, Tomlinson B, Chow AH, Waye MM and Chow MS (2004) Omeprazole as a CYP2C19 marker in Chinese subjects: assessment of its gene-dose effect and intrasubject variability. *J Clin Pharmacol*, **44**:582-589.

Yin OQ, Tomlinson B and Chow MS (2005b) CYP2C9, but not CYP2C19, polymorphisms affect the pharmacokinetics and pharmacodynamics of glyburide in Chinese subjects. *Clin Pharmacol Ther*, **78**:370-377.

Yoon YR, Cha IJ, Shon JH, Kim KA, Cha YN, Jang IJ, Park CW, Shin SG, Flockhart DA and Shin JG (2000) Relationship of paroxetine disposition to metoprolol metabolic ratio and CYP2D6\*10 genotype of Korean subjects. *Clin Pharmacol Ther*, 67:567-576.

Yu A, Dong H, Lang D and Haining RL (2001a) Characterization of dextromethorphan O- and N-demethylation catalyzed by highly purified recombinant human CYP2D6. *Drug Metab Dispos*, 29:1362-1365.

Yu A and Haining RL (2001) Comparative contribution to dextromethorphan metabolism by cytochrome P450 isoforms in vitro: can dextromethorphan be used as a dual probe for both CYP2D6 and CYP3A activities? *Drug Metab Dispos*, 29:1514-1520.

Yu KS, Cho JY, Jang IJ, Hong KS, Chung JY, Kim JR, Lim HS, Oh DS, Yi SY, Liu KH, Shin JG and Shin SG (2004) Effect of the CYP3A5 genotype on the pharmacokinetics of intravenous midazolam during inhibited and induced metabolic states. *Clin Pharmacol Ther*, 76:104-112.

Yu KS, Yim DS, Cho JY, Park SS, Park JY, Lee KH, Jang IJ, Yi SY, Bae KS and Shin SG (2001b) Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. *Clin Pharmacol Ther*, 69:266-273.

Zhang X, Liu ZH, Zheng JM, Chen ZH, Tang Z, Chen JS and Li LS (2005) Influence of CYP3A5 and MDR1 polymorphisms on tacrolimus concentration in the early stage after renal transplantation. *Clin Transplant*, 19:638-643.

Zhang YA, Reviriego J, Lou YQ, Sjoqvist F and Bertilsson L (1990) Diazepam metabolism in native Chinese poor and extensive hydroxylators of S-mephenytoin: interethnic differences in comparison with white subjects. *Clin Pharmacol Ther*, 48:496-502.

Zhao Y, Song M, Guan D, Bi S, Meng J, Li Q and Wang W (2005) Genetic polymorphisms of CYP3A5 genes and concentration of the cyclosporine and tacrolimus. *Transplant Proc*, 37:178-181.

Zhou Q, Yamamoto I, Fukuda T, Ohno M, Sumida A and Azuma J (1999) CYP2C19 genotypes and omeprazole metabolism after single and repeated dosing when combined with clarithromycin. *Eur J Clin Pharmacol*, 55:43-47.

Ziegler WH, Schalch E, Leishman B and Eckert M (1983) Comparison of the effects of intravenously administered midazolam, triazolam and their hydroxy metabolites. *Br J Clin Pharmacol*, 16 (S1):63S-69S.

Zineh I, Beitelshes AL, Gaedigk A, Walker JR, Pauly DF, Eberst K, Leeder JS, Phillips MS, Gelfand CA and Johnson JA (2004) Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. *Clin Pharmacol Ther*, 76:536-544.

**PAGE**

**NUMBERING**

**AS ORIGINAL**



Kaneko A, Bergqvist Y, Taleo G, Kobayakawa T, Ishizaki T and Bjorkman A (1999a) Proguanil disposition and toxicity in malaria patients from Vanuatu with high frequencies of CYP2C19 mutations. *Pharmacogenetics*, 9:317-326.

Kaneko A, Lum JK, Yaviong L, Takahashi N, Ishizaki T, Bertilsson L, Kobayakawa T and Bjorkman A (1999b) High and variable frequencies of CYP2C19 mutations: medical consequences of poor drug metabolism in Vanuatu and other Pacific islands. *Pharmacogenetics*, 9:581-590.

Karam WG, Goldstein JA, Lasker JM and Ghanayem BI (1996) Human CYP2C19 is a major omeprazole 5-hydroxylase, as demonstrated with recombinant cytochrome P450 enzymes. *Drug Metab Dispos*, 24:1081-1087.

Kartunnen P, Tukiainen H, Silvasti M and Kolonen S (1987) Antitussive effect of dextromethorphan and dextromethorphan-salbutamol combination in healthy volunteers with artificially induced cough. *Respiration*, 52:49-53.

Katashima M, Yamamoto K, Tokuma Y, Hata T, Sawada Y and Iga T (1998) Comparative pharmacokinetic/pharmacodynamic analysis of proton pump inhibitors omeprazole, lansoprazole and pantoprazole, in humans. *Eur J Drug Metab Pharmacokinet*, 23:19-26.

Katsuki H, Nakamura C, Arimori K, Fujiyama S and Nakano M (1997) Genetic polymorphism of CYP2C19 and lansoprazole pharmacokinetics in Japanese subjects. *Eur J Clin Pharmacol*, 52:391-396.

Kendall MJ (2003) Review article: esomeprazole--the first proton pump inhibitor to be developed as an isomer. *Aliment Pharmacol Ther*, 17 (S1):1-4.

Kerry NL, Somogyi AA, Bochner F and Mikus G (1994) The role of CYP2D6 in primary and secondary oxidative metabolism of dextromethorphan: in vitro studies using human liver microsomes. *Br J Clin Pharmacol*, 38:243-248.

Khan T, Wynne H, Wood P, Torrance A, Hankey C, Avery P, Kesteven P and Kamali F (2004) Dietary vitamin K influences intra-individual variability in anticoagulant response to warfarin. *Br J Haematol*, 124:348-354.

Kim KA, Shon JH, Park JY, Yoon YR, Kim MJ, Yun DH, Kim MK, Cha IJ, Hyun MH and Shin JG (2002) Enantioselective disposition of lansoprazole in extensive and poor metabolizers of CYP2C19. *Clin Pharmacol Ther*, 72:90-99.

King BP, Khan TI, Aithal GP, Kamali F and Daly AK (2004) Upstream and coding region CYP2C9 polymorphisms: correlation with warfarin dose and metabolism. *Pharmacogenetics*, 14:813-822.

Kirchheiner J, Bauer S, Meineke I, Rohde W, Prang V, Meisel C, Roots I and Brockmoller J (2002a) Impact of CYP2C9 and CYP2C19 polymorphisms on

tolbutamide kinetics and the insulin and glucose response in healthy volunteers. *Pharmacogenetics*, **12**:101-109.

Kirchheiner J, Brockmoller J, Meineke I, Bauer S, Rohde W, Meisel C and Roots I (2002b) Impact of CYP2C9 amino acid polymorphisms on glyburide kinetics and on the insulin and glucose response in healthy volunteers. *Clin Pharmacol Ther*, **71**:286-296.

Kirchheiner J, Heesch C, Bauer S, Meisel C, Seringer A, Goldammer M, Tzvetkov M, Meineke I, Roots I and Brockmoller J (2004a) Impact of the ultrarapid metabolizer genotype of cytochrome P450 2D6 on metoprolol pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther*, **76**:302-312.

Kirchheiner J, Klein C, Meineke I, Sasse J, Zanger UM, Murdter TE, Roots I and Brockmoller J (2003a) Bupropion and 4-OH-bupropion pharmacokinetics in relation to genetic polymorphisms in CYP2B6. *Pharmacogenetics*, **13**:619-626.

Kirchheiner J, Kudlicz D, Meisel C, Bauer S, Meineke I, Roots I and Brockmoller J (2003b) Influence of CYP2C9 polymorphisms on the pharmacokinetics and cholesterol-lowering activity of (-)-3S,5R-fluvastatin and (+)-3R,5S-fluvastatin in healthy volunteers. *Clin Pharmacol Ther*, **74**:186-194.

Kirchheiner J, Meineke I, Freytag G, Meisel C, Roots I and Brockmoller J (2002c) Enantiospecific effects of cytochrome P450 2C9 amino acid variants on ibuprofen pharmacokinetics and on the inhibition of cyclooxygenases 1 and 2. *Clin Pharmacol Ther*, **72**:62-75.

Kirchheiner J, Meineke I, Muller G, Bauer S, Rohde W, Meisel C, Roots I and Brockmoller J (2004b) Influence of CYP2C9 and CYP2D6 polymorphisms on the pharmacokinetics of nateglinide in genotyped healthy volunteers. *Clin Pharmacokinet*, **43**:267-278.

Kirchheiner J, Meineke I, Muller G, Roots I and Brockmoller J (2002d) Contributions of CYP2D6, CYP2C9 and CYP2C19 to the biotransformation of E- and Z-doxepin in healthy volunteers. *Pharmacogenetics*, **12**:571-580.

Kirchheiner J, Meineke I, Steinbach N, Meisel C, Roots I and Brockmoller J (2003c) Pharmacokinetics of diclofenac and inhibition of cyclooxygenases 1 and 2: no relationship to the CYP2C9 genetic polymorphism in humans. *Br J Clin Pharmacol*, **55**:51-61.

Kirchheiner J, Sasse J, Meineke I, Roots I and Brockmoller J (2003d) Trimipramine pharmacokinetics after intravenous and oral administration in carriers of CYP2D6 genotypes predicting poor, extensive and ultrahigh activity. *Pharmacogenetics*, **13**:721-728.

Kirchheiner J, Stormer E, Meisel C, Steinbach N, Roots I and Brockmoller J (2003e) Influence of CYP2C9 genetic polymorphisms on pharmacokinetics of celecoxib and its metabolites. *Pharmacogenetics*, **13**:473-480.

