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Evaluation of Cefmetazole Rectal Suppository Formulation(s)

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ABSTRACT

The objective of this study was to determine formulation parameters necessary to develop a cefmetazole suppository. Three 1 gram cefmetazole rectal suppository formulations were compared using in-vitro testing of melting behavior, dissolution times and fracture weight; and in-vivo dog studies of the three suppository formulations compared to IM single dose. The in-vivo study compared the dosage forms in four dogs by a cross-over design. The formulation containing one gram of sodium 5-methoxysalicylate as adjuvant gave a relative bioavailability of 29.4%, while the suppository containing sodium salicylate as adjuvant gave 17.5% relative bioavailability. The formulation which did not contain adjuvant neither dissolved properly in-vitro nor produced observable plasma levels during the in-vivo dog study. Despite the relatively large size (4.9 grams), the suppositories were easily inserted and no leakage occurred from medium-sized dogs. Proctoscopic examinations were performed following blood collection for each dose period. The suppositories were well tolerated as administered in this study. No clinical signs or symptoms of inflammation or irritation of the colon of the dogs dosed once weekly for four weeks with the suppository were noted. Blood levels obtained from the 1 g cefmetazole rectal suppositories are sufficient to be effective against many infectious diseases caused by certain pathogens. The data from the present investigation warrants further studies of the tolerance and pharmacokinetics of the 1 gram cefmetazole rectal suppository in man.

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†Deceased

INTRODUCTION

Recently, considerable advances have been realized in the rectal delivery of water soluble antibiotics. The work of Nishihata et al[1-10] has shown that a group of innocuous pharmaceutical adjuvants i.e. the salicylates and benzoates, can lead to enhanced rectal absorption of drug, particularly water soluble drugs such as cefmetazole and cefoxitin[3,4,6-10]. Such enhancement has been shown in rat[1-4,6-8,10], dog[5,8,9], and human[11]. New, improved and safe suppository bases (e.g. Witepsol® H-15) are now available and by adding an adjuvant (e.g. sodium salicylate or sodium 5-methylsalicylate, or another adjuvant) to the base, a dramatic increase of rectal uptake of water-soluble drugs which are ordinarily poorly absorbed after rectal administration, is achieved. Now it is more possible to develop an antibiotic suppository to be used in children who have a problem of swallowing tablets or capsules, to circumvent the taste problem, no need to interrupt sleep, etc. and in adults in debilitated patients, in nauseated patients, in patients with GI problems, or in patients with too many concomitant drugs. The rectal suppository could be an excellent route for those drugs which cannot be available in oral form. The rectal route could follow after IV or IM administration of the drug in the hospital. This will shorten the hospital stay and lower substantially the cost of hospitalization. It will be a very suitable drug to be prescribed in office practice.

The need for a safe and much less costly alternative to parenteral administration should prevail against any cultural reluctance to use this drug delivery form.

The interest by Upjohn in delivery of antibiotics via rectal administration includes the 1966 Lincocin Hydrochloride rectal absorption study. This study showed that rectal administration from an aqueous solution of 500 mg lincomycin hydrochloride gave average and median serum level responses in humans from about 50% to 100% of the response obtained following oral administration of the commercial capsule in the fasting state. When the subjects were in a fasting state and had received an enema the night before, serum level responses following the solution administered rectally were statistically equivalent to those following the capsule given to fasting subjects. The serum level response from the rectally delivered solution was considerably better than the response to the rectal suppository. Poor retention of the suppository was cited as a problem. In retrospect, since adjuvants were not used, and realizing

the improvements made in suppository bases, the serum level response obtained from the rectally administered suppository was surprisingly good (data on file - Upjohn).

