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Enhanced small intestinal absorption of cefmetazole and cefoxitin in rats in the presence of non-surfactant adjuvants

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Cefmetazole and cefoxitin, cefamycin antibiotics, are not readily absorbed after oral administration due to their high water solubility, consequently, intramuscular injection is extensively used. However, new dosage forms suitable for oral administration might alleviate any irritation problems caused by injections and potentially broaden the therapeutic use of the drugs.

In previous papers (Nishihata et al 1981a,b; 1982b,c), salicylate and its derivatives, such as 5-methoxysalicylate, were found to effectively promote the rectal absorption of insulin and theophylline. Furthermore, relatively high concentrations (up to 50 mg ml^{-1}) of salicylate did not cause any damage to the rectal mucosal membrane (Nishihata et al 1982a). 5-Methoxysalicylate has also been shown to aid in the absorption of insulin from the upper gastrointestinal tract of rats (Nishihata et al 1981c).

The enhanced absorption of cefmetazole and cefoxitin from the rat jejunum in the presence of the adjuvants sodium salicylate and sodium 5-methoxysalicylate is reported in this communication. Both cefmetazole (Sankyo Co., Tokyo, Japan) and cefoxitin (Merck, Rahway, NJ, USA) were administered into in-situ jejunal loops (Levine et al 1955) 5 cm in length by a microenema technique previously described (Kunze et al 1972). The microenema was prepared with 0.05 M phosphate buffer at pH 5.0 and delivered in dosage volumes of 1 ml kg^{-1}. Blood samples were taken from a jugular vein at designated time intervals. Plasma concentrations of cefmetazole and cefoxitin were measured by high pressure liquid chromatography (Nishihata et al unpublished data).

An in-situ jejunal-loop technique was used in order to maintain a high drug concentration at the absorption site. In an in-vivo gut preparation (Nishihata et al 1981c), plasma cefmetazole levels after intrajejunal injection of a microenema containing 30 mg of cefmetazole and 100 mg sodium salicylate ml^{-1} were quite low, 1.83 ± 0.47 μg ml^{-1} at peak concentration. However, using the in-situ loop technique, high cefmetazole plasma concentrations (6.18 ± 1.57 μg ml^{-1}) were obtained after administration of a similar microenema containing the drug and salicylate (Fig. 1A). Enhancement of cefmetazole absorption was dose-dependent with respect to the amount of salicylate present in the microenema, i.e., absorption of cefmetazole increased as the concentration of salicylate increased in the microenema, with a plateau occurring at a salicylate concentration of 100 mg ml^{-1}. 5-Methoxysalicylate also enhanced the jejunal absorption of cefmetazole. After administration of a microenema containing 50 mg of 5-methoxysalicylate and 30 mg of cefmetazole into the jejunal loop, an approximate 9-fold increase in the plasma peak concentrations of cefmetazole (4.86 ± 0.91 μg ml^{-1}, $P < 0.001$, $n = 5$) was observed compared with those obtained after microenema administration of 60 mg of cefmetazole ml^{-1} without any adjuvant (0.54 ± 0.31 μg ml^{-1}) (Fig. 1).

Salicylate and 5-methoxysalicylate both significantly facilitated the absorption of cefoxitin using the in-situ jejunal-loop technique. Administration of a microenema containing 40 mg cefoxitin ml^{-1} alone into the jejunal loop resulted in a low plasma cefoxitin level with a peak of 0.73 ± 0.24 μg ml^{-1} ($n = 5$). However, after administration of a microenema containing 50 mg ml^{-1} salicylate and 20 mg ml^{-1} cefoxitin into the loop, plasma cefoxitin levels increased almost 6-fold resulting in peak concentrations of 4.07 ± 1.13 μg ml^{-1} ($P < 0.001$, Student's t-test, $n = 5$).

Figure 1B shows the effect of varying concentrations of 5-methoxysalicylate on the plasma cefoxitin level after administration of a microenema into the in-situ jejunal loop. From these results, it appears that 5-methoxysalicylate-enhanced intestinal absorption of cefoxitin is also dependent upon the concentration of adjuvant in the microenema. Administration of a microenema containing 20 mg of cefoxitin ml^{-1} and 50 mg of 5-methoxysalicylate ml^{-1} produced peak plasma concentrations of 8.63 ± 1.27 μg ml^{-1} ($P > 0.001$, $n = 5$, as seen in Fig. 1B), an 11-fold improvement in the plasma peak concentrations of cefoxitin compared with those obtained after administration of a cefoxitin microenema without any adjuvant.

