

Original Article

Involvement of cytochrome P450 3A4 and P-glycoprotein in first-pass intestinal extraction of omeprazole in rabbits

Hai-ming FANG^{1,2,3}, Jian-ming XU^{1,*}, Qiao MEI¹, Lei DIAO¹, Mo-li CHEN¹, Juan JIN¹, Xin-hua XU¹

¹The Key Laboratory for Digestive Diseases of Anhui Province, Department of Gastroenterology, First Affiliated Hospital, Anhui Medical University, Hefei 230022, China; ²Department of Pharmacology, Anhui Medical University, Hefei 230022, China; ³Department of Gerontology, First Affiliated Hospital, Anhui Medical University, Hefei 230026, China

Aim: To quantitatively evaluate *in vivo* first-pass intestinal extraction of omeprazole and to investigate the possible involvement of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) in this process in rabbits.

Methods: Pharmacokinetic parameters were examined after intraduodenal (id), intraportal venous (ipv), and intravenous (iv) administration of omeprazole at various doses to intestinal and vascular access-porting rabbits. Extraction ratios in the liver and intestinal tract were determined from the area under the plasma concentration-time curve (AUC). In addition, omeprazole was administered by id or iv to rabbits alone or 30 min after the id administration of CYP3A4 or P-gp inhibitors (ketoconazole or verapamil, respectively).

Results: Pharmacokinetic parameters of omeprazole were dose-dependent after id, ipv, and iv administration at various doses. After id administration of 3 mg/kg omeprazole, the hepatic and intestinal extraction ratio was 57.18%±2.73% and 54.94%±1.85%, while the value was 59.29%±3.14% and 54.20%±1.53% after given 6 mg/kg, respectively. Compared with the control group, the presence of ketoconazole (60 mg/kg) or verapamil (9 mg/kg) significantly increased the area under the plasma concentration time curve (AUC) and the peak concentration (C_{max}) of id-administered omeprazole, while it had no significant effect on omeprazole administered by iv.

Conclusion: Oral omeprazole undergoes marked extraction in the small intestine, and increased bioavailability of the drug after id administration of ketoconazole and verapamil suggests that this increase results from inhibition of CYP3A4 and P-gp function in the intestine rather than the liver.

Keywords: omeprazole; pharmacokinetics; intestinal first-pass extraction; cytochrome P450 3A4; P-glycoprotein; ketoconazole; verapamil

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Introduction

The liver has long been thought to have a role during first-pass extraction of orally-administered drugs. However, the intestine has also been reported to be involved in first-pass extraction, and in some cases it is the major organ of drug metabolism^[1,2].

Omeprazole is an atypical proton pump inhibitor. It is prescribed for the treatment of various acid-related diseases, such as peptic ulcer, gastroesophageal reflux diseases, and Zollinger-Ellison syndrome^[3]. Although omeprazole can be rapidly absorbed from the gut lumen, the oral bioavailability of omeprazole is low and variable in humans. Its bioavail-

ability is only 35% after the first dose and about 60% with repeated doses. Thus, omeprazole seems to undergo extensive first-pass extraction before entering systemic circulation^[4]. Yet few studies have attempted to explore the influence of the intestine on the low bioavailability of omeprazole. Therefore, one goal of the present study was to quantitatively evaluate intestinal first-pass extraction of omeprazole.

A few methods are presently available to study drug metabolism *in vivo* or *in situ* in the intestine. However, most of them generally cannot discriminate the contribution of the liver and the intestine. Placement of a catheter into the portal vein provides a way to accurately quantify drug absorption from the gut lumen into portal venous circulation and distinguish intestinal extraction from liver extraction^[5]. Portal vein catheterization in the rat^[6], dog^[7] and monkey^[8] have been used to assess the intestinal extraction of drugs. However, these

* To whom correspondence should be addressed.

E-mail funhemon@163.com

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models have many limitations, including short life spans (such as rat models) or high costs of maintenance (such as dog and monkey models). The rabbit model has been commonly used for the pharmacokinetic evaluation of numerous drugs, and the rabbit intestine has been widely used to assess the membrane permeability characteristics of drugs. Kunta^[5] and colleagues used an intestinal and vascular access-ported (IVAP) rabbit model to differentiate intestinal and hepatic first-pass extraction of verapamil. They demonstrated that this direct measurement model can be used to study the intestinal and hepatic extraction of drugs and other xenobiotics. Therefore, we chose the IVAP rabbit model for our present study.

Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) are constitutively expressed in intestinal epithelial cells and form another obstacle for drug absorption. Moreover, P-gp may act with CYP3A4 to increase drug metabolism in the intestine^[9, 10]. To our knowledge, little information is known about the intestinal disposition characteristics of omeprazole in detail, especially the role of CYP3A4 in drug metabolism and P-gp-mediated drug efflux. Therefore, the second goal of the present study was to investigate whether CYP3A4 and P-gp are involved in intestinal disposition of omeprazole, which may help improve its oral bioavailability.

Materials and methods

Materials

Omeprazole was purchased from Changzhou Siyao Pharmaceutical Co, Ltd (Changzhou, China). Ketoconazole was obtained from Janssen Pharmaceutical Co, Ltd (Xi-an, China). Verapamil was obtained from Shanghai Pharmaceutical Co, Ltd (Shanghai, China). Intestinal and vascular access ports and 22 gauge Huber needles were obtained from B Braun Company (Melsungen, Germany). Other chemicals were of reagent grade or HPLC grade.

Animals

Male New Zealand white rabbits (purchased from Changlinghe Laboratory Animal Co, Ltd, Hefei, China) weighing 2.5–3.5 kg were given access to a normal standard chow diet and tap water. Throughout the experiment, the animals were housed, one per cage, in laminar flow cages maintained at 22±2 °C, 50%–60% relative humidity, under a 12-h light/12-h dark cycle (lights on at 7:00). The animals were kept in these facilities for at least 1 week prior to the experiment. The protocol for the animal study was approved by the Animal Care and Use Committee of Anhui Medical University.

Preparation of IVAP rabbits

The pretreatment and surgical procedures for intraportal (ipv) and intraduodenal (id) access ports were similar to previously reported methods^[11, 12]. In brief, through a survival surgery, catheters were placed into the pyloric vein (modified portal vein cannulation) and duodenal lumen. The catheters were tunneled out and affixed to a titanium reservoir in the subcutaneous layer on the dorsal side of the animals. After surgery, the catheters in the ipv and id ports were flushed with 1–2

mL of 5% dextrose solution and heparinized saline. The ports were accessed through a transdermal injection into the titanium reservoir using a 22 gauge Huber needle. The procedure was conducted under sterile conditions to prevent infection. After surgery, the animals were allowed to recover at least 2 weeks before the initiation of the pharmacokinetics studies. Six rabbits were used and fasted overnight prior to the experiments. Water was allowed *ad libitum*. The left auricular artery was cannulated for systemic sampling. The IVAP rabbits were used once every 2 weeks.

Drug administration to the IVAP rabbits

For iv infusion, omeprazole (omeprazole powder dissolved in injection saline) at doses of 1.5 mg/kg (*n*=6), 3 mg/kg (*n*=6), and 6 mg/kg (*n*=6) was injected over 1 min via the marginal ear vein. Approximately 2 mL of blood was collected via the auricular artery at 0 (to serve as a control), 1, 5, 10, 15, 30, 45, 60, 90, and 120 min after drug administration. The blood samples were centrifuged within 10 min of sampling at 3000×*g* for 10 min at 4 °C. The plasma was decanted and stored at -80 °C until analysis by HPLC.

For ipv infusion, omeprazole (omeprazole powder dissolved in injection saline) was infused at a dose of 1.5 mg/kg (*n*=6), 3 mg/kg (*n*=6), and 6 mg/kg (*n*=6) over 5 min via the ipv port with the assistance of an infusion pump (Modular Infusion Pump, Smiths Medical international Ltd, UK) followed by a 1–2 mL saline flush. Other procedures were similar to the iv infusion above.

For id instillation, the id catheter was flushed with 5 mL of saline 15 min before intestinal dosing, and omeprazole (suspended in 0.1% CMC-Na) at a dose of 3 mg/kg (*n*=6), 6 mg/kg (*n*=6), and 9 mg/kg (*n*=6) was infused via the id port, followed by a 1–2 mL saline flush. Approximately 2 mL of blood was collected via the auricular artery at 0 (to serve as a control), 1, 3, 6, 9, 12, 15, 30, 45, 60, 90, and 120 min after the administration. Other procedures were similar to the iv infusion described above.

The IVAP rabbits were allowed a 2 week washout time between different doses during the experiment.