The recent interest by Upjohn in a rectal antibiotic suppository is for cefmetazole, which has been licensed from Sankyo Co., LTD, Tokyo, Japan. Since oral administration is not an option for this drug, formulation of a rectal suppository may compliment the dosage forms currently being developed. A rectal dosage form is particularly attractive for short course perioperative antibiotic prophylaxis, where use of the suppository could follow initial IV administration of cefmetazole, potentially shortening hospital stays. Considering the possibly significant economical advantages and both improved compliance and ease of administration associated with a cefmetazole rectal suppository, in-vitro testing and an in-vivo investigation in dog was conducted comparing three suppository formulations with an IM injection. The formulations compared consisted of 1 gram of cefmetazole in Witepsol H-12 suppository base 1) without adjuvant, 2) with 1 gram sodium salicylate as adjuvant, and 3) with 1 gram of sodium 5-methoxysalicylate as adjuvant.

EXPERIMENTAL

Formulation

Materials used for suppository preparation were Cefmetazole Free Acid (lot 712), Sodium salicylate (Fisher S-395, Lot 723468), 5-methoxysalicylic acid (98%, Aldrich Chemical Co., Lot 04807EL), Witeposl H-12 (Kay-Fries, Inc., Lot 012415), and Lecithin (Fisher Purified Grad 0-3376, Lot 855684). The salicylates functioned as adjuvants in the formulation, while lecithin was used to reduce brittleness of the suppository which contained 1-2 grams of solids. The cefmetazole and lecithin were stored in vacuum, a desiccator for at least 48 hours before use. Powdered ingredients were passed through a 30-mesh security screen.

The Witepsol H-12 and lecithin were heated to a maximum of 70°C and stirred until the lecithin had dissolved. On a laboratory scale this required approximately 30 minutes. The cefmetazole and the absorption enhancing agent were added and stirred to uniformly disperse the powders. On a laboratory scale this required 5 minutes. The fused mass was then poured into an aluminum mold at room temperature. The same mold was used for all formulations. The mass was allowed to congeal at room temperature (20-30 minutes) and then it was transferred to a cool room (5°C). After 30 minutes in the cool room, the suppositories were

removed from the mold. Weight variation did not exceed ± 2% of the average weight. Dissolution of each suppository was conducted in USP apparatus 2 using 500 ml of distilled water at 37°C. This allowed sufficient water to immerse the paddle so that the paddle did not strike the suppository. A speed of 50 rpm was selected as a mild agitation which should allow observation of any major differences in the release from the suppository formulations. The pH of the dissolution solution was measured immediately after dissolution. The melting behavior and fracture load of each suppository was observed in the constricted glass column of a fracture apparatus immersed in a water bath at 37°C. The fracture apparatus is shown in Figure 1.

The intramuscular dose was prepared by adding 8.9 cc of sterile water for injection to a vial of Cefmetazole Sodium Sterile Powder (Lot 24,050) containing two grams of drug. 5 cc of the resulting 10 cc solution was injected into the hind quarter of the dog.

Assay Procedure

Principle of Assay

Cefmetazole, in both the suppository formulations and in the plasma, was quantitated using reverse-phase HPLC with spectrophotometric detection at 274 nm. Aprobarbital was used as the internal standard.

Chromatographic Conditions

Instrument:	Shimadzu HPLC with a LC-6A Pump, SPD-6A UV Detector and C-R3A Integrator
Injection Volume:	20 1
Detector:	UV at 274 nm
Column:	Phenomenex C^{18}, 10 particle size (30 cm x 3.9 nm (I.D.)
Flow:	1 ml/minute
Temperature:	Ambient
Detector Sensitivity:	0.04
Mobile Phase:	Acetonitrile:1%, Aqueous Acetic Acid (25:75)

Retention time for the cefmetazole is about 6.7 minutes, while that of aprobarbital is approximately 10.1 minutes.

