

Probing CYP2C19 and CYP3A4 activities in Chinese liver microsomes by quantification of 5-hydroxyomeprazole and omeprazole sulphone¹

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ABSTRACT

AIM: To develop an analytical method for simultaneous quantification of 5-hydroxyomeprazole (5-OH-OP) and omeprazole sulfone (OPS), and explore whether omeprazole (OP) is an appropriate phenotypic probe for CYP2C19 and CYP3A4 in Chinese liver microsomes.

METHODS: OP metabolism *in vitro* was conducted in Chinese liver microsomes, and the major metabolites 5-OH-OP and OPS were determined using high pressure liquid chromatography (HPLC). Monoclonal antibodies anti-CYP2C8/9/19 and anti-CYP3A4 were employed to conduct inhibition experiments. The protein contents of CYP2C19 and CYP3A4 were quantified using Western blot analysis and densitometric scanning. **RESULTS:** 5-OH-OP and OPS gave a baseline resolution in the HPLC analysis. The detection limits for both compounds were 0.01 nmol and the recovery (98 % - 102 %) had good precision with relative standard deviation of <9.5 %. Both anti-CYP2C8/9/19 and anti-CYP3A4 had a significant inhibitory effect ($P < 0.05$) on the 5-OH-OP formation in a substrate concentration-dependent manner, and anti-CYP3A4 alone could almost abolish the formation of OPS (>87 %). At a substrate concentration of 2 $\mu\text{mol/L}$ OP, good correlations were found between OP 5-hydroxylation and *S*-mephenytoin 4'-hydrox-

ylation activities ($r = 0.72$, $P < 0.01$), OP 5-hydroxylation activities and CYP2C19 contents ($r = 0.82$, $P < 0.01$), and OP sulfoxidation activities and CYP3A4 contents ($r = 0.78$, $P < 0.01$) in Chinese liver microsomes.

CONCLUSION: OP metabolism is mediated mainly by CYP2C19 and CYP3A4, and OP can be used to probe CYP2C19 and CYP3A4 activities in Chinese liver microsomes at appropriate substrate concentrations with the HPLC method presently developed.

INTRODUCTION

In recent years, the use of human liver microsomes to identify the P450 enzyme(s) responsible for a given metabolic pathway has increased greatly^[1]. One of the fundamental study approaches for such an end is to correlate the metabolism of the tested drug with the activities of each P450 enzyme possibly involved in a panel of liver microsomes from different subjects^[1]. This approach of correlation analysis necessitates characterizing the liver microsomes for metabolic competency with probe substrates of various P450 enzymes.

Omeprazole (OP), the prototypic gastric H⁺/K⁺-ATPase inhibitor, undergoes extensive and complete metabolism in the liver to yield two major metabolites: 5-hydroxyomeprazole (5-OH-OP) and omeprazole sulfone (OPS)^[2]. The formation of 5-OH-OP is mediated mainly by CYP2C19 with only a minor contribution of CYP3A4 in Japanese and Caucasian liver microsomes, while the formation of OPS is almost CYP3A4-dependent^[3-5]. OP thus may provide a convenient probe substrate for both CYP2C19 and CYP3A4 in drug metabolism studies *in vitro*. To assume this role, close relationships between the enzyme activities and/or protein contents of CYP2C19 and CYP3A4 and OP oxidative metabolism would have to be further established respectively. In fact, it has been suggested that OP can replace *S*-mephenytoin (*S*-MP) as an *in vivo* phenotypic probe for CYP2C19 in large population studies^[6]. OP metabolism has not been fully characterized in Chinese liver micro-

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somes. In consideration of the interethnic differences in the activities of CYP2C19^(7,8) and CYP3A4⁽⁹⁾, it is also necessary to further evaluate the relative contributions of these two enzymes to OP metabolism in Chinese liver microsomes. The present study was mainly to explore whether OP is suitable for determining CYP2C19 and CYP3A4 activities in Chinese liver microsomes as a probe substrate.

