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Effects of Enzyme Inducers and Inhibitors on the Pharmacokinetics of Intravenous Omeprazole in Rats

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ABSTRACT: A series of experiments using various inducers and inhibitors of the hepatic microsomal cytochrome P450 (CYP) isozymes were conducted to find CYP isozymes responsible for the metabolism of omeprazole in male Sprague–Dawley rats. Omeprazole, 20 mg/kg, was administered intravenously. In rats pretreated with SKF 525-A (a nonspecific CYP isozyme inhibitor in rats), the time-averaged nonrenal clearance (Cl_{nr}) was significantly slower (77.1% decrease) than that in untreated rats. This indicated that omeprazole is metabolized via CYP isozymes in rats. Hence, rats were pretreated with various enzyme inducers and inhibitors. In rats pretreated with 3-methylcholanthrene and dexamethasone (main inducers of CYP1A1/2 and 3A1/2 in rats, respectively), the Cl_{nr} values were significantly faster (43.8% and 26.3% increase, respectively). In rats pretreated with troleandomycin and quinine (main inhibitors of CYP3A1/2 and 2D1 in rats, respectively), the Cl_{nr} values were significantly slower (20.9% and 12.9% decrease, respectively). However, the Cl_{nr} values were not significantly different in rats pretreated with orphenadrine, isoniazid and sulfaphenazole (main inducers of CYP2B1/2 and 2E1, and a main inhibitor of 2C11, respectively, in rats) compared with those of respective control rats. The above data suggested that omeprazole could be mainly metabolized via CYP1A1/2, 3A1/2 and 2D1 in male rats. Copyright © 2006 John Wiley & Sons, Ltd.

Key words: omeprazole; CYP isozymes; enzyme inducers and inhibitors; pharmacokinetics; rats

Introduction

Omeprazole, 5-methoxy-2-[{(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl}sulphoxide]-1H-benzimidazole, is a proton pump inhibitor in gastric parietal cells. The drug has greater antisecretory activity than histamine H_2-receptor antagonists and has been widely used in the treatment of peptic ulcer, reflux oesophagitis and Zollinger-Ellison syndrome [1,2]. In humans, it is completely metabolized by the liver, and the two major plasma metabolites are 5′-hydroxyomeprazole (a main metabolite) and omeprazole sulfone [3,4]. The following results were reported by Karam *et al*. [5] using human recombinant hepatic microsomal P450 (CYP) enzymes and selective antibody inhibition. The CYP2C19 is a major high affinity omeprazole 5-hydroxylase and CYP3A4 is a low affinity omeprazole-hydroxylating enzyme. Other CYP2C enzymes (CYP2C8, 2C9 and 2C18) may contribute to omeprazole hydroxylation at high substance concentrations. In contrast, omeprazole sulfone is formed principally by CYP3A4. Balim *et al*. [6] supported the hypothesis that omeprazole 5′-hydroxylation cosegregates with the CYP2C19 metabolic polymorphism in 167 healthy volunteers. Andersson *et al*. [7] reported that in human liver microsomes, formation of hydroxyomeprazole was significantly correlated with CYP3A content, formation of omeprazole

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sulfone was mediated via CYP3A family, and 5′-O-desmethylomeprazole was mediated via the CYP2D6. Omeprazole is a substrate for CYP1A1/2 in humans [8]. Human CYP1A1, 1A2, 2C8, 2C9, 2D6 and 3A4 and rat CYP1A1, 1A2, 2C13, 2C11, 2D1 and 3A1(23) proteins have 78%, 70%, 68%, 77%, 71% and 73% homology, respectively [9]. A rat orthologue of human CYP2C19 seemed not to be found.

Some disease states, age, drugs and genetic factor could change CYP isozyme(s). These changes sometimes lead to adverse drug reaction [10,11] even with medications, such as omeprazole, which has a good safety profile. Although the CYP isozymes responsible for the metabolism of omeprazole in humans were studied as mentioned above [5–7], pharmacokinetic changes of omeprazole in patients, which may lead to adverse reactions, with respect to CYP isozyme changes seemed not to have been published. Therefore, the effects of various enzyme inducers and inhibitors on the pharmacokinetics of intravenous omeprazole in rats were measured in this study to find what types of CYP isozymes are involved in the metabolism of omeprazole and to explain the possible pharmacokinetic changes of omeprazole in rat disease models with respect to CYP isozyme changes. The aim of this paper is to report the types of CYP isozymes that are involved in the metabolism of omeprazole in male Sprague–Dawley rats.