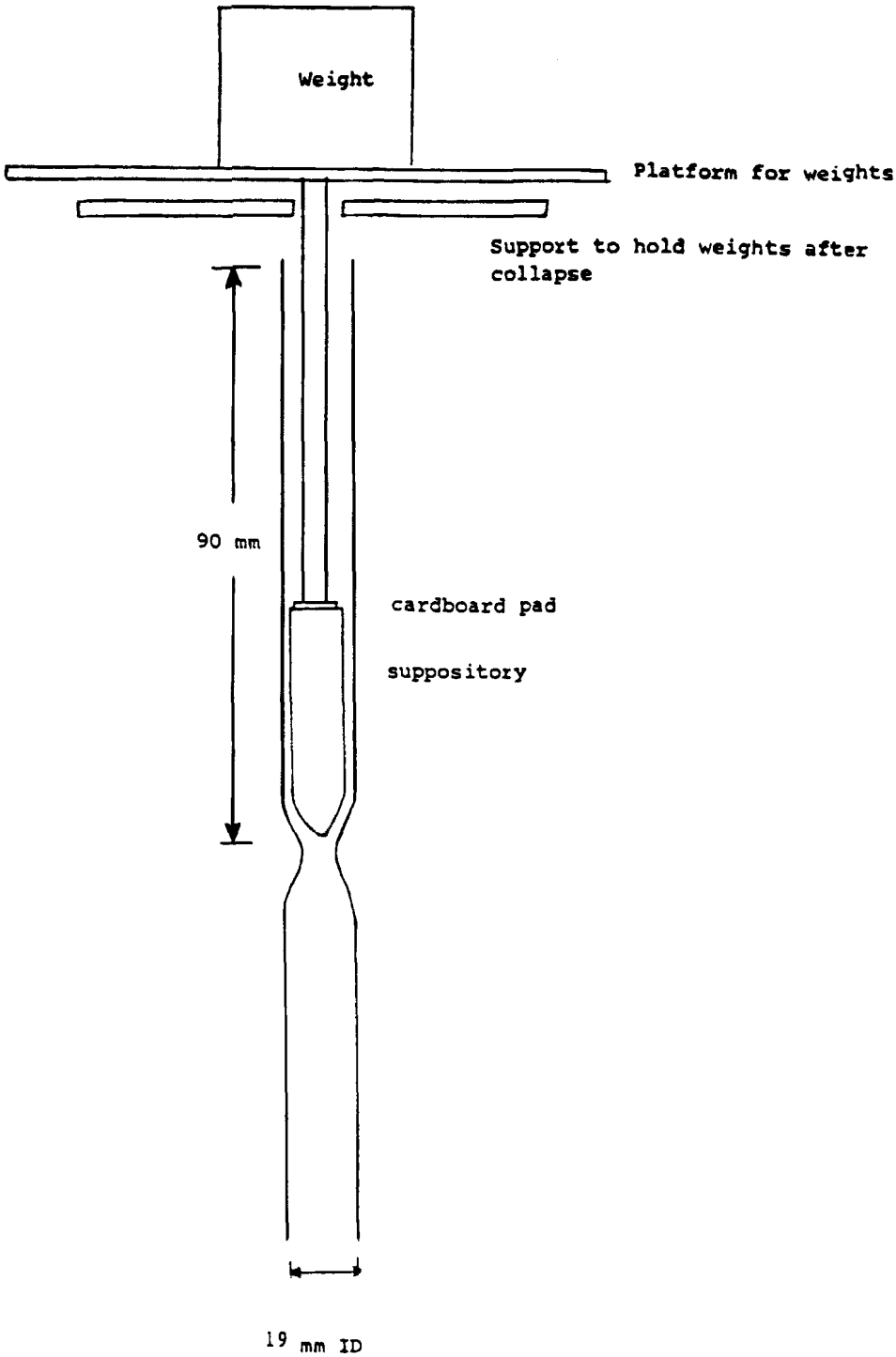

Figure 1. Apparatus for Determining Collapse Weight

Protocol

A complete crossover study design was used to test three suppository formulations and an intramuscular dose all of which contained one gram of drug. The design is shown in the table below.

	Period			
Dog	1	2	3	4
390	58	60	62	IM
300	60	62	IM	58
303	62	IM	58	60
296	IM	58	60	62

The dog weights at the beginning of the study were 390, 20.8 Kg; 300, 18.4 Kg; 303, 19.0 Kg; and 296, 20.09 Kg. The study lasted a total of 5 weeks with a one week washout between periods.

