J. Pharm. Pharmacol. 1988, 40: 329–332
Received December 11, 1987

Rate-controlled Absorption Enhancement of Rectally Administered Cefazolin in Rats by a Glyceride Mixture (MGK)

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Abstract—The enhancing effect of the medium chain glyceride preparation MGK on the rectal absorption of the cephalosporin antibiotic cefazolin sodium was evaluated in relation to the rate of delivery. Cefazolin sodium proved to be absorbed to a small extent (15 to 27%) after rectal administration without MGK. Bolus administration with MGK enhanced rate and extent of cefazolin sodium absorption, resulting in a bioavailability of 57 ± 26%. Linear infusion of 3 mg cefazolin sodium with MGK in 32 min produced complete absorption of the antibiotic (102 ± 7%), but absorption occurred slower in comparison with bolus delivery. The rate of administration proved to be an important variable of the absorption enhancing effect of MGK.

Many polar drugs can be given only by injection because of poor intestinal absorption after oral or rectal administration. Enhancement of absorption of such compounds would potentially represent a large benefit to practical therapy. Many attempts have been made to enhance the absorption of poorly absorbed compounds like β-lactam antibiotics by coadministration of an absorption promoter. Miyamoto et al (1983) reported an increase of the intestinal absorption of propicillin and cefazolin by ether-type non-ionic surfactants in rats. Rectal absorption of cefoxitin seems to be enhanced by phosphate derivatives (Nishihata et al 1984a) and acylcarnitines (Fix et al 1986), whereas cefmetazole absorption proved to be increased by salicylates (Nishihata et al 1984b), diethylethoxymethylene malonate and diethyl maleate (Nishihata et al 1984c), and by medium chain glycerides (Sekine et al 1985a) when given rectally. Similar observations were made for cefazolin by coadministration with medium chain glycerides (Sekine et al 1985b,c), sodium decanoate (Nishimura et al 1985), enamines (Murakami et al 1981), saponin A (Yata et al 1985) and mixed micelles (Muranishi 1985). The medium chain glyceride preparation, MGK, has been reported to be a suitable pharmaceutical vehicle for absorption enhancement with low oral acute toxicity and without causing notable morphological changes to the rectal membrane (Sekine et al 1985d).

In the studies referred to, no attention has been given to the influence of the rate of rectal administration in relation to the effect of the absorption promoter. The aim of the present study was to evaluate the enhancing effect of MGK on the rate and extent of rectal absorption of the cephalosporin antibiotic cefazolin when administered rectally in a rate-controlled fashion to rats.

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Materials and Methods

Chemicals

Cefazolin sodium (Kefzol) was a gift from Eli Lilly Nederland, Utrecht, The Netherlands. MGK (registered trade mark), a commercially available mixture of glycerol, octanoic acid and glyceryl mono-, di- and trioctanoate, was a gift from Nikko Chemicals Co. Ltd., Tokyo, Japan. Cefoxitin sodium (Mefoxin) was a gift from Merck, Sharp & Dohme, Haarlem, The Netherlands. All other chemicals were of analytical grade. Ethyl acetate was distilled before use.

Animals

The animal experiments performed were registered according to the Dutch Experimental Animals Act. Male Wistar rats of laboratory breed, 180–200 g, were used. From 16 h before the experiments until their completion only water was allowed.

Drug solutions

For i.v. administration solutions of cefazolin sodium 2·5 and 15 mg mL^{-1} were used. The solutions were made isotonic by addition of sodium chloride.

For rectal administration, solutions were used containing cefazolin sodium 15 mg mL^{-1} in MGK–water (13:1 w/w) or in 0·067 M phosphate buffer pH 7·4 with or without NaCl to an ionic strength of 0·75.

Drug administration and blood sampling

Drug administration and blood sampling were as described by van Hoogdalem et al (1988). 200 μL of solution were delivered 1 cm from the anus, as a bolus in 24 s or as a linear infusion over 32 min. Blood samples of 100 μL were taken from a cannulated carotid artery at regular intervals after starting the experiment.

Assay of cefazolin sodium

Cefazolin sodium was assayed in haemolysed blood samples by reversed phase high performance liquid chromatography

as described by van Hoogdalem et al (1988). As internal standard a solution of cefoxitin sodium (24 μg mL^{-1}) was used.

Data analysis

The areas under the individual blood concentration-time curves were calculated with the linear-logarithmic trapezoidal rule as described by van Hoogdalem et al (1988).

Systemic clearance of cefazolin sodium was calculated as D/AUC, where D is the administered i.v. dose of cefazolin sodium and AUC is the total area under the curve.

Using statistical moment theory (Gibaldi & Perrier 1982), the mean residence time (MRT) after i.v. and rectal administration of cefazolin sodium was calculated and corrected for the rate of zero-order delivery. The mean absorption time (MAT) after rectal administration was calculated by subtracting the mean MRT after i.v. administration from the individual MRT after rectal administration.

