J. Pharm. Pharmacol. 1996, 48: 371–374
Received June 5, 1995
Accepted December 5, 1995

Improving the Oral Bioavailability of Sulpiride by a Gastric-retained Form in Rabbits

NAONORI KOHRI, IMAD NAASANI, KEN ISEKI AND KATSUMI MIYAZAKI

Department of Pharmacy, Hokkaido University Hospital, School of Medicine, Hokkaido University, Nishi-5-chome, Kita-14-jo, Kita ku, Sapporo 060, Japan

Abstract

To improve the limited oral bioavailability of sulpiride, a gastric-retained form was developed and evaluated using gastric-emptying-controlled rabbits.

The AUC value after oral administration of sulpiride as an aqueous solution was less than that after oral administration of sulpiride original powder. The dissolution was not important as a rate limiting factor for sulpiride oral absorption. Sulpiride was absorbed predominantly from the upper part of the small intestine of the rabbit.

A gastric-retained tablet prepared from Carbopol 934P, with sustained-release characteristics, was found to be suitable for improving and extending the oral bioavailability of sulpiride.

Sulpiride, unlike most other neuroleptics, is a selective antagonist of the dopamine D_2 receptors and has a much lower incidence of extrapyramidal side effects. The clinical activity of sulpiride is dose-dependent. The antipsychotic effect occurs at doses generally ranging from 400 to 1800 mg day^{-1}, whereas antidepressant and anxiolytic activity is prevalent at lower doses (50–300 mg day^{-1}) (Yura et al 1976). Sulpiride is also given for gastric and duodenal ulcers at a dose of 150 mg daily (Martindale 1993).

Many reports have indicated that sulpiride has oral bioavailability problems including differences between species, erratic limited absorption, and a high dependence on the formulation factors (Mizuno et al 1986; Bressolle et al 1992). In our previous study, a significant increase in the oral bioavailability was achieved by incorporation of sodium oleate as an enhancer in enteric capsules (Naasani et al 1995). It seemed that the mechanism of enhancing the absorption was due to an improvement in the physicochemical properties of sulpiride toward a higher lipophilicity and a higher solubility as well as to a modification of the permeability of the biomembrane.

Gouda et al (1987) suggested that the delay in the gastrointestinal transit time due to food or an anticholinergic drug, propantheline bromide, allows for an improvement in the absorption of sulpiride from the human intestine. Based on these observations, an oral formulation with gastric-retained properties will offer the best conditions for increasing the absorption of sulpiride without using enhancers. In the present study, we prepared a gastric-retained formulation for sulpiride and evaluated the improvement of sulpiride oral bioavailability using gastric-emptying-controlled rabbits.

Correspondence: K. Miyazaki, Department of Pharmacy, Hokkaido University Hospital, School of Medicine, Hokkaido University, Nishi-5-chome, Kita-14-jo, Kita-ku, Sapporo 060, Japan.

Materials and Methods

Materials

(±)-Sulpiride was purchased from Sigma Chemical Co., USA. Carbopol 934P (carboxyvinyl polymer) was supplied by B. E. Goodrich Co., UK.

Dosage form preparation

Original powder. The original powder of sulpiride was administered as a fine powder (100-mesh) filled in hard gelatin capsules (Japanese Pharmacopeia XII, No. 5). Each rabbit received one capsule containing the administered dose.

Liquid form. The required dose of sulpiride was dissolved in 20 mL 0·1 M HCl and administered using a plastic stomach catheter.

Gastric-retained form. A physical mixture of sulpiride (100-mesh) with Carbopol 934P (100-mesh) was prepared and mixed again with a fine powder of magnesium stearate (as a lubricant). The ratio of the final mixture was sulpiride-Carbopol 934P-magnesium stearate = 1 : 18·8 : 0·2. Approximately 350 mg of the mixture were compressed into a cylindrical tablet by a single-punch machine (model KT-2, Okada Seiko Co., Japan). A tablet with a diameter of 5 mm, length 12 mm was used for the administration. Each rabbit received 2 tablets containing the required dose.