The dogs were fasted for 48 hours prior to dosing. A 10 cc blood sample was withdrawn from the jugular vein using a heparinized vacutainer tube. Samples were taken at times 0, 15, 30, 45, 60, 90, 120 and 180 minutes. Mucosal biopsies were taken from each dog prior to each administration of the experimental drug. Each biopsy was taken under intravenous thiopental sodium anaesthesia using an approximately 1 mm^3 ellipsoidal biopsy forceps 8-10 cm from the external anal sphincter. Proctoscopy was also done following the blood collection each day. Suppositories were inserted manually for a distance of 3 inches.

The following protocol deviation occurred. The dogs were given food inadvertently at midnight just prior to the dosing during period 2. The suppository formulations were readministered one week after period 4 as follows: Dog 390, Formulation 60; Dog 300, Formulation 62; and Dog 296, Formulation 58. Data given in this report as period 2R is from the readministered period 2. The IM dose was not readministered.

RESULTS AND DISCUSSION

Formulation

The suppository formulations used in this study weighed approximately 4.9 grams each being 28.5 mm long and having a diameter at the base of approximately 17 mm. Despite the relatively large size of the suppositories, they were easily inserted and no leakage occurred from

medium sized dogs. The lack of any clinical signs in these dogs which imply irritation or inflammation of the colon (tenesmus, mucus, fresh blood) suggests the suppositories used in the study are relatively non-irritating. Formulation composition, fracture load and dissolution results are given in Table 1. As seen, each formulation was firm enough to insert (fracture loads greater than 1.2 kg).

In formulations 58 and 62, which contain a sodium salt of an absorption enhancing agent, dissolution occurs completely and in the same pattern. The suppositories melt and dissolve simultaneously and retain their geometric shape as this occurs. The suppositories have a density greater than 1.0 g/cm^3 and sink to the bottom of the dissolution vessel. After 10 minutes only oil floats on the surface of the water as the suppository no longer exists. The pH of the solution is 3.2. It appears that two mechanisms--melting and dissolution--for release of cefmetazole occur simultaneously so that release from the suppository occurs readily.

In formulation 60, which does not contain an absorption enhancing agent, the dissolution behavior was not satisfactory. Formulation 60 had melted by 10 minutes, but a large pliable mass formed under the paddle and had not dissolved or dispersed at 40 minutes. If palpitated with a glass rod at 10 minutes, the conical mass broke into several pieces; however, after 20 more minutes the smaller pieces had combined into two large pieces. After 20 more minutes the two pieces remained unchanged. When the mass was removed and felt with the fingers a gritty sensation is experienced. This indicates that the cefmetazole was not completely dissolved. Obviously, this formulation is unacceptable as a product, and it is useful only as a reference.

When tested in a constricted glass column immersed in a 37°C water bath, formulations 58, 60 and 62 each demonstrated localized melting at the apex and base in 1-2 minutes. At 5 minutes sufficient melting had occurred so that the melted mass was completely immersed in the melt. At 10 minutes the entire mass had melted. The suppository melts readily so release is facilitated but not so quickly that it cannot be rapidly inserted.

There is considerable contraction of the mass as the suppository congeals. After the suppository has congealed, it has contracted completely away from the wall of the cavity of the mold and drops freely from the mold. This was an advantage of a laboratory scale. If in

Table 1--Cefmetazole Suppositories

Lot	Formula		Fracture Load, kg	Dissolution[a] Behavior	pH[b]
58	Cefmetazole (acid) Sodium salicylate Lecithin Witepsol	1.00 g 1.00 g 0.07 g 2.83 g	3.4	Simultaneous melting and dissolving with suppository maintaining its geometric shape; filaments of melted Witepsol float to surface; suppository remains on bottom of vessel; at 10 minutes there is no suppository	3.2
60	Cefmetazole (acid) Lecithin Witepsol H-12	1.00 g 0.07 g 3.47 g	3.4	At 10 minutes a pliable conical mass (if papitated with glass rod breaks into pieces). At 40 minutes pieces reform into two larger pieces	3.2
62	Cefmetazole (acid) Sodium 5-methoxysalicylate Lecithin Witepsol H-12	1.00 g 1.00 g 0.07 g 2.83 g	2.2	Simultaneous melting and dissolving with suppository maintaining its geometric shape; filaments of melted Witepsol float to surface; suppository remains on bottom of vessel; at 8.5 minutes there is no suppository	3.3
63	Lecithin Witepsol H-12	0.098 g 3.962 g	3.4	Suppository floats; melts maintaining its geometric shape; at 10 minutes there is no suppository	6.8