MATERIALS AND METHODS

Chemicals and materials OP, 5-OH-OP, OPS, and H259/36 (internal standard) were generous gifts from Astra Hässle AB (Mölnådal, Sweden). *S*-MP and 4'-hydroxymephenytoin were generously donated by Dr GR Wilkinson (Vanderbilt University School of Medicine, Nashville, TN, USA). NADP, glucose-6-phosphate and glucose-6-phosphate dehydrogenase were purchased from Sigma Chemical Co (St Louis, MO, USA). Acetonitrile and methanol of HPLC grade were from Linhan Chemical Factory (Zhejiang, China). Recombinant CYP2C19 and CYP3A4 expressed in human lymphoblast, and goat anti-rat CYP2C11 and anti-rat CYP3A2 were from Daiichi Pure Chemicals Co (Tokyo, Japan). Inhibitory monoclonal antibodies to human CYP2C8/9/19 and CYP3A4, and anti-lysozyme monoclonal antibody (HyHel, IgG) as a control were generously donated by Dr TJ Yang and Dr HV Gelboin (Laboratories of Molecular Carcinogenesis and Metabolism, NIH, Bethesda, MD, USA). All other supplies were of the highest grades available from commercial sources.

Preparation of human liver microsomes The twenty Chinese liver specimens used in this study were randomly selected from our liver bank. The collection and use of human liver tissue for studies had been approved by the Ethics Committee of Hunan Medical University. The collection procedures for liver tissue and its morphologic and biochemical characterization were described as elsewhere^(10,11). Microsomes were prepared by differential centrifugation^(10,11). And microsomal protein concentrations were determined by the method of Lowry⁽¹²⁾.

OP and *S*-MP metabolism *in vitro* The activities of OP 5-hydroxylase, OP sulfoxidase, and *S*-MP 4'-hydroxylase (CYP2C19) were measured in the microsomes of the twenty Chinese livers. The incubation medium contained 0.1 mol/L potassium-phosphate buffer (pH 7.4), 0.5 g/L of microsome protein, 0.5 mmol/L NADP, 5 mmol/L glucose-6-phosphate, 1 IU/mL glu-

cose-6-phosphate dehydrogenase, 5 mmol/L MgCl₂, 0.1 mmol/L edetic acid, and OP (2 μmol/L) or *S*-MP (250 μmol/L) in a final volume of 500 μL. Duplicate incubations were used for each liver specimen. Preliminary experiments showed that the formation rates of metabolites for both OP and *S*-MP were linear at 37 °C for the incubation time up to 60 min and microsomal protein concentration up to 1.0 g/L. Accordingly, the incubation time of 20 min for OP metabolism and 60 min for *S*-MP metabolism, and the microsomal protein concentration of 0.5 g/L for both were employed for the subsequent work. The enzyme reactions were terminated by cooling the samples in ice bath and by adding 3 mL of extraction solutions.

The inhibitory effect of monoclonal antibodies specific to CYP2C8/9/19 and CYP3A4 on OP metabolism was examined with five specimens at substrate concentrations of 2, 20, and 100 μmol/L, respectively. A ratio of 1:5 (antibody: microsomal protein) of anti-CYP2C8/9/19 and anti-CYP3A4 was used to ensure a maximal inhibitory effect on CYP2C19 and CYP3A4, respectively, which was tested on six specimens. Due to the limited quantities of the antibodies, single incubations were employed.

HPLC analysis After the enzyme reactions were terminated, 100 μL H259/36 (24.0 μmol/L) methanol solution was added to the samples as internal standard for assaying 5-OH-OP and OPS both of which were extracted with dichloromethane. The aliquot of organic layer after shaking vigorously for 1 min and centrifugation for 10 min (2500 × *g*) was transferred to another glass tube and evaporated to dryness under a gentle stream of nitrogen at 37 °C. Residues were reconstituted by 50 μL or 100 μL of HPLC mobile phase. The HPLC system consisted of an HP series of 1050 pump, online degasser, variable wavelength detector and manual injector (Hewlett-Packard Co, USA). The HPLC was performed on a 5 μm Kromasil C₁₈ column (4.6 mm × 250 mm, ID, Alltech, Dalian, China) at the wavelength of 302 nm at 40 °C of column temperature. The mobile phase was a mixture of acetonitrile, methanol, and phosphate buffer 0.01 mol/L pH 8.0 (43:100:100, vol:vol:vol) at a flow rate of 1.0 mL/min.

