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Pharmacokinetics of Alafosfalin, Alone and in Combination with Cephalexin, in Humans

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Alafosfalin is a phosphonodipeptide with significant activity as an antibacterial agent and as a potentiator of β-lactam antibiotics. Studies in humans showed that oral doses of 50 to 2,500 mg were well absorbed, but some metabolic hydrolysis occurred before the drug reached the general circulation. Oral bioavailability was approximately 50% and was largely independent of dose. Alafosfalin has an elimination half-life of about 60 min and does not accumulate during chronic administration. Healthy volunteers excreted intact phosphonodipeptide in the urine. The recovery was dose dependent and increased from 6 ± 1% after 50-mg doses to 17 ± 1% after 2,500-mg doses. This change with dose occurred because the human kidney has a small, saturable capacity for reabsorbing the phosphonopeptide. Less alafosfalin was excreted in the urine of subjects with impaired glomerular function. When alafosfalin was coadministered with cephalexin, both compounds were absorbed, distributed, and eliminated at virtually identical rates. Oral administration of 500 mg of the phosphonodipeptide plus 250 mg of the β-lactam antibiotic gave approximately equal concentrations of the drugs in plasma, with a fourfold excess of cephalexin in the urine. This 2:1 combination is being tested in the clinic.

Alafosfalin (L-alanyl-L-1-aminoethylphosphonic acid; Ro 03-7008) is a member of a series of antibacterial phosphonopeptides (4) which show good activity both in vitro and in vivo, particularly against *Enterobacteriaceae* (1). The compound acts by interfering with bacterial cell wall biosynthesis (3) and also potentiates the activity of β-lactam antibiotics (1).

Previous studies in human volunteers have shown that alafosfalin is absorbed well from the gastrointestinal tract (2), probably by a facilitated transport mechanism. During absorption, approximately half of a 500-mg dose is hydrolyzed to the component amino acids, L-alanine and L-1-aminoethylphosphonic acid [L-Ala(P)]. The remainder, however, reaches the general circulation as intact phosphonodipeptide (2). Unchanged drug and the metabolite are mainly excreted in the urine (2).

In this paper we describe studies to determine how the absorption, metabolism, and excretion vary with dose; whether the drug and its metabolite, L-Ala(P), accumulate during chronic administration; and what effect impaired renal function has on the pharmacokinetics. The rates of absorption and elimination are also compared with those of cephalexin when the two compounds are coadministered orally (p.o.). The tolerance to single and repeat doses of alafosfalin is also reported.

MATERIALS AND METHODS

Population studied. All studies were conducted with volunteers who had been given a comprehensive medical examination. Informed consent was obtained from all subjects. The trials were carried out in accordance with the Declaration of Helsinki (1975), under the direction of one of the following clinicians or pairs of clinicians: (i) G. S. Harris and L. J. Lees, Clinical Research Department, Roche Products Limited, Welwyn Garden City, England; (ii) E. Leicht, Medizinische Klinik und Poliklinik der Universität, Homburg-an-der-Saar, West Germany; and (iii) H. Beck, Hopital Charles Foix, 94203 Ivry, France. A total of 21 male and 5 female volunteers participated in the single-dose studies, and 20 males and 4 females participated in repeat-dose studies. Some volunteers took part in more than one trial.

Single-dose studies. The following trials were performed: (i) a randomized crossover study to compare urinary recoveries of alafosfalin when solutions containing 50-mg doses were taken during fasting and at 0.5 h after a standard English breakfast of cereal, bacon and eggs, toast, and coffee; (ii) an absolute bioavailability study to measure plasma levels in a human volunteer given 500-mg doses of alafosfalin intravenously (i.v.), intramuscularly (i.m.), and p.o.; (iii) measurement of plasma and urine levels in subjects dosed p.o. with 500 mg of alafosfalin in solution; (iv) a three-part randomized crossover study in which volunteers were dosed p.o. with alafosfalin (500-mg tablet), cephalexin (250-mg Ceporex [R] capsule), and both preparations simultaneously; (v) a comparative

bioavailability trial with 1,000-mg doses of alafosfalin in tablet form (2 × 500 mg) and capsule form (4 × 250 mg) on a randomized crossover basis; (vi) an ascending-dose study with doses of 1.5, 2.0, and 2.5 g of alafosfalin in tablet form; and (vii) administration of a 200-mg i.m. dose of alafosfalin to healthy volunteers and subjects with impaired glomerular function to compare urinary recoveries.