Release studies

The dissolution characteristics of the gastric-retained form or the original powder were assessed using the Japanese Pharmacopeia XII dissolution apparatus with a rotating basket method operating at 100 rev min^{-1}. The dissolution media employed were Japanese Pharmacopeia XII 1st (pH 1·2) and 2nd (pH 6·8) disintegration fluids. Five hundred milliliters of each medium was maintained at 37 ± 0·1°C.

An amount of the tested formulation corresponding to 15 mg sulpiride was added to each medium, and then samples of 5 mL were removed at predetermined intervals and filtered through membrane filters (pore size, 0·45 μm). Five milliliters of fresh medium was added to the dissolution vessel immediately to maintain the original volume. The removed samples were directly analysed by HPLC (Naasani et al 1995).

In-situ absorption studies

The absorption site of sulpiride in the intestinal tract of the rabbit was established by the in-situ loop method derived from the method of Levine & Pelikan (1961). Before experimentation, white male rabbits, 3–3·5 kg, were prevented from coprophagy using plastic collars, and fasted for 30 h with free access to water. After anaesthetization (sodium pentobarbitone, 0·3 mg kg^{-1}), a midline incision was made and intestinal loops of 20 cm were prepared and gently manipulated to clear the contents of the lumen. The loops were ligated at the upper, middle, and distal parts of the intestine. The proximal ligation of the upper loop was placed about 10 cm from the pylorus, and therefore the bile duct remained unligated. The proximal ligation of the middle loop was placed about 45 cm from the pylorus, and that of the distal loop was placed about 30 cm above the ileo-caecal junction. Five milliliters of drug solution (50 μg mL^{-1}) in an isotonic phosphate buffer, pH 7·0 was injected into the loop using a syringe. After 60 min, before the animal was killed, the loop was removed and the contents were emptied into a 25-mL volumetric flask. The lumen of the loop was rinsed to give a total volume of 25 mL with the isotonic phosphate buffer, pH 7·0. The samples were centrifuged at 1000 *g* for 10 min and 3 mL of each supernatant was mixed with 2 mL methanol and centrifuged again at 1000 *g* for 10 min. Twenty microliters of the supernatant was used for HPLC.

Animal treatment and dosage form administration

Gastric-emptying-controlled rabbits were prepared by the method of Takahashi et al (1983) to simulate gastric emptying in man. In this method, white male rabbits, 3–3·5 kg, were given doses corresponding to 10 mg sulpiride kg^{-1} in a cross-over manner with a 14-day washout period between dosing. Each formulation was inserted into the stomach of the rabbit with a plastic catheter attached to a syringe. The plastic catheter was inserted through a hole in a wooden bar which held the mouth open in such a way that the catheter passed through the oesophagus into the stomach. The dosage form which had been fixed to the inserted end of the plastic catheter was pushed out of it with 20-mL water into the stomach interior. For the intravenous administration, sulpiride sulphate solution (Dogmatil Injection) was injected through the ear marginal vein. For both intravenous and oral administrations, no water was given for the first 4 h and no food was allowed until the study was over. Plasma samples were collected from the ear vein with a heparinized syringe at predetermined intervals and 1 mL plasma was mixed with 2 mL carbonate buffer (0·2 M Na_2CO_3–0·2 M $NaHCO_3$, pH 9·8) and extracted with 6 mL chloroform. Five milliliters of the organic layer were evaporated and reconstituted with 0·2 mL internal standard solution (α-naphthylamine in mobile phase, 5 μg mL^{-1}). The resulting solution was used for HPLC.