4'-OH-MP formed in the incubations was also determined using HPLC as described by others⁽¹³⁾ except that microsomal incubation instead of blood samples was used.

Western blot analysis The protein contents of CYP2C19 and CYP3A4 were determined using Western

blot analysis and densitometric scanning with minor modifications^[14]. In the present study, the goat anti-rat CYP2C11 antibody was used to detect CYP2C19, and the anti-rat CYP3A2 antibody to detect CYP3A4 (antibody dilution 1:500). Recombinant CYP2C19 and CYP3A4 expressed in human lymphoblast were used as controls respectively.

Statistical analysis Data were expressed as $\bar{x} \pm s$. Pooled data were analyzed using worksheet program, Excel (version 7.0, Microsoft Inc, USA). A one-way *t*-test for unpaired and paired data was used to determine the significance of differences in the inhibitory effects of monoclonal antibodies. Correlation analyses were performed by least-squares linear regression. $P < 0.05$ was considered statistically significant.

RESULTS

Chromatographic quantification of 5-OH-OP and OPS The retention times of 5-OH-OP, internal standard, OP, and OPS were 5.5, 9.8, 12.2, and 13.5 min, respectively. No potential interfering peaks were found in the blank incubation buffers. 5-OH-OP, internal standard, OP and OPS gave fully resolved and symmetrical peaks (Fig 1). The relative recoveries of both 5-OH-OP and OPS derived from the found and spiked

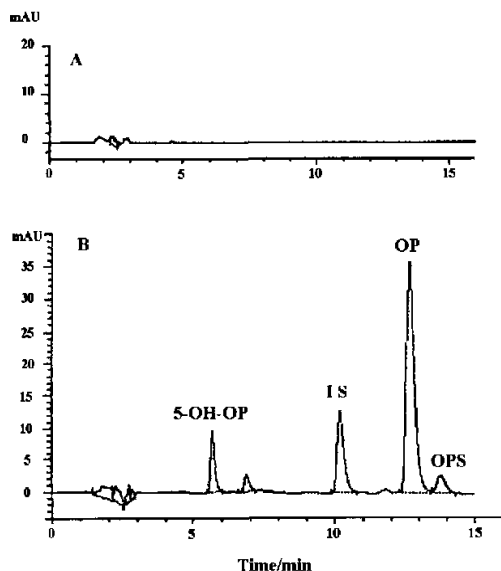


Fig 1. HPLC of extracted (A) blank incubation buffer and (B) incubation buffer of human liver microsomes with 2 μmol/L OP. IS: internal standard.

four levels ranged from 98 % - 102 %. The coefficients of variation for intra- and inter-day reproducibility were less than 9.5 %. 5-OH-OP and OPS were linear over the range of 0.02 - 5.0 nmol with a correlation coefficient of 0.999 and 0.998, respectively. This HPLC method showed a limit of detection of 0.01 nmol for both 5-OH-OP and OPS.

Inhibition study with monoclonal antibodies

Both anti-CYP2C8/9/19 and anti-CYP3A4 could cause a reduction in the formation of 5-OH-OP, and their inhibitory effects were substrate concentration-dependent but changed to an opposite manner with an increase of substrate concentrations (Fig 2). The addition of anti-CYP2C8/9/19 resulted in a mean 75.0 %, 56.4 %, and 42.0 % ($P < 0.01$) inhibition of the 5-OH-OP formation at 2, 20, and 100 μmol/L OP respectively, while anti-CYP3A4 correspondingly caused 22.2 % ($0.01 < P < 0.05$), 35.5 %, and 54.1 % ($P < 0.01$) inhibition at the three substrate concentrations. In addition, anti-CYP3A4 almost abolished the formation of OPS at all the substrate concentrations tested ($> 87 %$, $P < 0.05$), while anti-CYP2C8/9/19 had little inhibitory effect (Fig 3).