Multiple-dose studies. Groups of five or six volunteers were dosed p.o. with the following: 500 mg every 8 h for a total of 16 doses; 750 mg four times daily for 5 days; 1,000 mg three times daily for 4 days, plus 2 days of placebo dosing, randomized before or after the administration of an active drug; and 1,000 mg four times daily for 7 days.

Sample collection and analysis. Blood samples were collected by direct venipuncture or via an indwelling cannula. Samples for hematology and clinical chemistry were assayed within 4 h of collection. In the studies in England samples were analyzed by Searle Diagnostics with automated techniques which were subjected to recognized international quality control procedures. In single-dose studies hematology (Coulter count, reticulocyte counts) and clinical chemistry (blood urea nitrogen, alkaline phosphatase, serum glutamic oxalacetic transaminase, and total bilirubin, plus other parameters on occasions) were determined immediately before and at 24 or 48 h or both after dosing. In repeat-dose studies full hematological and clinical chemistry profiles (Coulter, reticulocyte, and platelet counts, serum electrolytes, creatinine, urea, bilirubin, alkaline phosphatase, serum glutamic oxalacetic transaminase, cholesterol, triglycerides, and total protein) were determined on at least four occasions. Plasma haptoglobin and Coombs' tests values were also determined before and after drug administration in three higher-dose studies. Clinical examinations were performed on all subjects before and after dosing and also upon the reporting adverse effects.

Blood samples for the drug level determination were transferred to lithium-heparin tubes and then cooled in ice water. After centrifugation, plasma was removed and stored at −20°C until analyzed. Care was taken to avoid hemolysis as erythrocytes contain enzymes that hydrolyze alafosfalin.

Urine samples were collected, and the volumes and pH were recorded. Portions were taken for urinalysis, urine microscopy, electrolyte excretion, and measurement of creatinine clearance. The remaining samples were stored frozen for subsequent measurement of drug levels.

Concentrations of alafosfalin in biological samples were measured by previously published methods, either microbiologically (1) or by amino acid analysis (2). The latter procedure could also be used to determine the levels of L-Ala(P), which is a metabolite of alafosfalin (2). Cephalexin concentrations were measured microbiologically with a cup-plate method on Oxoid diagnostic sensitivity test agar with a *Staphylococcus aureus* strain that was insensitive to alafosfalin as the test organism.

RESULTS

A preliminary study was performed to determine the effects of food on alafosfalin absorption and excretion. Volunteers were dosed p.o. with 50 mg in solution during fasting and after a meal. A microbiological analysis showed that the urinary recovery of intact phosphonopeptide was higher when the drug was taken after a meal (6.4 ± 0.9% of the dose as compared to 3.4 ± 0.4% of the dose; $P < 0.05$). An independent investigation also demonstrated that plasma concentrations of alafosfalin were higher when 500-mg p.o. doses were taken with milk or protein (8). In all subsequent studies, therefore, the drug was taken with a glass of milk or after a meal.

Single-dose studies; plasma levels. Figure 1 shows the plasma levels of alafosfalin when 500-mg doses were given i.v., i.m., and p.o. to a healthy male volunteer. Calculation of the areas under the plasma concentration-time curves (AUC values) showed values of 2.09 and 2.47 mg min ml^{-1} for the i.v. and i.m. doses. This demonstrated that the i.m. dose was completely absorbed as intact phosphonodipeptide. Lower values of 1.10 and 0.95 mg min ml^{-1} were found when the same dose was given p.o. in solution (not shown in Fig. 1) and in tablet form. In this subject, therefore, the p.o. bioavailability of alafosfalin (the proportion of the dose that reached the general circulation as intact drug) was approximately 50%.