Kirchheiner J, Ufer M, Walter EC, Kammerer B, Kahlich R, Meisel C, Schwab M, Gleiter CH, Rane A, Roots I and Brockmoller J (2004c) Effects of CYP2C9 polymorphisms on the pharmacokinetics of R- and S-phenprocoumon in healthy volunteers. *Pharmacogenetics*, 14:19-26.

Kita T, Tanigawara Y, Aoyama N, Hohda T, Saijoh Y, Komada F, Sakaeda T, Okumura K, Sakai T and Kasuga M (2001) CYP2C19 genotype related effect of omeprazole on intragastric pH and antimicrobial stability. *Pharm Res*, 18:615-621.

Kivisto KT, Niemi M, Schaeffeler E, Pitkala K, Tilvis R, Fromm MF, Schwab M, Eichelbaum M and Strandberg T (2004) Lipid-lowering response to statins is affected by CYP3A5 polymorphism. *Pharmacogenetics*, 14:523-525.

Klotz U, Schwab M and Treiber G (2004) CYP2C19 polymorphism and proton pump inhibitors. *Basic Clin Pharmacol Toxicol*, 95:2-8.

Klotz U and Ziegler G (1982) Physiologic and temporal variation in hepatic elimination of midazolam. *Clin Pharmacol Ther*, 32:107-112.

Knodell RG, Dubey RK, Wilkinson GR and Guengerich FP (1988) Oxidative metabolism of hexobarbital in human liver: relationship to polymorphic S-mephenytoin 4-hydroxylation. *J Pharmacol Exp Ther*, 245:845-849.

Knoester PD, Jonker DM, Van Der Hoeven RT, Vermeij TA, Edelbroek PM, Brekelmans GJ and de Haan GJ (2002) Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. *Br J Clin Pharmacol*, 53:501-507.

Kobayashi K, Morita J, Chiba K, Wanibuchi A, Kimura M, Irie S, Urae A and Ishizaki T (2004) Pharmacogenetic roles of CYP2C19 and CYP2B6 in the metabolism of R- and S-mephobarbital in humans. *Pharmacogenetics*, 14:549-556.

Koopmans R, Dingemans J, Danhof M, Horsten GP and van Boxtel CJ (1988) Pharmacokinetic-pharmacodynamic modeling of midazolam effects on the human central nervous system. *Clin Pharmacol Ther*, 44:14-22.

Koyama E, Tanaka T, Chiba K, Kawakatsu S, Morinobu S, Totsuka S and Ishizaki T (1996) Steady-state plasma concentrations of imipramine and desipramine in relation to S-mephenytoin 4'-hydroxylation status in Japanese depressive patients. *J Clin Psychopharmacol*, 16:286-293.

Kuang T-Y, Lou Y-C and Tao P (1994) Pharmacokinetics of propafenone and its relationship with debrisoquin and mephenytoin metabolism polymorphisms in healthy Chinese volunteers. *Chinese Journal of Pharmacology and Toxicology*, 8:13.

Kuehl P, Zhang J, Lin Y, Lamba J, Assem M, Schuetz J, Watkins PB, Daly A, Wrighton SA, Hall SD, Maurel P, Relling M, Brimer C, Yasuda K, Venkataramanan R, Strom S, Thummel K, Boguski MS and Schuetz E (2001) Sequence diversity in CYP3A

- promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat Genet*, **27**:383-391.
- Kupfer A and Branch RA (1985) Stereoselective mephobarbital hydroxylation cosegregates with mephenytoin hydroxylation. *Clin Pharmacol Ther*, **38**:414-418.
- Kvasz M, Allen IE, Gordon MJ, Ro EY, Estok R, Olkin I and Ross SD (2000) Adverse drug reactions in hospitalized patients: A critique of a meta-analysis. *MedGenMed*, **2**:E3.
- Kvist EE, Al-Shurbaji A, Dahl ML, Nordin C, Alvan G and Stahle L (2001) Quantitative pharmacogenetics of nortriptyline: a novel approach. *Clin Pharmacokinet*, **40**:869-877.
- Laine K, Anttila M, Nyman L, Wahlberg A and Bertilsson L (2001) CYP2C19 polymorphism is not important for the in vivo metabolism of selegiline. *Eur J Clin Pharmacol*, **57**:137-142.
- Lane HY, Liu YC, Huang CL, Chang YC, Wu PL, Lu CT and Chang WH (2006) Risperidone-related weight gain: genetic and nongenetic predictors. *J Clin Psychopharmacol*, **26**:128-134.
- Lasker JM, Wester MR, Aramsombatdee E and Raucy JL (1998) Characterization of CYP2C19 and CYP2C9 from human liver: respective roles in microsomal tolbutamide, S-mephenytoin, and omeprazole hydroxylations. *Arch Biochem Biophys*, **353**:16-28.
- Lazarou J, Pomeranz BH and Corey PN (1998) Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *Jama*, **279**:1200-1205.
- Le Meur Y, Djebli N, Szelag JC, Hoizey G, Toupance O, Rerolle JP and Marquet P (2006) CYP3A5\*3 influences sirolimus oral clearance in de novo and stable renal transplant recipients. *Clin Pharmacol Ther*, **80**:51-60.
- Lee CR, Goldstein JA and Pieper JA (2002a) Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. *Pharmacogenetics*, **12**:251-263.
- Lee CR, Pieper JA, Frye RF, Hinderliter AL, Blaisdell JA and Goldstein JA (2003) Tolbutamide, flurbiprofen, and losartan as probes of CYP2C9 activity in humans. *J Clin Pharmacol*, **43**:84-91.
- Lee CR, Pieper JA, Hinderliter AL, Blaisdell JA and Goldstein JA (2002b) Evaluation of cytochrome P450 2C9 metabolic activity with tolbutamide in CYP2C9 heterozygotes. *Clin Pharmacol Ther*, **72**:562-571.
- Lee EJ and Williams KM (1990) Chirality. Clinical pharmacokinetic and pharmacodynamic considerations. *Clin Pharmacokinet*, **18**:339-345.
- Lee JT, Kroemer HK, Silberstein DJ, Funck-Brentano C, Lineberry MD, Wood AJ, Roden DM and Woosley RL (1990) The role of genetically determined polymorphic drug metabolism in the beta-blockade produced by propafenone. *N Engl J Med*, **322**:1764-1768.

- Lennard MS, Tucker GT, Silas JH, Freestone S, Ramsay LE and Woods HF (1983) Differential stereoselective metabolism of metoprolol in extensive and poor debrisoquin metabolizers. *Clin Pharmacol Ther*, **34**:732-737.
- Lepper ER, Baker SD, Permenter M, Ries N, van Schaik RH, Schenk PW, Price DK, Ahn D, Smith NF, Cusatis G, Ingersoll RG, Bates SE, Mathijssen RH, Verweij J, Figg WD and Sparreboom A (2005) Effect of common CYP3A4 and CYP3A5 variants on the pharmacokinetics of the cytochrome P450 3A phenotyping probe midazolam in cancer patients. *Clin Cancer Res*, **11**:7398-7404.
- Li T, Lange LA, Li X, Susswein L, Bryant B, Malone R, Lange EM, Huang TY, Stafford DW and Evans JP (2006) Polymorphisms in the VKORC1 gene are strongly associated with warfarin dosage requirements in patients receiving anticoagulation. *J Med Genet*, **43**:740-744.
- Liggett SB (2000) The pharmacogenetics of beta2-adrenergic receptors: relevance to asthma. *J Allergy Clin Immunol*, **105**:S487-492.
- Lilja JJ, Backman JT and Neuvonen PJ (2005) Effect of gemfibrozil on the pharmacokinetics and pharmacodynamics of racemic warfarin in healthy subjects. *Br J Clin Pharmacol*, **59**:433-439.
- Lin JH and Lu AY (1997) Role of pharmacokinetics and metabolism in drug discovery and development. *Pharmacol Rev*, **49**:403-449.
- Lin YS, Dowling AL, Quigley SD, Farin FM, Zhang J, Lamba J, Schuetz EG and Thummel KE (2002) Co-regulation of CYP3A4 and CYP3A5 and contribution to hepatic and intestinal midazolam metabolism. *Mol Pharmacol*, **62**:162-172.
- Lind T, Cederberg C, Ekenved G, Haglund U and Olbe L (1983) Effect of omeprazole--a gastric proton pump inhibitor--on pentagastrin stimulated acid secretion in man. *Gut*, **24**:270-276.
- Lindh JD, Lundgren S, Holm L, Alfredsson L and Rane A (2005) Several-fold increase in risk of overanticoagulation by CYP2C9 mutations. *Clin Pharmacol Ther*, **78**:540-550.
- Lipsky MS and Sharp LK (2001) From idea to market: the drug approval process. *J Am Board Fam Pract*, **14**:362-367.
- Liu J, Liu ZQ, Tan ZR, Chen XP, Wang LS, Zhou G and Zhou HH (2003) Gly389Arg polymorphism of beta1-adrenergic receptor is associated with the cardiovascular response to metoprolol. *Clin Pharmacol Ther*, **74**:372-379.
- Liu ZQ, Cheng ZN, Huang SL, Chen XP, Ou-Yang DS, Jiang CH and Zhou HH (2001) Effect of the CYP2C19 oxidation polymorphism on fluoxetine metabolism in Chinese healthy subjects. *Br J Clin Pharmacol*, **52**:96-99.

