International Journal of Pharmaceutics, 21 (1984) 239–248
Elsevier

IJP 00726

Enhancement of rectal absorption of water-soluble antibiotics in dogs

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(Received November 1st, 1982)
(Modified version received May 15th, 1984)
(Accepted May 18th, 1984)

Summary

The effects of sodium 5-methoxysalicylate and sodium salicylate on the rectal absorption of sodium penicillin G, gentamicin sulfate, sodium cefoxitin and sodium cefmetazole are reported. It was found that both adjuvants improve the rectal absorption of these water-soluble antibiotics. However, sodium 5-methoxysalicylate was more effective. Rectal bioavailability of these antibiotics depends both on the concentration of the adjuvant used and on the dosage form. In these studies, a lipophilic suppository base seems to provide a satisfactory vehicle for delivery of the water-soluble drugs resulting in rectal bioavailabilities of ~ 85% for penicillin G, ~ 50% for cefoxitin, ~ 50% for cefmetazole and ~ 35% for gentamicin compared with intravenous administration over the time period of 0–120 min.

Introduction

Many water-soluble antibiotic agents are poorly absorbed from the digestive tract. Although some of these agents are used for clinical therapy, they are usually limited to parenteral administration. Recent studies in our laboratory have identified novel absorption adjuvants which improve rectal or oral drug delivery (Nishihata et

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al., 1980, 1981a, b and c; 1982a and b). These adjuvants, including various combinations of hydroxy-, carboxy- and methoxy-phenol derivatives were found to dramatically increase rectal or oral drug absorption for several water-soluble drugs with typically low bioavailabilities when administered orally or rectally. Some of these compounds were found to be more effective than others in promoting rectal absorption (Nishihata et al., 1982b).

From our previous studies using rats, it became apparent that a high local concentration of these adjuvants is necessary for rapid drug absorption in the rectal compartment. The rectal compartment, including the distal portion of the large bowel, presents an ideal situation for maintaining a high adjuvant concentration. In this region there is active absorption of water which also may aid in maintaining a high concentration of the dissolved adjuvants and/or drug substances.

In the present study, the effects of sodium salicylate and sodium 5-methoxysalicylate, one of the more effective absorption adjuvants, on the rectal uptake of several antibiotics in Beagle dogs is evaluated. The target drugs selected were: sodium pencillin G, a penicillin analog; gentamicin sulfate, an aminoglycoside; sodium cefoxitin and sodium cefmetazole, both cephalosporin compounds.

Materials and Methods

Eight male Beagle dogs, 9–12 kg, which were fasted for 16 h prior to an experiment, were divided into two groups of 4 and crossed over with respect to dosage form. Witepsol H-15 was used as an excipient to prepare 1 g suppositories. Microenema formulations were prepared with 4% gelatin in saline or with a simple physiological saline solution, or with 0.02 M phosphate buffer with a final pH of 7.4. Microenemas were administered with a volume of either 0.5 or 1 ml. Blood samples were taken at appropriate intervals from either the external jugular or foreleg vein. Blood samples were heparinized and centrifuged at $4000 \times g$ for 10 min. Plasma aliquots were assayed for drug concentrations.

The assay of plasma levels of cefoxitin and cefmetazole was carried out by an HPLC method (Nishihata et al., 1984a). Penicillin G and gentamicin were assayed with respect to plasma levels using a microbioassay slightly modified from Simon and Yin (1970). The organism used for the assay of penicillin G was *Micrococcus luteus* ATCC no. 9341 prepared according to the procedure outlined by Bennett et al. (1966). Penicillin G concentrations used to generate the standard curve were: 0.06, 0.10, 0.30, 0.60, 1.0 and 3.0 g/ml. The reference standard was 0.30 μg/ml. The organism used for the assay of gentamicin was *Bacillus subtilis* ATCC no. 6633 prepared as described by Simon and Yin (1970). Gentamicin concentrations used to generate the standard curve were: 0.1, 0.3, 1.0, 3.0, 10.0 and 30.0 μg/ml. The reference standard was 3.0 μg/ml. The limits in terms of sensitivity were as follows: penicillin G, 0.06 μg/ml; gentamicin, cefoxitin and cefmetazole, 0.1 μg/ml. The reproducibility, as indicated by coefficients of variation for the HPLC assays, were 3.2% for cefmetazole and 1.5% for cefoxitin on 5 replicate analyses of 1.0 μg/ml samples. The standard deviation for 24 replicate samples of gentamicin at 1 μg/ml was ±15% and for penicillin was ±2.5%.

