

Acknowledgements

We thank Dr. Joyce A. Goldstein and Dr. Yoshihiko Funae for providing CYP2C19*1A cDNA and pGYR1 vector, respectively. We also thank AstraZeneca R&D Mölndal (Mölndal, Sweden) for generously donating 5-hydroxyomeprazole. This work was supported in part by Health and Labor Sciences Research Grants from the Ministry of Health, Labor and Welfare, in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and in part by the Promotion of Fundamental Studies in Health Sciences from National Institute of Biomedical Innovation.

References

- Wilde MI, McTavish D. Omeprazole: an update of its pharmacology and therapeutic use in acid-related disorders. *Drugs* 1994;48:91-132.
- Smallwood RA, Berlin RG, Castagnoli N, Festen HP, Hawkey CJ, Lam SK *et al.* Safety of acid-suppressing drugs. *Dig Dis Sci* 1995;40:63S-80S.
- Renberg L, Simonsson R, Hoffmann KJ. Identification of two main urinary metabolites of [¹⁴C]omeprazole in humans. *Drug Metab Dispos* 1989;17:69-76.
- Andersson T, Miners JO, Veronese ME, Tassaneeyakul W, Tassaneeyakul W, Meyer UA *et al.* Identification of human liver cytochrome P450 isoforms mediating omeprazole metabolism. *Br J Clin Pharmacol* 1993;36:521-30.
- Chiba K, Kobayashi K, Manabe K, Tani M, Kamataki T, Ishizaki T. Oxidative metabolism of omeprazole in human liver microsomes: cosegregation with *S*-mephenytoin 4'-hydroxylation. *J Pharmacol Exp Ther* 1993;266:52-9.
- Andersson T, Miners JO, Veronese ME, Birkett DJ. Identification of human liver cytochrome P450 isoforms mediating secondary omeprazole metabolism. *Br J Clin Pharmacol* 1994;37:597-604.
- Åbelö A, Andersson TB, Antonsson M, Naudot AK, Skånberg I, Weidolf L. Stereoselective metabolism of omeprazole by human cytochrome P450 enzymes. *Drug Metab Dispos* 2000;28:966-72.
- Li XQ, Weidolf L, Simonsson R, Andersson TB. Enantiomer/enantiomer interactions between the *S*- and *R*-isomers of omeprazole in human cytochrome P450 enzymes: major role of CYP2C19 and CYP3A4. *J Pharmacol Exp Ther* 2005;315:777-87.
- de Morais SM, Wilkinson GR, Blaisdell J, Meyer UA, Nakamura K, Goldstein JA. Identification of a new genetic defect responsible for the polymorphism of (*S*)-mephenytoin metabolism in Japanese. *Mol Pharmacol* 1994;46:594-8.
- de Morais SM, Wilkinson GR, Blaisdell J, Nakamura K, Meyer UA, Goldstein JA. The major genetic defect responsible for the polymorphism of *S*-mephenytoin metabolism in humans. *J Biol Chem* 1994;269:15419-22.
- Goldstein JA. Clinical relevance of genetic polymorphisms in the human CYP2C subfamily. *Br J Clin Pharmacol* 2001;52:349-55.
- Kita T, Tanigawara Y, Aoyama N, Hohda T, Saijoh Y, Komada F *et al.* CYP2C19 genotype related effect of omeprazole on intragastric pH and antimicrobial stability. *Pharm Res* 2001;18:615-21.
- Ieiri I, Kubota T, Urae A, Kimura M, Wada Y, Mamiya K *et al.* Pharmacokinetics of omeprazole (a substrate of CYP2C19) and comparison with two mutant alleles, C gamma P2C19m1 in exon 5 and C gamma P2C19m2 in exon 4, in Japanese subjects. *Clin Pharmacol Ther* 1996;59:647-53.
- Furuta T, Ohashi K, Kamata T, Takashima M, Kosuge K, Kawasaki T *et al.* Effect of genetic differences in omeprazole metabolism on cure rates for *Helicobacter pylori* infection and peptic ulcer. *Ann Intern Med* 1998;129:1027-30.
- Furuta T, Ohashi K, Kobayashi K, Iida I, Yoshida H, Shirai N *et al.* Effects of clarithromycin on the metabolism of omeprazole in relation to CYP2C19 genotype status in humans. *Clin Pharmacol Ther* 1999;66:265-74.
- Wedlund PJ. The CYP2C19 enzyme polymorphism. *Pharmacology* 2000;61:174-83.
- Ferguson RJ, De Morais SM, Benhamou S, Bouchardy C, Blaisdell J, Ibeanu G *et al.* A new genetic defect in human CYP2C19: mutation of the initiation codon is responsible for poor metabolism of *S*-mephenytoin. *J Pharmacol Exp Ther* 1998;284:356-61.
- Ibeanu GC, Blaisdell J, Ghanayem BI, Beyeler C, Benhamou S, Bouchardy C *et al.* An additional defective allele, CYP2C19*5, contributes to the *S*-mephenytoin poor metabolizer phenotype in Caucasians. *Pharmacogenetics* 1998;8:129-35.
- Ibeanu GC, Goldstein JA, Meyer U, Benhamou S, Bouchardy C, Dayer P *et al.* Identification of new human CYP2C19 alleles (CYP2C19*6 and CYP2C19*2B) in a Caucasian poor metabolizer of mephenytoin. *J Pharmacol Exp Ther* 1998;286:1490-5.
- Ibeanu GC, Blaisdell J, Ferguson RJ, Ghanayem BI, Brosen K, Benhamou S *et al.* A novel transversion in the intron 5 donor splice junction of CYP2C19 and a sequence polymorphism in exon 3 contribute to the poor metabolizer phenotype for the anticonvulsant *S*-mephenytoin. *J Pharmacol Exp Ther* 1999;290:635-40.
- Blaisdell J, Mohrenweiser H, Jackson J, Ferguson S, Coulter S, Chanas B *et al.* Identification and functional characterization of novel potentially defective alleles of human CYP2C19. *Pharmacogenetics* 2002;12:703-11.
- Sim SC, Risinger C, Dahl ML, Aklillu E, Christensen M, Bertilsson L *et al.* A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther* 2006;79:103-13.
- Fukushima-Uesaka H, Saito Y, Maekawa K, Ozawa S, Hasegawa R, Kajio H *et al.* Genetic variations and haplotypes of CYP2C19 in a Japanese population. *Drug Metab Pharmacokin* 2005;20:300-7.
- Hanioka N, Tsuneto Y, Saito Y, Sumada T, Maekawa K, Saito K *et al.* Functional characterization of two novel CYP2C19 variants (CYP2C19*18 and CYP2C19*19) found in a Japanese population. *Xenobiotica* 2007;37:342-55.
- Sakaki T, Akiyoshi-Shibata M, Yabusaki Y, Ohkawa H. Organella-targeted expression of rat liver cytochrome P450c27 in yeast. Genetically engineered alteration of mitochondrial P450 into a microsomal form creates a novel functional electron transport chain. *J Biol Chem* 1992;267:16497-502.
- Romanos MA, Scorer CA, Clare JJ. Foreign gene expression in yeast: a review. *Yeast* 1992;8:423-88.
- Wan J, Imaoka S, Chow T, Hiroi T, Yabusaki Y, Funae Y. Expression of four rat CYP2D isoforms in *Saccharomyces cerevisiae* and their catalytic specificity. *Arch Biochem Biophys* 1997;348:383-90.
- Hichiya H, Takemi C, Tsuzuki D, Yamamoto S, Asaoka K, Suzuki S *et al.* Complementary DNA cloning and characterization of cytochrome P450 2D29 from Japanese monkey liver. *Biochem Pharmacol* 2002;64:1101-10.
- Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. *J Biol Chem* 1951;193:265-75.
- Omura T, Sato R. The carbon monoxide-binding pigment of liver microsomes. I. Evidence for its hemoprotein nature. *J Biol Chem* 1964;239:2370-8.
- Laemmli UK. Cleavage of structural proteins during the assembly of the head of bacteriophage T4. *Nature* 1970;227:680-5.