[a]USP Apt. 2, 500 ml distilled water at 37°C, 50 rpm

[b]of dissolution medium after suppository melted/dissolved

Table 2. Cefmetazole Content of the Suppository Formulations

	Formulation Mg Cefmetazole/Suppository			Standard Curve Parameters		
Assay Run	58	60	62	r^2	slope	intercept
1	861	928	891	.9994	.423	-1.99
2	907	950	952	.9992	.386	-1.20
3	826	857	926	.9971	.420	-0.67
Ave ± S.D.	865 ± 41	912 ± 49	922 ± 31			
CV	± 4.7%	± 5.4%	± 3.4%			

production a flash cooling process were used, cracking of the suppository may occur because of its large mass (4.9 g).

After manufacture, the suppositories were stored in a cool room until use. A total of three suppositories of each formulation were assayed for cefmetazole content. One suppository was assayed each time from each formulation along with a set of standards. This was repeated three times. The data is shown in Table 2. As seen, the suppositories were consistently sub-potent, tending to be 900 mg rather than 1 gram in strength. No interferences were observed in the chromatogram obtained from excretion of a blank suppository consisting only of vehicle components.

Bioavailability

There were no observable plasma levels from the suppository that did not contain adjuvant (Formulation 60). The average plasma concentration data is presented in Table 3 for the suppository using sodium salicylate as the adjuvant (Formulation 58) and in Table IV for the suppository containing sodium 5-methoxysalicylate (Formulation 62) as adjuvant. As seen, sodium 5-methoxysalicylate appears to function slightly better as an absorption enhancer. However, the significance of this difference is very questionable in view of the variability in plasma concentrations characteristic of this study. One potential contributing factor to the

Table 3. Plasma Concentrations from Suppository Formulation 58 (Cefmetazole plus Sodium Salicylate). Periods 1-2R-3-4. AUC: 1617 g·min/cc

Period-Dog

Time (Min)	1-390	2R-296	3-303	4-300	Ave ± S.D.
0	0.0	0.0	0.0	0.0	0.0
15	24.7	0.0	25.8	4.2	13.7 ± 13.5
30	28.9	0.0	31.0	5.3	16.4 ± 15.8
45	27.9	0.0	36.9	2.5	16.9 ± 18.2
60	22.3	0.0	26.4	1.6	12.7 ± 13.6
90	15.3	0.0	20.0	0.2	9.0 ± 10.2
120	11.1	0.0	11.7	0.0	5.8 ± 6.5
180	6.3	0.0	5.8	0.0	3.1 ± 3.4

Table 4. Plasma Concentrations from Suppository Formulation 62 (Cefmetazole plus Sodium 5-methoxy-Salicylate). Periods: 1-2R-3-4. AUC: 2716 g·min/cc

Period-Dog

Time (Min)	1-303	2R-300	3-390	4-296	Ave ± S.D.
0	0.0	0.0	0.0	0.0	0.0
15	13.7	24.8	3.1	32.1	18.4 ± 12.7
30	26.2	29.2	5.3	50.3	27.8 ± 18.4
45	29.7	24.3	9.5	39.3	25.7 ± 12.5
60	23.9	17.3	12.2	38.8	23.0 ± 11.5
90	19.7	9.3	8.0	24.1	15.3 ± 7.9
120	12.6	6.3	8.4	16.0	10.8 ± 4.3
180	7.1	3.6	5.9	6.3	5.7 ± 1.5

Table 5. Plasma Concentrations from Intramuscular Injection of 1.0 Gram of Cefmetazole. Periods: 1-2-3. AUC: 9234 g·min/cc