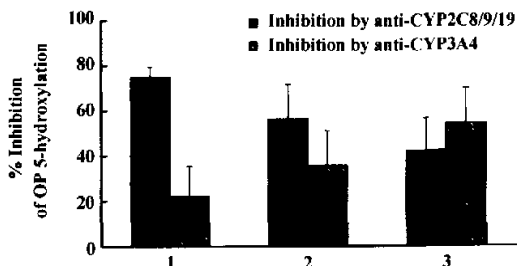


Fig 2. Effects of monoclonal antibodies anti-CYP2C8/9/19 and anti-CYP3A4 on the formation of 5-OH-OP in human liver microsomes at the substrate concentration of (1) 2, (2) 20, and (3) 100 μmol/L OP. The inhibition study was performed with five liver specimens. $\bar{x} \pm s$.

Correlation analysis The twenty Chinese livers were phenotyped with CYP2C19 putative probe substrate *S*-MP (250 μmol/L) at first. The formation of 4'-OH-MP was markedly deficient in three livers (less than 20 nmol · min⁻¹ · g⁻¹ microsomal protein). The microsomal activities of OP 5-hydroxylation and sulfoxidation in these livers were then measured at a substrate concentration of 2 μmol/L. Good correlation was found between the OP 5-hydroxylation and *S*-MP 4'-hydroxylation activities ($r =$

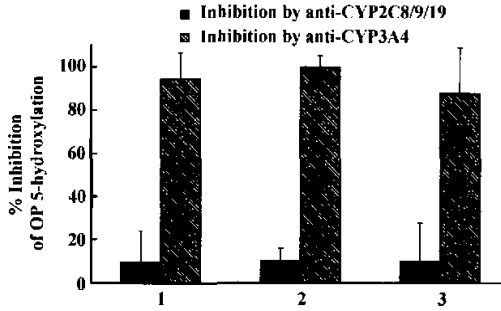


Fig 3. Effects of monoclonal antibodies anti-CYP2C8/9/19 and anti-CYP3A4 on the formation of OPS in human liver microsomes at the substrate concentration of (1) 2, (2) 20, and (3) 100 μmol/L OP. The inhibition study was performed with five liver specimens. $\bar{x} \pm s$.

0.71, $P < 0.01$; Fig 4). The average protein contents of CYP2C19 and CYP3A4 in these livers were 7.0 and 119.3 nmol/g microsomal protein, respectively. There was a 5-fold variation in the CYP3A4 content. Interestingly, the three livers deficient in *S*-MP 4'-hydroxylation activity had very low activities of OP 5-hydroxylation and lacked CYP2C19 protein. The OP 5-hydroxylation activities correlated well with the CYP2C19 contents ($r = 0.82$; $P < 0.01$; Fig 5), but not with the contents of

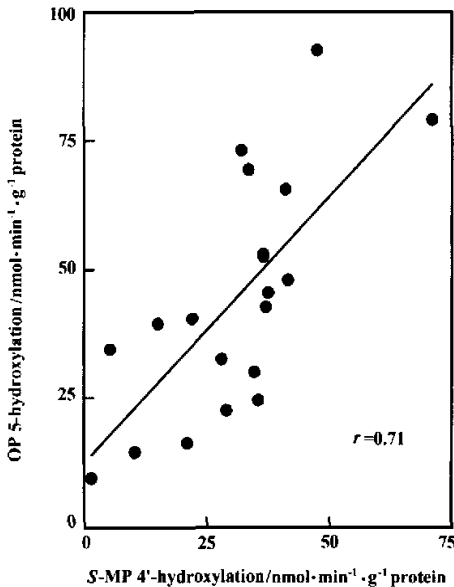


Fig 4. Correlation between OP 5-hydroxylation and *S*-MP 4'-hydroxylation activities in the microsomes of 20 Chinese livers. The substrate concentrations were 2 μmol/L OP and 250 μmol/L *S*-MP, respectively.