Materials and Methods

Chemicals

Omeprazole was donated from the Yungjin Pharmaceutical Company (Seoul, Republic of Korea). 3-Methylcholanthrene (a main inducer of CYP1A1/2 in rats [12]), SKF 525-A (a nonspecific CYP isozyme inhibitor in rats [12]), dexamethasone phosphate (a main inducer of CYP3A1/2 in rats [12]), orphenadrine citrate (a main inducer of CYP2B1/2 in rats [13]), isoniazid (a main inducer of CYP2E1 in rats [12]), troleandomycin (a main inhibitor of CYP3A1/2 in rats [14]), sulfaphenazole (a main inhibitor of CYP2C11 in rats [15]) and quinine hydrochloride (a main inhibitor of CYP2D1 in rats [16,17]) were purchased from Sigma–Aldrich Corporation (St Louis, MO). Other chemicals were of reagent grade or high-performance liquid chromatographic (HPLC) grade.

Animals

Male Sprague–Dawley rats (weighing 250–310 g) purchased from the Charles River Company Korea (Orient, Seoul, Republic of Korea) were housed in a light-controlled room (light: 0700–1900, dark: 1900–0700) kept at a temperature of $22 \pm 2\,^{\circ}C$ and a relative humidity of $55 \pm 5\%$ (The Animal Center for Pharmaceutical Research, College of Pharmacy, Seoul National University, Seoul, Republic of Korea). Rats were housed in metabolic cages (Tecniplast, Varese, Italy) under a supply of filtered pathogen-free air and with food (Samyang Company, Seoul, Republic of Korea) and water *ad libitum*. The protocol of this study was approved by the Animal Care and Use Committee of the College of Pharmacy, Seoul National University.

Administration of enzyme inducers and inhibitors in rats

Rats received a single intraperitoneal injection of 50 mg (3.3 ml)/kg of SKF 525-A (SK-T group) [18], 500 mg (5 ml)/kg of troleandomycin (TM-T group) [14], or 20 mg (5 ml)/kg of quinine hydrochloride (QN-T group) [16], a single intravenous injection of 80 mg (2 ml)/kg of sulfaphenazole (SP-T group) [15], three daily intraperitoneal injections of 50 mg (5 ml)/kg of dexamethasone phosphate (DX-T group) [19,20], 150 mg (3 ml)/kg of isoniazid (IN-T group) [21], or 60 mg (5 ml)/kg of orphenadrine citrate (OP-T group) [13], four daily intraperitoneal injections of 20 mg (3.3 ml)/kg of 3-methylcholanthrene (MC-T group) [22,23], or intraperitoneal (or intravenous) injection of 5 ml/kg of 0.9% NaCl-injectable solution (OP-C, IN-C, DX-C, SK-C, QN-C, SP-C and TM-C groups) or 3.3 ml/kg of corn oil (MC-C group). During the pretreatment, rats had free access to food and water.

Sulfaphenazole was dissolved in distilled water with a minimum amount of NaOH to produce a pH of approximately 8.0. SKF 525-A, quinine hydrochloride, dexamethasone phosphate, isoniazid and orphenadrine citrate were

dissolved in 0.9% NaCl-injectable solution. Troleandomycin was dissolved in 0.9% NaCl-injectable solution acidified to pH 4.0 with HCl, and 3-methylcholanthrene was dissolved in corn oil.

Intravenous study

The procedures for the pretreatment of rats including the cannulation of the carotid artery (for blood sampling) and the jugular vein (for drug administration) were similar to the previously reported methods [24]. An experiment was performed just after for the SP-T and SP-C groups [15], during the first hour for the SK-T and SK-C groups [18] and QN-T and QN-C groups [16], 2 h for the TM-T and TM-C groups [18], on day 4 for the DX-T and IN-T groups [20,21,25], and day 5 for the MC-T, MC-C, OP-C, IN-C and DX-C groups [13,20–23,25] as the commencement of respective pretreatment.