To estimate the bioavailability of the drugs after rectal administration, a comparison was made between the $AUC_{0-120\,min}$ determined using a trapezoidal integration after rectal administration versus intravenous injection. The intravenous injection consisted of 0.5 ml of saline solution containing 50 mg of drug. Blood samples subsequent to i.v. injection were processed as previously described. The comparative bioavailabilities obtained are reported in Tables 1 and 2.

The respective bioavailabilities for suppositories and microenemas containing 5-methoxysalicylate calculated against i.v. administration are summarized in Tables

TABLE 1

COMPARATIVE BIOAVAILABILITY OF SODIUM PENICILLIN G, SODIUM CEFOXITIN, SODIUM CEFMETAZOLE AND GENTAMICIN SULFATE FOLLOWING RECTAL ADMINISTRATION IN 4 DOGS (CROSS-OVER STUDY) USING SODIUM 5-METHOXYSALICYLATE AS ADJUVANT

Dose of drug (mg)	Dose of adjuvant (mg)	AUC [a] ($\mu g \cdot min \cdot ml^{-1}$) (comparative bioavailability [b,c])			
		Penicillin G	Cefoxitin	Cefmetazole	Gentamicin
Intravenous injection					
50	0	357 ± 33	1358 ± 80	1118 ± 81	1577 ± 140
Rectal suppository with Witepsol H-15 as base					
150	0	38 ± 2	82 ± 17	-	13 ± 3
300	0	-	-	96 ± 24	-
75	75	249 ± 11 (13)	324 ± 76 (8)	303 ± 59 (13)	-
75	150	462 ± 83 (24)	828 ± 133 (20)	615 ± 68 (25)	713 ± 42 (109)
75	300	446 ± 62 (23)	1105 ± 123 (27)	801 ± 65 (33)	848 ± 162 (130)
150	200	912 ± 71 (24)	1804 ± 159 (22)	1653 ± 800 (34) [d]	-
150	300	893 ± 103 (24)	2095 ± 169 (25)	1658 ± 206 (34)	-
0.02 M phosphate buffer solution (pH = 7.4) or 0.9 % saline [e] microenema					
300	0	52 ± 10	114 ± 12	71 ± 14	58 ± 9
75	150	149 ± 17 (11)	-	168 ± 20 (9)	-
75	300	296 ± 39 (23)	189 ± 30 (7)	201 ± 25 (11)	233 ± 35 (16)
150	150	342 ± 59 (13)	-	330 ± 38 (9)	-
150	300	586 ± 65 (23)	-	656 ± 89 (18)	-
4 % gelatin microenema					
300	0	68 ± 13	138 ± 27	83 ± 19	65 ± 18
75	150	301 ± 28 (18) [f]	-	302 ± 50 (15)	-
75	200	-	481 ± 71 (14)	435 ± 87 (21)	357 ± 149 (22)
75	300	497 ± 62 (29)	-	482 ± 61 (23)	521 ± 47 (32)
75	400	-	1242 ± 53 (36)	-	-
150	200	563 ± 91 (21)	-	645 ± 50 (16)	-
150	400	745 ± 73 (22)	1388 ± 140 (20)	985 ± 79 (24)	-

[a] AUC = $AUC_{0-120\,min}$, uncertainties expressed as standard errors of the mean.

[b] Numbers in parentheses = $\frac{[AUC]_p (dose)_a}{[AUC]_a (dose)_p}$ where a = adjuvant absent, p = adjuvant present.