- Loboz KK, Gross AS, Williams KM, Liauw WS, Day RO, Blievernicht JK, Zanger UM and McLachlan AJ (2006) Cytochrome P450 2B6 activity as measured by bupropion hydroxylation: effect of induction by rifampin and ethnicity. *Clin Pharmacol Ther*, **80**:75-84.
- Loebstein R, Yonath H, Peleg D, Almog S, Rotenberg M, Lubetsky A, Roitelman J, Harats D, Halkin H and Ezra D (2001) Interindividual variability in sensitivity to warfarin--Nature or nurture? *Clin Pharmacol Ther*, **70**:159-164.
- Lotsch J, Skarke C, Grosch S, Darimont J, Schmidt H and Geisslinger G (2002) The polymorphism A118G of the human mu-opioid receptor gene decreases the pupil constrictory effect of morphine-6-glucuronide but not that of morphine. *Pharmacogenetics*, **12**:3-9.
- Lutz U, Volkel W, Lutz RW and Lutz WK (2004) LC-MS/MS analysis of dextromethorphan metabolism in human saliva and urine to determine CYP2D6 phenotype and individual variability in N-demethylation and glucuronidation. *J Chromatogr B Analyt Technol Biomed Life Sci*, **813**:217-225.
- Macphee IA, Fredericks S, Mohamed M, Moreton M, Carter ND, Johnston A, Goldberg L and Holt DW (2005) Tacrolimus pharmacogenetics: the CYP3A5\*1 allele predicts low dose-normalized tacrolimus blood concentrations in whites and South Asians. *Transplantation*, **79**:499-502.
- Mahgoub A, Idle JR, Dring LG, Lancaster R and Smith RL (1977) Polymorphic hydroxylation of Debrisoquine in man. *Lancet*, **2**:584-586.
- Mamiya K, Hadama A, Yukawa E, Ieiri I, Otsubo K, Ninomiya H, Tashiro N and Higuchi S (2000) CYP2C19 polymorphism effect on phenobarbitone. Pharmacokinetics in Japanese patients with epilepsy: analysis by population pharmacokinetics. *Eur J Clin Pharmacol*, **55**:821-825.
- Mamiya K, Ieiri I, Shimamoto J, Yukawa E, Imai J, Ninomiya H, Yamada H, Otsubo K, Higuchi S and Tashiro N (1998) The effects of genetic polymorphisms of CYP2C9 and CYP2C19 on phenytoin metabolism in Japanese adult patients with epilepsy: studies in stereoselective hydroxylation and population pharmacokinetics. *Epilepsia*, **39**:1317-1323.
- Mandema JW, Tuk B, van Steveninck AL, Breimer DD, Cohen AF and Danhof M (1992) Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite alpha-hydroxymidazolam in healthy volunteers. *Clin Pharmacol Ther*, **51**:715-728.
- Mankowski DC, Lawton MP and Ekins S (2000) Characterization of transgenic mouse strains using six human hepatic cytochrome P450 probe substrates. *Xenobiotica*, **30**:745-754.

- Margaglione M, Colaizzo D, D'Andrea G, Brancaccio V, Ciampa A, Grandone E and Di Minno G (2000) Genetic modulation of oral anticoagulation with warfarin. *Thromb Haemost*, **84**:775-778.
- Martinez C, Garcia-Martin E, Blanco G, Gamito FJ, Ladero JM and Agundez JA (2005) The effect of the cytochrome P450 CYP2C8 polymorphism on the disposition of (R)-ibuprofen enantiomer in healthy subjects. *Br J Clin Pharmacol*, **59**:62-69.
- Masica AL, Mayo G and Wilkinson GR (2004) In vivo comparisons of constitutive cytochrome P450 3A activity assessed by alprazolam, triazolam, and midazolam. *Clin Pharmacol Ther*, **76**:341-349.
- Mathijssen RH, Marsh S, Karlsson MO, Xie R, Baker SD, Verweij J, Sparreboom A and McLeod HL (2003) Irinotecan pathway genotype analysis to predict pharmacokinetics. *Clin Cancer Res*, **9**:3246-3253.
- Matthys H, Bleicher B and Bleicher U (1983) Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. *J Int Med Res*, **11**:92-100.
- McGinnity DF, Parker AJ, Soars M and Riley RJ (2000) Automated definition of the enzymology of drug oxidation by the major human drug metabolizing cytochrome P450s. *Drug Metab Dispos*, **28**:1327-1334.
- Meibohm B and Derendorf H (1997) Basic concepts of pharmacokinetic /pharmacodynamic (PK/PD) modelling. *Int J Clin Pharmacol Ther*, **35**:401-413.
- Meyer UA (1991) Genotype or Phenotype: the Definition of a Pharmacogenetic Polymorphism. *Pharmacogenetics*, **1**:66-67.
- Mihara K, Otani K, Tybring G, Dahl ML, Bertilsson L and Kaneko S (1997) The CYP2D6 genotype and plasma concentrations of mianserin enantiomers in relation to therapeutic response to mianserin in depressed Japanese patients. *J Clin Psychopharmacol*, **17**:467-471.
- Min DI, Ellingrod VL, Marsh S and McLeod H (2004) CYP3A5 polymorphism and the ethnic differences in cyclosporine pharmacokinetics in healthy subjects. *Ther Drug Monit*, **26**:524-528.
- Miura M, Tada H, Yasui-Furukori N, Uno T, Sugawara K, Tateishi T and Suzuki T (2004) Pharmacokinetic differences between the enantiomers of lansoprazole and its metabolite, 5-hydroxylansoprazole, in relation to CYP2C19 genotypes. *Eur J Clin Pharmacol*, **60**:623-628.
- Miyoshi M, Mizuno M, Ishiki K, Nagahara Y, Maga T, Torigoe T, Nasu J, Okada H, Yokota K, Oguma K and Tsuji T (2001) A randomized open trial for comparison of proton pump inhibitors, omeprazole versus rabeprazole, in dual therapy for Helicobacter pylori infection in relation to CYP2C19 genetic polymorphism. *J Gastroenterol Hepatol*, **16**:723-728.

Moghadamnia AA, Rostami-Hodjegan A, Abdul-Manap R, Wright CE, Morice AH and Tucker GT (2003) Physiologically based modelling of inhibition of metabolism and assessment of the relative potency of drug and metabolite: dextromethorphan vs. dextrorphan using quinidine inhibition. *Br J Clin Pharmacol*, **56**:57-67.

Molden E, Johansen PW, Boe GH, Bergan S, Christensen H, Rugstad HE, Rootwelt H, Reubsæet L and Lehne G (2002) Pharmacokinetics of diltiazem and its metabolites in relation to CYP2D6 genotype. *Clin Pharmacol Ther*, **72**:333-342.

Morin S, Bodin L, Lorient MA, Thijssen HH, Robert A, Strabach S, Verstuyft C, Tregouet DA, Dubert L, Laurent-Puig P, Funck-Brentano C, Jaillon P, Beaune PH and Becquemont L (2004) Pharmacogenetics of acenocoumarol pharmacodynamics. *Clin Pharmacol Ther*, **75**:403-414.

Morin S, Lorient MA, Poirier JM, Tenneze L, Beaune PH, Funck-Brentano C, Jaillon P and Becquemont L (2001) Is diclofenac a valuable CYP2C9 probe in humans? *Eur J Clin Pharmacol*, **56**:793-797.

Morinobu S, Tanaka T, Kawakatsu S, Totsuka S, Koyama E, Chiba K, Ishizaki T and Kubota T (1997) Effects of genetic defects in the CYP2C19 gene on the N-demethylation of imipramine, and clinical outcome of imipramine therapy. *Psychiatry Clin Neurosci*, **51**:253-257.

Moschitto LJ and Greenblatt DJ (1983) Concentration-independent plasma protein binding of benzodiazepines. *J Pharm Pharmacol*, **35**:179-180.

Mould DR, DeFeo TM, Reece S, Milla G, Limjuco R, Crews T, Choma N and Patel IH (1995) Simultaneous modeling of the pharmacokinetics and pharmacodynamics of midazolam and diazepam. *Clin Pharmacol Ther*, **58**:35-43.

Mouly SJ, Matheny C, Paine MF, Smith G, Lamba J, Lamba V, Pusek SN, Schuetz EG, Stewart PW and Watkins PB (2005) Variation in oral clearance of saquinavir is predicted by CYP3A5\*1 genotype but not by enterocyte content of cytochrome P450 3A5. *Clin Pharmacol Ther*, **78**:605-618.

Murphy GM, Jr., Kremer C, Rodrigues HE and Schatzberg AF (2003) Pharmacogenetics of antidepressant medication intolerance. *Am J Psychiatry*, **160**:1830-1835.

Naganuma M, Shiga T, Nishikata K, Tsuchiya T, Kasanuki H and Fujii E (2001) Role of desethylamiodarone in the anticoagulant effect of concurrent amiodarone and warfarin therapy. *J Cardiovasc Pharmacol Ther*, **6**:363-367.

Nagashima R, O'Reilly RA and Levy G (1969) Kinetics of pharmacologic effects in man: the anticoagulant action of warfarin. *Clin Pharmacol Ther*, **10**:22-35.

Nakajima M, Fujiki Y, Kyo S, Kanaya T, Nakamura M, Maida Y, Tanaka M, Inoue M and Yokoi T (2005) Pharmacokinetics of paclitaxel in ovarian cancer patients and



genetic polymorphisms of CYP2C8, CYP3A4, and MDR1. *J Clin Pharmacol*, **45**:674-682.

Nakajima Y, Yoshitani T, Fukushima-Uesaka H, Saito Y, Kaniwa N, Kurose K, Ozawa S, Aoyagi N, Kamatani N, Yamamoto N, Kunitoh H, Ohe Y, Tamura T, Yoshida T, Minami H, Saijo N, Katori N and Sawada J (2006) Impact of the haplotype CYP3A4\*16B harboring the Thr185Ser substitution on paclitaxel metabolism in Japanese patients with cancer. *Clin Pharmacol Ther*, **80**:179-191.

Nebert DW (1999) Pharmacogenetics and pharmacogenomics: why is this relevant to the clinical geneticist? *Clin Genet*, **56**:247-258.