Bioavailability data analysis

The peak concentration (C_{max}) and the time-to-peak concentration (t_{max}) were observed from the plasma profile. The area under the plasma concentration–time curve from 0 to 28 h (AUC_{0-28h}) was calculated according to the trapezoidal rule. The mean residence time (MRT) and the mean absorption time (MAT) were calculated using statistical moment theory

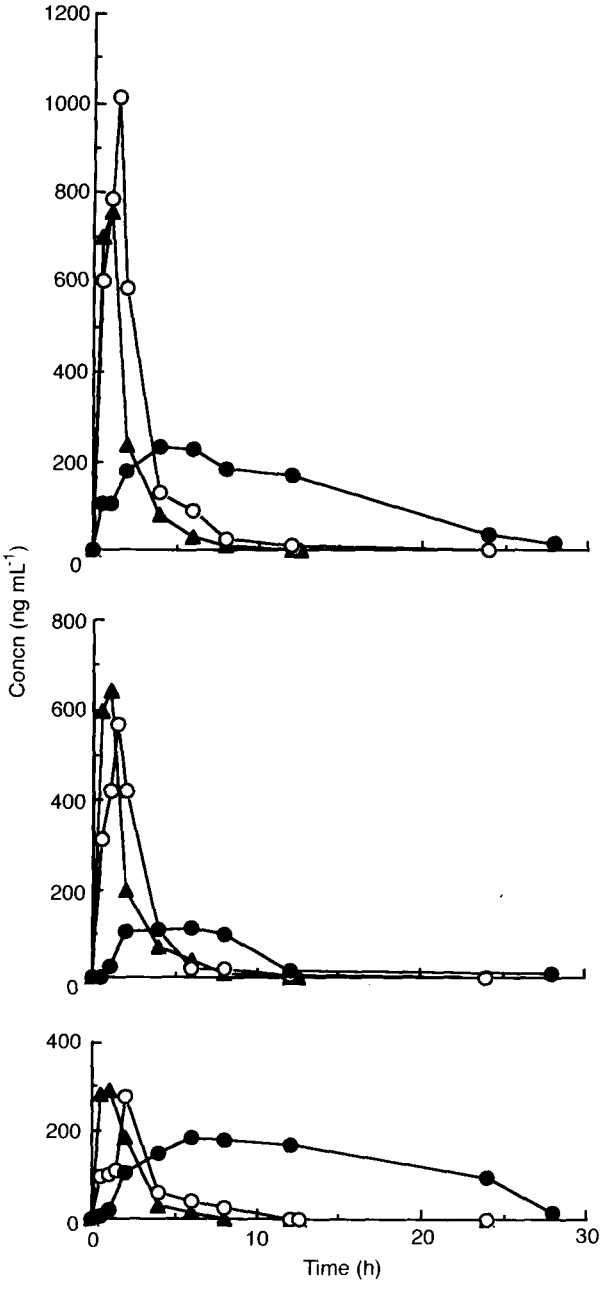


FIG. 1. Individual plasma concentrations of sulpiride after oral administration of the liquid form (▲), the original powder (○) and the gastric-retained tablet (●) to each rabbit at a dose of 10 mg kg^{-1} body weight in a cross-over study.

Table 1. Bioavailability parameters after sulpiride administration to rabbits at a dose of 10 mg kg^{-1} body weight in a cross-over study.

Formulation	t_{max} (h)	C_{max} (ng mL^{-1})	AUC_{0-28} (ng h mL^{-1})	MRT (h)	MAT (h)	F (%)
Solution	1·0 ± 0·00	562 ± 172·1	1201 ± 283·4	1·9 ± 0·08	0·3 ± 0·28	18·1 ± 5·90
Original powder	1·7 ± 0·20	620 ± 262·1	1605 ± 602·2	2·8 ± 0·43	1·2 ± 0·68	24·7 ± 11·82
Gastric-retained tablet	5·3 ± 0·82	175 ± 41·9	3098 ± 696·5	11·1 ± 1·09	9·4 ± 1·33	45·9 ± 13·13
Intravenous injection			6944 ± 726·0	1·7 ± 0·26		

Each value represents the mean ± s.e.m. of 3 animals.

