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Improvement of Bioavailability of Poorly Intestinally Absorbed Drugs from Medium-Chain Glyceride Base. Enhancement of the Rectal Absorption of Cefmetazole Sodium in Rabbits

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Medium-chain glyceride (MCG) enhanced the bioavailability of cefmetazole sodium, a water-soluble β-lactam antibiotic, after rectal administration to rabbits. The promoting effect of MCG on the rectal absorption of cefmetazole sodium was observed to be much larger than that on cefmetazole. The plasma concentration–time profile after rectal administration of cefmetazole sodium in MCG solution was similar to that after intramuscular administration.

Keywords——cefmetazole sodium; medium-chain glyceride; rectal absorption; bioavailability

In general, few injectable β-lactam antibiotics are absorbed satisfactorily when they are administered by the oral route because of their low lipophilic character and their ionization at the physiological pH levels in the gastrointestinal tract, as expected from their low pK_a values. Therefore, poorly intestinally absorbed β-lactam antibiotics are administered parenterally.

Recently, many attempts have been made to improve the absorption of β-lactam antibiotics from the rectum. Murakami *et al.* studied the effect of enamine derivatives on the rectal absorption of β-lactam antibiotics in rabbits.[1] Nishihata *et al.* reported the promoting effect of salicylic acid on the rectal absorption of cefmetazole sodium.[2] However, there are few reports on the effect of suppository base on the absorption of β-lactam antibiotics. Therefore, we attempted to improve the absorption of cefmetazole sodium as a model drug by using various kinds of suppository base.

Cefmetazole sodium, a semisynthetic derivative of cephamycin, has broad spectrum antibacterial activity against gram-positive and gram-negative bacteria.

Materials and Methods

Materials——Cefmetazole and its sodium salt were synthesized in the central research laboratories of Sankyo Co., Ltd. The following materials were used for the preparation of suppositories: MGK® is a commercial product of Nikko Chemicals. It is available in liquid form and is a mixture of glyceryl mono-, di- and tricaprylate. Glycerylmonooleate (MGO®) and glyceryltrioleate were supplied by Nikko Chemicals. Glycerylmonolaurate was supplied by Taiyo Kagaku. Witepsol H15® (Dynamit Nobel), a semisynthetic medium chain triglyceride base, was a commercial product.

Test Preparations——To prepare an aqueous solution of cefmetazole sodium, cefmetazole sodium was dissolved in saline to a concentration of 125 mg/ml for intravenous administration and 500 mg/ml for intramuscular and rectal administrations.

To prepare suppositories, cefmetazole sodium was suspended in melted adeps solidus at about 40 °C and molded. Two grams of each suppository contained 250 mg of cefmetazole sodium. In the case of the MGK® suppository, 250 mg of cefmetazole sodium was dissolved in 1750 mg of MGK® by sonication (type 72, Branson) in a water bath at 25 °C for 5 min. However, cefmetazole (which is insoluble in MGK®) was used as an MGK®

suspension.

Animal Experiments——Male white rabbits weighing 2.6—2.9 kg were fasted for about 40 h prior to experiments, but with free access to water. These rabbits were accustomed to remaining quietly in pyrogen test boxes. Cefmetazole sodium, 250 mg/body, was administered intravenously or intramuscularly to 4 rabbits. In the case of rectal administration, the suppository was inserted just inside the internal sphincter. The aqueous solution and MGK® solution were administered about 3 cm inside from the anus using a 2 ml syringe. After administration into the rectum, the anus was sealed with Aronalpha A® (Sankyo Co., Ltd.), an adhesive agent, to prevent leakage. Four rabbits were used in each of these experiments.

At given times, blood samples were taken from the ear into heparinized test tubes. Plasma samples were obtained by centrifugation and frozen until required for analysis.

Analytical Method——Cefmetazole in plasma samples was determined according to the microbiological assay of Sahashi *et al.*[3] The microbiological assay was performed by the thin-layer disk plate method using *Micrococcus luteus* ATCC 9341 as the test organism. The standard solution was prepared by using rabbit plasma from animals which had not received any drug.