Doses of 500 to 2,500 mg of alafosfalin were administered p.o. to further volunteers. The mean concentrations of alafosfalin in plasma are shown in Fig. 2, and the results are summarized in Table 1. Alafosfalin was rapidly absorbed and was generally detected in plasma at 20 min after dosing. Maximum concentrations were normally reached at between 1 and 2 h, and then the levels declined exponentially with a half-life of 63 min (range, 40 to 120 min). Both the peak plasma concentrations and the AUC values increased linearly with dose. No significant differences were found between the AUC values ob-

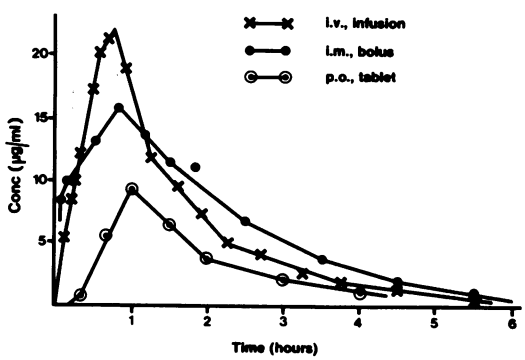

FIG. 1. *Concentrations of alafosfalin in plasma of a human volunteer given 500-mg doses by different routes.*

tained for capsule, tablet, and solution doses, and the p.o. bioavailability of alafosfalin was therefore independent of the dose and formulation. The metabolite L-Ala(P) was also detected in the plasma of volunteers dosed p.o. with alafosfalin. Measurable concentrations were first detected at 40 min; maximum amounts were reached by 2 to 3 h, and the levels then declined relatively slowly (Fig. 3). Comparison of peak concentrations showed that the mean values increased linearly with dose, from 3.6 μg/ml after the administration of 500 mg of alafosfalin to 18.5 μg/ml after the administration of 2,500 mg (Table 1). Accurate AUC values for the metabolite could not be calculated because the plasma concentration-time curves were incompletely measured.

Single-dose studies; urinary excretions. After p.o. administration of alafosfalin, the recovery of unchanged drug in the urine was essentially complete by 8 h (Table 2). L-Ala(P) was excreted, but at a slower rate. During the first 8 h, 30 to 40% of the dose was excreted as this compound in the urine. More of the metabolite, representing approximately 20 and 5% of the dose, was also recovered in the 8- to 24- and 24- to 48-h collections, respectively. The total excretion of drug-related material [alafosfalin plus L-Ala(P)] in 48 h was independent of dose (Table 2). The relative recovery of the drug and the metabolite was, however, dose dependent as the proportion excreted as intact phosphonopeptide increased progressively from 6 ± 1% after a 50-mg dose to 17 ± 1% after a 2,500-mg dose (Table 2).

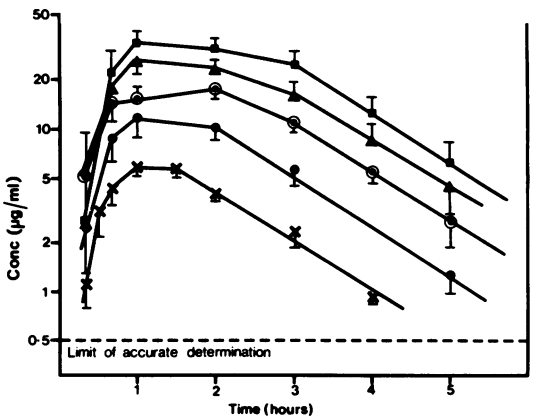

FIG. 2. *Mean concentrations (±SE) of intact phosphonodipeptide in plasma of human volunteers dosed p.o. with alafosfalin in capsule and tablet form. Symbols for dose (in milligrams): ×——×, 500; ●——●, 1,000; ●——●, 1,500; ▲——▲, 2,000; ■——■, 2,500.*