[c] $P < 0.001$ compared with rectal administration in the absence of adjuvant, Student's t-test.

[d] Experimental number = 2.

[e] Gentamicin.

[f] Experimental number = 8, 2 sets of 4 dogs.

3 and 4. These bioavailabilities are based on the AUCs from 0–2 h (due to the volume of blood being removed, data were collected only for 2 h). Such data shows an inordinately larger portion of the curve for intravenous administration than that for rectal administration. If one were to extrapolate the data to $t = \infty$ assuming a one-compartmental model, the data would predict, higher bioavailability for rectal administration than reported in Table 3. For example, for gentamicin the following

TABLE 2

COMPARATIVE BIOAVAILABILITY OF SODIUM PENICILLIN G, SODIUM CEFOXITIN, SODIUM CEFMETAZOLE AND GENTAMICIN SULFATE AFTER RECTAL ADMINISTRATION IN SUPPOSITORY (WITEPSOL H-15) IN THE PRESENCE OF SODIUM SALICYLATE AS ADJUVANT IN 4 DOGS (CROSS-OVER STUDY)

Dose of drug (mg)	Dose of adjuvant (mg)	AUC [a] ($\mu g \cdot min \cdot ml^{-1}$) (comparative bioavailability [b,c])			
		Penicillin G	Cefoxitin	Cefmetazole	Gentamicin
150	0	38 ± 2	82 ± 17	50 ± 12	13 ± 3
150	150	528 ± 116 (14)	1015 ± 123 (12)	604 ± 186 (12)	673 ± 116 (52)
150	200	795 ± 108 (21)	1528 ± 214 (19)	1011 ± 380 (21)	1186 ± 143 (91)
150	300	862 ± 149 (23)	1675 ± 158 (20)	1477 ± 357 (30)	1125 ± 119 (86)

[a] $AUC = AUC_{0-120\,min}$.

[b] Numbers in parentheses $= \frac{[AUC]_p(dose)_a}{[AUC]_a(dose)_p}$ where a = adjuvant absent, p = adjuvant present.

[c] $P < 0.001$ versus rectal administration in absence of adjuvant, Student's *t*-test.

TABLE 3

BIOAVAILABILITY OF 4 ANTIBIOTICS AFTER RECTAL ADMINISTRATION FROM SUPPOSITORY (WITEPSOL H-15 AS BASE) COMPARED TO INTRAVENOUS ADMINISTRATION

Dose of drug (mg)	Dose of adjuvant (mg)	Bioavailability [a] (%)			
		Penicillin G	Cefoxitin	Cefmetazole	Gentamicin
No adjuvant					
150	0	3.5	2	–	0.3
300	0	–	–	1.4	–
5-Methoxysalicylate					
75	150	86	41	37	30
75	300	83	54	48	36
150	200	85	44	49	–
150	300	83	51	49	–
Salicylate					
150	150	49	25	18	14
150	200	74	38	30	25
150	300	80	41	44	24

[a] $\frac{[AUC]_r(dose)_{iv}}{[AUC]_{iv}(dose)_r} \times 100$, $[AUC]_{r\,or\,iv} = AUC_{0-120\,min}$ where r is rectal and iv is intravenous.

was observed. After i.v. administration, the average AUC_{0-2h} was 1580 μg min/ml while the $AUC_{0-\infty}$ was 2100 μg min/ml. The AUCs following rectal administration of gentamicin in a suppository were 848 and 1680, respectively, and following rectal administration as a 4% gelatin microenema the AUC_{0-2h} was 521 and $AUC_{0-\infty}$ was 975. For the rectal suppository, the bioavailability based on AUC_{0-2h} was 36% while based on the estimated $AUC_{0-\infty}$ it would be 53% an increase of approximately 50%. In general, the bioavailabilities reported in Tables 3 and 4 for rectal administration should be considered as minimum values with the actual bioavailabilities being somewhat greater.

