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Intestinal absorption of sodium cefoxitin in rats: effect of formulation

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The absorption of cefoxitin from rat intestine, rectum and small intestine was greater when the powdered form was administered than when an aqueous solution was given. Cefoxitin absorption from the small intestine was significantly increased after its administration in suppository form prepared with a triglyceride base, although rectal absorption from the suppository did not differ from that of the drug in powdered form. The increase in absorption by the small intestine from the suppository form may be due to fatty acids produced from triglyceride by lipase.

Formulation design (Marshall 1979) can markedly influence drug absorption from the intestinal tract. In the present study, we examined the effect of three fomulations, solution, powdered form and solid vehicle prepared with a triglyceride base, on the intestinal absorption of sodium cefoxitin, an antibiotic of low lipophilicity. Since the transit of administered drugs and lipase activity in the rectum can be ignored in comparison with those in the small intestine, we investigated the cefoxitin absorption at both sites.

Materials and methods

Sodium cefoxitin in fine powder form was supplied by Merck Sharp & Dohme (Rahway, NJ, USA). The triglyceride base, Witepsol H-15, was purchased from Chemishe Werk (Witten, West Germany). Other reagents used were of analytical grade.

For the preparation of suppositories, 30 mg of cefoxitin were combined with 970 mg of melted triglyceride base. The mixture was poured into polytef tubing (3 mm $\phi \times 100$ mm). After solidifying, the solid form, weighing approximately 0·5 g, was extruded and kept at 4 °C until use. Cefoxitin solutions were prepared by dissolving sodium cefoxitin in distilled water (30 mg ml^{-1}).

Male, Sprague-Dawley rats (200–250 g) were fasted for 18 h before the experiment. Rats were anaesthetized with sodium pentobarbitone (60 mg kg^{-1}) and body temperature was maintained at 38 °C. In the in-vivo small intestinal absorption study, the intestine was exposed by a ventral midline incision and another incision made in the fundus of the stomach, through which each test formulation was introduced into the duodenum. After administration of the formulation, the pylorus was ligated as also was the anus in in-vivo rectal absorption studies.

For rectal and intestinal administration, the aqueous solution was injected through polyethylene tubing (PE 50). Cefoxitin in a powder or suppository vehicle was administered via polytef tubing (3 mm $\phi \times 100$ mm) through which the formulations were extruded by a stainless steel rod. At designated times after administration of a test formulation, blood samples were collected from the internal jugular vein and plasma separated by centrifugation and its cefoxitin concentration was determined by HPLC (Nishihata et al 1984).

To evaluate the effect of formulations on cefoxitin absorption by the small intestine, the following investigations were carried out as preliminary studies. The transit rate of cefoxitin from an upper small intestine, including duodenum (about 15 cm), 1 h after administration of each formulation was determined by assessing the percent cefoxitin remaining in the upper intestine against the total cefoxitin remaining in the whole intestine. The percentage (mean ± s.d.) of the total cefoxitin remaining in the whole small intestine against the cefoxitin dose was 93·6 ± 5·7% (n = 4) for an aqueous solution, 82·7 ± 5·9% (n = 4) for a powder formulation and 26·2 ± 7·9% (n = 4) for the suppository formulation. However, no cefoxitin was found in the large intestine. The cefoxitin remaining in the upper small intestine against total cefoxitin remaining (described above) in the intestine was 17·1 ± 5·8% of the dose for an aqueous solution, 32·6 ± 6·2% for a powder formulation ($P < 0.05$ versus aqueous solution, Student's t-test) and 36·2 ± 9·1% for the suppository formulation ($P < 0.05$ versus an aqueous solution). Furthermore, an in-situ small intestinal loop study (Nishihata et al 1983) was carried out to determine cefoxitin absorption from the upper, middle and lower regions of the small intestine by measuring the remaining cefoxitin in each loop 1 h after administration of 0·5 ml aqueous solution containing 30 mg ml^{-1} of sodium cefoxitin. Disappearance of cefoxitin determined from the cefoxitin amounts remaining was 6·9 ± 3·7% (n = 4) from the upper, 5·3 ± 2·4% (n = 4) from the middle and 5·9 ± 3·1% (n = 4) from the lower region. These preliminary findings indicate that the

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intestinal absorption of cefoxitin by itself was little affected by the site in the small intestine, though the transit rate of cefoxitin was affected by formulation, with rapid transit rate of an aqueous solution.