Pharmacokinetic Analysis——The plasma concentrations of cefmetazole were determined up to 2 h after administration. The observed plasma concentrations after intravenous administration were fitted to a one-compartment model. When cefmetazole sodium was administered intramuscularly or rectally, the plasma concentration data were well described by a one-compartment model. The pharmacokinetic constants were obtained by the least-squares method. The values of C_{max} and T_{max} were calculated from the individual data for each rabbit by using the pharmacokinetic parameters calculated above. The extent of bioavailability was calculated as the ratio of the area under the plasma concentration *vs.* time curve (AUC) for rectal administration to that for intravenous administration.

Results and Discussion

The effects of various suppository bases on the rectal absorption of cefmetazole sodium from rabbits are summarized in Table I. As shown in Table I, cefmetazole was not detected in plasma after rectal administration of an aqueous solution of cefmetazole sodium at a dose of 250 mg. Cefmetazole sodium was apparently not absorbed because of its low lipophilicity and its ionization at the physiological pH in the rectum. Cefmetazole sodium from Witepsol H15® suppository was not detected in plasma either. Glycerylmonolaurate–glycerylmonooleate and glyceryltrioleate–glycerylmonooleate (used as suppository bases) were also ineffective. However, when MGK® solution containing cefmetazole sodium was administered into the rectum, absorption of the drug was significantly increased; the bioavailability of the drug from MGK® was calculated to be about 65.9%. MGK®–glycerylmonooleate was almost equally effective.

The plasma concentration–time profiles were measured after rectal administration of

Table I. Rectal Absorption of Cefmetazole Sodium from Various Suppository Bases in Rabbits[a]

Base	AUC (μg·h/ml)	Bioavailability (%)
MGK®	79.2±2.7	65.9±2.2
G.[b] monolaurate–G. monooleate (80:20)	2.3±0.1	1.9±0.1
G. trioleate–G. monooleate (80:20)	N.D.[c]	
MGK®–G. monooleate (80:20)	76.3±5.0	63.5±4.2
Witepsol H15®	N.D.	
Water	N.D.	

a) Each value is the mean±S.E. for 4 animals.
b) Glyceryl-. *c*) Not detected.

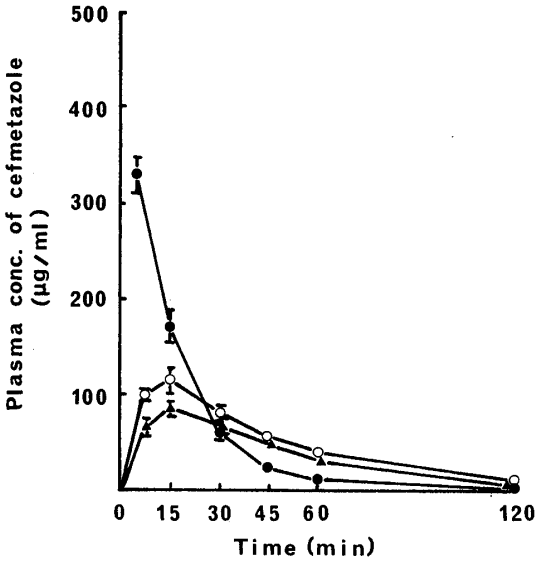

Fig. 1. Mean Plasma Concentrations of Cefmetazole after Intravenous, Intramuscular and Rectal Administrations of 250 mg of Cefmetazole Sodium to Rabbits

Each value is the mean ± S.E. of 4-experiments. ●, intravenous; ○, intramuscular; ▲, rectal administration.