Effect of ketoconazole on id or iv pharmacokinetics of omeprazole

Briefly, 3 mg/kg of omeprazole was administered to rabbits (*n*=6) via the id port in the presence or absence of ketoconazole (60 mg/kg via the id port 30 min prior to omeprazole administration) with a dosing volume of 1 mL. Approximately 2 mL of blood was collected via the auricular artery at 0 (to serve as a control), 1, 3, 6, 9, 12, 15, 30, 45, 60, 90, and 120 min after administration of the drug.

After a 2-week washout, 1.5 mg/kg of omeprazole was administered to rabbits via the marginal ear vein in the presence or absence of ketoconazole (60 mg/kg via the id port 30 min prior to omeprazole administration). Approximately 2 mL of blood was collected via the auricular artery at 0 (to serve as a control), 1, 5, 10, 15, 30, 45, 60, 90, and 120 min after the administration.

Effect of verapamil on id or iv pharmacokinetics of omeprazole

Briefly, 3 mg/kg of omeprazole was administered to rabbits ($n=6$) via the id port in the presence and absence of verapamil (9 mg/kg via the id port 30 min prior to omeprazole administration) with a dosing volume of 1 mL. Approximately 2 mL of blood was collected via the auricular artery at 0 (to serve as a control), 1, 3, 6, 9, 12, 15, 30, 45, 60, 90, and 120 min after administration.

After a 2-week washout, 1.5 mg/kg of omeprazole was administered to rabbits via the marginal ear vein in the presence or absence of verapamil (9 mg/kg via the id port 30 min prior to omeprazole administration). Approximately 2 mL of blood was collected via the auricular artery at 0 (to serve as a control), 1, 5, 10, 15, 30, 45, 60, 90, and 120 min after administration.

HPLC analysis of omeprazole

The plasma concentrations of omeprazole were determined by a modified HPLC assay^[13]. The chromatographic system was composed of a LC-20AT liquid chromatograph pump, SIL-20A auto injector, SPD-20AV UV detector, LC solution module (Shimadzu, Japan). The detector wavelength was 302 nm and the column, a Shimadzu VP-ODS C₁₈ (250 L×46 mm, 5 μm, Shimadzu, Japan), was used at 40 °C. A mixture of methanol, acetic acid and triethylamine (60:40:0.1, *v/v/v*, pH=4.3, adjusted with acetic acid) was used as the mobile phase at a flow rate of 1 mL/min. The concentration detection limit of omeprazole in rabbit plasma was 20 ng/mL. Good linearity was observed for 20 ng/mL to 10 000 ng/mL of omeprazole with a correlation coefficient of 0.9989. The recovery from this method ranged from 64.73% to 72.37%. The intraday coefficient of variation of omeprazole was 4.82%, 8.59%, 4.19%, and the interday coefficient of variation was 7.97%, 4.04%, and 8.42% at concentration levels of 100 ng/mL, 500 ng/mL, and 5000 ng/mL, respectively.

Pharmacokinetic analysis

Non-compartmental pharmacokinetic analysis was performed using the DAS 2.0 software. Pharmacokinetic parameters of omeprazole, containing the area under the plasma concentration–time curve (AUC), plasma clearance (CL) and half-life time ($t_{1/2}$) were calculated. Maximum plasma concentration (C_{max}) and the time to reach maximum plasma concentration (t_{max}) were determined by visual inspection of the experimental data.

The absolute bioavailability (BA), hepatic extraction ratio (EH), and intestinal extraction ratio (EI) were calculated as follows^[14]:

$$BA = (AUC_{id} / Dose_{id}) / (AUC_{iv} / Dose_{iv}) \quad (1)$$

$$EH = 1 - (AUC_{ipv} / AUC_{iv}) \quad (2)$$

$$EI = 1 - (AUC_{id} / AUC_{ipv}) \quad (3)$$

Where AUC_{id} , AUC_{iv} , and AUC_{ipv} correspond to the AUC of id, iv, and ipv administration, respectively. $Dose_{id}$ and $Dose_{iv}$ correspond to the dose of id and iv administration, respectively.

The relative bioavailability of omeprazole was calculated

directly by the AUC value.

Statistical analysis

All mean values were presented with their standard deviation (mean±SD). Pharmacokinetic parameters were compared using a one way ANOVA. Differences were considered to be significant at a level of $P < 0.05$. Statistical calculations were performed using the SPSS 11.0 software.