Neymour R (1993) Gastric pH and stomach contents. *Anesth Analg*, **76**:906-907.

Nielsen F, Rosholm JU and Brosen K (1995) Lack of relationship between quinidine pharmacokinetics and the sparteine oxidation polymorphism. *Eur J Clin Pharmacol*, **48**:501-504.

Niemi M, Cascorbi I, Timm R, Kroemer HK, Neuvonen PJ and Kivisto KT (2002) Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. *Clin Pharmacol Ther*, **72**:326-332.

Niemi M, Leathart JB, Neuvonen M, Backman JT, Daly AK and Neuvonen PJ (2003) Polymorphism in CYP2C8 is associated with reduced plasma concentrations of repaglinide. *Clin Pharmacol Ther*, **74**:380-387.

Nieminen T, Uusitalo H, Maenpaa J, Turjanmaa V, Rane A, Lundgren S, Ropo A, Rontu R, Lehtimaki T and Kahonen M (2005) Polymorphisms of genes CYP2D6, ADRB1 and GNAS1 in pharmacokinetics and systemic effects of ophthalmic timolol. A pilot study. *Eur J Clin Pharmacol*, **61**:811-819.

Nishimura N, Naora K, Hirano H and Iwamoto K (1998) Effects of Sho-saiko-to on the pharmacokinetics and pharmacodynamics of tolbutamide in rats. *J Pharm Pharmacol*, **50**:231-236.

Niu C, Luo J and Wang X (2004) Effects of cytochrome P450 2C19 genetic polymorphism on the acid-suppression of rabeprazole. *Chinese journal of gastroenterology*, **9**:17-20.

O'Reilly RA (1974) Studies on the optical enantiomorphs of warfarin in man. *Clin Pharmacol Ther*, **16**:348-354.

Oates NS, Shah RR, Idle JR and Smith RL (1983) Influence of oxidation polymorphism on phenformin kinetics and dynamics. *Clin Pharmacol Ther*, **34**:827-834.

Obach RS (1999) Prediction of human clearance of twenty-nine drugs from hepatic microsomal intrinsic clearance data: An examination of in vitro half-life approach and nonspecific binding to microsomes. *Drug Metab Dispos*, **27**:1350-1359.

Odani A, Hashimoto Y, Otsuki Y, Uwai Y, Hattori H, Furusho K and Inui K (1997) Genetic polymorphism of the CYP2C subfamily and its effect on the pharmacokinetics of phenytoin in Japanese patients with epilepsy. *Clin Pharmacol Ther*, **62**:287-292.

Ohara K, Tanabu S, Ishibashi K, Ikemoto K, Yoshida K and Shibuya H (2003) CYP2D6\*10 alleles do not determine plasma fluvoxamine concentration/dose ratio in Japanese subjects. *Eur J Clin Pharmacol*, **58**:659-661.

Ohkusa T, Maekawa T, Arakawa T, Nakajima M, Fujimoto K, Hoshino E, Mitachi Y, Hamada S, Mine T, Kawahara Y, Nagai T, Aoyama N, Yoshida N, Tadokoro K, Chida N, Konda Y, Seno H, Shimatani T, Inoue M and Sato N (2005) Effect of CYP2C19 polymorphism on the safety and efficacy of omeprazole in Japanese patients with recurrent reflux oesophagitis. *Aliment Pharmacol Ther*, **21**:1331-1339.

Ohnishi A, Murakami S, Akizuki S, Mochizuki J, Echizen H and Takagi I (2005) In vivo metabolic activity of CYP2C19 and CYP3A in relation to CYP2C19 genetic polymorphism in chronic liver disease. *J Clin Pharmacol*, **45**:1221-1229.

Otton SV, Schadel M, Cheung SW, Kaplan HL, Busto UE and Sellers EM (1993) CYP2D6 phenotype determines the metabolic conversion of hydrocodone to hydromorphone. *Clin Pharmacol Ther*, **54**:463-472.

Ozdemir M, Crewe KH, Tucker GT and Rostami-Hodjegan A (2004) Assessment of in vivo CYP2D6 activity: differential sensitivity of commonly used probes to urine pH. *J Clin Pharmacol*, **44**:1398-1404.

Paine MF, Hart HL, Ludington SS, Haining RL, Rettie AE and Zeldin DC (2006) The human intestinal cytochrome P450 "pie". *Drug Metab Dispos*, **34**:880-886.

Paine MF, Khalighi M, Fisher JM, Shen DD, Kunze KL, Marsh CL, Perkins JD and Thummel KE (1997) Characterization of interintestinal and intrainestinal variations in human CYP3A-dependent metabolism. *J Pharmacol Exp Ther*, **283**:1552-1562.

Palamanda J, Feng WW, Lin CC and Nomeir AA (2000) Stimulation of tolbutamide hydroxylation by acetone and acetonitrile in human liver microsomes and in a cytochrome P-450 2C9-reconstituted system. *Drug Metab Dispos*, **28**:38-43.

Pan L, Vander Stichele R, Rosseel MT, Berlo JA, De Schepper N and Belpaire FM (1999) Effects of smoking, CYP2D6 genotype, and concomitant drug intake on the steady state plasma concentrations of haloperidol and reduced haloperidol in schizophrenic inpatients. *Ther Drug Monit*, **21**:489-497.

Park JY, Kim KA, Park PW, Lee OJ, Kang DK, Shon JH, Liu KH and Shin JG (2006) Effect of CYP3A5\*3 genotype on the pharmacokinetics and pharmacodynamics of alprazolam in healthy subjects. *Clin Pharmacol Ther*, **79**:590-599.

Peart GF, Boutagy J and Shenfield GM (1987) Lack of relationship between tolbutamide metabolism and debrisoquine oxidation phenotype. *Eur J Clin Pharmacol*, **33**:397-402.

Pedersen RS, Damkier P and Brosen K (2006) Enantioselective pharmacokinetics of tramadol in CYP2D6 extensive and poor metabolizers. *Eur J Clin Pharmacol*, 62:513-521.

Perini JA, Vianna-Jorge R, Brogliato AR and Suarez-Kurtz G (2005) Influence of CYP2C9 genotypes on the pharmacokinetics and pharmacodynamics of piroxicam. *Clin Pharmacol Ther*, 78:362-369.

Peyvandi F, Spreafico M, Siboni SM, Moia M and Mannucci PM (2004) CYP2C9 genotypes and dose requirements during the induction phase of oral anticoagulant therapy. *Clin Pharmacol Ther*, 75:198-203.

Pieri L, Schaffner R, Scherschlicht R, Polc P, Sepinwall J, Davidson A, Mohler H, Cumin R, Da Prada M, Burkard WP, Keller HH, Muller RK, Gerold M, Pieri M, Cook L and Haefely W (1981) Pharmacology of midazolam. *Arzneimittelforschung*, 31:2180-2201.

Polonsky KS, Licinio-Paixao J, Given BD, Pugh W, Rue P, Galloway J, Karrison T and Frank B (1986) Use of biosynthetic human C-peptide in the measurement of insulin secretion rates in normal volunteers and type I diabetic patients. *J Clin Invest*, 77:98-105.

Pope LE, Khalil MH, Berg JE, Stiles M, Yakatan GJ and Sellers EM (2004) Pharmacokinetics of dextromethorphan after single or multiple dosing in combination with quinidine in extensive and poor metabolizers. *J Clin Pharmacol*, 44:1132-1142.

Poulin P and Theil FP (2002) Prediction of pharmacokinetics prior to in vivo studies. II. Generic physiologically based pharmacokinetic models of drug disposition. *J Pharm Sci*, 91:1358-1370.

Powers WF, Abbrecht PH and Covell DG (1980) Systems and microcomputer approach to anticoagulant therapy. *IEEE Trans Biomed Eng*, 27:520-523.

Priskorn M, Sidhu JS, Larsen F, Davis JD, Khan AZ and Rolan PE (1997) Investigation of multiple dose citalopram on the pharmacokinetics and pharmacodynamics of racemic warfarin. *Br J Clin Pharmacol*, 44:199-202.

Proctor NJ, Tucker GT and Rostami-Hodjegan A (2004) Predicting drug clearance from recombinantly expressed CYPs: intersystem extrapolation factors. *Xenobiotica*, 34:151-178.

Qiao HL, Hu YR, Tian X, Jia LJ, Gao N, Zhang LR and Guo YZ (2006) Pharmacokinetics of three proton pump inhibitors in Chinese subjects in relation to the CYP2C19 genotype. *Eur J Clin Pharmacol*, 62:107-112.

Qin XP, Xie HG, Wang W, He N, Huang SL, Xu ZH, Ou-Yang DS, Wang YJ and Zhou HH (1999) Effect of the gene dosage of CYP2C19 on diazepam metabolism in Chinese subjects. *Clin Pharmacol Ther*, 66:642-646.