Results and discussion

The effects of sodium 5-methoxysalicylate on the absorption of sodium penicillin G after rectal administration are shown in Fig. 1. Rectal administration of 150 mg of sodium penicllin G to the dog did not produce appreciable plasma levels (Fig. 1A). Based on the projected area under the curve after i.v. injection, the bioavailability of rectally administered pencillin G in the absence of 5-methoxysalicylate was approximately 4%. When 75 mg of sodium penicillin G was rectally administered in a suppository formulation using Witepsol H-15 as a base and containing 150 mg of sodium 5-methoxysalicylate, the bioavailability was significantly increased compared

TABLE 4

BIOAVAILABILITY OF 4 ANTIBIOTICS AFTER RECTAL ADMINISTRATION AS A MICROENEMA COMPARED TO INTRAVENOUS ADMINISTRATION USING SODIUM 5-METHOXYSALICYLATE AS ADJUVANT

Dose of drug (mg)	Dose of adjuvant (mg)	Bioavailability [a] (%)			
		Penicillin G	Cefoxitin	Cefmetazole	Gentamicin
0.02 phosphate buffer solution (pH = 7.4) or 0.9% saline [b] microenema					
300	0	2.4	1.4	1.1	0.6
75	150	28	-	10	-
75	300	55	9.3	12	10
150	150	31	-	10	-
150	300	55	-	20	-
4% gelatin microenema					
300	0	3	1.7	1.2	0.7
75	150	56	-	18	-
75	200	-	24	26	15
75	300	93	-	29	22
75	400	-	61	-	-
150	200	53	-	19	-
150	400	70	34	29	-

[a] $\frac{[AUC]_r(dose)_{iv}}{[AUC]_{iv}(dose)_r} \times 100$, $[AUC]_{r \text{ or } iv} = AUC_{0-120\,min}$ where r is rectal and iv is intravenous.

[b] Gentamicin.

to rectal administration without 5-methoxysalicylate (Fig. 1B). The inclusion of 150 mg of 5-methoxysalicylate increased rectal bioavailability 20-fold to about 85%, based on blood levels obtained after i.v. administration (Table 3) from time 0 to 120 min. In addition, the facilitation of penicillin G absorption increased as the absolute amount of sodium 5-methoxysalicylate increased (Table 1, Fig. 1B).

Plasma levels of penicillin G after administration of a microenema containing 75 mg of drug and 150 mg of adjuvant was significantly increased (based on Student's *t*-test) in comparison with those after microenema administration without the absorption adjuvant. However, bioavailability from the microenema formulation was less than that from the Witepsol suppository formulation (Fig. 1B and C). The administration of a microenema containing 75 mg of drug and 150 mg of 5-methoxysalicylate produced only 30% bioavailability compared to i.v. administration (Table 4). The administration of a gelatin microenema containing 75 mg of penicillin G with 150 mg of 5-methoxysalicylate showed some improvement in bioavailability (i.e. 56%, Table 4) over that from a solution microenema. However, when this gelatin formulation was compared to the suppository formulation, the bioavailability was consistently less than 70% of that found for the suppository formulation.