Results and discussion

Plasma cefoxitin concentration after rectal or small intestinal administration of 0·5 ml of cefoxitin solution was low (Fig. 1) as reported previously (Nishihata et al 1983, 1984). As seen in Fig. 2, the plasma peak concentration of cefoxitin was dependent on the cefoxitin concentration in solution. This concentration dependency was more evident after rectal administration than after administration into the small intestine. When powdered cefoxitin was administered, the rectal plasma peak concentration was significantly higher than that obtained at the intestinal site (Figs 1b, 2). This difference between drug uptake from the rectal and intestinal lumens could be related to the volume of luminal fluid secreted at each site.

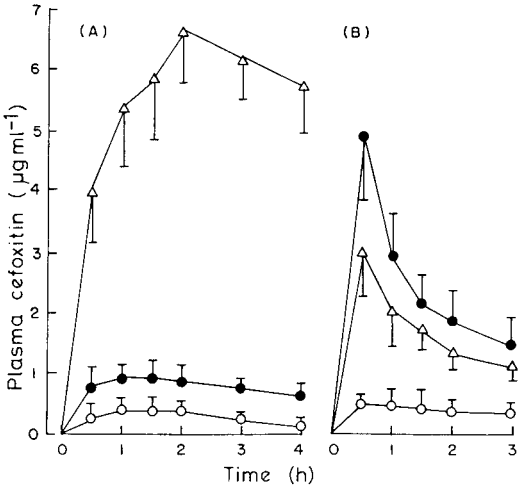

FIG. 1. Plasma cefoxitin concentration after administration into (A) rat small intestine or (B) rat rectum of a sodium cefoxitin dose of 15 mg kg^{-1} in aqueous solution (○), powdered form (●), or suppository formulation with a triglyceride base (△). Each value represents the mean ± s.d. ($n \geq 5$).

Plasma concentration after rectal administration of a cefoxitin suppository was lower than that obtained after administration of cefoxitin in powdered form (Fig. 1B). The exact opposite results were obtained at the small intestinal administration site with the suppository formulation producing higher plasma drug concentrations (Fig. 1A). The presence of the triglyceride base in the

FIG. 2. Relation between plasma peak cefoxitin concentration and the dosage volume after administration of an aqueous solution containing a cefoxitin dose of 15 mg kg^{-1} into rat small intestine (○) or rectum (●). The zero value for the dosage volume represents sodium cefoxitin administered in powdered form. Data are expressed as the mean ± s.d. ($n \geq 5$).

suppository vehicle may be the key factor responsible for the differing absorption rates from the rectal and intestinal lumens. The triglyceride base can be degraded by lipase predominantly into a fatty acid and monoglyceride. It is well known tht fatty acids act as surfactants in ionized form upon dissolution in luminal fluid, and that lipase activity in rectal luminal fluid is absent. The fatty acid product may therefore alter the permeability of the small intestinal membrane to cefoxitin. Using the triglyceride base employed in this study as an excipient in tablet form (coated with sugar, unpublished data), small intestinal absorption of low lipophilic drugs can possibly be enhanced, provided normal lipase activity in the small intestinal fluid is present.

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REFERENCES

Marshall, K. (1979) in: Banker, G. S., Rhodes, C. T. (eds) Modern Pharmaceutics. Marcel Dekker, Inc., New York, p. 359

Nishihata, T., Takahagi, H., Higuchi, T. (1983) J. Pharm. Pharmacol. 35: 124–125

Nishihata, T., Takahagi, H., Yamamoto, M. Tomida, H., Rytting, J. H., Higuchi, T. (1984) J. Pharm. Sci. 73: 109–112