Omeprazole (dissolved in 0.1 M carbonate buffer of pH 9.8 with a minimum amount of 10 N NaOH, and adjusted to a final pH of approximately 10 with HCl) at a dose of 20 mg/kg was administered intravenously over 1 min via the jugular vein of each group ($n = 7$ for IN-T, DX-T and SK-T groups; $n = 9$ for MC-T, OP-T and TM-T groups; $n = 10$ for MC-C, OP-C, IN-C and DX-C groups; $n = 11$ for QN-T, SP-C and SP-T groups; $n = 12$ for SK-C, QN-C and TM-C groups). The total injection volume was 2 ml/kg. Approximately 0.22 ml aliquot of blood sample was collected via the carotid artery at 0 (to serve as a control), 1 (at the end of the infusion), 3, 7, 15, 30, 40, 50, 60, 70 and 80 min after intravenous administration of omeprazole. Approximately 0.25 ml aliquot of the heparinized 0.9% NaCl-injectable solution (20 units/ml) was used to flush the cannula after each blood sampling to prevent blood clotting. Blood samples were centrifuged immediately at 9000*g* for 10 min and a 100 µl aliquot of each plasma sample was stored in a –70 °C freezer (Model DF8517; Ilshin Laboratory Company, Seoul, Republic of Korea) until HPLC analysis of omeprazole. At the end of 24 h, each metabolic cage was rinsed with 10 ml of distilled water and the rinsed materials were combined with the 24 h urine sample. After measuring the exact volume of the combined urine sample, two 0.1 ml aliquots of the combined urine sample were stored in a −70 °C freezer until HPLC analysis of omeprazole. At the same time (24 h), each rat was exsanguinated and killed by cervical dislocation, and then the entire gastrointestinal tract (including its contents and faeces) was removed, transferred into a beaker containing 50 ml of methanol (to facilitate the extraction of omeprazole), and cut into small pieces using scissors. After stirring with a glass rod for 1 min, two 100 µl aliquots of the supernatant were collected from each beaker and stored in a –70 °C freezer until HPLC analysis of omeprazole.

Omeprazole at a dose of 20 mg/kg was also administered via the jugular vein in control rats ($n = 10$) after bile duct cannulation without cannulation of the carotid artery [26]. A bile sample was collected between 0–24 h.

Measurement of plasma protein binding of omeprazole using an equilibrium dialysis technique

The procedures were similar to those reported previously [27]. One ml of plasma of an additional control, SK-T, QN-T and SP-T rats ($n = 3$, each) was dialysed against 1 ml of isotonic Sørensen phosphate buffer of pH 7.4 containing 3% dextran in a 1 ml dialysis cell (Spectrum Medical Industries, Los Angeles, CA) using a Spectra/Por 4 membrane (mol. wt. cutoff of 12000–14000; Spectrum Medical Industries). In the preliminary study, binding of omeprazole to 4% human serum albumin was constant, $91.7 \pm 0.785\%$, at omeprazole concentrations ranging from 1 to 200 µg/ml. Therefore, the omeprazole concentration of 10 µg/ml was arbitrarily chosen in this study.

HPLC analysis of omeprazole

Concentrations of omeprazole in the above samples were determined by a slight modification of the reported HPLC method [28]. Torasemide instead of lansoprazole was used as an internal standard. In a 2.2 ml eppendorf tube containing a 100 µl aliquot of sample, a 50 µl aliquot of methanol containing an internal standard (torasemide; 50 µg/ml) and a 50 µl aliquot of 0.2 M phosphate buffer (pH 7.0) were added. Then the mixture was extracted with a 1 ml aliquot of diethylether. The organic layer was transferred into a clean

eppendorf tube and a 150 µl aliquot of 0.1 N NaOH was added. After vortex-mixing for 30 s, the aqueous layer was collected and a 75 µl aliquot was injected directly onto the reversed-phase (C_8) column. The mobile phase, phosphate buffer (0.2 M KH_2PO_4; pH of 7.0):acetonitrile (77:23; v/v) was run at a flow-rate of 1.4 ml/min and the column effluent was monitored by an UV detector set at 302 nm. The retention times of omeprazole and the internal standard were approximately 10.2 and 8.1 min, respectively. The detection limits of omeprazole in rat plasma and urine were 20 and 50 ng/ml, respectively. Coefficients of variation of omeprazole in plasma and urine were below 5.34% and 7.90%, respectively.

Pharmacokinetic analysis

The total area under the plasma concentration–time curve from time zero to time infinity (*AUC*) was calculated by the trapezoidal rule-extrapolation method; this method uses the logarithmic trapezoidal rule for the calculation of the area during the declining plasma level phase [29] and the linear trapezoidal rule for the rising plasma level phase. The area from the last datum point to time infinity was estimated by dividing the last measured plasma concentration by the terminal rate constant.