To determine why the urinary recovery of alafosfalin was dependent upon the amount of drug administered, renal clearance studies were performed in the volunteer given 500-mg doses i.v. and i.m. Plotting the rate of excretion in the urine against the mid-point plasma concentrations (Fig. 4; only the i.v. data are shown) gave curves which were characteristic of clearance by glomerular filtration, followed by saturable reabsorption at the renal tubule (7). When the plasma concentration exceeded 5 μg/ml, there was a linear relationship between urine clearance and plasma level, and the gradient of this line (109 ml/min) was very similar to the glomerular filtration rate of 112 ml/min determined by creatinine clearance. At concentrations below 5 μg/ml, the urinary recovery declined towards zero, demonstrating that the reabsorption process was no longer saturated. Back projection of the linear portion of the curve gave an intercept on the ordinate which indicated that the maximum reabsorption rate in this particular subject was approximately 200 μg/min.

Four patients with urinary tract infections were given a single 200-mg i.m. dose of alafos-

TABLE 1. *Plasma levels (mean ± standard error [SE]) for dose-response bioavailability studies with alafosfalin*

Dose (mg)	Form	No. of subjects	Maximum concn (μg ml^{-1})		AUC[b] for alafosfalin (mg min ml^{-1})
			Alafosfalin	Metabolite[a]	
500	Solution	6	6.5 ± 1.3	NM[c]	1.00 ± 0.15
500	Tablet	9	7.1 ± 0.6	2.8 ± 0.3	0.86 ± 0.07
1,000	Tablets	5	17.1 ± 3.1	9.2 ± 1.6	1.92 ± 0.23
1,000	Capsules	5	14.5 ± 1.6	7.4 ± 0.7	1.83 ± 0.21
1,500	Tablets	5	19.9 ± 1.8	10.3 ± 1.0	3.12 ± 0.18
2,000	Tablets	5	32.0 ± 2.2	14.0 ± 0.8	4.92 ± 0.57
2,500	Tablets	4	39.1 ± 3.5	18.5 ± 1.6	6.18 ± 0.57

[a] L-Ala(P).
[b] AUC values determined trapezoidally with extrapolation to infinite time.
[c] NM, Not measured.

falin, and the urinary recoveries of drug-related material were compared with those of healthy volunteers (Table 3). These preliminary results suggest that simple, uncomplicated urinary tract infections may not change the excretion of alafosfalin, but the elimination of both intact phosphonopeptide and L-Ala(P) may be considerably reduced in subjects with impaired renal function. This would be consistent with the mechanism for renal clearance of alafosfalin.

Single-dose studies; co-administration with cephalexin. Volunteers were dosed p.o. with cephalexin and alafosfalin, both separately and simultaneously. Measurement of the cephalexin levels in plasma and urine (Fig. 5 and Table 4) showed that they were not altered by the coadministration of alafosfalin. Thus, there were no significant differences (paired Student's t tests) in the times to reach peak concentration, the peak levels, the elimination rates, the AUC values, and the urinary recoveries of the intact β-lactam antibiotic. The pharmacokinetics of alafosfalin were also not affected by the coadministration of cephalexin.

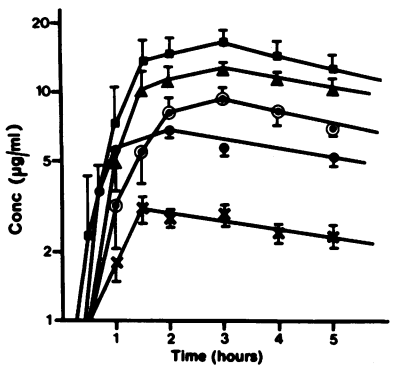

FIG. 3. *Mean concentrations (±SE) of L-Ala(P) in plasma of human volunteers dosed p.o. with alafosfalin. Symbols same as in Fig. 2.*

When cephalexin and alafosfalin were administered simultaneously, all nine volunteers absorbed and eliminated the drugs at virtually identical rates (Fig. 5A). In every subject both compounds were present in the general circulation at 40 min after dosing, both reached maximum concentrations at between 60 and 90 min, and both could still be detected at 4 h.

