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Urinary Recovery of *N*-Formimidoyl Thienamycin (MK0787) as Affected by Coadministration of *N*-Formimidoyl Thienamycin Dehydropeptidase Inhibitors

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N-Formimidoyl thienamycin (MK0787) undergoes renal metabolism by a dipeptidase, dehydropeptidase I, located on the brush border of the proximal tubular cells. The effects of two inhibitors (MK-789 and MK-791) of dehydropeptidase I on the pharmacokinetics of *N*-formimidoyl thienamycin were studied in 41 healthy subjects receiving various combinations of *N*-formimidoyl thienamycin and MK-789 or MK-791. Both inhibitors affected the plasma kinetics of *N*-formimidoyl thienamycin only to a small extent. Plasma concentrations and the area under the plasma concentration curve increased about 20% with a proportional decrease in plasma clearance. Plasma half-life was not altered significantly. Coadministration of MK-789 or MK-791 resulted in uniform and marked increases in urinary recovery and renal clearance of *N*-formimidoyl thienamycin. Thus, at an *N*-formimidoyl thienamycin/MK-791 ratio of 1:0.25 or higher, the urinary recovery was about 72% in all subjects, whereas it varied between 7.7 and 43% when *N*-formimidoyl thienamycin was given alone. The ratio of the *N*-formimidoyl thienamycin and MK-791 doses affected response. At relatively higher doses of MK-791, significant increases of *N*-formimidoyl thienamycin urinary recovery, renal clearance, and urine concentrations occurred during the later part of the 10-h observation period after each administration. At a 1:1 ratio of the two drugs, the inhibition of renal metabolism of *N*-formimidoyl thienamycin was maintained for at least 8 h, whereas renal clearance declined as soon as 4 h after the administration of a 1:0.25 ratio. The results indicated that MK-789 and MK-791 alter the renal excretion of *N*-formimidoyl thienamycin from glomerular filtration plus tubular secretion to glomerular filtration only, possibly by competitively inhibiting the penetration of *N*-formimidoyl thienamycin into the proximal tubular cells.

The human pharmacokinetics of *N*-formimidoyl thienamycin (MK0787) are characterized by high plasma concentrations and rapid elimination via the kidneys (3). The urinary recovery (UR) of *N*-formimidoyl thienamycin varies considerably between subjects, whereas the within-subject variation is very small (3). The probable reason for the varying urinary recovery is a renal metabolism by a dipeptidase, dehydropeptidase I, located at the brush border of the proximal tubular cell and inactivating *N*-formimidoyl thienamycin by breaking the β-lactam bond (2). Since the various degrees of renal metabolism make the urinary excretion of intact *N*-formimidoyl thienamycin in humans unpredictable and since unnecessarily high doses of *N*-formimidoyl thienamycin may have to be used to guarantee sufficient urinary concentrations of the antibiotic, it was considered worthwhile to investigate the effect of inhibitors of dehydropeptidase I on the pharmacokinetics of *N*-formimidoyl thienamycin in humans.

(These studies were reported at the 21st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill., November 1981.)

MATERIALS AND METHODS

Subjects. A total of 41 healthy, male Caucasian subjects with a mean age of 24.6 (range, 19 to 38 years) and a mean body weight of 75.0 kg (range, 60 to 89 kg) were included in the studies described in this report. All subjects gave their informed written consent to participate, and the protocols for the studies were

TABLE 1. Pharmacokinetic variables for *N*-formimidoyl thienamycin administered alone or together with a dehydropeptidase inhibitor (MK-789 or MK-791)

Dose (mg) of:			No. of subjects	AUC (μg · h/ml)	VCl_p (ml/min 1.73 m^{-2})	$T_{1/2}$ (h)
N-formimidoyl thienamycin	MK-789	MK-791				
150	0	—	15	9.6 ± 1.2	231.6 ± 37.5	1.0 ± 0.1
150	25	—	5	10.5 ± 0.6	205.4 ± 14.2	1.0 ± 0.2
150	75	—	5	10.3 ± 1.0	220.8 ± 30.6	1.0 ± 0.1
150	150	—	5	10.9 ± 2.4	206.9 ± 19.2	1.0 ± 0.1
500	—	0	8	34.3 ± 3.8	207.2 ± 15.1	1.0 ± 0.1
500	—	250	8	39.8 ± 3.7	171.6 ± 9.5	1.0 ± 0.1
500	—	500	8	37.3 ± 3.8	174.9 ± 9.7	1.0 ± 0.1
500	—	1,000	8	40.7 ± 4.8	167.1 ± 7.4	1.0 ± 0.1
1,000	—	0	8	62.3 ± 7.6	220.0 ± 36.3	1.0 ± 0.1
1,000	—	250	8	73.7 ± 7.6	176.5 ± 15.2	1.0 ± 0.1
1,000	—	500	8	78.1 ± 11.0	171.4 ± 15.6	1.0 ± 0.1
1,000	—	1,000	8	81.9 ± 13.5	167.5 ± 18.1	1.0 ± 0.1

