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Rate-controlled rectal absorption enhancement of cefoxitin by co-administration of sodium salicylate or sodium octanoate in healthy volunteers

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1 The effects of sodium octanoate and sodium salicylate on the rectal absorption of cefoxitin were investigated in healthy volunteers. Drug solutions were given either as a bolus or as a zero-order infusion.

2 On rectal infusion sodium octanoate and sodium salicylate both enhanced mean cefoxitin bioavailability (± s.d.) from 5.0 ± 1.2% to 9.1 ± 1.3% and 9.2 ± 1.5%, respectively. After rectal bolus delivery octanoate increased the mean cefoxitin bioavailability from 7 ± 3% to 17 ± 3%, whereas bolus salicylate did not produce a statistically significant effect. All formulations were well tolerated by the volunteers.

3 It is concluded that both octanoate and salicylate are capable of enhancing rectal cefoxitin absorption in man; rate of delivery seems to be an important factor.

Keywords absorption cefoxitin salicylate octanoate volunteers

Introduction

In order to provide alternative methods for the parenteral delivery of poorly absorbed drugs, various studies have been undertaken to develop effective oral and rectal formulations containing drug absorption-enhancing agents. For instance the intestinal absorption of β-lactam antibiotics in rats has been reported to be promoted by co-administration of enamines (Choh *et al.*, 1985), acylcarnitines (Fix *et al.*, 1986), polyoxyethylene ethers (Miyamoto *et al.*, 1983; Nishihata *et al.*, 1985), sodium salicylate (Nishihata *et al.*, 1985; Van Hoogdalem *et al.*, 1988c), fractionated coconut oil (Palin *et al.*, 1986), medium chain glycerides (Sekine *et al.*, 1985; Van Hoogdalem *et al.*, 1988b), saponins (Yata *et al.*, 1986), medium chain fatty acids (Yoshitomi *et al.*, 1987; Nishimura *et al.*, 1985; Van Hoogdalem *et al.*, 1988a) and *N*-acyl derivatives of amino acids (Wu *et al.*, 1987). In these animal experiments beneficial effects of the various enhancers on drug uptake have been demonstrated unambiguously. However, there have been few reports on the action of absorption promoters in man. Davis *et al.* (1985) observed an increase of cefoxitin bioavailability from 3% to 20% in man following rectal delivery with a combination of sodium salicylate and polyoxyethylene-23-lauryl ether in fatty suppositories.

In the present study the effects of sodium salicylate and sodium octanoate on rectal absorption of cefoxitin sodium were investigated in healthy male volunteers. Because delivery rate was shown to be an important determinant of the action of absorption promoters in rats (Van Hoogdalem *et al.*, 1988b,c), the preparations were given either as a bolus or as a zero-order infusion.

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Methods

Chemicals

Cefoxitin sodium (Mefoxin) was a generous gift from Merck, Sharp & Dohme (Haarlem, The Netherlands). Cefazolin sodium (Kefzol) was purchased from Eli Lilly & Co. (Nieuwegein, The Netherlands). Octanoic acid was obtained from Janssen Chimica (Beerse, Belgium), sodium salicylate was supplied by OPG (Utrecht, The Netherlands). 3,4,5-Trimethoxybenzoic acid was obtained from Sigma Chemicals Co. (St Louis, USA). All reagents were analytical grade. Ethyl acetate was distilled before use.

Drug preparations

For i.v. infusion solutions containing 1 g of cefoxitin as its sodium salt in 50 ml of saline were used. All preparations for rectal administration contained 1 g of cefoxitin as sodium salt in 5 ml of aqueous solution. Preparations without enhancer contained 0.36 g of sodium chloride to adjust the ionic strength to 1.70. Formulations with salicylate contained 1 g of sodium salicylate, resulting in an ionic strength of 1.72. Cefoxitin preparations with octanoate contained 0.5 g of octanoic acid, dissolved by titration with NaOH 1 N (pH < 8). The ionic strength of the latter solution was 1.16 and this value could not be adjusted by adding sodium chloride, owing to precipitation of sodium octanoate.

Subjects

Twelve male volunteers (aged 20–28 years, body weight 64–90 kg) participated in the study. At a pre-study visit they received a full explanation of the nature and purpose of the study and the risks involved, and all subjects gave their consent. They were subjected to a medical interview and a physical examination and they underwent haematology and biochemistry screening. Volunteers with no abnormalities of clinical importance were entered into the study. The study protocol was approved by the Ethics Committee of the University Hospital of Leiden.