(Yamaoka et al 1978) according to the following equations:

$$MRT = \int_0^t tCdt \Big/ \int_0^t Cdt \quad (1)$$

$$MAT = MRT_{p.o.} - MRT_{i.v.} \quad (2)$$

$$F = AUC_{p.o.}/AUC_{i.v.} \quad (3)$$

where p.o. and i.v. represent the oral and the intravenous administrations, respectively. The MAT expresses the average time needed for the drug molecule to reach the general circulation following oral administration.

Results and Discussion

As we have mentioned in our preceding paper (Naasani et al 1995), sulpiride does not undergo a marked first-pass effect when administered to rabbits orally. Moreover, in a preliminary experiment, we found that sulpiride does not have any tendency to bind to the gastrointestinal mucin (data not shown). Therefore, the poor oral bioavailability of sulpiride seems to be attributed either to the solubility or to the membrane permeability. We found that the solubility of sulpiride in an isotonic phosphate buffer (pH 7·0) at 37°C was about 8 mg mL^{-1} and that in the distilled water was about 0·8 mg mL^{-1}. Since the gastrointestinal fluids do have some buffering and surfactant capacity, the solubility of sulpiride in these media will be at least that in the distilled water, and as such, the extent of solubility is unlikely to be the reason for reduced physiological bioavailability (Fincher 1968). We further examined the relationship between the dissolution and the oral bioavailability of sulpiride. After oral administration of sulpiride as an aqueous solution, reduced values of t_{max} and AUC_{0-28} were observed when compared with the original powder (Fig. 1, Table 1).

The lesser absorbability of the aqueous solution as well as the enhancing effect of food and anticholinergics in man (Gouda et al 1987) could be indications for the presence of an absorption window for sulpiride. We investigated the gastrointestinal absorption site for sulpiride by the in-situ loop technique. The percentage of recovered sulpiride at different sites in the intestine is shown in Table 2. Sulpiride was found to be preferably absorbed from the upper intestine in rabbit as in the case of man (Gouda et al 1987). Therefore it would be suitable to increase the transit time of the formulation along the upper part of the gastrointestinal tract to create a better opportunity for the drug to be absorbed from the effective site of absorption.

Table 2. Disappearance of sulpiride (%) from different sites of rabbit small intestinal loop for 60 min.

Upper	Middle	Distal
51·2 ± 2·5	36·4 ± 2·4	22·1 ± 6·1

Drug concentration of the solution in each loop was 50 μg mL^{-1} of isotonic phosphate buffer, pH 7·0. Each value represents the mean ± s.e.m. of 3 animals.

For this purpose, a drug mixture with a bioadhesive and swellable polymer, Carbopol 934P (Hunt et al 1987), was prepared and compressed into a cylindrical matrix tablet (5 mm × 12 mm). The release profiles of sulpiride from this tablet and from the original powder are shown in Fig. 2. At pH 1·2 and after 10 h release period, about 70% of the amount of sulpiride incorporated in the tablet was released and an elastic gelatinous matrix with an enlarged volumetric size to more than 8 times that of the original remained in the basket of the release apparatus. On the other hand, the original powder showed complete dissolution in less than 30 min. We concluded that this tablet would release sulpiride mostly in the stomach. The release at pH 6·8 was determined because of the possibility that after a certain extent of erosion, the remainder of the matrix might pass to the intestine.