- Rane A, Wilkinson GR and Shand DG (1977) Prediction of hepatic extraction ratio from in vitro measurement of intrinsic clearance. *J Pharmacol Exp Ther*, **200**:420-424.
- Rau T, Heide R, Bergmann K, Wuttke H, Werner U, Feifel N and Eschenhagen T (2002) Effect of the CYP2D6 genotype on metoprolol metabolism persists during long-term treatment. *Pharmacogenetics*, **12**:465-472.
- Regardh CG, Andersson T, Lagerstrom PO, Lundborg P and Skanberg I (1990) The pharmacokinetics of omeprazole in humans--a study of single intravenous and oral doses. *Ther Drug Monit*, **12**:163-172.
- Rendell M (2004) Advances in diabetes for the millennium: drug therapy of type 2 diabetes. *MedGenMed*, **6**:9.
- Rendic S (2002) Summary of information on human CYP enzymes: human P450 metabolism data. *Drug Metab Rev*, **34**:83-448.
- Rettie AE, Korzekwa KR, Kunze KL, Lawrence RF, Eddy AC, Aoyama T, Gelboin HV, Gonzalez FJ and Trager WF (1992) Hydroxylation of warfarin by human cDNA-expressed cytochrome P-450: a role for P-450C9 in the etiology of (S)-warfarin-drug interactions. *Chem Res Toxicol*, **5**:54-59.
- Rettie AE, Wienkers LC, Gonzalez FJ, Trager WF and Korzekwa KR (1994) Impaired (S)-warfarin metabolism catalysed by the R144C allelic variant of CYP2C9. *Pharmacogenetics*, **4**:39-42.
- Riedel M, Schwarz MJ, Strassnig M, Spellmann I, Muller-Arends A, Weber K, Zach J, Muller N and Moller HJ (2005) Risperidone plasma levels, clinical response and side-effects. *Eur Arch Psychiatry Clin Neurosci*, **255**:261-268.
- Rolan P, Atkinson AJ, Jr. and Lesko LJ (2003) Use of biomarkers from drug discovery through clinical practice: report of the Ninth European Federation of Pharmaceutical Sciences Conference on Optimizing Drug Development. *Clin Pharmacol Ther*, **73**:284-291.
- Rooney KF, Snoeck E and Watson PH (2001) Modelling and simulation in clinical drug development. *Drug Discov Today*, **6**:802-806.
- Rosemary J, Surendiran A, Rajan S, Shashindran CH and Adithan C (2006) Influence of the CYP2C9 AND CYP2C19 polymorphisms on phenytoin hydroxylation in healthy individuals from south India. *Indian J Med Res*, **123**:665-670.
- Rostami-Hodjegan A, Abdul-Manap R, Wright CE, Tucker GT and Morice AH (2001) The placebo response to citric acid-induced cough: pharmacodynamics and gender differences. *Pulm Pharmacol Ther*, **14**:315-319.
- Rostami-Hodjegan A, Peacey SR, George E, Heller SR and Tucker GT (1998) Population-based modeling to demonstrate extrapancreatic effects of tolbutamide. *Am J Physiol*, **274**:E758-771.

Rostami-Hodjegan A and Tucker G (2004) 'In silico' simulations to assess the 'in vivo' consequences of 'in vitro' metabolic drug–drug interactions. *Drug Discovery Today: Technologies*, **1**:441-448.

Rostami-Hodjegan A and Tucker GT (2002) The effects of portal shunts on intestinal cytochrome P450 3A activity. *Hepatology*, **35**:1549-1550; author reply 1550-1541.

Rowland M and Tozer TN (1995) *Clinical Pharmacokinetics: Concepts and Applications*, third edition. Lippincott Williams & Wilkins, Philadelphia.

Rowland-Yeo K, Rostami-Hodjegan A and Tucker GT (2004) Abundance of cytochromes P450 in human liver: a meta-analysis. *Br J Clin Pharmacol*, **57**:687-688.

Sachs G, Shin JM, Briving C, Wallmark B and Hersey S (1995) The pharmacology of the gastric acid pump: the H<sup>+</sup>,K<sup>+</sup> ATPase. *Annu Rev Pharmacol Toxicol*, **35**:277-305.

Sachse C, Brockmoller J, Bauer S and Roots I (1997) Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. *Am J Hum Genet*, **60**:284-295.

Sagar M, Seensalu R, Tybring G, Dahl ML and Bertilsson L (1998) CYP2C19 genotype and phenotype determined with omeprazole in patients with acid-related disorders with and without *Helicobacter pylori* infection. *Scand J Gastroenterol*, **33**:1034-1038.

Sakai T, Aoyama N, Kita T, Sakaeda T, Nishiguchi K, Nishitora Y, Hohda T, Sirasaka D, Tamura T, Tanigawara Y, Kasuga M and Okumura K (2001) CYP2C19 genotype and pharmacokinetics of three proton pump inhibitors in healthy subjects. *Pharm Res*, **18**:721-727.

Sandberg M, Johansson I, Christensen M, Rane A and Eliasson E (2004) The impact of CYP2C9 genetics and oral contraceptives on cytochrome P450 2C9 phenotype. *Drug Metab Dispos*, **32**:484-489.

Schadel M, Wu D, Otton SV, Kalow W and Sellers EM (1995) Pharmacokinetics of dextromethorphan and metabolites in humans: influence of the CYP2D6 phenotype and quinidine inhibition. *J Clin Psychopharmacol*, **15**:263-269.

Schalekamp T, Brasse BP, Roijers JF, Chahid Y, van Geest-Daalderop JH, de Vries-Goldschmeding H, van Wijk EM, Egberts AC and de Boer A (2006) VKORC1 and CYP2C9 genotypes and acenocoumarol anticoagulation status: interaction between both genotypes affects overanticoagulation. *Clin Pharmacol Ther*, **80**:13-22.

Scheinin H, Anttila M, Dahl ML, Karnani H, Nyman L, Taavitsainen P, Pelkonen O and Bertilsson L (1998) CYP2D6 polymorphism is not crucial for the disposition of selegiline. *Clin Pharmacol Ther*, **64**:402-411.

Schellens JH, van der Wart JH and Breimer DD (1990) Relationship between mephenytoin oxidation polymorphism and phenytoin, methylphenytoin and

phenobarbitone hydroxylation assessed in a phenotyped panel of healthy subjects. *Br J Clin Pharmacol*, 29:665-671.

Schmid E and Smith D (2005) Is declining innovation in the pharmaceutical industry a myth? *Drug Discovery Today*, 10:1031-1039.

Schmider J, Greenblatt DJ, Fogelman SM, von Moltke LL and Shader RI (1997) Metabolism of dextromethorphan in vitro: involvement of cytochromes P450 2D6 and 3A3/4, with a possible role of 2E1. *Biopharm Drug Dispos*, 18:227-240.

Schwab M, Schaeffeler E, Klotz U and Treiber G (2004) CYP2C19 polymorphism is a major predictor of treatment failure in white patients by use of lansoprazole-based quadruple therapy for eradication of *Helicobacter pylori*. *Clin Pharmacol Ther*, 76:201-209.

Schwabedissen CM, Mevissen V, Schmitz F, Woodruff S, Langebartels G, Rau T, Zerres K, Hoffmann R and Ortlepp JR (2006) Obesity is associated with a slower response to initial phenprocoumon therapy whereas CYP2C9 genotypes are not. *Eur J Clin Pharmacol*, 62:713-720.

Sconce EA, Khan TI, Wynne HA, Avery P, Monkhouse L, King BP, Wood P, Kesteven P, Daly AK and Kamali F (2005) The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. *Blood*, 106:2329-2333.

Scordo MG, Pengo V, Spina E, Dahl ML, Gusella M and Padrini R (2002) Influence of CYP2C9 and CYP2C19 genetic polymorphisms on warfarin maintenance dose and metabolic clearance. *Clin Pharmacol Ther*, 72:702-710.

Sekino K, Kubota T, Okada Y, Yamada Y, Yamamoto K, Horiuchi R, Kimura K and Iga T (2003) Effect of the single CYP2C9\*3 allele on pharmacokinetics and pharmacodynamics of losartan in healthy Japanese subjects. *Eur J Clin Pharmacol*, 59:589-592.

Seo JS, Lee SY, Won KJ, Kim DJ, Sohn DS, Yang KM, Cho SH, Park JD, Lee KH and Kim HD (2000) Relationship between normal heart size and body indices in Korean. *J Korean Med Sci*, 15:641-646.

Shams ME, Arneith B, Hiemke C, Dragicevic A, Muller MJ, Kaiser R, Lackner K and Hartter S (2006) CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. *J Clin Pharm Ther*, 31:493-502.

Shargel L and Yu ABC (1999) Applied Biopharmaceutics and Pharmacokinetics, Fourth. Appleton and Lange, Stamford.

Sheiner LB (1969) Computer-aided long term anticoagulation therapy. *Computers and Biomedical Research*, 2:519-536.

Shih PS and Huang JD (2002) Pharmacokinetics of midazolam and 1'-hydroxymidazolam in Chinese with different CYP3A5 genotypes. *Drug Metab Dispos*, **30**:1491-1496.

Shimamoto J, Ieiri I, Urae A, Kimura M, Irie S, Kubota T, Chiba K, Ishizaki T, Otsubo K and Higuchi S (2000) Lack of differences in diclofenac (a substrate for CYP2C9) pharmacokinetics in healthy volunteers with respect to the single CYP2C9\*3 allele. *Eur J Clin Pharmacol*, **56**:65-68.

Shimatani T, Inoue M, Kuroiwa T, Horikawa Y, Mieno H and Nakamura M (2003) Effect of omeprazole 10 mg on intragastric pH in three different CYP2C19 genotypes, compared with omeprazole 20 mg and lafutidine 20 mg, a new H<sub>2</sub>-receptor antagonist. *Aliment Pharmacol Ther*, **18**:1149-1157.

Shimoda K, Someya T, Yokono A, Morita S, Hirokane G, Takahashi S and Okawa M (2002) The impact of CYP2C19 and CYP2D6 genotypes on metabolism of amitriptyline in Japanese psychiatric patients. *J Clin Psychopharmacol*, **22**:371-378.

Shirai N, Furuta T, Moriyama Y, Okochi H, Kobayashi K, Takashima M, Xiao F, Kosuge K, Nakagawa K, Hanai H, Chiba K, Ohashi K and Ishizaki T (2001) Effects of CYP2C19 genotypic differences in the metabolism of omeprazole and rabeprazole on intragastric pH. *Aliment Pharmacol Ther*, **15**:1929-1937.

Shon JH, Yoon YR, Kim KA, Lim YC, Lee KJ, Park JY, Cha IJ, Flockhart DA and Shin JG (2002) Effects of CYP2C19 and CYP2C9 genetic polymorphisms on the disposition of and blood glucose lowering response to tolbutamide in humans. *Pharmacogenetics*, **12**:111-119.