Standard methods [30] were used to calculate the time-averaged total body (*Cl*), renal (Cl_r) and nonrenal (Cl_{nr}) clearances, terminal half-life, total area under the first moment of the plasma concentration–time curve from time zero to time infinity (*AUMC*), mean residence time (*MRT*) and apparent volume of distribution at steady state (V_{ss}) [24].

The mean values of each clearance [31], V_{ss} [32] and terminal half-life [33] were calculated by the harmonic mean method.

Statistical analysis

A p value of less than 0.05 was considered to be statistically significant using the unpaired t-test. All results are expressed as mean $\pm$ standard deviation.

Results

Measurement of plasma protein binding of omeprazole

The plasma protein binding values of omeprazole were significantly smaller after treatment with SKF 525-A (SK-T), quinine (QN-T) and sulfaphenazole (SP-T); the values were $80.8 \pm 4.40\%$, $71.3 \pm 6.00\%$, $52.2 \pm 2.26\%$ and $40.0 \pm 1.73\%$ for control, SK-T, QN-T and SP-T rats, respectively. This could be due to displacement of the binding of omeprazole by the enzyme inhibitors. Displacement of plasma (serum) protein binding of tolbutamide [34] and cefazolin [35] by sulfaphenazole, and of oxprenolol and propranolol by SKF 525-A [36] were also reported. The time intervals between pretreatment of enzyme inhibitors and omeprazole dosing are short (0, 1, 1 and 2 h for sulfaphenazole, SKF 525-A, quinine and troleandomycin, respectively), therefore, it could be expected that the inhibitors were present in the plasma. Hence, the significantly smaller plasma protein binding of omeprazole could be due to displacement effect of the enzyme inhibitors.

Pharmacokinetics of omeprazole in rats pretreated with enzyme inducers

The mean arterial plasma concentration–time profiles of omeprazole after 1 min intravenous administration in rats pretreated with 3-methylcholanthrene (MC-T), orphenadrine (OP-T), isoniazid (IN-T) and dexamethasone (DX-T), and their respective control rats are shown in Figure 1, and some relevant pharmacokinetic parameters are listed in Table 1. After intravenous administration, the plasma concentrations of omeprazole declined in a polyexponential manner for all groups of rats studied. Omeprazole was below the detection limit in the gastrointestinal tract at 24 h for all rats studied.

In MC-T and DX-T rats, the *AUC* values were significantly smaller (30.2% and 20.7% decrease for MC-T and DX-T, respectively), *Cl* (43.1%, 25.8% increase, respectively) and Cl_{nr} (43.8% and 26.3% increase, respectively) values were significantly faster, and *MRT* values were significantly shorter (26.8% and