From the plasma profile, it is clear that sustained plasma levels with improved bioavailability were achieved. After administration of this tablet at 8 h post-dosing, we surgically

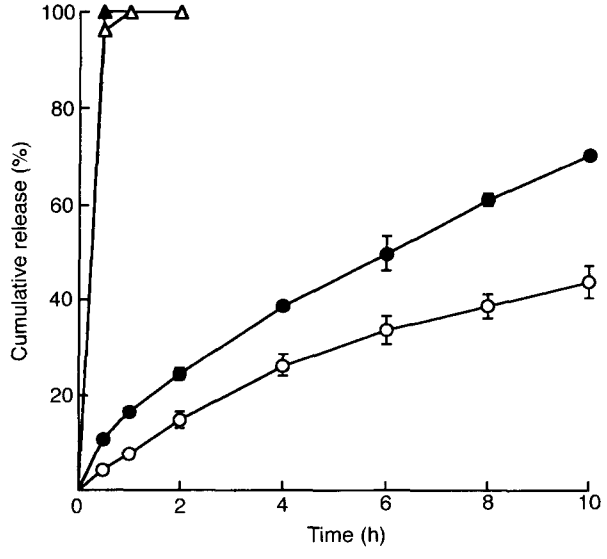
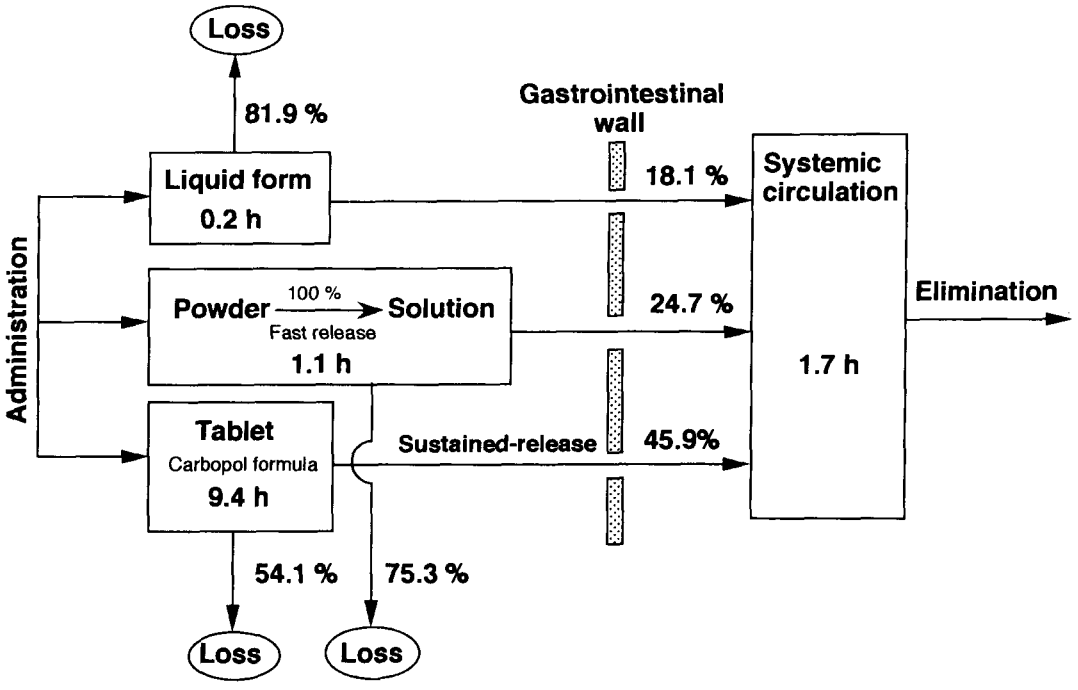


FIG. 2. Release profiles of sulpiride from the original powder (△, ▲) and the gastric-retained tablet (○, ●) in Japenese Pharmacopeia XII 1st (pH 1·2) (▲, ●) and 2nd (pH 6·8) (△, ○) disintegration fluids at 37°C. Each value represents the mean ± s.d. of three experiments.



SCHEME 1. Drug flow diagram of sulpiride original powder, liquid form and gastric-retained tablet.

assessed the retention behaviour of the tablet. The tablet enlarged and assumed a sponge-like adherent structure. This structure allowed a long retention in the stomach cavity. During this period, the drug was released slowly from the matrix and a sustained profile with a higher absorption ratio was achieved.