Comparison of the plasma concentrations (paired Student's t tests) showed that the peak levels of cephalexin were slightly higher than those of alafosfalin (9.4 ± 0.6 μg/ml as compared to 7.3 ± 0.5 μg/ml; $P < 0.01$). The AUC values for cephalexin were also slightly greater than those of alafosfalin (Table 4; $P < 0.01$), but the individual phosphonopeptide values were always more than half those of the β-lactam antibiotic (range of ratios, 0.56 to 1.00).

Analysis of urine samples showed that the two compounds were also excreted at very similar rates. During the first 2 h, the mean excretion rate for cephalexin was 63 ± 5 mg/h, compared with 16 ± 2 mg/h for alafosfalin. The corresponding values for the 2- to 4- and 4- to 6-h collections were 34 ± 3 and 9 ± 0.5 mg/h, respectively, for cephalexin and 7 ± 1 and 1.5 ± 0.2 mg/h, respectively, for alafosfalin.

Repeat-dose studies. The concentrations of alafosfalin and L-Ala(P) in plasma from volunteers given 500-mg doses p.o. every 8 h are shown in Fig. 6. Alafosfalin AUC values after the first and last doses were not significantly different (0.91 ± 0.16 mg min ml^{-1} as compared to 0.85 ± 0.15 mg min ml^{-1}, demonstrating that the phosphonopeptide did not accumulate during chronic administration. In contrast, there was a small increase in L-Ala(P) concentrations during the course of the trial, and levels at the end of the study were approximately 20% higher than

TABLE 2. *Recovery (% of dose) of drug-related material in the urine of volunteers dosed p.o. with alafosfalin*

Dose (mg)	Form	No. of subjects	Alafosfalin (0 to 8 h)	Total[a] (0 to 48 h)
50	Solution	6	6.4 ± 0.9	NM
500	Solution	6	10.8 ± 1.0	72.1 ± 1.6
500	Tablet	9	9.7 ± 0.8	60.2 ± 4.0[b]
1,000	Tablets	5	13.6 ± 0.9	66.1 ± 1.4
1,000	Capsules	5	13.0 ± 1.4	68.8 ± 4.0
1,500	Tablets	5	14.6 ± 1.6	60.7 ± 3.3
2,000	Tablets	5	16.0 ± 1.6	67.5 ± 8.2
2,500	Tablets	4	17.2 ± 0.9	75.2 ± 6.3

[a] Unchanged drug plus L-Ala(P). NM, Not measured.
[b] 0- to 24-h collection only.

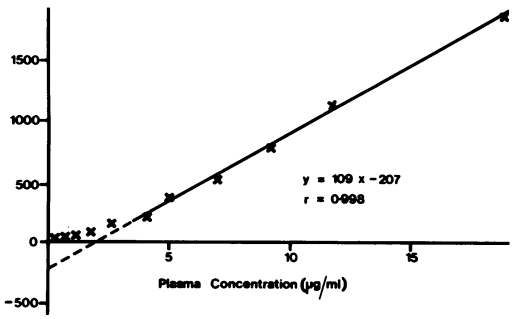

FIG. 4. *Rate of excretion of alafosfalin (µg/min) in human urine as a function of plasma concentration.*

TABLE 3. *Recovery (% of dose) of drug-related material in 6-h urine samples collected from healthy volunteers and patients with urinary tract infections dosed i.m. with alafosfalin (200 mg)*

Subject no.[a]	Age (yr)	Creatinine clearance (ml min^{-1})	Recovery (% of dose) of:	
			Alafosfalin	Total[b]
1	36	110	30.6	NM
2	37	119	23.1	NM
3	62	92	17.8	NM
4	54	68	32.4	48.6
5	64	89	13.2	42.0
6	82	23	7.1	14.5
7	84	10	2.3	8.2

[a] Subjects no. 1 to 3 were healthy volunteers, and subjects no. 4 to 7 were patients with infections of the urinary tract.