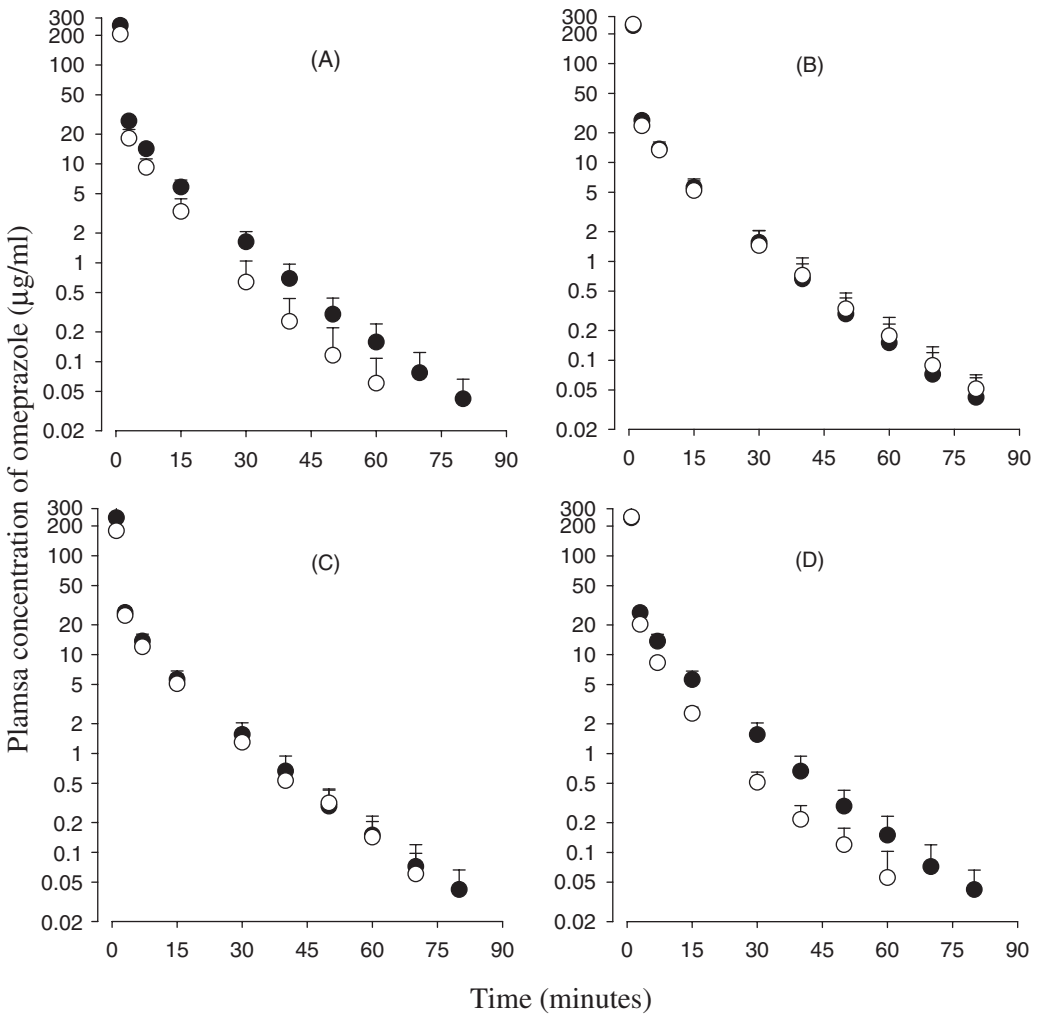

Figure 1. Mean arterial plasma concentration–time profiles of omeprazole after 1 min intravenous administration at a dose of 20 mg/kg to rats pretreated with enzyme inducers (○), 3-methylcholanthrene (A), orphenadrine (B), isoniazid (C) and dexamethasone (D), and their respective control rats (●). Vertical bars represent standard deviation

40.4% decrease, respectively) than those in respective controls. In MC-T rats, the terminal half-life and percentage of dose excreted in 24 h urine as unchanged omeprazole ($Ae_{0-24\,h}$) were significantly shorter (27.2% decrease) and smaller (56.8% decrease), respectively, than those in the respective controls. In OP-T and IN-T rats, the pharmacokinetic parameters of omeprazole listed in Table 1 were not significantly different compared with those in the controls except significantly smaller $Ae_{0-24\,h}$ in IN-T rats (54.2% decrease).

Pharmacokinetics of omeprazole in rats pretreated with enzyme inhibitors

The mean arterial plasma concentration–time profiles of omeprazole after 1 min intravenous administration in rats pretreated with SKF 525-A (SK-T), quinine (QN-T), sulfaphenazole (SP-T) and troleandomycin (TM-T), and their respective control rats are shown in Figure 2, and some relevant pharmacokinetic parameters are listed in Table 2. After intravenous administration, the plasma concentrations of omeprazole declined in

Table 1. Mean (± standard deviation) pharmacokinetic parameters of omeprazole after intravenous administration at a dose of 20 mg/kg to rats pretreated with 3-methylcholanthrene (MC-T), orphenadrine (OP-T), isoniazid (IN-T) and dexamethasone (DX-T), and their respective control rats (MC-C, OP-C, IN-C and DX-C)

Parameter	MC-C ($n = 10$)	MC-T ($n = 9$)	OP-C, IN-C, DX-C ($n = 10$)	OP-T ($n = 9$)	IN-T ($n = 7$)	DX-T ($n = 7$)
AUC (μg min/ml)	550 ± 104	384 ± 91.1[a]	532 ± 116	512 ± 232	437 ± 76.0	422 ± 64.2[b]
Terminal half-life (min)	9.45 ± 1.92	6.88 ± 1.55[a]	8.91 ± 2.23	9.38 ± 1.40	8.14 ± 1.93	9.12 ± 2.97
MRT (min)	6.05 ± 1.31	4.43 ± 1.41[b]	5.98 ± 1.26	6.41 ± 2.86	6.22 ± 0.831	3.71 ± 0.700[c]
V_{ss} (ml/kg)	204 ± 86.9	212 ± 120	210 ± 85.4	210 ± 200	281 ± 75.5	170 ± 45.2
Cl (ml/min/kg)	36.4 ± 7.52	52.1 ± 13.4[a]	37.6 ± 9.36	39.0 ± 16.7	45.7 ± 10.7	47.3 ± 6.20[b]
Cl_r (ml/min/kg)	0.273 ± 0.117	0.158 ± 0.0672[a]	0.134 ± 0.204	0.230 ± 0.328	0.101 ± 0.0881[b]	0.215 ± 0.205
Cl_{nr} (ml/min/kg)	36.1 ± 7.51	51.9 ± 13.4[a]	37.3 ± 9.38	44.3 ± 15.1	44.8 ± 11.6	47.1 ± 6.09[b]
$Ae_{0-24\,h}$ (% of dose)	0.810 ± 0.261	0.335 ± 0.135[c]	0.740 ± 0.340	0.921 ± 0.558	0.339 ± 0.177[b]	0.593 ± 0.373