Because of the effect of the gastrointestinal secretions and peristalsis, the matrix would be expected to be slowly eroded and loosened until it is emptied from the stomach; following surgery, we confirmed that the matrix disappeared completely from the stomach within 2 days after oral administration.

The results are summarized in Scheme 1 by moment analysis (Yamaoka et al 1978). Scheme 1 depicts the drug flow diagram after oral administration of three kinds of sulpiride formulations. An interesting finding is that the MAT and the F values for the liquid form are the smallest. This means that the liquid form passes over the effective absorption site more rapidly than does the original powder. This provides an additional indication that sulpiride has an absorption window in the gastrointestinal tract. The MAT and the F values of the gastric-retained form showed, respectively, about 8·5- and 2-fold increase when compared with the original powder.

Combining the results of the present and previous study (Naasani et al 1995), we conclude that both the gastric-retained form and the enteric form in combination with sodium oleate are promising approaches for improving the oral bioavailability of sulpiride. However, considering the inter- and intra-subject variance of the gastric emptying and its effect on the release onset from enteric-soluble formulations, the gastric-retained form is superior in limiting the bioavailability variance, extending the effective plasma levels and thus achieving better therapy.

References

Bressolle, F., Bres, J., Faure-Jeastis, A. (1992) Absolute bioavailability, rate of absorption, and dose proportionality of sulpiride in humans. J. Pharm. Sci. 81: 26–32

Fincher, J. H. (1968) Particle size of drugs and its relationship to absorption and activity. J. Pharm. Sci. 57: 1825–1835

Gouda, M. W., Babhair, S. A., Al-Angary, A. A., El-Hofy, S. A., Mahrous, G. M. (1987) Effect of dosage form, food, and an anticholinergic drug on the bioavailability of sulpiride. Int. J. Pharm. 37: 227–231

Hunt, G., Kearney P., Kellaway, I. W. (1987) Mucoadhesive polymers in drug delivery systems. In: Johnson, P., Lloyd-Jones, J. G. (eds) Drug Delivery Systems, Ellis Horwood, London, pp 180–199

Japanese Pharmacopeia XII (1991) Hirokawa Publishing, Tokyo

Levine, R. R., Pelikan, E. W. (1961) The influence of experimental procedures and dose on the intestinal absorption of an onium compound, benzomethamine. J. Pharmacol. Exp. Ther. 131: 319–327.

Martindale, The Extra Pharmacopoeia, 30th edn. In: Reynolds, J. E. F. (ed.) (1993) The Pharmaceutical Press, London, pp 615–616

Mizuno, N., Morita, E., Nishikata, M., Shinkuma, D., Yamanaka, Y. (1986) Gastrointestinal absorption of sulpiride in rat. Arch. Int. Pharmacodyn. 283: 30–38

Naasani, I., Kohri, N., Iseki, K., Miyazaki, K. (1995) Improving the oral bioavailability of sulpiride by sodium oleate in rabbits. J. Pharm. Pharmacol. 47: 469–473

Takahashi, T., Uezono, Y., Fujioka, H. (1983) Gastric-acidity controlled rabbits for evaluation of bioavailability. Yakuzaigaku 43: 61–67

Yamaoka, K., Nakagawa, T., Uno, T. (1978) Statistical moments in pharmacokinetics. J. Pharmacokin. Biopharm. 6: 547–558

Yura, R., Kato, Y., Shibahara, Y., Fukushima, Y., Sasaki, K., Sato, M., Kawamura, K., Miyoshi, K., Nakajima, H., Furuyabu, S., Matsuda, Y., Kasahara, Y. (1976) A double-blind comparative study of the effects of sulpiride and imipramine on depression. Seishin-Igaku 18: 89–102