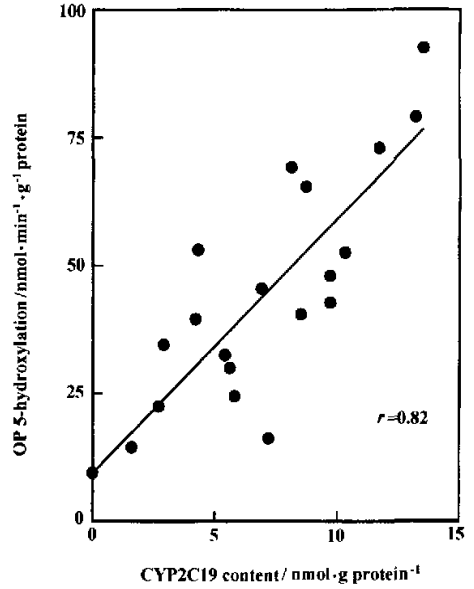


Fig 5. Correlation between OP 5-hydroxylation activities and CYP2C19 protein contents in the microsomes of 20 Chinese livers. The substrate concentration for OP 5-hydroxylation was 2 μmol/L OP.

CYP3A4 ($r = -0.33$, $P > 0.10$). However, good correlation was found between OP sulfoxidation activities and the CYP3A4 contents ($r = 0.78$, $P < 0.01$; Fig 6).

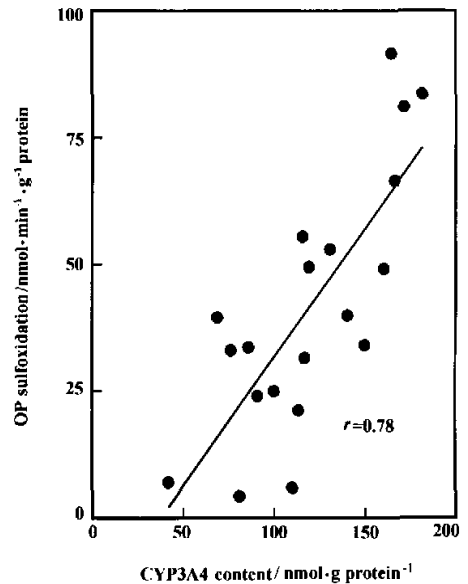


Fig 6. Correlation between OP sulfoxidation activities and CYP3A4 protein contents in the microsomes of 20 Chinese livers. The substrate concentration for OP sulfoxidation is 2 μmol/L OP.

DISCUSSION

The extractor, mobile phase, and/or internal standard employed in this study to determine the 5-OH-OP and OPS formed in liver microsomes were different from those reported previously^[3-5]. However, good precision was still achieved for the recoveries of OP and OPS. Furthermore, the simple and convenient HPLC method had a wide linear range and excellent sensitivity for quantification of these two compounds, which met well with the analytical demands for studying drug metabolism *in vitro*^[15].

Consistent with the previous findings from Japanese and Caucasian liver microsomes^[3-5], our results from inhibition experiments indicated that both CYP2C and CYP3A4 were responsible for OP 5-hydroxylation in Chinese liver microsomes. The sum of the inhibitory effects of anti-CYP2C8/9/19 and anti-CYP3A4 was more than 90 % at each substrate concentration tested, suggesting little contribution of other P450 enzymes except CYP2C and CYP3A4. We could not discriminate the roles of CYP2C8, 2C9, 2C18 and 2C19, but it has been reported, by using human recombinant P450 enzymes, that the former three may only contribute to the reaction at high substrate concentrations^[16]. In this study, at a low substrate concentration (2 $\mu\text{mol/L}$) that is close to *in vivo* therapeutic plasma levels, the 5-OH-OP formation was inhibited by anti-CYP2C8/9/19 to an extent of 75.0 % extent, and correlated well with the CYP2C19-mediated 4'-hydroxymephenytoin formation and the CYP2C19 protein contents respectively. These *in vitro* results indicate clearly that 5-OH-OP is formed mainly by CYP2C19 in Chinese liver microsomes at such a low substrate concentration, consistent with *in vivo* results of cosegregation of OP 5-hydroxylation with S-MP 4'-hydroxylation in Chinese subjects^[17]. In addition, the substrate concentration-dependent inhibition of OP 5-hydroxylation by anti-CYP2C8/9/19 and anti-CYP3A4 showed that with the increase of substrate concentration, the relative contribution of CYP2C to the reaction decreased while that of CYP3A4 increased.