	Period-Dog			
Time (Min)	1-296*	2-303	3-300	Ave ± S.D.
0	0.0	0.0	0.0	0.0
15	98.9	121.0	121.6	113.8 ± 12.9
30	100.4	112.6	117.8	110.3 ± 8.9
45	88.9	94.1	84.8	89.3 ± 4.7
60	76.3	71.5	60.8	69.5 ± 7.9
90	43.3	46.5	34.0	41.3 ± 6.5
120	31.2	30.1	26.1	29.1 ± 2.7
180	13.7	15.8	12.6	14.0 ± 1.6

variation in plasma levels was the presence of stool in the rectum. Even though the dogs were fasted for 48 hours, there were still significant amounts present. The IM data in Table 5 was much less scattered until the period 4 data was collected. This period was not included in the IM data but rather is presented by itself in Table 6. Figure 2 shows the data plotted, while Table 7 provides a compilation of the average pharmacokinetic parameters. These results clearly show that the formulation must contain an adjuvant for cefmetazole to be delivered to detectable levels systemically. However, it should be noted that the suppositories were slightly sub-potent (Table 2), indicating the bioavailability from the suppositories is slightly greater (~10% greater) than listed in Table 7).

Table 8 gives the MIC90 values for cefmetazole against major pathogenic bacteria. As it can be seen in this table the MIC values for many important pathogens are very low (e.g. *Staph. aureus*, *Streptococcus* spp., *E. coli*, *K. pneumoniae*, *Salminella* spp., *Proteus* spp., etc.). Therefore the concentration of cefmetazole from a 1 g suppository could yield sufficient drug concentrations to be effective against many infectious diseases caused by these pathogens. The concentrations after 1 g of cefmetazole administered intramuscularly to healthy male volunteers in the serum were as follows: 20 min. - 17.3 mcg/ml; 60 min. - 30.0 mcg/ml; 2.0 hr. - 25 mcg/ml; 3.0 hr. - 19.0 mcg/ml and 4.0 hr. - 13.0 mcg/ml.

Table 6. Plasma Concentration from Intramuscular Injection of 1.0 Gram of Cefmetazole. Period: 4.
AUC: 6461 g·min/cc

Time (Min)	4-390
0	0.0
15	35.1
30	37.7
45	43.6
60	38.5
90	42.6
120	39.3
180	36.0

* March 12, 1987 70296 Pre- This dog was in pro-estrus and there was some generalized, mild hyperemia of the rectal mucosa.

Post - Same

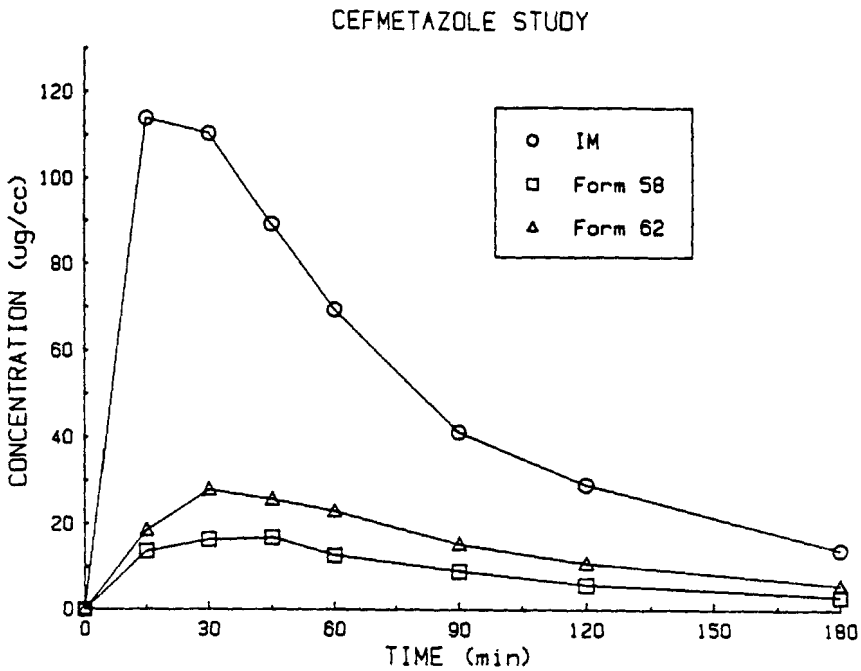

Figure 2. Plasma data for Periods 1-2R-3 and 4 for Formulations 58, 62 and IM dose.