Results

Pharmacokinetic features of omeprazole after iv administration of different doses

The mean arterial plasma drug concentration–time profiles of omeprazole after iv administration of various doses to rabbits are illustrated in Figure 1, and some relevant pharmacokinetic parameters are listed in Table 1. As shown, the $AUC_{(0-t)}$ values of omeprazole increased proportionally to the dose, and the values were $0.42 \pm 0.51 \mu\text{g} \cdot \text{mL}^{-1} \cdot \text{h}^{-1}$, $1.02 \pm 0.22 \mu\text{g} \cdot \text{mL}^{-1} \cdot \text{h}^{-1}$, and $2.48 \pm 0.07 \mu\text{g} \cdot \text{mL}^{-1} \cdot \text{h}^{-1}$ for 1.5 mg/kg, 3 mg/kg, and 6 mg/kg, respectively. However, dose-normalized (based on 1.5 mg/kg) $AUC_{(0-t)}$ values were independent of the doses studied. The values of terminal half-life and total clearance (CL) of different doses also exhibited dose-independent characteristics.

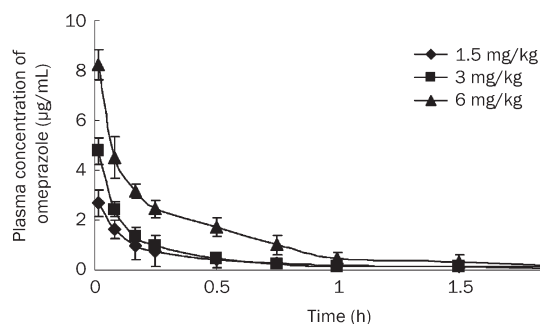


Figure 1. Mean plasma concentration–time profiles of omeprazole after iv administration of different doses (1.5, 3, and 6 mg/kg) to rabbits. Each point indicates the Mean±SD ($n=6$). (◆) 1.5 mg/kg; (■) 3 mg/kg; (▲) 6 mg/kg.

Pharmacokinetic features of omeprazole after ipv administration of different doses.

The mean arterial plasma drug concentration–time profiles of omeprazole after ipv administration of various doses to rabbits are illustrated in Figure 2, and some relevant pharmacokinetic parameters are listed in Table 2. The $AUC_{(0-t)}$ values of omeprazole increased proportionally, but dose-normalized (based on 1.5 mg/kg) $AUC_{(0-t)}$ values were independent of the doses studied, and the values were significantly smaller than that of the corresponding doses for iv administration ($0.27 \pm 0.06 \mu\text{g} \cdot \text{mL}^{-1} \cdot \text{h}^{-1}$ vs $0.42 \pm 0.51 \mu\text{g} \cdot \text{mL}^{-1} \cdot \text{h}^{-1}$ for 1.5 mg/kg; $0.43 \pm 0.11 \mu\text{g} \cdot \text{mL}^{-1} \cdot \text{h}^{-1}$ vs $1.02 \pm 0.22 \mu\text{g} \cdot \text{mL}^{-1} \cdot \text{h}^{-1}$ for 3 mg/kg; $1.01 \pm 0.07 \mu\text{g} \cdot \text{mL}^{-1} \cdot \text{h}^{-1}$ vs $2.48 \pm 0.07 \mu\text{g} \cdot \text{mL}^{-1} \cdot \text{h}^{-1}$ for 6 mg/kg, respectively. $P < 0.05$). The values of terminal half-life and total clearance (CL) of different doses was dose-independent.

Table 1. Mean pharmacokinetic parameters of omeprazole administered iv to rabbits alone or 30 min after the id administration of 60 mg/kg ketoconazole or 9 mg/kg verapamil. *n*=6. Mean±SD.