Siguret V, Gouin I, Golmard JL, Geoffroy S, Andreux JP and Pautas E (2004) [Cytochrome P450 2C9 polymorphisms (CYP2C9) and warfarin maintenance dose in elderly patients]. *Rev Med Interne*, **25**:271-274.

Sim SC, Risinger C, Dahl ML, Aklillu E, Christensen M, Bertilsson L and Ingelman-Sundberg M (2006) A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther*, **79**:103-113.

Simonson SG, Martin PD, Mitchell PD, Lasseter K, Gibson G and Schneck DW (2005) Effect of rosuvastatin on warfarin pharmacodynamics and pharmacokinetics. *J Clin Pharmacol*, **45**:927-934.

Sindrup SH, Broesen K, Hansen MG, Aaes-Jorgensen T, Overo KF and Gram LF (1993) Pharmacokinetics of citalopram in relation to the sparteine and the mephenytoin oxidation polymorphisms. *Ther Drug Monit*, **15**:11-17.

Skjelbo E, Mutabingwa TK, Bygbjerg I, Nielsen KK, Gram LF and Broosen K (1996) Chloroguanide metabolism in relation to the efficacy in malaria prophylaxis and the S-mephenytoin oxidation in Tanzanians. *Clin Pharmacol Ther*, **59**:304-311.

Smith DA (2002) Hello Drug Discovery, I am from *insilico*, take me to your president. *Drug Discov Today*, 7:1080-1081.

Soga Y, Nishimura F, Ohtsuka Y, Araki H, Iwamoto Y, Naruishi H, Shiomi N, Kobayashi Y, Takashiba S, Shimizu K, Gomita Y and Oka E (2004) CYP2C polymorphisms, phenytoin metabolism and gingival overgrowth in epileptic subjects. *Life Sci*, 74:827-834.

Sohn DR, Kusaka M, Ishizaki T, Shin SG, Jang IJ, Shin JG and Chiba K (1992) Incidence of S-mephenytoin hydroxylation deficiency in a Korean population and the interphenotypic differences in diazepam pharmacokinetics. *Clin Pharmacol Ther*, 52:160-169.

Sohn DR, Kwon JT, Kim HK and Ishizaki T (1997) Metabolic disposition of lansoprazole in relation to the S-mephenytoin 4'-hydroxylation phenotype status. *Clin Pharmacol Ther*, 61:574-582.

Spigset O, Granberg K, Hagg S, Norstrom A and Dahlqvist R (1997) Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms. *Eur J Clin Pharmacol*, 52:129-133.

Steimer W, Zopf K, von Amelunxen S, Pfeiffer H, Bachofer J, Popp J, Messner B, Kissling W and Leucht S (2004) Allele-specific change of concentration and functional gene dose for the prediction of steady-state serum concentrations of amitriptyline and nortriptyline in CYP2C19 and CYP2D6 extensive and intermediate metabolizers. *Clin Chem*, 50:1623-1633.

Streetman DS, Bleakley JF, Kim JS, Nafziger AN, Leeder JS, Gaedigk A, Gotschall R, Kearns GL and Bertino JS, Jr. (2000) Combined phenotypic assessment of CYP1A2, CYP2C19, CYP2D6, CYP3A, N-acetyltransferase-2, and xanthine oxidase with the "Cooperstown cocktail". *Clin Pharmacol Ther*, 68:375-383.

Sullivan-Klose TH, Ghanayem BI, Bell DA, Zhang ZY, Kaminsky LS, Shenfield GM, Miners JO, Birkett DJ and Goldstein JA (1996) The role of the CYP2C9-Leu359 allelic variant in the tolbutamide polymorphism. *Pharmacogenetics*, 6:341-349.

Suzuki K, Yanagawa T, Shibasaki T, Kaniwa N, Hasegawa R and Tohkin M (2006) Effect of CYP2C9 genetic polymorphisms on the efficacy and pharmacokinetics of glimepiride in subjects with type 2 diabetes. *Diabetes Res Clin Pract*, 72:148-154.

Svec JM, Coleman RW, Mungall DR and Ludden TM (1985) Bayesian pharmacokinetic/pharmacodynamic forecasting of prothrombin response to warfarin therapy: preliminary evaluation. *Ther Drug Monit*, 7:174-180.

Swaisland HC, Cantarini MV, Fuhr R and Holt A (2006) Exploring the relationship between expression of cytochrome P450 enzymes and gefitinib pharmacokinetics. *Clin Pharmacokinet*, 45:633-644.



Tabrizi AR, Zehnbaauer BA, Borecki IB, McGrath SD, Buchman TG and Freeman BD (2002) The frequency and effects of cytochrome P450 (CYP) 2C9 polymorphisms in patients receiving warfarin. *J Am Coll Surg*, **194**:267-273.

Tada H, Tsuchiya N, Satoh S, Kagaya H, Li Z, Sato K, Miura M, Suzuki T, Kato T and Habuchi T (2005) Impact of CYP3A5 and MDR1(ABCB1) C3435T polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients. *Transplant Proc*, **37**:1730-1732.

Taguchi M, Nozawa T, Mizumaki K, Inoue H, Tahara K, Takesono C and Hashimoto Y (2004) Nonlinear mixed effects model analysis of the pharmacokinetics of metoprolol in routinely treated Japanese patients. *Biol Pharm Bull*, **27**:1642-1648.

Takada K, Arefayene M, Desta Z, Yarboro CH, Boumpas DT, Balow JE, Flockhart DA and Illei GG (2004) Cytochrome P450 pharmacogenetics as a predictor of toxicity and clinical response to pulse cyclophosphamide in lupus nephritis. *Arthritis Rheum*, **50**:2202-2210.

Takahashi H, Kashima T, Kimura S, Murata N, Takaba T, Iwade K, Abe T, Tainaka H, Yasumori T and Echizen H (1999) Pharmacokinetic interaction between warfarin and a uricosuric agent, bucolome: application of In vitro approaches to predicting In vivo reduction of (S)-warfarin clearance. *Drug Metab Dispos*, **27**:1179-1186.

Takahashi H, Kashima T, Nomoto S, Iwade K, Tainaka H, Shimizu T, Nomizo Y, Muramoto N, Kimura S and Echizen H (1998) Comparisons between in-vitro and in-vivo metabolism of (S)-warfarin: catalytic activities of cDNA-expressed CYP2C9, its Leu359 variant and their mixture versus unbound clearance in patients with the corresponding CYP2C9 genotypes. *Pharmacogenetics*, **8**:365-373.

Takahashi H, Wilkinson GR, Caraco Y, Muszkat M, Kim RB, Kashima T, Kimura S and Echizen H (2003) Population differences in S-warfarin metabolism between CYP2C9 genotype-matched Caucasian and Japanese patients. *Clin Pharmacol Ther*, **73**:253-263.

Takanashi K, Tainaka H, Kobayashi K, Yasumori T, Hosakawa M and Chiba K (2000) CYP2C9 Ile359 and Leu359 variants: enzyme kinetic study with seven substrates. *Pharmacogenetics*, **10**:95-104.

Takekuma Y, Takenaka T, Kiyokawa M, Yamazaki K, Okamoto H, Kitabatake A, Tsutsui H and Sugawara M (2006) Contribution of polymorphisms in UDP-glucuronosyltransferase and CYP2D6 to the individual variation in disposition of carvedilol. *J Pharm Pharm Sci*, **9**:101-112.

Tang C, Shou M, Rushmore TH, Mei Q, Sandhu P, Woolf EJ, Rose MJ, Gelmann A, Greenberg HE, De Lepeleire I, Van Hecken A, De Schepper PJ, Ebel DL, Schwartz JI and Rodrigues AD (2001) In-vitro metabolism of celecoxib, a cyclooxygenase-2 inhibitor, by allelic variant forms of human liver microsomal cytochrome P450 2C9: correlation with CYP2C9 genotype and in-vivo pharmacokinetics. *Pharmacogenetics*, **11**:223-235.

Tanigawara Y, Aoyama N, Kita T, Shirakawa K, Komada F, Kasuga M and Okumura K (1999) CYP2C19 genotype-related efficacy of omeprazole for the treatment of infection caused by *Helicobacter pylori*. *Clin Pharmacol Ther*, 66:528-534.

Tassies D, Freire C, Pijoan J, Maragall S, Monteagudo J, Ordinas A and Reverter JC (2002) Pharmacogenetics of acenocoumarol: cytochrome P450 CYP2C9 polymorphisms influence dose requirements and stability of anticoagulation. *Haematologica*, 87:1185-1191.

Tate SK, Depondt C, Sisodiya SM, Cavalleri GL, Schorge S, Soranzo N, Thom M, Sen A, Shorvon SD, Sander JW, Wood NW and Goldstein DB (2005) Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin. *Proc Natl Acad Sci U S A*, 102:5507-5512.

Tateishi T, Watanabe M, Nakura H, Asoh M, Shirai H, Mizorogi Y, Kobayashi S, Thummel KE and Wilkinson GR (2001) CYP3A activity in European American and Japanese men using midazolam as an in vivo probe. *Clin Pharmacol Ther*, 69:333-339.

Taube J, Halsall D and Baglin T (2000) Influence of cytochrome P-450 CYP2C9 polymorphisms on warfarin sensitivity and risk of over-anticoagulation in patients on long-term treatment. *Blood*, 96:1816-1819.

Tenneze L, Tarral E, Ducloux N and Funck-Brentano C (2002) Pharmacokinetics and electrocardiographic effects of a new controlled-release form of flecainide acetate: comparison with the standard form and influence of the CYP2D6 polymorphism. *Clin Pharmacol Ther*, 72:112-122.

