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Rectal Absorption of Omeprazole from Suppositories in Rabbits

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Rectal absorption of omeprazole, a proton pump inhibitor, from suppositories was studied in rabbits. The suppositories were prepared by the conventional melting method with two types of bases, water-soluble polyethylene glycol (PEG) 4000 and oil-soluble Witepsol H15 bases, and administered intrarectally (ir) to rabbits at a dose of 10 mg omeprazole/kg. The plasma omeprazole concentration-time profiles of the two suppositories were compared with those following intravenous (iv) administration of the same dose. There were no significant differences between the two suppositories in bioavailabilities and peak plasma concentrations (C_{max}). Bioavailabilities and C_{max} of PEG- and Witepsol suppositories were 30.3 and 33.9%, and 7.0 and 5.6 μg/ml, respectively. However, PEG suppository showed significantly ($P<0.05$) shorter time to reach peak plasma concentration (T_{max}), mean absorption time (MAT) and mean residence time in the plasma (MRT) than Witepsol suppository. The T_{max}, MRT and MAT were 25.0, 83.0 and 38.5 min for PEG suppository, but were 90.0, 122.5 and 78.0 min for Witepsol suppository, respectively. These differences between the two suppositories could be explained by the difference in the in vitro dissolution rates between the suppositories. The dissolution of omeprazole from PEG suppository was reportedly much faster than that from Witepsol suppository. It suggests that plasma profiles of omeprazole, especially C_{max}, MAT and MRT, could be controlled by modifying the *in vitro* dissolution rate of the drug from the suppositories. Above results suggest that rectal suppository is worth developing as an alternative dosage form of omeprazole to the conventional oral preparations which need sophisticated treatments, such as enteric coating, to prevent acid degradation of the drug in the stomach fluid.

Key words : Omeprazole, Rectal absorption, Suppository, Rabbit, Bioavailability, PEG base, Witepsol base

INTRODUCTION

Omeprazole, 5-methyl-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazole, is a substituted benzimidazole which suppresses gastric acid secretion by inhibiting the H^+/K^+-ATPase (a proton pump) in the gastric mucosa (Wallmark *et al.*, 1985; Larsson *et al.*, 1985). Clinical studies have shown that omeprazole is superior to H2 receptor antagonists in the healing of peptic ulcers (Classen *et al.*, 1985a; Classen *et al.*, 1985b), reflux oesophagitis (Dammann *et al.*, 1985a; Classen *et al.*, 1985b), reflux oesophagitis (Dammann *et al.*, 1986), and the Zollinger-Ellison syndrome (Vezzadini *et al.*, 1984).

The oral bioavailability of omeprazole is complicated by the fact that it was 40-50% in humans (Pilbrant and Cederberg, 1985; Regardh *et al.*, 1985), 15% in dogs (Regardh *et al.*, 1985), 6-13% (Watanabe *et al.*, 1994) or 40% in rats (Choi *et al.*, 1995). It increased dose-dependently in all the species. For example, it was only 6-13% at 10-40 mg/kg dose (Watanabe *et al.*, 1994), but increased up to 40% at 72 mg/kg dose (Choi *et al.*, 1995) in rats.

Omeprazole degrades very rapidly in water solutions at low pH-values (Pilbrant and Cederberg, 1985). The acid-instability, at least in part, may be responsible for the low oral bioavailability. Thus, various oral formulations of the drug have been developed to limit preabsorptive degradation. Most early studies introduced suspensions containing alkaline buffers, while more recent studies developed an enteric-coated formulation (Pilbrant and Cederberg, 1985). The reported oral bioavailability of 40-50% in humans (Pilbrant and Cederberg, 1985; Regardh *et al.*, 1985) was a result from the enteric-coated for-

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mulation.