[a] Significantly different ($p < 0.01$) from respective control.
[b] Significantly different ($p < 0.05$) from respective control.
[c] Significantly different ($p < 0.001$) from respective control.

a polyexponential manner for all groups of rats studied. Omeprazole was also below the detection limit in the gastrointestinal tract at 24 h for all rats studied.

In SK-T, QN-T and TM-T rats, the *AUC* values were significantly greater (331%, 16.7% and 28.2% increase for SK-T, QN-T and TM-T, respectively), and *Cl* values based on total (76.7%, 14.6% and 22.0% decrease for SK-T, QN-T and TM-T, respectively) and free (unbound to plasma proteins) fractions of omeprazole in plasma (84.4% and 65.7% decrease for SK-T and QN-T, respectively), and Cl_{nr} values based on total (77.1%, 12.9% and 20.9% decrease for SK-T, QN-T and TM-T, respectively) and free fractions (68.7% and 65.0% decrease for SK-T and QN-T, respectively) were significantly slower than controls. In SK-T, QN-T and SP-T rats, the *MRT* values were significantly longer (573%, 65.1% and 69.2% increase for SK-T, QN-T and SP-T, respectively) and V_{ss} values based on total plasma concentration were significantly larger (52.7%, 43.9% and 97.7%, respectively) than controls. However, the V_{ss} values based on free fractions were smaller in QN-T and SP-T rats (42.4% and 36.5% decrease, respectively), but the values were comparable between SK-C and SK-T rats (1380 and 1400 ml/kg). In SK-T and SP-T rats, the terminal half-lives were significantly longer (143% and 23.6% increase for SK-T and SP-T, respectively) than controls.

Biliary excretion of omeprazole after intravenous administration in rats

The 24 h biliary excretion of omeprazole after intravenous administration at a dose of 20 mg/kg after bile duct cannulation in control rats was almost negligible; the mean value was only 0.0436 ± 0.0159% of dose.

Discussion

After intravenous administration of omeprazole at doses of 2.5, 5 and 10 mg/kg in rats, the $AUC_{0-2\,h}$ (the plasma concentrations of omeprazole were measured up to 1.25, 2.0 and 2.0 h for 2.5, 5 and 10 mg/kg, respectively) values were dose-proportional [37]. Moreover, the terminal half-life, V_{ss}, and *Cl* values were also dose-independent [37]. In the present control rats, the $AUC_{0-2\,h}$ values of omeprazole after intravenous administration at a dose of 20 mg/kg were approximately 2-times that of $AUC_{0-2\,h}$ obtained after intravenous administration at a dose of 10 mg/kg in rats [37]. Hence, the intravenous dose of omeprazole, 20 mg/kg, was arbitrarily chosen in the present study.

After intravenous administration of omeprazole in rats, the contribution of biliary excretion of omeprazole to Cl_{nr} of omeprazole was also negligible; only 0.0436% of dose was excreted as unchanged omeprazole in 24 h bile after