In contrast to 5-hydroxylation, OP sulfoxidation was almost inhibited by anti-CYP3A4 alone. And good correlation was found between the sulfoxidation activities and the CYP3A4 protein contents. These data showed that OPS was formed principally by CYP3A4 in Chinese liver microsomes, which is also in line with the previous results^[3-5].

CYP2C19 has recently become a subject of extensive

studies concerning individual and ethnic variation of drug metabolism^[7,8]. And CYP3A4 has been shown to be the most abundant P450 enzyme in human liver microsomes^[18] and has been shown to be involved in the biotransformations of numerous xenobiotic and endobiotic chemicals^[18,19]. It is thus of interest to use a single probe to phenotype livers with respect to these two important P450 enzymes. The present results indicated that when an appropriate substrate concentration was used, for example 2 $\mu\text{mol/L}$, the activities of OP 5-hydroxylation and sulfoxidation can reflect well the CYP2C19 and CYP3A4 activities in Chinese liver microsomes respectively.

In summary, this study indicated that OP 5-hydroxylation was mediated by both CYP2C19 and CYP3A4, while OP sulfoxidation was principally CYP3A4-dependent in Chinese liver microsomes. Consequently, OP could be used as a probe substrate to phenotype Chinese livers regarding CYP2C19 and CYP3A4 activities when an appropriate substrate concentration was employed. In addition, we developed a simple and sensitive HPLC method for such *in vitro* phenotyping procedures and for studying OP metabolism *in vitro*.

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REFERENCES

- 1 Rodrigues D. Use of *in vitro* human metabolism studies in drug development. *Biochem Pharmacol* 1994; 48: 2147-56.
- 2 Regårdh CG, Andersson T, Lagerstrom PO, Lundborg P, Skanberg I. The pharmacokinetics of omeprazole in humans—a study of single intravenous and oral dose. *Ther Drug Monit* 1990; 12: 163-72.
- 3 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.
- 4 Andersson T, Miners JO, Veronese ME, Tassaneeyakul W, Meyer UA, Birkett DJ. Identification of human liver cytochrome P450 isoforms mediating omeprazole metabolism. *Br J Clin Pharmacol* 1993; 36: 521-30.
- 5 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.
- 6 Balian JD, Sukhova N, Harris JW, Hewett J, Pickle L,

Golestein JA, *et al.* The hydroxylation of omeprazole correlates with S-mephenytoin metabolism; A population study. *Clin Pharmacol Ther* 1995; 57: 662-9.

7 Bertilsson L. Geographical/interracial differences in polymorphic drug oxidation: Current state of knowledge of CYP2D6 and CYP2C19. *Clin Pharmacokinet* 1995; 29: 192-209.

8 Shu Y, Zhou HH. Individual and ethnic differences in CYP2C19 activity in Chinese populations. *Acta Pharmacol Sin* 2000; 21: 193-9.

9 Sowunmi A, Rashid TJ, Akinyinka OO, Renwick AG. Ethnic differences in nifedipine kinetics; comparisons between Nigerians, Caucasians and south Asians. *Br J Clin Pharmacol* 1995; 40: 489-93.

10 von Bahr C, Groth CG, Jansson H, Lundgren G, Lind M, Glaumann H. Drug metabolism in Human liver *in vitro*: Establishment of a human liver bank. *Clin Pharmacol Ther* 1960; 27: 711-25.

11 Shu Y, Xu ZH, Xie HG, Zhu RH, Zhao JP, Zhou HH. Enzyme kinetic analysis and inhibition of amitriptyline N-demethylation in human liver microsomes *in vitro*. *Chin J Pharmacol Toxicol* 1998; 12: 260-5.