Table 7. Average Pharmacokinetic Parameters for each Formulation. Periods: 1-2R-3-4.

Parameter	Formulation 58	60	62	IM*
t_p (min)	45	0	30	15
C_{max} (g/cc)	16.9	0	27.9	113.8
AUC (g¯min/cc	1617	0	2716	9234
% Relative Bioavailability	17.5	0	29.4	100.0

* Does not include data from Period 4, Dog 390.

Proctoscopic Examination

Proctoscopic examinations in the dogs dosed with suppositories were also done. We believe that lack of any clinical signs in these dogs which imply irritation or inflammation of the colon (tenesmus, mucus, fresh blood) suggest that the suppositories used in the study are relatively non-irritating when given once weekly for four weeks in a cross-over study design. Rectal biopsy histopathology also showed no evidence of direct mucosal injury, inflammation, or altered mucin production resulting from the cefmetazole suppositories.

Clinical Laboratory Evaluation

No clinically meaningful changes or trends in the assay results between pretreatment and during treatment were found in this study after the administration of a 1.0 g cefmetazole suppository to the experimental dogs.

Comparison With Literature

Reviewing the literature, some published animal data with cefotaxime and potassium penicillin G administered by the rectal route are available[3,7,8]. These 3 antibiotics are marked for parenteral use only and none of them displays appreciable absorption when administered rectally without an absorption adjuvant. The experiments were conducted using Beagle dogs as an animal model[5]. A Conventional base material (Witepsol® H-15) was used to form the bulk of the suppository. Either antibiotic alone, or antibiotic plus sodium 5-methoxysalicylate, was

Table 8
CEFMETAZOLE

MIC_{90} (μg/ml)

≤ 16		≤ 32	
Species	MIC_{90} (Source)	Species	MIC_{90} (Source)
Clostridium spp.	8 (TUC)	Listeria monocytogenes	32 (TUC)
Clostridium difficile	16 (TUC)		32 (CAST)
S. aureus ($meth^S$)	2 (TUC)	Staphylococcus spp ($meth^R$)	>32 (CAST)
Staphylococcus sp ($meth^S$)	2 (CAST)	Acinetobacter spp.	128 (TUC)
S. aureus ($meth^R$)	16 (TUC)		>32 (CAST)
S. epidermidis	4 (TUC	Yersinia enterocolitica	32 (TUC)
Streptococcus spp. (Grp A)	0.5 (TUC)		
	0.5 (CAST)		
Streptococcus spp. (Grp B)	2 (TUC)		
Streptococcus agalactiae	2 (CAST)	> 64	
S. pneumoniae	0.5 (TUC)	Ps. aeruginosa	>128 (TUC)
S. pneumoniae	8 (CAST)		>32 (CAST)
B. fragilis	16 (TUC)	S. faecalis	>128 (TUC)
C. diversus	1 (TUC)	Bacteroides spp	64 (TUC)
	0.5 (CAST)	C. freundii	64 (TUC)
E. coli	4 (TUC)		>32 (CAST)
	1 (CAST)	E. aerogenes	>128 (TUC)
H. influenzae (amp^S)	16 (TUC)		>32 (CAST)
	2 (ACST)	E. cloacae	>128 (TUC)
H. influenzae (amp^R)	16 (TUC)	S. cloacae	>32 (CAST)
	4 (CAST)	S. marcescens	>32 (CAST)
K. pneumoniae	1 (TUC)		
	2 (CAST)		
M. morganii	16 (TUC)		
	8 (CAST)		
N. gonorrhoeae (amp^S)	2 (TUC)		
	16 (CAST)		
N. gonorrhoeae (amp^R)	8 (TUC)		
	1 (CAST)		
P. mirabilis	2 (TUC)		
	4 (CAST)		
P. rettgeris	16 (TUC)		
	2 (CAST)		
P. vulgaris	16 (TUC)		
	2 (CAST)		
Providencia stuartii	2 (TUC)		
	4 (CAST)		
Salmonella spp.	1 (TUC)		
S. marcescens	16 (TUC)		
Shigella spp.	1 (TUC)		
B. Cattharalis	0.5 (CAST)		
N. meningitidis	0.12 (CAST)		