Study design and treatments

All volunteers were studied on four separate occasions at intervals of 1 week. On the first occasion all volunteers received 1 g of cefoxitin by i.v. infusion over 60 min. On the next three occasions they received cefoxitin rectally without enhancer, with salicylate and with octanoate in a double-blind balanced cross-over design. The subjects were randomly assigned to two groups: six subjects received all of the rectal formulations as an infusion over 60 min; the others received all of the preparations as a bolus.

All experiments started at 08.00 h after an overnight fast. Following collection of a urine sample, an indwelling cannula (Venflon 2, Viggo Products, Sweden) was inserted into a forearm vein. For i.v. infusion a second cannula was inserted into a superficial vein of the opposite arm. For rectal infusion a delivery device was assembled by connecting the tip of an enema container to a 10 ml syringe filled with drug solution, using 1.25 m of teflon tubing (i.d. 0.9 mm, o.d. 1.5 mm; Talas, Ommen, The Netherlands). After rectal insertion of the tip of the enema holder, 5 ml of drug solution were delivered at a constant rate over 60 min using an infusion pump (Syringe infusion pump 22, Harvard Apparatus Ltd, Edenbridge, England). Bolus delivery was achieved by administering 5 ml of the drug solution as a microenema. Rectal infusions and bolus solutions were delivered at a distance of approximately 4 cm from the external anal sphincter.

At appropriate intervals after starting drug delivery blood samples of 6 ml were collected into heparinized tubes (Li-heparin Monovettes, Sarstedt B.V., Eindhoven, The Netherlands). After centrifugation the plasma was collected and stored at −20° C until analysis. During the experiments urine was collected over 0–6 h and 6–24 h after starting drug delivery. The total weight of the fractions was measured and samples were stored at −20° C until analysis.

Subjective effects

Rectal discomfort was assessed using a visual analogue scale comprising three horizontal lines of 100 mm, representing irritation, defaecation urge and pain. Measurements were recorded at 0, 5, 15, 30, 60, 120, 240 and 360 min after rectal drug administration. Spontaneous reports of side effects were also noted.

Analytical methods

Sodium salicylate and cefoxitin sodium were measured in plasma (100–200 μl) by reversed phase h.p.l.c. as described previously by Van Hoogdalem *et al.* (1988c). Total salicylate in urine (1 ml) was measured by reversed phase h.p.l.c. (Van Hoogdalem *et al.*, 1988c) after acid hydrolysis (Levy & Procknal, 1968).

Data analysis

The area under the individual plasma drug concentration-time curves from 0 to 360 min (AUC) was calculated using the linear-logarithmic trapezoidal rule (Chiou, 1978). Assuming linearity of cefoxitin elimination kinetics in the dose range used (Schrogie *et al.*, 1978), cefoxitin bioavailability was calculated as $AUC_{rect}/AUC_{i.v.}$, the subscripts rect and i.v. indicating rectal and i.v. delivery, respectively. The mean residence time (MRT) was calculated by statistical moment theory and was corrected for the zero-order delivery rate when applicable (Gibaldi & Perrier, 1982).

The ratings on the visual analogue lines in mm were plotted against time and the areas under the individual rating-time curves were calculated using the linear trapezoidal rule. The score was expressed as a percentage of the maximal possible area under the rating-time curve.

Paired comparison of adjuvant effects on bioavailability, MRT and scores of subjective effects was made using the extended paired rank test (Wilcoxon & Wilcox, 1964). Unpaired comparison of the effects of delivery rate on cefoxitin bioavailability and total salicylate excretion was made using the Wilcoxon rank sum test. In both procedures a *P*-value less than 0.05 was considered as statistically significant.

Results

The mean plasma drug concentration-time curve obtained after i.v. infusion of cefoxitin is shown in Figure 1. Rectal infusion and bolus delivery without enhancer resulted in considerably lower mean plasma drug concentrations, which were

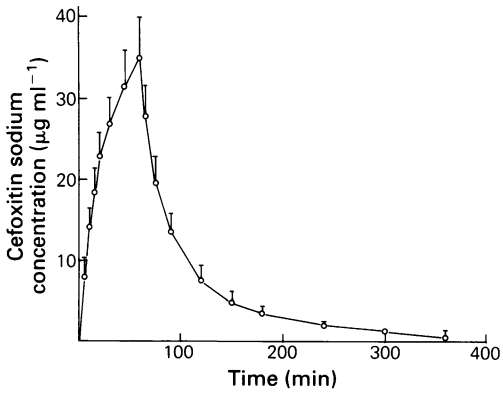

Figure 1 Mean plasma concentrations (± s.d.) of cefoxitin sodium after i.v. infusion of 1 g of cefoxitin over 60 min (n = 12).