[b] Alafosfalin plus L-Ala(P). NM, Not measured; however, a group of five healthy subjects, aged 24 to 27 years, excreted 47 ± 4% of a 100-mg dose in 6 h.

those found after the first dose. Once drug administration was discontinued, the metabolite levels declined exponentially, with half-lives of 4 to 5 h, and concentrations of <0.5 µg/ml were found at 24 h after the last dose.

Analysis of urine samples (Fig. 7) showed that the excretion of the intact phosphonopeptide did not change during the study. The recovery of L-Ala(P) also reached a steady state after day 2, and, once this had been established, the urinary recovery of drug-related material corresponded to 84 ± 3% of the standard dose.

Further groups of subjects were also given repeat doses of alafosfalin (either 0.75 or 1.0 g, 4 times daily) to assess tolerance. To minimize the trauma of these studies, blood samples were not collected for drug analysis. However, complete urine collection was made between the last dose on day 3 and the first morning dose on day 4 of the study. Samples collected from subjects taking 750-mg doses contained 86 ± 4% of the standard dose, of which 17 ± 1% was excreted as alafosfalin. This clearly showed that a steady state had been established and the volunteers had, therefore, followed the study protocol. Similarly, the recovery for five of the volunteers taking 1,000-mg doses four times daily was 82 ± 5% of the standard dose, with 17 ± 2% being alafosfalin. However, the specimen supplied by the sixth subject contained only 28% of the standard dose (8% phosphonopeptide). It is not clear whether this subject did not collect all the urine, did not take all the doses, or was unable to absorb p.o. administered alafosfalin.

Tolerance of alafosfalin. Alafosfalin appeared to be exceptionally well tolerated during the preclinical evaluation. Three subjects each given a 500-mg dose in solution after a large fatty meal reported some gastrointestinal disturbance. It was felt that this could be attributed to the food. One subject reported slight diarrhea after a single 2,000-mg dose, and one subject experienced some indigestion when a 500-mg dose was coadministered with 250 mg of cephalexin. In repeat-dose studies no increase in bowel frequency or flatus was reported, although one subject taking 1,000 mg four times daily had lower abdominal discomfort. This subject was subsequently found to have a very low recovery of drug and metabolite in the urine. Otherwise, only the minor symptoms of slight headache, light-headedness, and urine odor were reported.

During repeat-dose studies, a slight, transitory elevation in serum glutamic pyruvic transaminase was reported in two subjects on a single occasion. In one subject the creatinine clearance

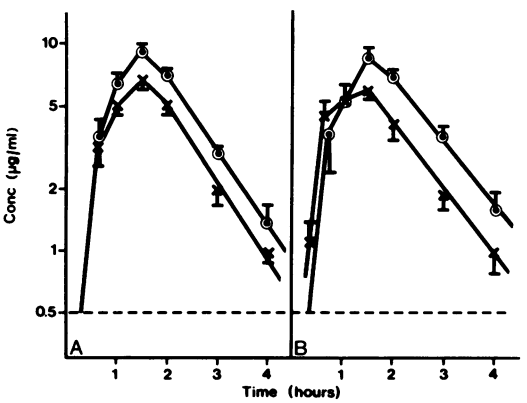

FIG. 5. *Mean concentrations (±SE) of cephalexin (250-mg Ceporex capsule; ●—●) and alafosfalin (500-mg tablet; ×——×) in plasma of human volunteers after administration together (A) and separately (B).*