The chelating agent, sodium EDTA, is known to improve the absorption of hydrophilic substances such as salicylate, possibly by removal of Ca^{2+} ions from the intestine interluminal surface (Windsor & Cronheim 1961). From the EDTA effects on salicylate absorption, it has been speculated (Kunze et al 1972) that salicylic acid itself may chelate Ca^{2+} ions at the border of the intestinal epithelium thereby increasing its own per-

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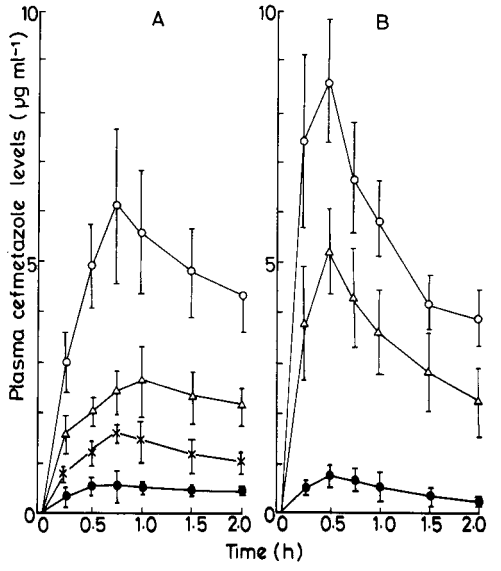

FIG. 1. Plasma profile of (A) cefmetazole and (B) cefoxitin after administration of a microenema into an in-situ rat jejunal loop. The ionic strength of the microenema was adjusted to 0.75 μ with sodium chloride.

In Fig. 1(A), 30 mg of cefmetazole ml^{-1} kg^{-1} were administered in a microenema containing 100 mg of sodium salicylate ml^{-1} (○), 50 mg of sodium salicylate ml^{-1} (△), or 30 mg of sodium salicylate ml^{-1} (X). A cefmetazole concentration of 60 mg ml^{-1} kg^{-1} was administered in a microenema without any adjuvant as a control experiment (●).

In Fig. 1(B), 20 mg of cefoxitin were administered in a microenema containing either 50 mg sodium 5-methoxysalicylate ml^{-1} (○) or 30 mg of sodium 5-methoxysalicylate ml^{-1} (△). A microenema containing 40 mg of cefoxitin ml^{-1} kg^{1} was administered without any adjuvant as a control (●).

Each value represents the mean with s.d. ($n > 5$). Each plasma level obtained in the presence of adjuvant has a significant difference of $P<0.001$ (Student's t-test) compared with the plasma levels obtained when no adjuvant was present.

meability through the epithelial membrane. Moreover, in the present study, the enhancing effects of salicylate, 5-methoxysalicylate and EDTA were inhibited by the addition of Ca^{2+} to the microenema (Table 1). However, the enhancing mechanism of salicylate and 5-methoxysalicylate may not necessarily involve the same Ca^{2+} chelating ability associated with the EDTA enhancing effect (Nishihata et al unpublished data).

Table 1. Effect of calcium chloride on the peak plasma concentrations of cefmetazole after rectal administration in rats of a microenema containing 60 mg cefmetazole and no adjuvant or 30 mg cefmetazole plus adjuvant.

	Plasma peak concn levels of cefmetazole, μg ml^{-1}			
50 mg of calcium chloride kg^{-1}	No adjuvant	Sodium salicylate (100 mg kg^{-1})	Sodium 5-methoxy salicylate (50 mg kg^{-1})	Disodium EDTA (40 mg kg^{-1})
Absent	0·54 ± 0.31	6·18 ± 1·57	4·86 ± 0·91	6·74 ± 2·13
Present	0·59 ± 0·28	1·93 ± 0·23*	1·82 ± 0·31*	0·47 ± 0·26*

* P <0·001 versus without $CaCl_2$, Student's t-test, $n > 5$.

The adjuvant-enhanced absorption of cefmetazole and cefoxitin from the intestine of rat may make oral administration of both drugs possible. However, for oral administration of either drug in conjunction with an adjuvant to be effective, a high concentration of drug and adjuvant must be maintained at the absorption site in the intestine.

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