Omeprazole undergoes extensive first-pass hepatic metabolism before entering the systemic circulation, and the metabolism decreases dose-dependently (Watanabe *et al.*, 1994). The hepatic extraction ratio in rats decreased from 0.8 to 0.59 when the dose was elevated from 2.5 to 10 mg/kg. The dose-dependent increase in the oral bioavailability was attributable to this dose-dependent hepatic metabolism (Watanabe *et al.*, 1994).

When a drug is unstable in the gastric fluid, and suffers extensive hepatic first-pass metabolism, rectal route can be considered as an alternative to the oral route of the drug administration, since the acid-degradation and first-pass metabolism can usually be avoided through this route. Rectal administration is also favored for patients who cannot swallow drogs. Omeprazole may be prescribed for a certain period of time to peptic ulcer patients, for example, who feel difficulty in swallowing oral preparations. Therefore, rectal administration of omeprazole seems to be worthy of consideration.

In this study, we examined the rectal route for its feasibility as an alternative to oral route of administration of omeprazole. Two types of suppositories, hydrophilic polyethylene glycol 4000 (PEG) and semisynthetic glyceride (Witepsol H15) bases, were prepared and administered intrarectally (ir), respectively. For intravenous (iv) administration, water solution of omeprazole without any buffers was prepared. And the plasma profiles of the drug following each administration were compared in terms of bioavailability. Oral absorption of omeprazole in rabbits was not examined in this study, since the rabbit has been known not to be a suitable animal for the evaluation of gastrointestinal absorption characteristics of drugs (Chiou *et al.*, 1969).

MATERIALS AND METHODS

Materials

Omeprazole was obtained from Han-Mi Pharmaceutical Inc., (Seoul, Korea). PEG 4000 and Witepsol H15 were purchased from BASFAG (UK) and Huls America, Germany. 1-Chloro-2,4-dinitrobenzene was purchased from Aldrich. Methanol and acetonitrile (Fisher) were HPLC grade. All other reagents were analytical grade and used as purchased.

Animals

Male albino rabbits (New Zealand breed) weighing 1.5-2.3 kg were used in all experiments. They were fed with a standard diet and were fasted for 48 hrs prior to experiments permitting free access to 10% (w/v) dextrose solution (Choong-Wae Pharm. Co., Seoul, Korea).

Preparation of suppositories

Fresh suppositories containing 10 mg of omeprazole were prepared by conventional molding method utilizing the PEG 4000 or Witepsol H15 (Huls America, Germany) as a base. A torpedo-shaped mold, made of a stainless steel, was used. After volumes of the mold openings was pre-calibrated with each base, the base was melted and required amount of omeprazole was incorporated by mixing at 67°C. Arginine was added to the mixture to yield 1.0% (w/w). The addition was found to protect omeprazole from a chemical degradation during storage or absorption process (Shim *et al.*, 1993). The resulting mixture was, then, poured into the mold and allowed to cool and congeal into suppositories at room temperature. Then, the mold was opened and the formed suppositories (0.5 g) were removed and stored in an airtight container. The contents of omeprazole in the suppository was 20 mg.

Intravenous (iv) administration

Rabbits (n=5) were injected bolusly via the marginal ear vein with a 0.4% (w/v) omeprazole solution at a dose of 2.5 ml/kg (10 mg/kg). The solution for iv administration was prepared by dissolving omeprazole in 0.1 M sodium bicarbonate containing 20% (v/v) PEG 400.

Rectal (ir) administration

Omeprazole was administered intrarectally to rabbits as suppositories. Witepsol or PEG suppository was administered into the rectum of rabbits (n=5 for each suppository) at the omeprazole dose of 10 mg/kg. The dose was controlled by adjusting the size of the suppositories.