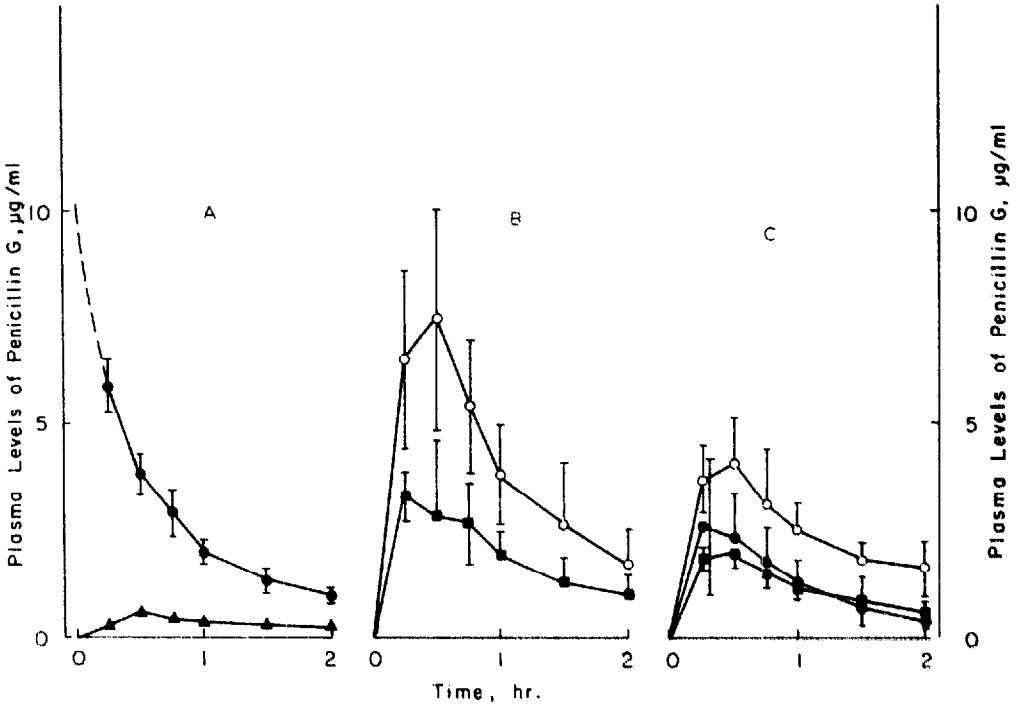

Fig. 1. Plasma concentrations of penicillin G (µg/ml): (A) following intravenous injection (●) of 50 mg of sodium penicillin G and following administration of a rectal Witepsol H-15 suppository (▲) containing 150 mg of sodium pencillin G; (B) following the administration of rectal Witepsol H-15 suppositories containing 75 mg of sodium pencillin G and 150 mg (○) and 75 mg (■) of 5-methoxysalicylate. (C) following the administration of a rectal microenema containing 75 mg sodium penicillin G with 300 mg 5-methoxysalicylate in a 0.02 M phosphate buffer solution at pH = 7.4 (■), with 300 mg 5-methoxysalicylate in a 4% gelatin solution (○) or with 150 mg 5-methoxysalicylate in a 4% gelatin solution (●). The error bars represent standard deviations with n = 4 or 8.

From these results, the use of a suppository formulation appears to provide better drug absorption than the use of an aqueous microenema. This suggestion is supported by data obtained (Nishihata et al., 1984b) on rectal absorption of ampicillin in rabbits in which suppositories also yielded higher plasma levels than did a microenema. However, it is contrary to insulin absorption data (Nishihata et al., 1983) which showed lower absorption from suppositories than from a microenema, probably due to slow release and dissolution of crystalline insulin from the suppository formulation. These observations probably also reflect the adjuvant concentration at the absorption site. It is conceivably easier to maintain high drug and adjuvant concentration at the mucosal surface of the rectum when the drug is presented as a suspension dispersed in a lipid matrix if dissolution of the drug is also relatively rapid.

Rectal administration of 300 mg of gentamicin sulfate in the absence of 5-methoxysalicylate produced plasma levels of less than 0.4 μg/ml (Fig. 2A). The inclusion of sodium 5-methoxysalicylate in the suppository of microenema formulation significantly increased the plasma levels of gentamicin in comparison to those formulations without absorption adjuvants. The suppository formulation using Witepsol H-15 as an excipient was again superior in terms of peak blood levels of