- 32 Towbin H, Staehelin T, Gordon J. Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: procedure and some applications. *Proc Natl Acad Sci USA* 1979;**76**:4350-4.
- 33 Yamazaki H, Inoue K, Shaw PM, Checovich WJ, Guengerich FP, Shimada T. 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* 1997;**283**:434-42.
- 34 Hofmann U, Schwab M, Treiber G, Klotz U. Sensitive quantification of omeprazole and its metabolites in human plasma by liquid chromatography-mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 2006;**83**:85-90.
- 35 Shimizu M, Uno T, Niioka T, Yauji-Furukori N, Takahata T, Sugawara K *et al.* Sensitive determination of omeprazole and its two main metabolites in human plasma by column-switching high-performance liquid chromatography: application to pharmacokinetic study in relation to CYP2C19 genotypes. *J Chromatogr B Analyt Technol Biomed Life Sci* 2006;**832**:241-8.
- 36 Goldstein JA, Faletto MB, Romkes-Sparks M, Sullivan T, Kitareewan S, Raucy JL *et al.* Evidence that CYP2C19 is the major (*S*)-mephenytoin 4'-hydroxylase in humans. *Biochemistry* 1994;**33**:1743-52.
- 37 Rendic S, Di Carlo FJ. Human cytochrome P450 enzymes: a status report summarizing their reactions, substrates, inducers, and inhibitors. *Drug Metab Rev* 1997;**29**:413-580.