Blood sampling

After each administration, blood samples (3 ml) were collected from each rabbit from the marginal ear vein by the aid of heparinized syringe. The heparinization was conducted by treating the syringes with 10 μl of heparinized saline (5000 IU/ml) and successive drying the saline. Blood samples were withdrawn at 0 and 2, 5, 10 30, 60, 90, 120, 170, 240 and 360 min after each administration. Physiological saline (3 ml) was injected after each blood sampling to maintain biological homeostasis. Plasma samples were separated by centrifuging the blood samples at 6000 g for 1 min and were stored at -20°C until HPLC assay.

HPLC assay of omeprazole

Plasma samples were analyzed for omeprazole by

published HPLC methods (Amantea and Narang, 1988; Nakashima *et al.*, 1988) with a slight modification. Briefly, carbonate buffer (pH 9.3, 1 M, 150 μl) and 1-chloro-2,4 dinitrobenzene (internal standard, 1 μg/ml, 100 μl) were added to plasma sample (1.0 ml) in 15-ml screw-cap polypropylene tube. Subsequently, omeprazole was extracted with 3.0 ml of hexane and 3.0 ml of methylenechloride by vortexing for 30 s. After centrifugation at 1,000 g for 5 min, the tubes were placed in a beaker of methanol in which dry ice had been added to freeze the aqueous layer (bottom layer). The organic layer (5.0 ml) was transferred into another tube and evaporated under nitrogen. The residue was reconstituted in 300 μl of mobile phase, and the solution (50 μl) was directly injected onto a Nova-Pak Phenyl column (Waters, 4-μm, 15-cm×3.9-mm id). The chromatograph consisted of a Shimadzu high-performance chromatograph (model LC 9A) and a variable ultraviolet spectrophotometric detector (model SPD-6A). Mobile phase was a mixture of methanol and triethylamine (99 : 1 volume ratio), pH of which was adjusted to 7.7 with 85% (w/v) phosphoric acid. The flow rate of the mobile phase was 0.7 ml/min and the wavelength of the detector was set at 302 nm, the absorption maxima of omeprazole. Separation of omeprazole was acceptable under this condition with a retention time of 7 min. Total run time of 15 min per injection was necessary to eliminate any possible interfering peaks. Plasma omeprazole was quantitated by comparison of the peak height of omeprazole to the internal standard using a calibration curve. The peak height ratio was linear in the range of 0.01-300 μg/ml (r=0.99, P<0.0001). Extraction recovery of omeprazole from the plasma was highly dependent on the concentration of carbonate buffer at pH 9.3; The recovery was less than 15% with the buffer below 0.5 M. Under the condition we report here, typical recovery was more than 90%, intra- and Inter-day variations of the assay were less than 5.0%, and the detection limit was 5 ng/ml.

Pharmacokinetic analysis

Total-body clearance (CL_t) and distribution volume at steady-state (Vd_{ss}) of omeprazole were calculated using iv data by Eqs. (1)-(2). Mean residence time (MRT) of omeprazole following each administration was calculated by Eq. (3) using respective AUC and AUMC data. Mean absorption time (MAT) of omeprazole following ir administration was calculated by Eq. (4)

$$CL_t = D/AUC \quad (1)$$

$$Vd_{ss} = D \cdot AUMC/AUC^2 \quad (2)$$

$$MRT = AUMC/AUC \quad (3)$$

$$MAT = MRT_{ir} - MRT_{iv} \quad (4)$$

where D, AUC and AUMC, respectiviely, denote dose, area under the plasma omeprazole concentration-time curve from time 0 to infinity and area under the first moment of the plasma omeprazole concentration-time curve from time 0 to infinity. The AUC and AUMC were calculated by the trapezoidal method from time 0 to the final sampling point and extrapolated from there to infinity using the elimination rate constant (β). β was obtained after fitting the plasma concentration data to a conventional two-compartment model using program MULTI (Yamaok *et al.*, 1981).

Statistical analysis

The statistical significance of the differences in the pharmacokinetic parameters was determined using the one-way analysis of variance (ANOVA) for unpaired data. A P value of <0.05 was chosen as the level of statistical significance. All results are expressed as mean±standard deviation.