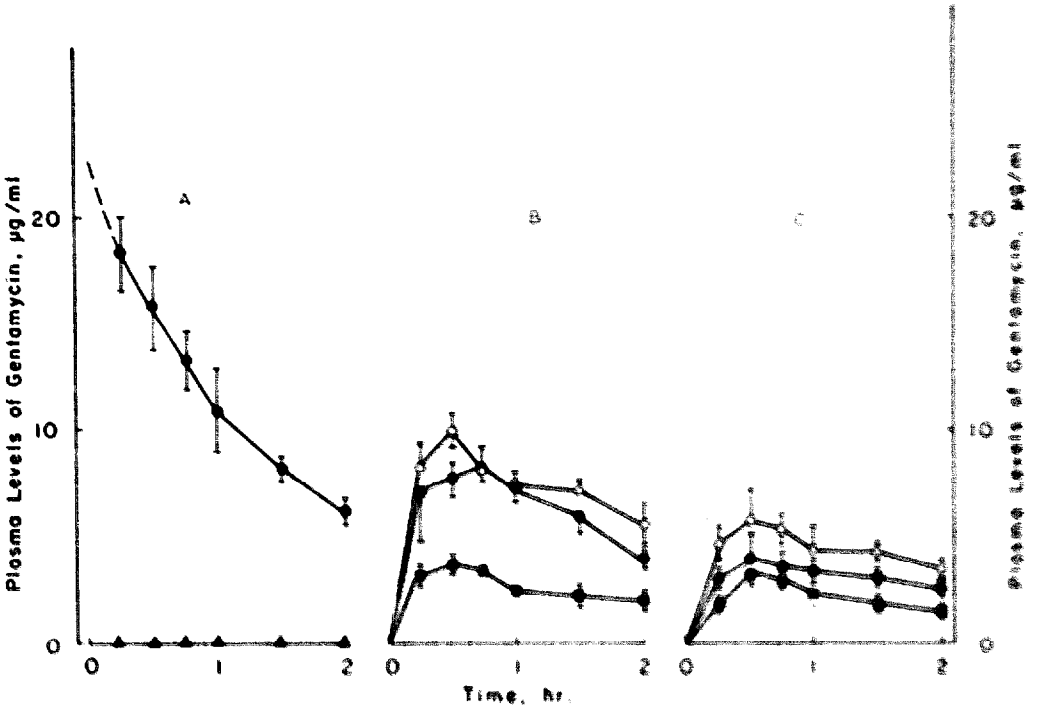

Fig. 2. Plasma concentrations of gentamicin (μg/ml): (A) following intravenous injection (●) of 50 mg of gentamicin and following administration of a rectal Witepsol H-15 suppository (▲) containing 150 mg of gentamicin; (B) following the administration of rectal Witepsol H-15 suppositories containing 75 mg of gentamicin and 300 mg (○), 150 mg (●) or 75 mg (■) 5-methoxysalicylate; (C) following the administration of a rectal microenema containing 75 mg gentamicin with 300 mg 5-methoxysalicylate in saline solution (■), with 300 mg 5-methoxysalicylate in a 4% gelatin solution (○) or with 200 mg 5-methoxysalicylate in a 4% gelatin solution (●). The error bars represent standard deviations with n = 4.

gentamicin compared with the microenema formulations. The bioavailability of gentamicin from rectal administration appears to increase as the amount of sodium 5-methoxysalicylate co-administered increases (Fig. 2B). Again, the use of 4% gelatin as a vehicle for drug and adjuvant appeared to improve the absorption of gentamicin above that obtained from a strictly aqueous formulation. However, the bioavailability when compared to that after i.v. injection was not impressive, i.e. approximately 20% (Table 1, Fig. 2C).

The rectal absorption of sodium cefoxitin was also improved in the presence of sodium 5-methoxysalicylate (Fig. 3). The suppository formulation containing 75 mg of cefoxitin and 300 mg of sodium 5-methoxysalicylate resulted in about 55% bioavailability compared to i.v. injection. The administration of a gelatin microenema containing 75 mg of cefoxitin and 400 mg of 5-methoxysalicylate resulted in nearly 60% bioavailability (Table 1). In the case of cefoxitin, the differences between the suppository formulation and the microenemas were not as dramatic as with penicillin G and gentamicin.