For statistical evaluation of the results, the Wilcoxon rank sum test was used. A P value smaller than 0·05 was considered as a significant difference.

Results

Intravenous infusion of 0·5 and 3 mg cefazolin sodium resulted in identical systemic clearance values of 1·9 ± 0·5 mL min^{-1} (n = 7) and 1·9 ± 0·6 mL min^{-1} (n = 7), respectively, indicating linear kinetics in this dose range.

Rectal bolus delivery of cefazolin sodium in phosphate buffer and in phosphate buffer with NaCl resulted in relatively low blood concentrations, whereas in combination with MGK much higher blood concentrations were achieved (Fig. 1). The rectal infusion experiments also exhibited large differences with and without coadministration of MGK (Fig. 2).

The results of the AUC-values obtained in these studies are summarized in Fig. 3. Rectal bolus delivery of cefazolin in phosphate buffer with or without NaCl resulted in significantly lower mean values of AUC/D, compared with those obtained with MGK or with the values obtained after i.v. infusion. Coadministration of sodium chloride did not influence AUC/D. The influence of MGK, when administered as a bolus, was significantly smaller than when it was administered by rectal infusion, absorption in the latter experiment appearing to be complete (Fig. 3).

Regarding absorption rate, rectal bolus delivery with MGK significantly reduced the mean MAT compared with bolus delivery in phosphate buffer with or without sodium chloride (Fig. 4). After rectal infusion, MAT was not significantly reduced by MGK. MAT of bolus delivery with MGK was significantly shorter than with rectal infusion.

Discussion

Without the absorption enhancer MGK, cefazolin sodium proved to be absorbed rectally to a very limited extent (Fig. 3). Sodium chloride has been suggested to increase rectal absorption of gentamicin sulphate (Fix et al 1983) and sodium ampicillin (Nishihata et al 1984d) in the absence and presence of other absorption promoters. In the present experiments the addition of sodium chloride to an ionic strength of 0·75 resulted in neither enhanced rectal absorption of cefazolin sodium after bolus administration in phosphate buffer (Fig. 3), nor in a higher absorption rate (Fig. 4). For this reason the solution in phosphate buffer was chosen as reference in the rectal infusion experiments.

The complete absorption of cefazolin achieved when given rectally by infusion in combination with MGK clearly indicates that rate control is essential in achieving optimal effects of the absorption enhancer. Apparently, the presence of an effective luminal concentration of MGK is required for complete absorption of cefazolin. Because of the poor rectal absorption of MGK (Sekine et al 1985b), this requirement can be met provided that the absorption enhancer is delivered at a low infusion rate. The influence of delivery rate on rectal spreading behaviour of a bromophenol blue solution has been studied in anaesthetized rats (van Hoogdalem et al 1988). On administration as an infusion, a shorter

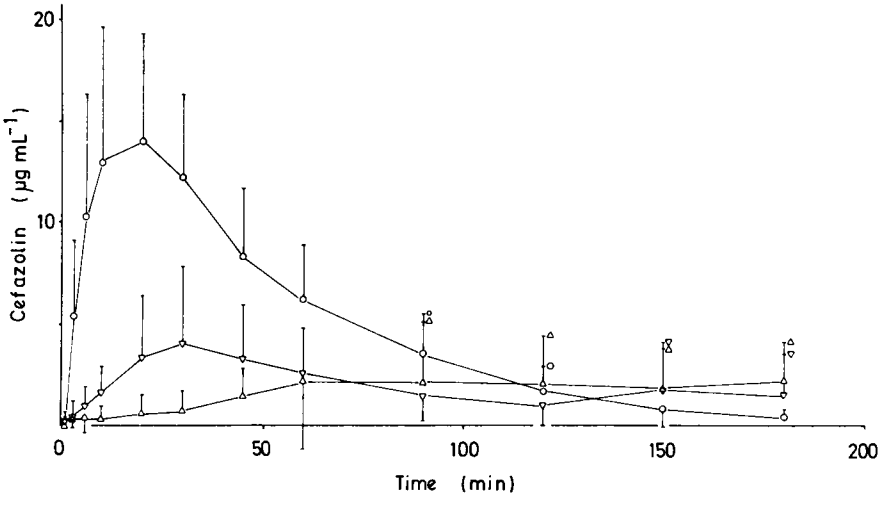

FIG. 1. Mean blood levels of cefazolin sodium ± s.d. after rectal bolus delivery of 3 mg cefazolin sodium in phosphate buffer (△, n = 7), in phosphate buffer with sodium chloride to an ionic strength of 0·75 (▽, n = 10) and in MGK–water (13:1 w/w) (○, n = 9).