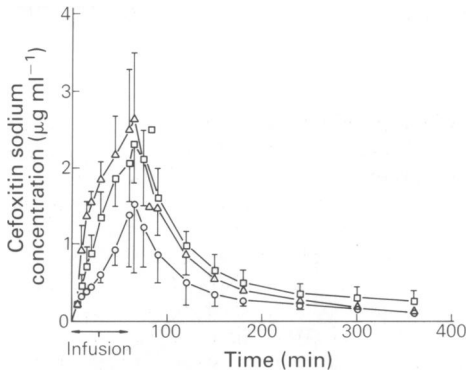

Figure 2 Mean plasma concentrations (± s.d.) of cefoxitin sodium after rectal infusion over 60 min of 1 g of cefoxitin without enhancer (○), with 0.5 g of octanoic acid as sodium salt (△) and with 1 g of sodium salicylate (□) (n = 6).

increased after co-administration with octanoate or salicylate (Figures 2 and 3). After bolus delivery (Figure 3) the effects of the enhancers on plasma drug concentrations appeared to be more pronounced, compared with rectal infusion (Figure 2). Following infusion the mean cefoxitin bioavailability (± s.d.) was significantly increased from 5.0 ± 1.2% to 9.1 ± 1.3% and 9.2 ± 1.5% by co-administration of octanoate and salicylate, respectively (Figure 4). Bolus delivery without enhancer resulted in a mean bioavailability (± s.d.) of 7 ± 3%, which was significantly increased by octanoate to 17 ± 3%. Administration with salicylate resulted in a bioavailability of 13 ± 5%, which did not differ significantly from the mean bioavailability obtained without enhancer (Figure 4). Concerning the influence of delivery rate, rectal infusion with octanoate resulted in a significantly lower mean bioavailability of cefoxitin, compared with bolus delivery, whereas administration without enhancer and with salicylate showed no delivery rate dependence (Figure 5).

Rectal infusion without enhancer and with salicylate resulted in significantly prolonged MRT-values, compared with i.v. infusion (Figure 6). However, bolus delivery resulted in variable MRT-values and no significant changes in MRT were observed following any treatment (Figure 6).

Both after rectal infusion and after bolus delivery plasma concentration-time curves of sodium salicylate were obtained which clearly indicated slow salicylate absorption (Figure 7); after infusion and bolus administration mean t_{max} values (± s.d.) of 210 ± 60 min and 150 ± 70 min, respectively, were found. No differences between infusion and bolus delivery were

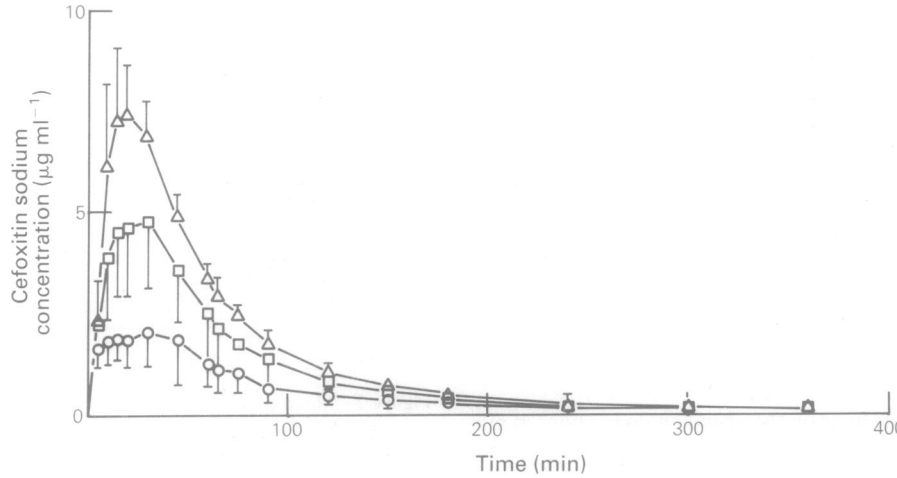

Figure 3 Mean plasma concentrations (± s.d.) of cefoxitin sodium after rectal bolus delivery of 1 g of cefoxitin in various formulations (n = 6); symbols as in Figure 2.