Tenneze L, Verstuyft C, Becquemont L, Poirier JM, Wilkinson GR and Funck-Brentano C (1999) Assessment of CYP2D6 and CYP2C19 activity in vivo in humans: a cocktail study with dextromethorphan and chloroguanide alone and in combination. *Clin Pharmacol Ther*, 66:582-588.

Thakor NV and Tong S (2004) Advances in quantitative electroencephalogram analysis methods. *Annu Rev Biomed Eng*, 6:453-495.

Tham LS, Goh BC, Nafziger A, Guo JY, Wang LZ, Soong R and Lee SC (2006) A warfarin-dosing model in Asians that uses single-nucleotide polymorphisms in vitamin K epoxide reductase complex and cytochrome P450 2C9. *Clin Pharmacol Ther*, 80:346-355.

Theofanous TG and Barile RG (1973) Multiple-dose kinetics of oral anticoagulants: methods of analysis and optimized dosing. *J Pharm Sci*, 62:261-266.

Thervet E, Anglicheau D, King B, Schlageter MH, Cassinat B, Beaune P, Legendre C and Daly AK (2003) Impact of cytochrome p450 3A5 genetic polymorphism on tacrolimus doses and concentration-to-dose ratio in renal transplant recipients. *Transplantation*, 76:1233-1235.

- Thijssen HH, Drittij MJ, Vervoort LM and de Vries-Hanje JC (2001) Altered pharmacokinetics of R- and S-acenocoumarol in a subject heterozygous for CYP2C9\*3. *Clin Pharmacol Ther*, **70**:292-298.
- Thummel KE, O'Shea D, Paine MF, Shen DD, Kunze KL, Perkins JD and Wilkinson GR (1996) Oral first-pass elimination of midazolam involves both gastrointestinal and hepatic CYP3A-mediated metabolism. *Clin Pharmacol Ther*, **59**:491-502.
- Timm R, Kaiser R, Lotsch J, Heider U, Sezer O, Weisz K, Montemurro M, Roots I and Cascorbi I (2005) Association of cyclophosphamide pharmacokinetics to polymorphic cytochrome P450 2C19. *Pharmacogenomics J*, **5**:365-373.
- Tsuchiya N, Satoh S, Tada H, Li Z, Ohyama C, Sato K, Suzuki T, Habuchi T and Kato T (2004) Influence of CYP3A5 and MDR1 (ABCB1) polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients. *Transplantation*, **78**:1182-1187.
- Tucker GT (2004) Pharmacogenetics - expectations and reality. *British Medical Journal*, **329**:4-6.
- Tucker GT, Houston JB and Huang SM (2001) Optimizing drug development: strategies to assess drug metabolism/transporter interaction potential--toward a consensus. *Pharm Res*, **18**:1071-1080.
- Tucker GT, Silas JH, Iyun AO, Lennard MS and Smith AJ (1977) Polymorphic hydroxylation of debrisoquine. *Lancet*, **2**:718.
- Tybring G, Bottiger Y, Widen J and Bertilsson L (1997) Enantioselective hydroxylation of omeprazole catalyzed by CYP2C19 in Swedish white subjects. *Clin Pharmacol Ther*, **62**:129-137.
- Ufer M, Kammerer B, Kahlich R, Kirchheiner J, Yasar U, Brockmoller J and Rane A (2004) Genetic polymorphisms of cytochrome P450 2C9 causing reduced phenprocoumon (S)-7-hydroxylation in vitro and in vivo. *Xenobiotica*, **34**:847-859.
- Vadher B, Patterson DL and Leaning M (1999) Prediction of the international normalized ratio and maintenance dose during the initiation of warfarin therapy. *Br J Clin Pharmacol*, **48**:63-70.
- Valetin J (2002) Basic anatomical and physiological data for use in radiological protection: Reference values. A report of age- and gender-related differences in the anatomical and physiological characteristics of reference individuals. *Annals of the ICRP, Publication 89*, **32**:5-265.
- van der Weide J, Steijns LS and van Weelden MJ (2003) The effect of smoking and cytochrome P450 CYP1A2 genetic polymorphism on clozapine clearance and dose requirement. *Pharmacogenetics*, **13**:169-172.

van der Weide J, Steijns LS, van Weelden MJ and de Haan K (2001) The effect of genetic polymorphism of cytochrome P450 CYP2C9 on phenytoin dose requirement. *Pharmacogenetics*, **11**:287-291.

Varsaldi F, Miglio G, Scordo MG, Dahl ML, Villa LM, Biolcati A and Lombardi G (2006) Impact of the CYP2D6 polymorphism on steady-state plasma concentrations and clinical outcome of donepezil in Alzheimer's disease patients. *Eur J Clin Pharmacol*, **62**:721-726.

Vecsler M, Loebstein R, Almog S, Kurnik D, Goldman B, Halkin H and Gak E (2006) Combined genetic profiles of components and regulators of the vitamin K-dependent gamma-carboxylation system affect individual sensitivity to warfarin. *Thromb Haemost*, **95**:205-211.

Venkatakrishnan K, von Moltke LL, Obach RS and Greenblatt DJ (2003) Drug metabolism and drug interactions: application and clinical value of in vitro models. *Curr Drug Metab*, **4**:423-459.

Veronese ME, Doecke CJ, Mackenzie PI, McManus ME, Miners JO, Rees DL, Gasser R, Meyer UA and Birkett DJ (1993) Site-directed mutation studies of human liver cytochrome P-450 isoenzymes in the CYP2C subfamily. *Biochem J*, **289** (Pt 2):533-538.

Verstuyft C, Morin S, Robert A, Loriot MA, Beaune P, Jaillon P and Becquemont L (2001) Early acenocoumarol overanticoagulation among cytochrome P450 2C9 poor metabolizers. *Pharmacogenetics*, **11**:735-737.

Veyrat-Follet C, Bruno R, Olivares R, Rhodes GR and Chaikin P (2000) Clinical trial simulation of docetaxel in patients with cancer as a tool for dosage optimization. *Clin Pharmacol Ther*, **68**:677-687.

Visser LE, van Vliet M, van Schaik RH, Kasbergen AA, De Smet PA, Vulto AG, Hofman A, van Duijn CM and Stricker BH (2004) The risk of overanticoagulation in patients with cytochrome P450 CYP2C9\*2 or CYP2C9\*3 alleles on acenocoumarol or phenprocoumon. *Pharmacogenetics*, **14**:27-33.

Visser SA, Wolters FL, Gubbens-Stibbe JM, Tukker E, Van Der Graaf PH, Peletier LA and Danhof M (2003) Mechanism-based pharmacokinetic/pharmacodynamic modeling of the electroencephalogram effects of GABAA receptor modulators: in vitro-in vivo correlations. *J Pharmacol Exp Ther*, **304**:88-101.

Von Moltke L, Greenblatt D, Grassi J and al e (1998a) Reevaluation of the specificity of dextromethorphan as an index substrate. *Clinical pharmacology and therapeutics*, **63**:227.

Von Moltke LL, Greenblatt DJ, Grassi JM, Granda BW, Venkatakrishnan K, Schmider J, Harmatz JS and Shader RI (1998b) Multiple human cytochromes contribute to biotransformation of dextromethorphan in vitro: role of CYP2C9, CYP2C19, CYP2D6, and CYP 3A. *Journal of Pharmacy and Pharmacology*, **50**:997-1004.

von Moltke LL, Greenblatt DJ, Schmider J, Duan SX, Wright CE, Harmatz JS and Shader RI (1996) Midazolam hydroxylation by human liver microsomes in vitro: inhibition by fluoxetine, norfluoxetine, and by azole antifungal agents. *J Clin Pharmacol*, **36**:783-791.

Vormfelde SV, Engelhardt S, Zirk A, Meineke I, Tuchen F, Kirchheiner J and Brockmoller J (2004) CYP2C9 polymorphisms and the interindividual variability in pharmacokinetics and pharmacodynamics of the loop diuretic drug torsemide. *Clin Pharmacol Ther*, **76**:557-566.

Wan J, Xia H, He N, Lu YQ and Zhou HH (1996) The elimination of diazepam in Chinese subjects is dependent on the mephenytoin oxidation phenotype. *Br J Clin Pharmacol*, **42**:471-474.

Wandel C, Witte JS, Hall JM, Stein CM, Wood AJ and Wilkinson GR (2000) CYP3A activity in African American and European American men: population differences and functional effect of the CYP3A4\*1B5'-promoter region polymorphism. *Clin Pharmacol Ther*, **68**:82-91.

Wang JH, Liu ZQ, Wang W, Chen XP, Shu Y, He N and Zhou HH (2001) Pharmacokinetics of sertraline in relation to genetic polymorphism of CYP2C19. *Clin Pharmacol Ther*, **70**:42-47.

Wang R, Chen K, Wen S, Li J and Wang S (2005a) Relationship of the P450 2C9 genetic polymorphisms in Chinese healthy volunteers and the pharmacokinetic of tolbutamide. *Chinese Journal of Clinical Pharmacology*, **21**:255-259.

Wang R, Chen K, Wen SY, Li J and Wang SQ (2005b) Pharmacokinetics of glimepiride and cytochrome P450 2C9 genetic polymorphisms. *Clin Pharmacol Ther*, **78**:90-92.

Wang Y and Unadkat JD (1999) Enzymes in addition to CYP3A4 and 3A5 mediate N-demethylation of dextromethorphan in human liver microsomes. *Biopharm Drug Dispos*, **20**:341-346.

Watanabe M, Iwahashi K, Kugoh T and Suwaki H (1998) The relationship between phenytoin pharmacokinetics and the CYP2C19 genotype in Japanese epileptic patients. *Clin Neuropharmacol*, **21**:122-126.

Wedlund PJ (2000) The CYP2C19 enzyme polymorphism. *Pharmacology*, **61**:174-183.

Wedlund PJ and Wilkinson GR (1996) In vivo and in vitro measurement of CYP2C19 activity. *Methods Enzymol*, **272**:105-114.