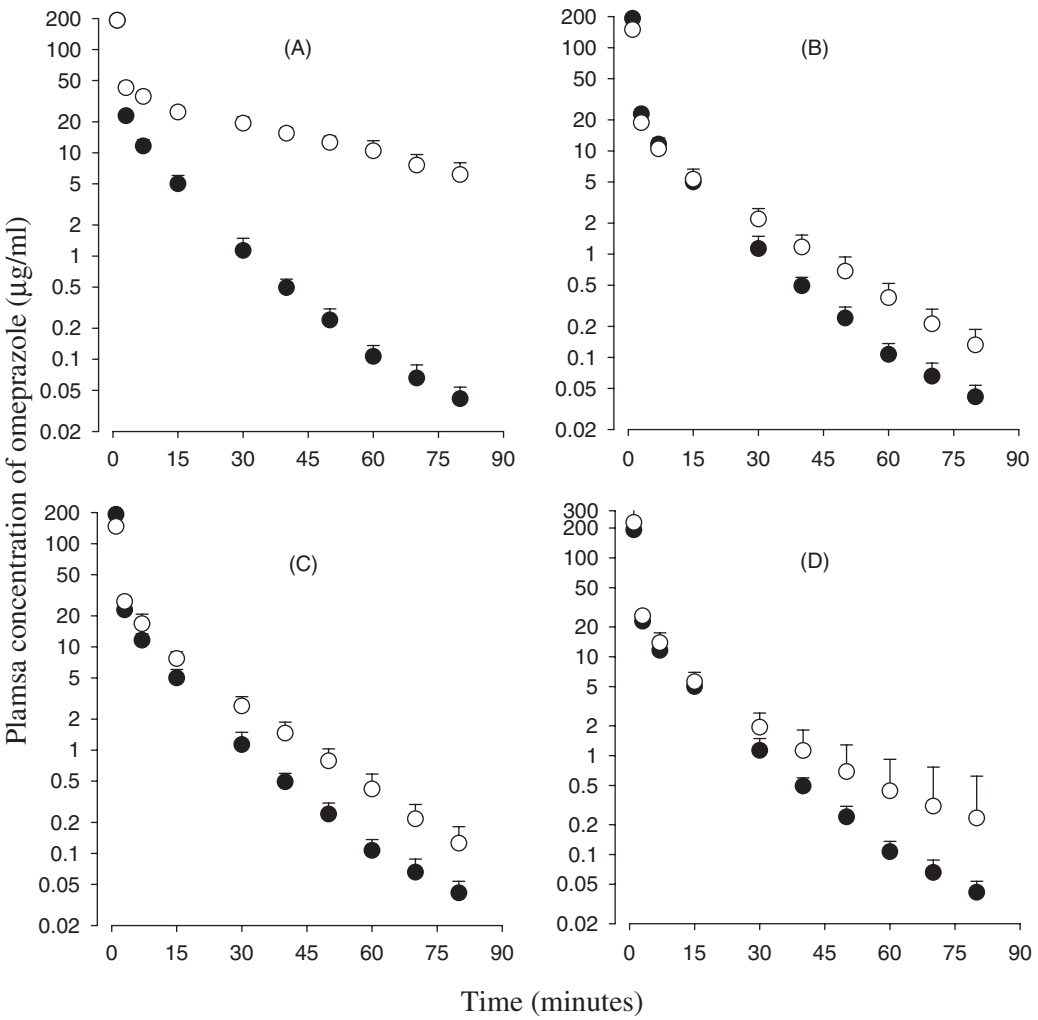

Figure 2. Mean arterial plasma concentration–time profiles of omeprazole after 1 min intravenous administration at a dose of 20 mg/kg to rats pretreated with enzyme inhibitors (○), SKF 525-A (A), sulfaphenazole (B), quinine (C) and troleandomycin (D), and their respective control rats (●). Vertical bars represent standard deviation

intravenous administration of omeprazole at a dose of 20 mg/kg in control rats after bile duct cannulation. This suggested that omeprazole is almost completely metabolized in rats. Hence, the Cl_{nr} values of omeprazole listed in Tables 1 and 2 could represent metabolic clearance values of omeprazole in rats. Therefore, the changes in Cl_{nr} values could represent changes in metabolism of omeprazole in rats. The hepatic extraction ratio of omeprazole was estimated in an other rat study after intravenous and intraportal administration; the value was 59% [37]. This indicated that omeprazole is an intermediate extraction ratio drug in rats [38]. Hence, the hepatic clearance of omeprazole in rats depends on hepatic blood flow rate, intrinsic clearance and free fractions of omeprazole in plasma.