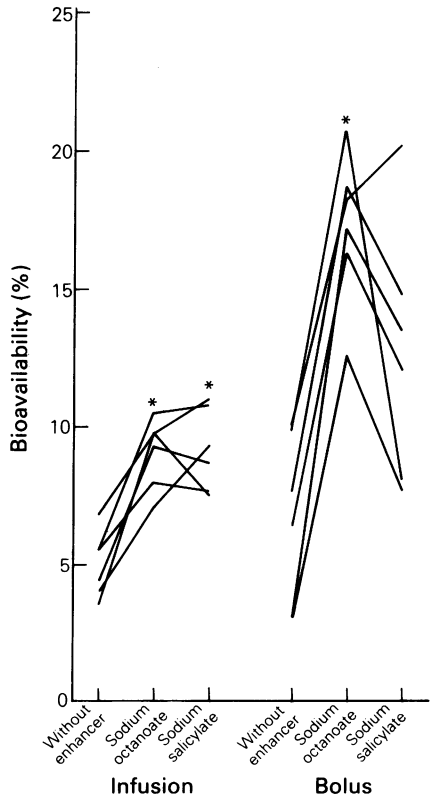

Figure 4 Effects of formulation on cefoxitin bioavailability; individual bioavailabilities of cefoxitin sodium after rectal infusion and after rectal bolus delivery of 1 g of cefoxitin in various formulations; *: significantly different from delivery without enhancer ($P < 0.05$, extended paired rank test).

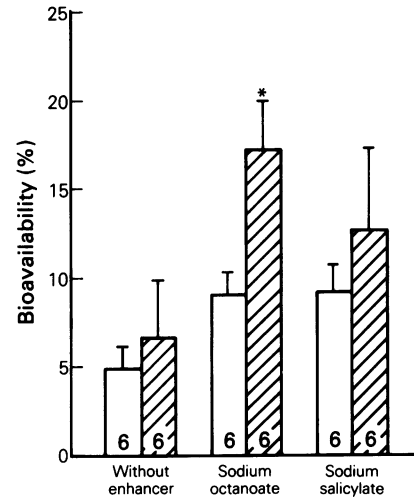

Figure 5 Effects of delivery rate on cefoxitin bioavailability; mean bioavailabilities (± s.d.) of cefoxitin sodium after rectal infusion (open bars) and after rectal bolus delivery (hatched bars) of 1 g of cefoxitin in various formulations; *: significantly different from infusion ($P < 0.05$, Wilcoxon rank sum test).

observed concerning the amount of total salicylate excreted in the urinary fractions; mean total salicylate (± s.d.) recovered in 24 h amounted to 64 ± 9% and 60 ± 4%, respectively.

All of the formulations were well tolerated by the volunteers. Scores of rectal irritation, defaecation urge and pain were 0–9%, 1–51% and 0–5% of the maximal possible scores, respectively, and no statistically significant differences