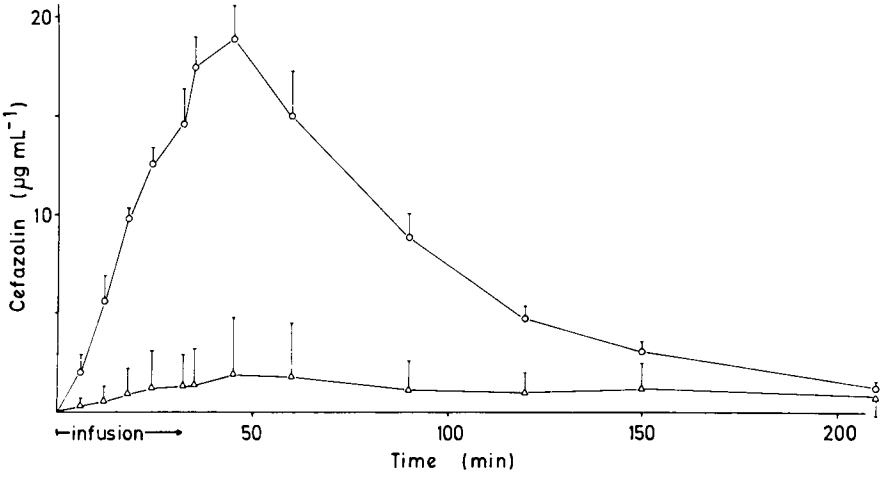

FIG. 2. Mean blood levels of cefazolin sodium ± s.d. after rectal infusion of 3 mg cefazolin sodium in phosphate buffer (△, n = 8) and in MGK-water (13:1 w/w) (○, n = 5).

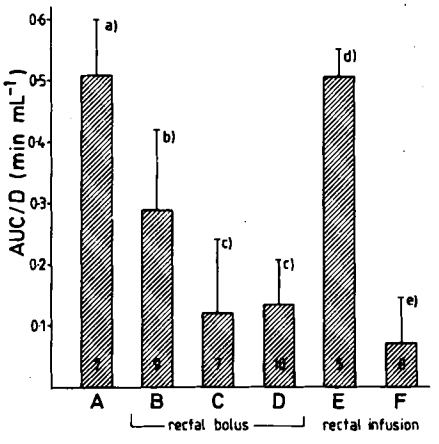

FIG. 3. Histogram of the mean value of AUC/D ± s.d of cefazolin sodium after i.v. and rectal administration of 3 mg cefazolin sodium under various circumstances. a) significantly different from bolus deliveries and from infusion in phosphate buffer, b) significantly different from i.v., bolus delivery in phosphate buffer with and without sodium chloride and from infusion with MGK, c) significantly different from i.v. and from bolus with MGK, d) significantly different from bolus with MGK and from infusion in phosphate buffer, e) significantly different from i.v. and from infusion with MGK (Wilcoxon rank sum test). A, i.v.; B, MGK/water; C, phosphate buffer; D, NaCl/phosphate buffer; E and F are identical to B and C, respectively.

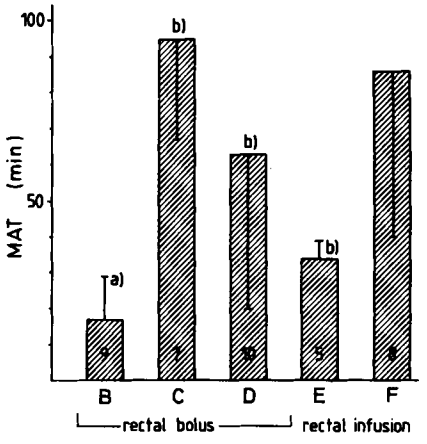

FIG. 4. Histogram of the mean mean absorption time ± s.d. of cefazolin sodium after rectal administration of 3 mg cefazolin sodium under various circumstances. a) significantly different from bolus in phosphate buffer with and without sodium chloride and from infusion with MGK, b) significantly different from bolus with MGK (Wilcoxon rank sum test), B–F as in Fig. 3.

length of rectum is filled with solution compared with bolus delivery of the same volume. As a consequence the amount of enhancer is delivered to a smaller mucosal area. The greater the amount of enhancer per unit area results in a more prolonged enhancing effect and a higher bioavailability of cefazolin. Because, after infusion, the mucosal area available for absorption is smaller, the rate of cefazolin absorption is lower compared with bolus delivery.

Concerning the mechanism of the absorption-enhancing action of MGK, a transcellular effect by interaction with phospholipids has been suggested (Sekine et al 1985b). As glycerol monooctanoate dissolves cholesterol-containing gall stones (Jarrett et al 1981), a transcellular effect by dissolving the membrane-stabilizing agent cholesterol out of the rectal membrane cannot be excluded.

Acknowledgements

The authors wish to thank Nikko Chemicals Co. Ltd. (Tokyo, Japan), Eli Lilly Nederland (Utrecht, The Netherlands) and Merck, Sharp & Dohme (Haarlem, The Netherlands) for kindly supplying MGK, cefazolin sodium and cefoxitin sodium, respectively.

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