Table 9

Rectal Bioavailability of Antibiotics in Dogs*

Target Date	Adjuvant Amount (sodium 5-methoxysalicylate)	Bioavailability** Mean ± SD	n
Sodium Cefmetazole 150 mg	0 mg	Not Detectable	4
	75 mg	0.31 ± 0.05	4
	100 mg	0.93 ± 0.17	2
Sodium Cefoxitin 75 mg	0 mg	0.05 ± 0.02	4
	50 mg	0.36 ± 0.17	4
	75 mg	0.51 ± 0.14	4
	100 mg	0.65 ± 0.16	4
Potassium Penicillin G 75 mg	0 mg	0.04 ± 0.003	4
	50 mg	0.41 ± 0.04	4
	75 mg	0.58 ± 0.13	4
	100 mg	1.04 ± 0.46	8

* Suppository formulations are drug-adjuvant suspensions in Witepsol® H-15, 1 gram suppositories

** Bioavailability compared to IV $\frac{[AUC]\ rectal}{[AUC]\ IV} \times \frac{dose\ IV}{dose\ rectal}$

added as a suspension prior to solidification of the suppository mass. Results presented in Table 9 relate increasing amounts of absorption adjuvant to increasing rectal bioavailability of the target drug. Bioavailability was calculated as a fraction of the normalized AUC obtained after IV dosing. These results clearly demonstrate that sodium 5-methoxysalicylate, when administered together with a water-soluble form of the antibiotic, can dramatically improve the rectal bioavailability. In some cases, equivalence to IV injection was observed.

There were a variety of experiments conducted to assess the cytologic effects of sodium salicylate and sodium 5-methoxysalicylate on the rectal mucosa of rats. These studies were both acute and chronic, acute being 10-20 minute exposure of a microenema in a ligated section of the distal bowel, and chronic being once daily administration of the particular adjuvant in the amount of 50 mg/kg bodyweight for a period for 30 days. The microenema consisted of either an aqueous solution (5% W/V) or a suspension in molten Witepsol® H-15 (15% W/V).

Tissue samples from the treated areas of the lower bowel were evaluated by a certified pathologist who did not know which samples were control and which were experimental. At

the light microscopic level, adjuvant treated tissue was not distinguishable from sham-treated and untreated controls.

Sodium salicylate in the rectal mucosa of the rat, has caused a transient increase in cell membrane permeability. Furthermore, even at the electron microscopic level, the only obvious effect of salicylate treatment at neutral pH was a "thinning" of the glycocalyx coat on the surface of the epithelial cell membrane. The altered mucosal permeability upon exposure to sodium salicylate is a transient phenomenon and lasts as long as the adjuvant is present. Once the salicylate (adjuvant) has been absorbed, the effect is lost almost immediately.

These experiments, when taken together with the observation that aspirin suppositories have successfully utilized for years in some countries, indicate that salicylate is not harmful when administered rectally as the sodium salt.

CONCLUSION

A 1 gram cefmetazole rectal suppository can be formulated that also contains one gram of salicylate adjuvant. Although relatively large in size (4.9 grams) the suppositories were easily inserted and no leakage occurred from medium sized dogs. Melting behavior, dissolution, and fracture weights of the suppositories containing adjuvant were acceptable. Dissolution testing indicated that an adjuvant was necessary for drug release and this was confirmed by the absence of observable plasma levels from the suppository that did not contain adjuvant. Percent relative bioavailability was determined to be 17.5% when sodium salicylate was the adjuvant and 29.4% when sodium 5-methoxysalicylate was the adjuvant.

The suppositories were well tolerated as administered in this study. No clinical signs or symptoms of inflammation or irritation of the colon of the dogs dosed once weekly for four weeks with the suppository were noted. Blood levels obtained from the 1 g cefmetazole rectal suppositories were sufficient to be effective against many infectious diseases caused by certain pathogens. The data warrant further study of the tolerance and pharmacokinetics of the 1 gram cefmetazole rectal suppository in man.

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