RESULTS AND DISCUSSION

Plasma levels of omeprazole following iv and ir administrations at a dose of 10 mg/kg are plotted as a function of time in Fig. 1.

The plasma profile of omeprazole following iv administration showed biexponential decay. The pharmacokinetic parameters following iv administration are summarized in Table I. The volume of distribution at steady state (Vd_{ss}) in this study was only 0.43 l/kg. It is inconsistent with those in humans (0.19-0.45 l/kg,

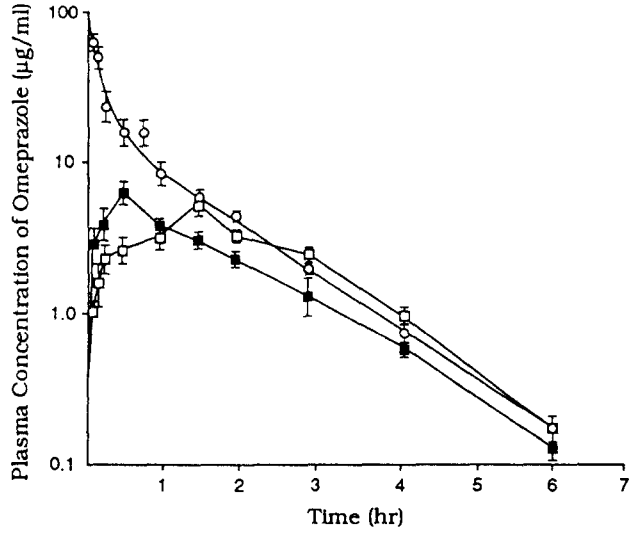

Fig. 1. Plasma concentration profiles of omeprazole following administration via various routes to rabbits at a dose of 10 mg/kg (Mean±S. D., n=5). ○: iv (water solution), □: ir (PEG 4000 suppository), ■: ir (Witepsol H15 suppository)

Table I. Pharmacokinetic parameters (mean±S.D., n=5) of omeprazole following iv and ir administration to rabbits at a dose of 10 mg/kg

Parameters	iv	ir	
		PEG base	Witepsol base
Vd_{ss} (ml/kg)	427.8 (±58.0)	–	–
CL_t (ml/min/kg)	9.6 (±0.8)	–	–
AUC (min. μg/ml)	2105.3 (±171.4)	638.3[a] (±31.3)	714.5[a] (±43.2)
MRT (min)	44.5 (±2.5)	83.0[a] (±2.7)	122.5[a,b] (±6.5)
C_{max} (μg/ml)	–	7.0 (±1.2)	5.6 (±1.0)
T_{max} (min)	–	25.0 (±0.0)	90.0[b] (±0.0)
MAT (min)	–	38.5	78.0
Bioavailability (%)	–	30.3	33.9

[a]Significantly different from iv administration.
[b]Significantly different from PEG suppository.

Regardh *et al.*, 1990) and rats (0.64-0.75 l/kg, Watanabe *et al.* 1994; 0.18 l/kg, Choi *et al.*, 1995). Choi *et al.* (1995) suggested dose-dependent pharmacokinetic characteristics of the drug (Regardh *et al.*, 1990, Watanabe *et al.*, 1994), in addition to species-difference, as a possible explanation of the difference between reports in Vd_{ss}. High plasma protein binding of the drug seemed responsible for the poor body distribution (Regardh *et al.*, 1985).

The total plasma clearance (CL_t) of omeprazole in this study (9.6 ml/min/kg) is comparable with those in rats (4.9 ml/min/kg, choi *et al.*, 1995) and humans (8.8 ml/min/kg), but much smaller than that of Watanabe *et al.*, (1994), in which CL_t of 38-39 ml/min/kg was reported for 2.5-10 mg/kg dose to rats. The discrepancy in CL_t between studies seems to be related with the dose-dependent hepatic metabolism (Regardh *et al.*, 1990, Watanabe *et al.*, 1994) and species-difference.