The effects of sodium 5-methoxysalicylate on the absorption of sodium cefmetazole after rectal administration are shown in Table 1 and Fig. 4. Less than 1.0 μg/ml

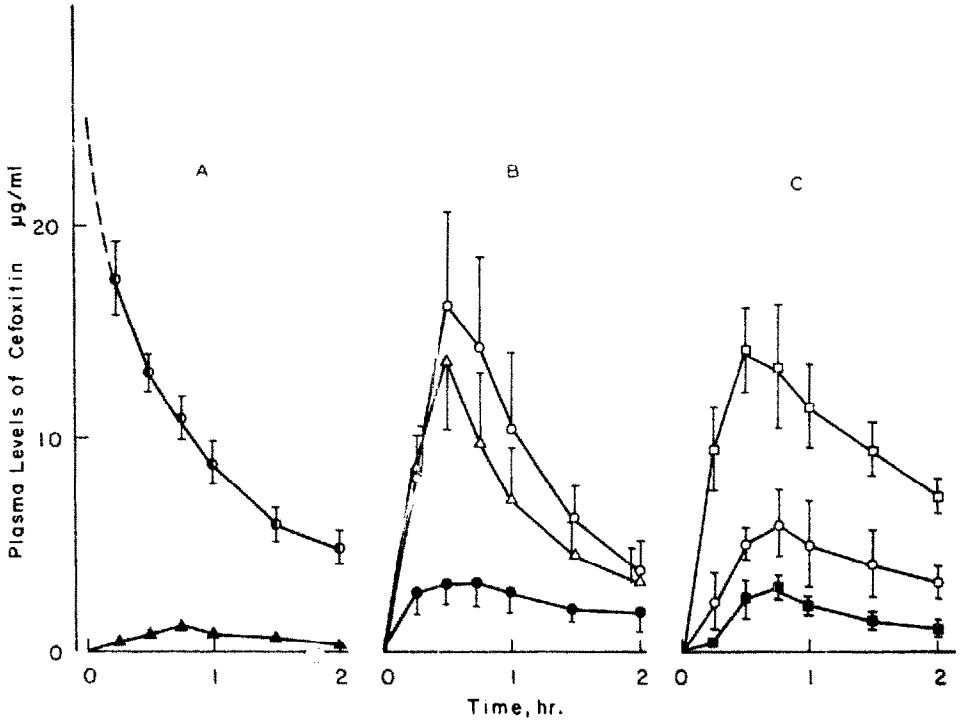

Fig. 3. Plasma concentrations of cefoxitin (μg/ml): (A) following intravenous injection (◐) of 50 mg of cefoxitin and following administration of a rectal Witepsol H-15 suppository (▲) containing 150 mg cefoxitin; (B) following the administration of rectal Witepsol H-15 suppositories containing 75 mg cefoxitin and 300 mg (○), 150 mg (△) or 75 mg (●) 5-methoxysalicylate; (C) following administration of a rectal microenema containing 75 mg cefoxitin with 300 mg 5-methoxysalicylate in buffer solution (■), with 400 mg 5-methoxysalicylate in a 4% gelatin solution (□) or with 200 mg 5-methoxysalicylate in a 4% gelatin solution (○). The error bars represent standard deviations with n = 4.

cefmetazole was found in the plasma after rectal administration of either the suppository or microenema of sodium cefmetazole containing no absorption adjuvants. Plasma levels of cefmetazole after administration of the suppository containing 150 mg of sodium cefmetazole and 150, 200 or 300 mg of sodium 5-methoxysalicylate increased significantly and were higher than those obtained from the administration of a microenema containing the same amount of both drug and adjuvant. This suppository formulation containing 5-methoxysalicylate produced relatively high plasma levels of cefmetazole, the peak levels occurring between 15 and 30 min.