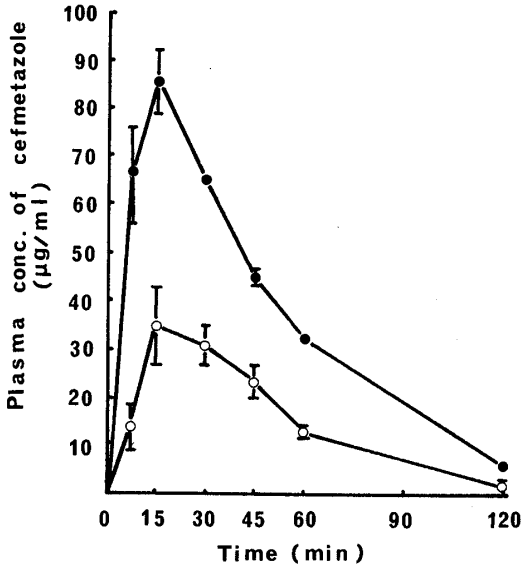

Fig. 2. Comparison of Rectal Absorptions of Cefmetazole and Cefmetazole Sodium in MGK®

Each value is the mean ± S.E. of 4 experiments. ○, cefmetazole; ●, cefmetazole sodium.

TABLE II. Comparison of the Pharmacokinetic Parameters Following Intravenous (*i.v.*), Intramuscular (*i.m.*) and Rectal (*i.r.*) Administrations of Cefmetazole Sodium to Rabbit[a]

Parameters	*i.v.*	*i.m.*	*i.r.*
C_{max}[b] (μg/ml)		122.1 ± 21.3	99.6 ± 2.6
T_{max}[c] (h)		0.20 ± 0.01	0.19 ± 0.01
k_a[d] (h^{-1})		9.362 ± 0.419	9.038 ± 2.644
k_{el}[e] (h^{-1})	3.969 ± 0.266	1.416 ± 0.183	1.556 ± 0.109
AUC[f] (μg·h/ml)	120.2 ± 8.5	102.4 ± 10.6	79.2 ± 2.7

a) Each value is the mean ± S.E. for 4 animals.
b) The plasma concentration peak. *c*) The time to reach the peak.
d) The absorption rate constant. *e*) The apparent elimination rate constant.
f) *AUC* was calculated by means of the trapezoidal rule from zero to infinite time.

MGK® solution of cefmetazole sodium. Figure 1 shows the mean plasma concentration–time profiles obtained after intravenous, intramuscular and rectal administrations of cefmetazole sodium (250 mg/body) to 4 rabbits. As shown in Fig. 1, the plasma concentrations of cefmetazole increased rapidly and reached maximum levels at 15 min after rectal administration. The plasma concentration–time profiles of cefmetazole sodium after rectal and intramuscular administrations were found to be similar.

The average values of individual pharmacokinetic parameters calculated from the plasma concentration–time profiles after intravenous, intramuscular and rectal administrations are summarized in Table II. No statistically significant differences were found between the pharmacokinetic parameters of rectal and intramuscular absorptions of cefmetazole sodium. These results show that the rectal absorption of cefmetazole sodium from MGK® solution is as fast as the absorption after intramuscular administration. Therefore, it was concluded that

not only the extent of bioavailability but also the rate of bioavailability of cefmetazole from MGK® solution in the rectum were not significantly different from those of the drug injected intramuscularly in saline solution.

The absorption of cefmetazole and its sodium salt from MGK® solution in the rabbit rectum was investigated. Figure 2 shows the plasma concentration–time profiles after rectal administration as MGK® suspension for cefmetazole and as MGK® solution for its sodium salt. The plasma concentration–time profiles after rectal administration of cefmetazole sodium were much higher than in the case of cefmetazole. This result indicates that the absorption-promoting effect of MGK® is much larger for cefmetazole sodium than for cefmetazole.

It was confirmed that MGK® significantly increased the absorption of cefmetazole sodium after rectal administration. MGK®, a mixture of glyceryl mono-, di- and tricaprylate, belongs to the medium-chain group of glycerides. Since medium-chain glycerides are in common use as emulsifying and solubilizing agents for various organic compounds in the pharmaceutical and food industries, and further they were reported to show low toxicity in rats by Yamashita *et al.*[4,5] MGK® might be suitable for therapeutic use.

The mechanism of the promoting effect of MGK® on rectal absorption of cefmetazole sodium will be discussed in detail in a subsequent paper.

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