	Omeprazole 1.5 mg/kg	Omeprazole 3 mg/kg	Omeprazole 6 mg/kg	Ketoconazole+ Omeprazole 1.5 mg/kg	Verapamil+ Omeprazole 1.5 mg/kg
AUC _(0-t) (µg/mL·h)	0.42±0.51	1.02±0.22	2.48±0.07	0.45±0.46	0.43±0.54
<i>t</i> _{1/2} (h)	0.96±0.54	0.93±0.55	1.07±0.82	0.92±0.17	0.94±0.47
CL (L·h ⁻¹ ·kg ⁻¹)	3.59±0.87	2.95±0.41	2.41±0.10	3.31±0.42	3.48±0.21

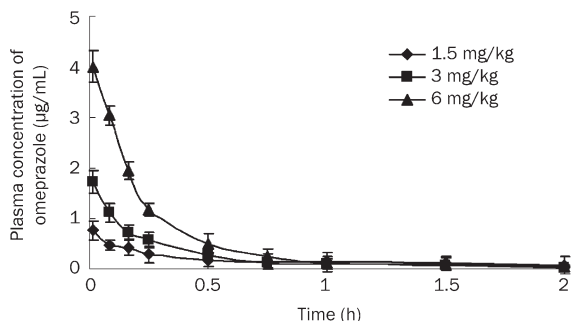


Figure 2. Mean plasma concentration-time profiles of omeprazole after ipv administration of different doses (1.5, 3, and 6 mg/kg) to rabbits. Each point indicates the Mean±SD (*n*=6). (◆) 1.5 mg/kg; (■) 3 mg/kg; (▲) 6 mg/kg.

Table 2. Pharmacokinetic parameters of omeprazole administered ipv in rabbits. *n*=6. Mean±SD.

	Omeprazole 1.5 mg/kg	Omeprazole 3 mg/kg	Omeprazole 6 mg/kg
AUC _(0-t) (µg/mL·h)	0.27±0.06	0.43±0.11	1.01±0.07
<i>t</i> _{1/2} (h)	1.02±0.58	0.84±0.32	0.84±0.12
CL (L·h ⁻¹ ·kg ⁻¹)	6.21±0.42	6.13±0.47	5.78±0.43

Pharmacokinetic features of omeprazole after id administration of different doses

The mean arterial plasma drug concentration-time profiles of

omeprazole after id administration of various doses to rabbits are illustrated in Figure 3, and some relevant pharmacokinetic parameters are listed in Table 3. As shown, after id administration of different doses of omeprazole, the plasma concentration of omeprazole rapidly increased and peaked at about 15 min, suggesting omeprazole can cross the rabbit intestinal epithelial cell layer rapidly. However, absolute bioavailability ranged from 18.64% to 19.29% (Table 4). The AUC_(0-t) values of omeprazole increased proportionally, but dose-normalized (based on 3 mg/kg) AUC_(0-t) values were independent of the doses studied. Moreover, the values were significantly smaller than those of corresponding doses administered by ipv (0.19±0.02 µg·mL⁻¹·h⁻¹ vs 0.43±0.11 µg·mL⁻¹·h⁻¹ for 3 mg/kg; 0.46±0.19 µg·mL⁻¹·h⁻¹ vs 1.01±0.07 µg·mL⁻¹·h⁻¹ for 6 mg/kg,

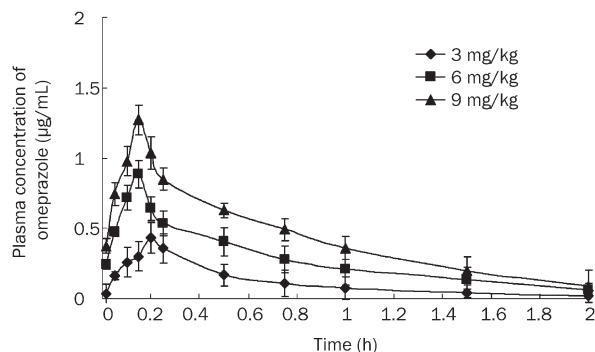


Figure 3. Mean plasma concentration-time profiles of omeprazole after id administration of different doses (3, 6, and 9 mg/kg) to rabbits. Each point indicates the Mean±SD (*n*=6). (◆) 3 mg/kg; (■) 6 mg/kg; (▲) 9 mg/kg.

Table 3. Mean pharmacokinetic parameters of omeprazole administered id to rabbits alone or 30 min after the id administration of 60 mg/kg ketoconazole or 9 mg/kg verapamil. *n*=6. Mean±SD. ^b*P*<0.05 vs the control (given omeprazole alone). CL/F: F is corresponded to the bioavailability.