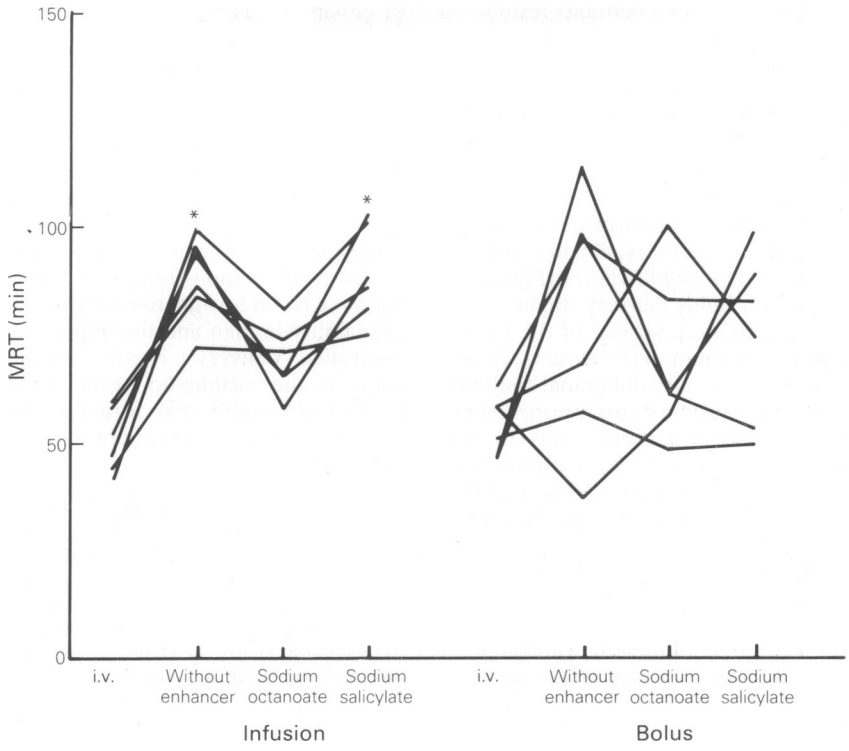

Figure 6 Individual mean residence time (MRT)-values of cefoxitin after i.v. infusion and after rectal delivery as infusion or bolus of 1 g of cefoxitin in various formulations; *: significantly different from i.v. administration ($P < 0.05$, extended paired rank test).

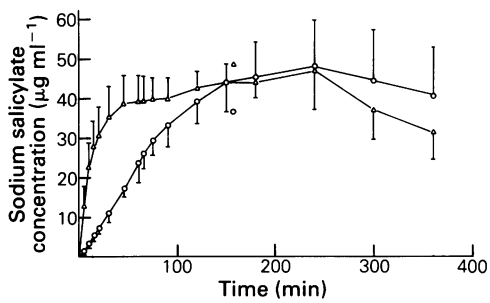

Figure 7 Mean plasma concentrations (± s.d.) of sodium salicylate after rectal infusion (○) and after rectal bolus delivery (△) of 1 g of sodium salicylate with 1 g of cefoxitin.

were found between the various treatments. No other side effects were reported, except for one subject who experienced irritation and slight blood loss on defaecation on the third and fifth day after octanoate administration and on the day after salicylate delivery. This volunteer experienced no symptoms on defaecation on two occasions after drug administration. Subsequent rectal examination and sigmoidoscopy did not reveal any abnormalities and the symptoms were ascribed to an anal fissure.

Discussion

Previous studies in rats have demonstrated a promoting effect of salicylate and octanoate on rectal cefoxitin absorption (Van Hoogdalem *et al.*, 1988a,c), the salicylate effect being dependent on delivery rate. Therefore, it was decided to study the influence of these enhancers on rectal cefoxitin absorption after rectal administration at two delivery rates in man.

Cefoxitin was poorly absorbed rectally, irrespective of the rate of delivery (Figures 2, 3, 4 and 5). Delivery rate appeared to be an important variable for absorption enhancement, since on infusion both enhancers promoted cefoxitin bioavailability, whereas on bolus delivery only octanoate exerted a significant effect (Figure 4), which exceeded the effect after infusion (Figure 5). Plasma drug concentration-time curves (Figure 7) and urinary excretion data indicated

that salicylate is well absorbed and results did not show any dependence of the extent of salicylate absorption on delivery rate.

The extent of cefoxitin absorption after bolus delivery with enhancer was associated with a large variability when compared with infusion (Figures 4 and 5). Moreover, afer rectal infusion without enhancer and with salicylate a significantly delayed cefoxitin absorption, expressed as increased MRT, was observed, whereas bolus delivery resulted in variable values (Figure 6). This variability on bolus delivery might be explained by a pronounced spread of the instantaneously delivered solution in the rectal cavity, giving rise to interactions with luminal contents. Consequently, circumstances for absorption enhancement and cefoxitin uptake may be less standardized compared with the infusion group and larger variability is observed. The fact that octanoate, in spite of these unfavorable conditions, considerably increased cefoxitin absorption after bolus delivery, is probably caused by the large amount of enhancer delivered per area and per time.

Subjective side effects during the various treatments were mild and unrelated to the addition of enhancers. However, future studies require more objective assessment of the effect of drug and enhancer on the rectal mucosa.

In rats the effects of salicylate (Van Hoogdalem *et al.*, 1988c) and octanoate (Van Hoogdalem *et al.*, 1988a) on rectal cefoxitin uptake were more pronounced, compared with the effects in man described in the present study. This demonstrates the necessity of human research to validate animal experiments. Nevertheless, the results obtained in this study demonstrate the feasibility of developing rectal formulations with enhanced bioavailability in man and the importance of rate-controlled delivery. Further studies should concern the scaling-up from small animals to clinically applicable formulations and the evaluation of the effects of absorption promoters on mucosal integrity.

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