TABLE 4. *Plasma and urine levels (mean ± SE) in volunteers dosed with alafosfalin and cephalexin*[a]

Drug	Pharmacokinetic parameter			
	Maximum concn (μg/ml)	Half-life (min)	AUC values (mg min ml^{-1})	Drug in urine (% of dose)
Cephalexin				
Alone	9.3 ± 0.9	55 ± 3	1.19 ± 0.07	86.6 ± 1.7
Combination	9.4 ± 0.6	56 ± 4	1.16 ± 0.05	91.8 ± 4.0
Alafosfolin				
Alone[b]	7.1 ± 0.6	50 ± 2	0.86 ± 0.07	9.7 ± 0.8
Combination	7.3 ± 0.5	50 ± 2	0.84 ± 0.05	10.5 ± 0.6

[a] Alafosfolin, 500-mg tablet; cephalexin, 250-mg Ceporex capsule.
[b] Data are also shown in Tables 1 and 2.

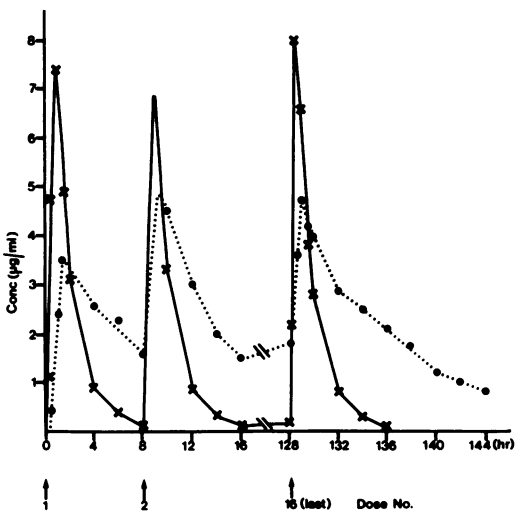

FIG. 6. *Mean concentrations of intact phosphonodipeptide (alafosfalin; ×——×) and L-Ala(P) (●···●) in plasma of five volunteers dosed p.o. with alafosfalin (500 mg every 8 h).*

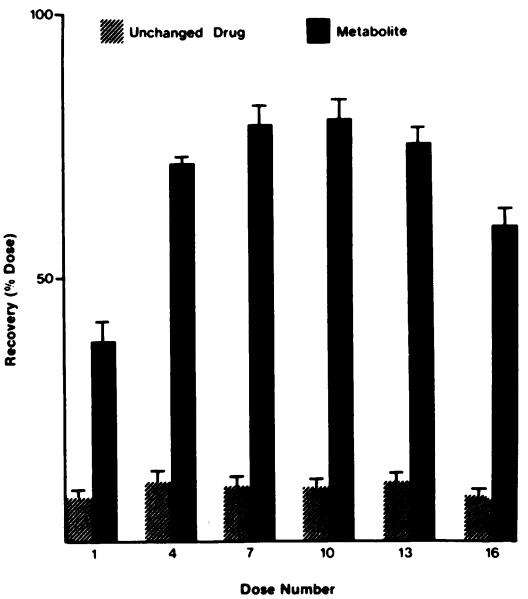

FIG. 7. *Urinary recoveries (% of dose ± SE) of unchanged drug and L-Ala(P) for five volunteers dosed p.o. with alafosfalin (500 mg every 8 h).*

value was low, possibly due to incomplete urine collection. In one subject polyuria with natriuresis occurred on the day 3 of dosage with 1,000 mg three times daily. During the study in which 500 mg was administered three times daily, hematology results showed a mild (5%) and transitory reduction in erythrocyte values in all subjects on days 2 and 3 of the trial. This was attributed to the large volumes of blood withdrawn during day 1 for biochemical monitoring and drug level determination. The reduction was not observed in other studies, in which higher doses were administered, but blood samples were not collected for drug analysis. During these studies, all hematological values remained within the normal range for healthy volunteers, and haptoglobin and Coombs' tests values were unchanged. The only possible effect observed was a 1% increase in reticulocyte counts on day 3 of the study in which 1,000 mg was administered four times daily. In view of the small hematological changes observed in rats after repeated administration of alafosfalin (2), these parameters will continue to be very closely monitored during clinical trials.