	Omeprazole 3 mg/kg	Omeprazole 6 mg/kg	Omeprazole 9 mg/kg	Ketoconazole+ Omeprazole 3 mg/kg	Verapamil+ Omeprazole 3 mg/kg
AUC _(0-t) (µg/mL·h)	0.19±0.02 ^b	0.46±0.19	0.68±0.17	0.92±0.23 ^b	0.43±0.18 ^b
<i>C</i> _{max} (µg/mL)	0.24±0.04 ^b	0.88±0.31	1.22±0.21	1.29±0.18 ^b	0.86±0.16 ^b
<i>t</i> _{max} (h)	0.2	0.15	0.15	0.15	0.2
<i>t</i> _{1/2} (h)	0.63±0.12	0.53±0.07	0.59±0.06	0.59±0.47	0.56±0.57
CL (L·h ⁻¹ ·kg ⁻¹)	15.32±1.12 ^b	12.91±4.51	13.21±1.81	3.25±0.29 ^b	6.85±0.58 ^b

Table 4. Bioavailability, hepatic and intestinal extraction ratios of omeprazole in rabbits. $n=6$. Mean \pm SD.

	Omeprazole	
	3 mg/kg	6 mg/kg
BA (%)	19.29 \pm 3.39	18.64 \pm 2.73
EH (%)	57.18 \pm 2.73	59.29 \pm 3.14
EI (%)	54.94 \pm 1.85	54.20 \pm 1.53

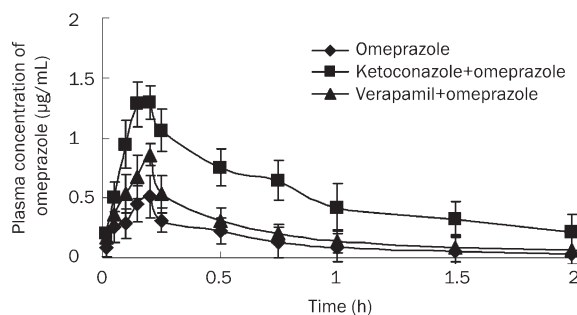
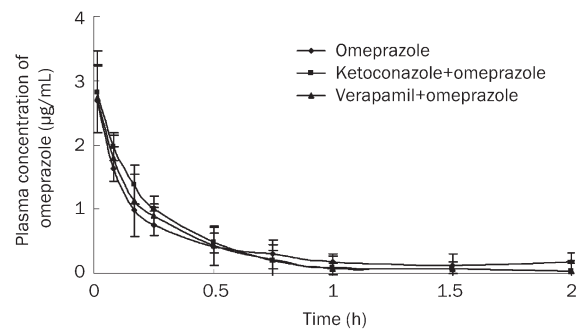
respectively. $P<0.05$). The values of terminal half-life and total clearance (CL/F) of different doses also exhibited dose-independent characteristics.

Differentiation of intestinal and hepatic first-pass extraction of omeprazole

A comparison of intestinal and hepatic extraction is shown in Table 4. EH and EI values calculated using the indirect method were based on the current rabbit data using 3 mg/kg and 6 mg/kg doses of id, ipv and iv administration. According to equations (2) and (3), the values of EH were estimated to be 57.18 \pm 2.73% and 59.29 \pm 3.14%, respectively, and the values of EI were estimated to be 54.94 \pm 1.85% and 54.20 \pm 1.53%, respectively.

Effect of ketoconazole or verapamil on id and iv pharmacokinetics of omeprazole

The mean plasma concentration-time profiles of omeprazole following id administration to rabbits in the presence or absence of ketoconazole or verapamil are illustrated in Figure 4, and some relevant pharmacokinetic parameters are listed in Table 3. The presence of ketoconazole (60 mg/kg) or verapamil (9 mg/kg) significantly increased the id plasma concentration of omeprazole compared with the control group, which received omeprazole alone. The relative bioavailability of omeprazole pretreated with ketoconazole or verapamil was 4.84 or 2.26 times higher than the control, respectively. The

**Figure 4.** Mean plasma concentration-time profiles of omeprazole after id administration of omeprazole (3 mg/kg) to rabbits in the presence of ketoconazole (60 mg/kg, administered intraduodenally) or verapamil (9 mg/kg, administered intraduodenally) respectively. Each point indicates the Mean \pm SD ($n=6$). (◆) Control (alone); (■) Coadministered with ketoconazole; (▲) Coadministered with verapamil.**Figure 5.** Mean plasma concentration-time profiles of omeprazole after iv administration of omeprazole (1.5 mg/kg) to rabbits in the presence of ketoconazole (60 mg/kg, administered intraduodenally) or verapamil (9 mg/kg, administered intraduodenally) respectively. Each point indicates the Mean \pm SD ($n=6$). (◆) Control (alone); (■) Coadministered with ketoconazole; (▲) Coadministered with verapamil.