12 Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. *J Biol Chem* 1951; 193: 265-75.

13 Xie HG, Huang SL, Zhou HH. High-performance liquid chromatographic determination of urinary 4'-hydroxymephenytoin, a metabolic marker for the hepatic enzyme CYP2C19, in humans. *J Chromatogr B: Biomed Appl* 1995; 668: 125-31.

14 Guengerich FP, Turvy CG. Comparison of levels of several human microsomal cytochrome P-450 enzymes and epoxide hydrolase in normal and disease states using immunochemical analysis of surgical liver samples. *J Pharmacol Ther Exp* 1990; 256: 1189-94.

15 Shu Y, Zhu RH, Xu ZH, Zhou HH. Determination of amitriptyline and nortriptyline in human liver microsomes with reversed-phase HPLC *in vitro*. *Acta Pharmacol Sin* 1998; 19: 343-6.

16 Karam WG, Goldstein JA, Lasker JM, Ghanayem BI. Human CYP2C19 is a major omeprazole 5-hydroxylase, as demonstrated with recombinant cytochrome P450 enzymes. *Drug Metab Dispos* 1996; 24: 1081-7.

17 Andersson T, Regårdh CG, Lou YQ, Zhang Y, Dahl ML, Bertilsson L. Polymorphic hydroxylation of S-mephenytoin and omeprazole metabolism in Caucasian and Chinese subjects. *Pharmacogenetics* 1992; 2: 25-31.

18 Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J Pharmacol Exp Ther* 1994; 270: 414-23.

19 Wrighton SA, Stevens JC. The human hepatic cytochrome

P450 involved in drug metabolism. *Crit Rev Toxicol* 1992; 22: 1-21.

定量 5-羟奥美拉唑和奥美拉唑砒以探测中国人肝微粒体中 CYP2C19 和 CYP3A4 的活性¹

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关键词 肝微粒体; 细胞色素 P-450 CYP2C19; 细胞色素 P-450 CYP3A4; 高压液相色谱法; 奥美拉唑; 美芬妥英; 代谢

目的: 建立同时定量 5-羟奥美拉唑(5-OH-OP)和奥美拉唑砒(OPS)的分析方法, 探讨奥美拉唑(OP)在中国人肝微粒体中能否作为细胞色素 P450 2C19 (CYP2C19)及 3A4 (CYP3A4)的活性表型探针药。
方法: 在中国人肝微粒体中进行 OP 的体外代谢, 以高压液相色谱法(HPLC)检测主要代谢产物 5-OH-OP 及 OPS; 抗 CYP2C8/9/19 及抗 CYP3A4 的单克隆抗体被用于抑制实验; 以 Western 斑点法和光密度扫描定量肝微粒体中 CYP2C19 及 CYP3A4 的含量。
结果: 在 HPLC 分析中 5-OH-OP 及 OPS 有很好的洗脱, 二者检测限均为 0.01 nmol, 回收率为 98% - 102% 并且变异系数小于 9.5%; 抗 CYP2C8/9/19 及抗 CYP3A4 均对 5-OH-OP 的生成有显著的抑制作用 ($P < 0.05$), 二者的抑制作用呈底物浓度依赖, 并且抗 CYP3A4 几乎可单独去除 OPS 的生成 ($> 87\%$); 在底物浓度为 2 $\mu\text{mol/L}$ OP 时, 中国人肝微粒体中 OP 的 5-羟化与美芬妥英的 4'-羟化活性之间 ($r = 0.72, P < 0.01$)、OP 的 5-羟化活性与 CYP2C19 含量之间 ($r = 0.82, P < 0.01$)以及 OP 的硫代氧化活性与 CYP3A4 含量之间 ($r = 0.78, P < 0.01$)均有很好的相关性。
结论: 中国人肝微粒体中 OP 的代谢主要由 CYP2C19 和 CYP3A4 介导; 采用本研究建立的 HPLC 方法, 在适当的底物浓度下, OP 能用于体外探测中国人肝微粒体中 CYP2C19 及 CYP3A4 的活性。

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