Wiegman H and Vossepoel AM (1977) A computer program for long term anticoagulation control. *Comput Programs Biomed*, **7**:71-84.

Wilkinson GR and Shand DG (1975) Commentary: a physiological approach to hepatic drug clearance. *Clin Pharmacol Ther*, **18**:377-390.

- Williams JA, Hyland R, Jones BC, Smith DA, Hurst S, Goosen TC, Peterkin V, Koup JR and Ball SE (2004) Drug-drug interactions for UDP-glucuronosyltransferase substrates: a pharmacokinetic explanation for typically observed low exposure (AUC<sub>i</sub>/AUC) ratios. *Drug Metab Dispos*, **32**:1201-1208.
- Williams JA, Johnson K, Paulauskis J and Cook J (2006) So many studies, too few subjects: establishing functional relevance of genetic polymorphisms on pharmacokinetics. *J Clin Pharmacol*, **46**:258-264.
- Williams JA, Ring BJ, Cantrell VE, Jones DR, Eckstein J, Ruterbories K, Hamman MA, Hall SD and Wrighton SA (2002) Comparative metabolic capabilities of CYP3A4, CYP3A5, and CYP3A7. *Drug Metab Dispos*, **30**:883-891.
- Williams PJ and Ette EI (2000) The role of population pharmacokinetics in drug development in light of the Food and Drug Administration's 'Guidance for Industry: population pharmacokinetics'. *Clin Pharmacokinet*, **39**:385-395.
- Wilson ZE, Rostami-Hodjegan A, Burn JL, Tooley A, Boyle J, Ellis SW and Tucker GT (2003) Inter-individual variability in levels of human microsomal protein and hepatocellularity per gram of liver. *Br J Clin Pharmacol*, **56**:433-440.
- Wong M, Balleine RL, Collins M, Liddle C, Clarke CL and Gurney H (2004) CYP3A5 genotype and midazolam clearance in Australian patients receiving chemotherapy. *Clin Pharmacol Ther*, **75**:529-538.
- Wrighton SA, Brian WR, Sari MA, Iwasaki M, Guengerich FP, Raucy JL, Molowa DT and Vandenberg M (1990) Studies on the expression and metabolic capabilities of human liver cytochrome P450III<sub>A5</sub> (HLp3). *Mol Pharmacol*, **38**:207-213.
- Wu XP, Liao EY, Liu SP, Zhang H, Shan PF, Cao XZ and Jiang Y (2004) Relationship of body surface area with bone density and its risk of osteoporosis at various skeletal regions in women of mainland China. *Osteoporos Int*, **15**:751-759.
- Wuttke H, Rau T, Heide R, Bergmann K, Bohm M, Weil J, Werner D and Eschenhagen T (2002) Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. *Clin Pharmacol Ther*, **72**:429-437.
- Xie HG, Prasad HC, Kim RB and Stein CM (2002) CYP2C9 allelic variants: ethnic distribution and functional significance. *Adv Drug Deliv Rev*, **54**:1257-1270.
- Xie HG, Xu ZH, Huang SL, Liu JH, Wu JX, Jiang CH and Zhou HH (1997) No correlation between side-chain of propranolol oxidation and S-mephenytoin 4'-hydroxylase activity. *Zhongguo Yao Li Xue Bao*, **18**:216-218.
- Yacobi A, Lampman T and Levy G (1977) Frequency distribution of free warfarin and free phenytoin fraction values in serum of healthy human adults. *Clin Pharmacol Ther*, **21**:283-286.

- Yamashiro W, Maeda K, Hirouchi M, Adachi Y, Hu Z and Sugiyama Y (2006) Involvement of transporters in the hepatic uptake and biliary excretion of valsartan, a selective antagonist of the angiotensin II AT1-receptor, in humans. *Drug Metab Dispos*, **34**:1247-1254.
- Yamazaki H, Inoue K, Chiba K, Ozawa N, Kawai T, Suzuki Y, Goldstein JA, Guengerich FP and Shimada T (1998) Comparative studies on the catalytic roles of cytochrome P450 2C9 and its Cys- and Leu-variants in the oxidation of warfarin, flurbiprofen, and diclofenac by human liver microsomes. *Biochem Pharmacol*, **56**:243-251.
- Yamazaki H, Inoue K, Shaw PM, Checovich WJ, Guengerich FP and Shimada T (1997) Different contributions of cytochrome P450 2C19 and 3A4 in the oxidation of omeprazole by human liver microsomes: effects of contents of these two forms in individual human samples. *J Pharmacol Exp Ther*, **283**:434-442.
- Yang J, Tucker GT and Rostami-Hodjegan A (2004) Cytochrome P450 3A expression and activity in the human small intestine. *Clin Pharmacol Ther*, **76**:391.
- Yasar U, Eliasson E, Forslund-Bergengren C, Tybring G, Gadd M, Sjoqvist F and Dahl ML (2001) The role of CYP2C9 genotype in the metabolism of diclofenac in vivo and in vitro. *Eur J Clin Pharmacol*, **57**:729-735.
- Yasar U, Forslund-Bergengren C, Tybring G, Dorado P, Llerena A, Sjoqvist F, Eliasson E and Dahl ML (2002) Pharmacokinetics of losartan and its metabolite E-3174 in relation to the CYP2C9 genotype. *Clin Pharmacol Ther*, **71**:89-98.
- Yasuda S, Horai Y, Tomono Y, Nakai H, Yamato C, Manabe K, Kobayashi K, Chiba K and Ishizaki T (1995) Comparison of the kinetic disposition and metabolism of E3810, a new proton pump inhibitor, and omeprazole in relation to S-mephenytoin 4'-hydroxylation status. *Clin Pharmacol Ther*, **58**:143-154.
- Yasui-Furukori N, Mihara K, Kondo T, Kubota T, Iga T, Takarada Y, De Vries R, Kaneko S and Tateishi T (2003) Effects of CYP2D6 genotypes on plasma concentrations of risperidone and enantiomers of 9-hydroxyrisperidone in Japanese patients with schizophrenia. *J Clin Pharmacol*, **43**:122-127.
- Yin OQ, Shi XJ, Tomlinson B and Chow MS (2005a) Effect of cyp2d6\*10 allele on the pharmacokinetics of loratadine in chinese subjects. *Drug Metab Dispos*, **33**:1283-1287.
- Yin OQ, Tomlinson B, Chow AH, Waye MM and Chow MS (2004) Omeprazole as a CYP2C19 marker in Chinese subjects: assessment of its gene-dose effect and intrasubject variability. *J Clin Pharmacol*, **44**:582-589.
- Yin OQ, Tomlinson B and Chow MS (2005b) CYP2C9, but not CYP2C19, polymorphisms affect the pharmacokinetics and pharmacodynamics of glyburide in Chinese subjects. *Clin Pharmacol Ther*, **78**:370-377.

Yoon YR, Cha IJ, Shon JH, Kim KA, Cha YN, Jang IJ, Park CW, Shin SG, Flockhart DA and Shin JG (2000) Relationship of paroxetine disposition to metoprolol metabolic ratio and CYP2D6\*10 genotype of Korean subjects. *Clin Pharmacol Ther*, 67:567-576.

Yu A, Dong H, Lang D and Haining RL (2001a) Characterization of dextromethorphan O- and N-demethylation catalyzed by highly purified recombinant human CYP2D6. *Drug Metab Dispos*, 29:1362-1365.

Yu A and Haining RL (2001) Comparative contribution to dextromethorphan metabolism by cytochrome P450 isoforms in vitro: can dextromethorphan be used as a dual probe for both CYP2D6 and CYP3A activities? *Drug Metab Dispos*, 29:1514-1520.

Yu KS, Cho JY, Jang IJ, Hong KS, Chung JY, Kim JR, Lim HS, Oh DS, Yi SY, Liu KH, Shin JG and Shin SG (2004) Effect of the CYP3A5 genotype on the pharmacokinetics of intravenous midazolam during inhibited and induced metabolic states. *Clin Pharmacol Ther*, 76:104-112.

Yu KS, Yim DS, Cho JY, Park SS, Park JY, Lee KH, Jang IJ, Yi SY, Bae KS and Shin SG (2001b) Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. *Clin Pharmacol Ther*, 69:266-273.

Zhang X, Liu ZH, Zheng JM, Chen ZH, Tang Z, Chen JS and Li LS (2005) Influence of CYP3A5 and MDR1 polymorphisms on tacrolimus concentration in the early stage after renal transplantation. *Clin Transplant*, 19:638-643.

Zhang YA, Reviriego J, Lou YQ, Sjoqvist F and Bertilsson L (1990) Diazepam metabolism in native Chinese poor and extensive hydroxylators of S-mephenytoin: interethnic differences in comparison with white subjects. *Clin Pharmacol Ther*, 48:496-502.

Zhao Y, Song M, Guan D, Bi S, Meng J, Li Q and Wang W (2005) Genetic polymorphisms of CYP3A5 genes and concentration of the cyclosporine and tacrolimus. *Transplant Proc*, 37:178-181.

Zhou Q, Yamamoto I, Fukuda T, Ohno M, Sumida A and Azuma J (1999) CYP2C19 genotypes and omeprazole metabolism after single and repeated dosing when combined with clarithromycin. *Eur J Clin Pharmacol*, 55:43-47.

Ziegler WH, Schalch E, Leishman B and Eckert M (1983) Comparison of the effects of intravenously administered midazolam, triazolam and their hydroxy metabolites. *Br J Clin Pharmacol*, 16 (S1):63S-69S.

Zineh I, Beitelshees AL, Gaedigk A, Walker JR, Pauly DF, Eberst K, Leeder JS, Phillips MS, Gelfand CA and Johnson JA (2004) Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. *Clin Pharmacol Ther*, 76:536-544.