AUC and C_{max} of omeprazole increased significantly, while there was no significant change in t_{max} and the terminal plasma half-life of omeprazole. Compared with the control, the total clearance (CL/F) significantly decreased after concurrent administration of ketoconazole and verapamil.

The iv pharmacokinetic profiles of omeprazole were also evaluated in the presence and absence of ketoconazole or verapamil in rabbits (Figure 5 and Table 1), respectively. As summarized in Table 1, ketoconazole and verapamil had no significant effect on the pharmacokinetic parameters of iv omeprazole.

Discussion

Oral administration is the most common route for drug administration. Orally-administered drugs have to cross the gastrointestinal epithelial cell membrane and are then transported into the port vein to the liver and eventually into the systemic circulation to exhibit their pharmacological effects.

In the present study, after id administration of different doses to rabbits, the plasma concentration of omeprazole peaked within 15 min, indicating omeprazole is rapidly absorbed from the intestinal lumen in rabbits. However, the bioavailability of omeprazole was low and dose-independent (from 18.64% to 19.29%). The AUC values were significantly smaller than those seen after ipv administration. This suggests that orally administered omeprazole undergoes poor gastrointestinal absorption and/or considerable first-pass extraction in rabbits. After iv administration of different doses of omeprazole, the CL values (2.41 L \cdot h $^{-1}$ \cdot kg $^{-1}$ to 3.59 L \cdot h $^{-1}$ \cdot kg $^{-1}$) were considerably smaller than the reported cardiac output in rabbits: 12.72 L \cdot h $^{-1}$ \cdot kg $^{-1}$ based on blood data^[15]. This suggests that the first-pass extraction of omeprazole in the lung and heart is negligible. The AUC values of ipv administration were significantly smaller than those for iv administration, suggesting omeprazole undergoes significant hepatic first-pass extraction in rabbits.

In short, the pharmacokinetic analysis of id, ipv and iv

omeprazole disposition in rabbits suggests that the low oral bioavailability observed for this drug results from comparable extraction by the liver and intestine.

Omeprazole is extensively metabolized by CYP2C19 and CYP3A4, and the pharmacokinetics and pharmacodynamics of omeprazole significantly depend on the CYP2C19 genotype status. Nevertheless, CYP3A4 is considered to account for about 70% of CYP enzymes expressed in the small intestine^[16]. *In vitro* (isolated enzyme preparations and specific transporters over-expressed cell lines) and *in vivo* (specific inhibitors, and *mdr1a/b* (-/-) mice) tools are available to study the role of transporters and drug-metabolizing enzymes^[17-19]. However, the gene knockout mice display increased expression of CYP enzymes^[20]. These suggest that models with a disease condition or altered gene expression may underestimate or overestimate the significance of intestine extraction on drug bioavailability. Therefore, in the present study we used specific CYP3A4 and P-gp inhibitors, ketoconazole and verapamil^[21] *in vivo* to evaluate the role of intestinal CYP3A and P-gp on the oral bioavailability of omeprazole.

In our study, pretreatment of ketoconazole or verapamil significantly increased the plasma concentration of omeprazole after id administration in rabbits. Increased AUC and decreased CL/F values were observed, but the slopes of the plasma concentration time curves were similar in all tested cases. Moreover, the iv pharmacokinetic parameters of the drug in the pretreated group were not significantly different from the control. These results suggest that both CYP3A and P-gp in the liver and kidney are not markedly inhibited by ketoconazole or verapamil during iv administration of omeprazole, and extraction of omeprazole in the small intestine after id administration is greater than that after iv administration, which is consistent with previous reports^[22].

In conclusion, oral omeprazole undergoes marked extraction in the small intestine, and the increased bioavailability of the drug after id administration of ketoconazole and verapamil results from CYP3A4 mediated metabolism and P-gp mediated efflux of the drug in the intestine, rather than in the liver.

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Author contribution

Hai-ming FANG, Jian-ming XU, Qiao MEI designed research; Hai-ming FANG performed research, analyzed data and wrote the paper; Lei DIAO, Mo-li CHEN, Juan JIN and Xin-hua XU performed part of the research together with Hai-ming FANG.

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