In order to find whether CYP isozymes are involved in the metabolism of omeprazole in male rats, SKF 525-A (a nonspecific CYP isozyme inhibitor in rats) was pretreated in rats. In SK-T rats, the Cl_{nr} was significantly slower than that in untreated rats (Table 2), indicating that omeprazole is metabolized via CYP isozymes in rats. Hence, various enzyme inducers and inhibitors of CYP isozymes were pretreated to find

Table 2. Mean (± standard deviation) pharmacokinetic parameters of omeprazole after intravenous administration at a dose of 20 mg/kg to rats pretreated with SKF 525-A (SK-T), quinine (QN-T), troleandomycin (TM-T) and sulfaphenazole (SP-T), and their respective control rats (SK-C, QN-C, TM-C and SP-C)

Parameter	SK-C, QN-C, TM-C ($n = 12$)	SK-T ($n = 7$)	QN-T ($n = 11$)	TM-T ($n = 8$)	SP-C ($n = 11$)	SP-T ($n = 11$)
AUC (μg min/ml)	436 ± 53.3	1880 ± 313[a]	509 ± 60.5[b]	559 ± 134[b]	439 ± 54.6	405 ± 80.1
Terminal half-life (min)	10.3 ± 2.13	25.0 ± 13.9[a]	11.3 ± 3.45	11.5 ± 11.5	10.6 ± 2.05	13.1 ± 3.05[c]
MRT (min)	5.93 ± 0.896	39.9 ± 12.8[a]	9.79 ± 1.24[a]	8.98 ± 5.45	5.91 ± 0.937	10.0 ± 3.00[a]
V_{ss} (ml/kg)	264 ± 61.2	403 ± 98.6[a]	380 ± 63.8[a]	261 ± 138	260 ± 63.3	514 ± 220[b]
Cl (ml/min/kg)	45.9 ± 5.49	10.7 ± 2.03[a]	39.2 ± 5.42[b]	35.8 ± 7.75[b]	45.5 ± 5.64	51.6 ± 9.81
Cl_r (ml/min/kg)	0.175 ± 0.323	0.0720 ± 1.11	0.0833 ± 0.485	0.130 ± 0.246	0.178 ± 0.347	0.246 ± 0.275
Cl_{nr} (ml/min/kg)	45.0 ± 5.81	10.3 ± 1.98[a]	39.2 ± 5.68[c]	35.6 ± 6.82[c]	44.4 ± 6.00	51.3 ± 9.82
$Ae_{0-24\ h}$ (% of dose)	0.661 ± 0.554	1.55 ± 1.11	0.228 ± 0.835	0.578 ± 0.497	0.711 ± 0.579	0.779 ± 0.493

[a] Significantly different ($p < 0.001$) from respective control.
[b] Significantly different ($p < 0.01$) from respective control.
[c] Significantly different ($p < 0.05$) from respective control.

what types of CYP isozymes are involved in the metabolism of omeprazole in rats. In MC-T and DX-T rats (main inducers of CYP1A1/2 and 3A1/2, respectively, in rats), the Cl_{nr} values were significantly faster than those in respective untreated rats (Table 1). This suggested that the contribution of CYP1A1/2 and 3A1/2 to the metabolism of omeprazole were considerable in rats. In TM-T and QN-T rats (main inhibitors of CYP3A1/2 and 2D1, respectively, in rats), the Cl_{nr} values were significantly slower than those in respective untreated rats (Table 2). This suggested that the contribution of CYP3A1/2 and 2D1 to the metabolism of omeprazole were considerable in rats. However, in OP-T, IN-T and SP-T rats (main inducers of CYP2B1/2 and 2E1, and a main inhibitor of CYP2C11, respectively, in rats), the Cl_{nr} values were not significantly different compared with those in the respective untreated rats. This suggested that the contribution of CYP2B1/2, 2E1 and 2C11 to the metabolism of omeprazole seemed to be almost negligible in rats. The above data suggested that omeprazole could be metabolized mainly via CYP1A1/2, 2D1 and 3A1/2 in male Sprague–Dawley rats. Note that the various enzyme inducers and inhibitors studied had activities to various CYP isozymes, however, the main CYP isozyme was only mentioned in this study. Hence, the results are confined to the main CYP isozymes. More studies are required to further evaluate what types of other CYP isozymes are more involved in the metabolism of omeprazole in rats.

The present results will play an important role in explaining the possible pharmacokinetic changes of omeprazole in various rat disease models where the CYP isozymes are changed. For example, in rats with protein–calorie malnutrition (the expressions and mRNA levels of CYP1A2 and 3A1/2 decreased [39]), acute renal failure induced by uranyl nitrate (the expressions and mRNA levels of CYP3A1(23) increased [40]), diabetes mellitus induced by alloxan or streptozotocin (the expressions and mRNA levels of CYP1A2 and 3A1(23) increased [41]), and mutant Nagase analbuminemic rats, an animal model for human familial analbuminemia (the expression and mRNA level of CYP1A2 increased [42]).

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