Following ir administration of suppositories, omeprazole appeared in the plasma immediately, and the terminal slopes of the plasma concentration-time curves of both suppositories were almost identical to that of iv administration. There were no significant differences in peak plasma concentrations(C_{max}) and AUC between the suppositories. So, the bioavailability of omeprazole from both suppositories was almost identical at around 30% of the iv administration. It indicates that omeprazole is efficiently absorbed from the rectal route. The rectal bioavailability in this study is consistent with that in rat study (39%, Choi *et al.*, 1994) and comparable to the oral bioavailabilities: 6-13% in rats (Watanabe *et al.*, 1994), 15% in dogs (Regardh *et al.*, 1985), 40-50% in humans (Regardh *et al*, 1990) and 41% in rats (Choi *et al.*, 1995). Here, it should be noted again that the discrepancy in oral bioavailabilities between reports, especially between Watanabe *et al.* (1994) and Choi *et al.* (1995), is attributed to the dose-dependent hepatic metabolism of the drug (Regardh *et al.*, 1990; Watanabe *et al.*, 1994). The low rectal bioavailability of omeprazole can be attributed to poor absorption of the drug from the rectum, since acidic degradation and/or first-pass metabolism will not be significant, if any, in rectal administration.

Contrary to C_{max} and AUC, the time to reach the peak concentration (T_{max}) following ir administration was significantly different ($p<0.05$) between the suppositories; it was 25.0 min for PEG suppository and 90.0 min for Witepsol suppository. Similarly, the mean absorption time (MAT) of omeprazole from Witepsol suppository (78.0 min) was 2-fold larger than that from PEG suppository (38.5 min). It indicates that the rectal absorption of omeprazole is faster from PEG suppository than from Witepsol suppository. As a result of different absorption, the mean residence time (MRT) of omeprazole from Witepsol suppository (122.5 min) was significantly larger ($p<0.05$) than that from PEG suppository.

The differences between the two suppositories in T_{max}, MAT and MRT may be attributed to the different dissolution of omeprazole from the suppositories in the rectal fluid. Lee *et al.*, (1993) reported that omeparzole release from the PEG suppository was much faster than from the Witepsol suppository when determined in water at 37°C by USP paddle method in vitro: the diffusion rate constant of the drug from the PEG- and Witepsol suppositories were 1.63 and 0.38 $mg \cdot min^{1/2}$, respectively, when analyzed according to the Higuchi's diffusion model. The different solubility of the two bases may be responsible for the different dissolution in the release medium; PEG base is hydrophilic and dissolves in water, while Witepsol base, a semi-synthetic glyceride, does not dissolve in water and just melts at the rectum temperature (around 37°C). Thus, it could be concluded that slower release of the drug from Witepsol suppository in the rectal fluid retarded the rectal absorption resulting larger T_{max}, MAT and MRT than PEG suppository. It was also found that *in vitro* release rate of omeprazole from the suppository is reflected on the *in vivo* absorption rate of omeprazole from the rectum.

Considering together with the fact that omeprazole in PEG and Witepsol suppositories does not irritate

rectal mucosa (Kim *et al.*, 1993), above results in this study suggest that ir route can be developed as a new alternative to oral route of administration of omeprazole which needs some sophisticated treatments such as enteric coating of the drug to prevent acidic degradation in the gastric fluid. Absorption rate of omeprazole from the suppository may be modified, without affecting the extent of bioavailability and peak plasma concentration significantly, by controlling *in vitro* dissolution rate of the drug from the dosage from. The dissolution rate could be controlled easily by selecting an appropriate suppository base such as hydrophilic PEG 4000 or hydrophobic Witepsol H15. Addition of appropriate absorption enhancer (s) to the rectal preparations is expected to improve the rectal bioavailability of omeprazole.

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