The adjuvant effect of sodium 5-methoxysalicylate with regard to rectal absorption of cefmetazole also increases as the dose increases, as shown in Table 1. Administration of the same suppository containing 150 mg of sodium cefmetazole but only 75 mg of sodium 5-methoxysalicylate produced a significantly lower AUC for cefmetazole when compared to the suppository containing 150 mg of absorption adjuvant. The suppository formulations of sodium cefmetazole containing 200 mg or more of sodium 5-methoxysalicylate provided approximately 50% bioavailability of cefmetazole. However, the bioavailability of cefmetazole (Table 4) was much lower after administration of the microenema formulation (~ 15% for buffer solutions containing 300 mg of adjuvant and ~ 30% for gelatin formulations containing 300 mg of sodium 5-methoxysalicylate).

Sodium salicylate was also evaluated as an absorption adjuvant in the suppository formulations of penicillin G, cefoxitin, cefmetazole and gentamicin (Table 2). These

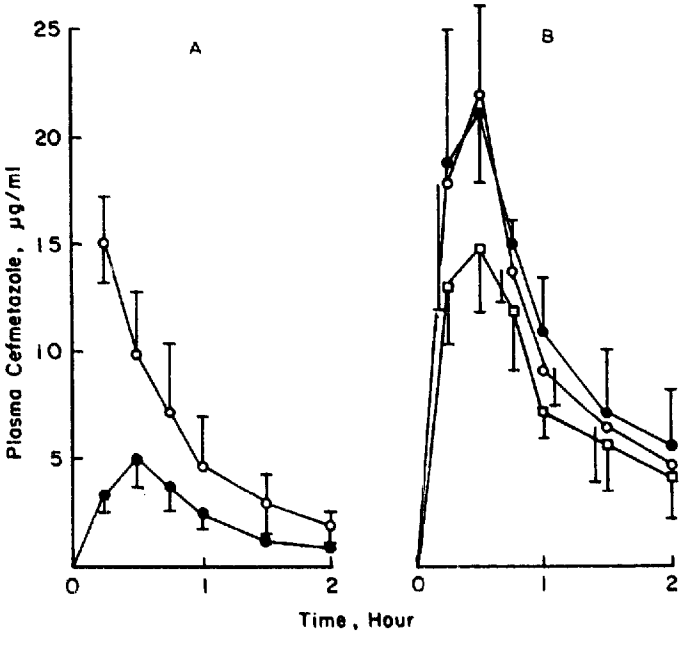

Fig. 4. Plasma concentrations of cefmetazole (µg/ml): (A) following intravenous injection (○) of 50 mg sodium cefmetazole and from rectal buffer microenema containing 150 mg sodium cefmetazole and 150 mg sodium 5-methoxysalicylate (●); (B) following the administration of rectal Witepsol H-15 suppositories containing 150 mg, sodium cefmetazole and 300 mg (●) or 200 mg (○) sodium 5-methoxysalicylate and 200 mg sodium salicylate (□). The error bars represent standard deviations with n = 4.

formulations containing 150, 200 or 300 mg of salicylate and 150 mg of the antibiotic showed improved bioavailability relative to the same formulations with no adjuvant. However, the effect of sodium salicylate as an absorption adjuvant was less pronounced than that of sodium 5-methoxysalicylate. Table 3 shows several examples of these differences.

It has been shown that sodium 5-methoxysalicate and sodium salicylate dramatically improve the rectal absorption of the water-soluble antibiotics penicillin G, gentamicin, sodium cefmetazole and sodium cefoxitin in dogs. Rectal bioavailability of these drugs depends on both the adjuvant concentration and the dosage form. A lipophilic suppository excipient seems to provide a satisfactory matrix for delivery of the water-soluble drugs and water soluble absorption adjuvants. These data suggest that high rectal bioavailability of these 4 water-soluble antibiotic compounds is possible. Rectal dosage forms of these drugs may offer distinct advantages over a parenteral route and broaden their use to include administration as an outpatient.

Acknowledgements

Supported in part by grants from INTER$_x$, Merck, Sharp and Dohme, Lawrence, Kansas; R.P. Scherer, North America, Detroit, MI and Eagle's Max Baer Heart Fund. The authors also acknowledge the support provided by the Center for Biomedical Research, The University of Kansas.

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