DISCUSSION

Biochemical studies (3) have shown that the antibacterial activity of phosophonopeptides is due to the aminoalkylphosphonic acid that is released within the cell. In the case of alafosfalin, the L-Ala(P) released inhibits the enzyme alanine racemase (EC 5.1.1.1.), and this prevents

the formation of cross-links in the bacterial cell wall (3). As this enzyme has no counterpart in the biochemistry of mammalian cells, both the phosphonopeptides and aminoalkylphosphonic acids are very nontoxic, even when extremely high doses are administered to animals (2). The results of the present studies also demonstrate that alafosfalin is well tolerated by humans.

Although the antibacterial action of alafosfalin is due to the L-Ala(P) portion of the molecule, the false amino acid is only weakly active because it is poorly transported into microorganisms (3). The phosphonopeptides, therefore, are needed for drug delivery, and for the compounds to be clinically effective, they must survive hydrolysis by human peptidases. The volunteer studies described in this report demonstrate that alafosfalin is fairly resistant to hydrolysis by these enzymes. The drug is well absorbed after p.o. administration, and approximately half the dose reaches the general circulation as intact phosphonopeptide. It has a plasma half-life of approximately 1 h, and healthy subjects also excrete unchanged drug in the urine. Alafosfalin is not, however, totally resistant to hydrolysis as substantial amounts of L-Ala(P) are found in plasma, and this metabolite accounts for most of the drug-related material excreted in the urine.

Alafosfalin is particularly active against those gram-negative organisms which infect the urinary tract. Although only about 10% of a p.o. dose is excreted unchanged in the urine, preliminary clinical studies suggest that this is sufficient for the treatment of simple urinary tract infections (unpublished data). The urinary recovery of intact phosphonopeptide is, however, very dependent upon kidney function. Clearance studies demonstrate that alafosfalin is removed from the general circulation by glomerular filtration but is then reabsorbed at the renal tubule, and high urinary excretion is only achieved when this reabsorption process has been saturated. Patients with impaired renal blood flow and impaired glomerular function will clear less alafosfalin through their kidneys in unit time. This should, in turn, make the drug more available for metabolism by tissue peptidases, thus further reducing the amounts of intact phosphonopeptide that can be excreted in the urine. The compound alone may, therefore, not be suitable for the treatment of more complicated renal infections, particularly in elderly subjects.

Alafosfalin not only has a broad spectrum of antibacterial activity, but also acts synergistically with other inhibitors of cell wall biosynthesis (1). In particular, even very small amounts of the phosphonopeptide have been shown to convert cephalexin from a bacteriostatic into a bactericidal agent (D. Greenwood and R. Vincent, Program Abstr. Int. Congr. Chemother. 11th, Boston, Mass., abstr. no. 239, 1979). The use of such combinations has also been shown to suppress the development of resistance to both the phosphonopeptide and the β-lactam antibiotic (M. J. Hall, M. Arisawa, S. W. Holmes, H. B. Maruyama, and L. J. Nisbet, Progr. Abstr. Int. Congr. Chemother. 11th, Boston, Mass., abstr. no. 238, 1979). Comparison of the pharmacokinetics of alafosfalin with data published for cephalexin (5, 6) also suggested that the two compounds would be absorbed, distributed, and eliminated at virtually identical rates in humans. Direct evidence that this is the case has been obtained in the present study. The synergistic activity, which has been demonstrated both in vitro and in vivo with animal models (11th ICC, abstr. no. 238) should therefore be reproduced under clinical conditions, and this 2:1 combination is being evaluated in the clinic.

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