[a] All values are given as means ± standard deviations. Abbreviations: $T_{1/2}$, half-life in the β-phase; VCl_P, plasma clearance.

approved by the Ethical Review Committees at the Faculties of Medicine of the Universities of Gothenburg and Umeå, Sweden.

Study no. 1. Fifteen subjects were included in the study and received single intravenous injections of 150 mg of *N*-formimidoyl thienamycin (Merck, Sharp & Dohme Research Laboratories, Rahway, N.J.) alone and together with 25 mg (five subjects), 75 mg (five subjects), or 150 mg (five subjects) of a dehydropeptidase inhibitor (MK-789 [3-pentyl-2-{dimethylcyclopropyl-carboxoxamido}-propenoate], Merck, Sharp & Dohme Research Laboratories). Each subject also received the same dose of MK-789 alone. All doses were administered as intravenous injections over 3 min in 15 ml of sterile physiological saline. At least 1 week elapsed between the doses administered to each subject. Blood for the analysis of plasma concentration was drawn before and at 6, 12, 30, and 45 min and 1, 1.5, 2, 3, 4, 5, and 6 h after the beginning of the administration of *N*-formimidoyl thienamycin. Urine for concentration and creatinine assays was collected before and at 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 5, 5 to 6, and 6 to 8 h after the beginning of the administration. Safety tests, including routine hematological and biochemical tests and urinalysis, were performed before and after each test dose. All volunteers were closely watched for local and systemic adverse reactions to the test drugs.

Study no. 2. In this study, 26 subjects were included for the screening of *N*-formimidoyl thienamycin UR. They all received single doses of 250 mg of *N*-formimidoyl thienamycin in 100 ml of sterile physiological saline infused intravenously at a constant rate of 5 ml/min over 20 min. Urine samples were collected before and at 0 to 2, 2 to 4, and 4 to 6 h after the beginning of the infusions. Safety samples were obtained as in study no. 1.

From this group of subjects 16 volunteers were selected: 8 with a low degree of renal metabolism of *N*-formimidoyl thienamycin (UR, >16% of the dose) and 8 with a high degree of metabolism (UR, <16% of the dose). In each of these two subgroups, the subjects received four consecutive doses of 500 mg (four subjects) or 1,000 mg (four subjects) of *N*-formimidoyl thienamycin and a dehydropeptidase inhibitor [MK-791; L-642, 957, {*S*,*Z*}-S-{6-carboxy-6-{{(2,2-dimethylcyclopropyl)carbonyl}amino}5-hexenyl}-L cysteine monosodium salt] in *N*-formimidoyl thienamycin/MK-791 ratios of 1:0, 1:0.5, 1:1, and 1:2 in the subjects receiving the 500-mg *N*-formimidoyl thienamycin dose and 1:0, 1:0.25, 1:0.5, and 1:1 in the subjects receiving the 1,000-mg *N*-formimidoyl thienamycin dose. The allocation of the various treatments was open and nonrandomized, and the subjects received increasing doses of MK-791. All doses were administered as constant-rate intravenous infusions in 100 ml of sterile physiological saline over 20 min.

Blood samples were collected before and at 0 and 20 min and at 1, 2, 4, 6, and 8 h after the initiation of the infusions. Urine was collected before and at intervals of 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 8, and 8 to 10 h after the initiation of the infusions. In each subject, at least 1 week elapsed between two consecutive infusions. Safety tests were performed before and after each dose.

Assay *N*-formimidoyl thienamycin. The methods used for the assay of *N*-formimidoyl thienamycin have been described in the accompanying manuscript (3).

Assay of dehydropeptidase inhibitors. MK-789 was assayed in selected blood and urine samples by a spectrophotometric technique measuring the inactivation of purified enzyme substrate, dehydropeptidase I. Concentrations of MK-789 were expressed as MK-789 equivalents since the drug is oxidized through keto and dicarboxylic acid intermediates, all of which are active inhibitors of *N*-formimidoyl thienamicin (2). Analyses of MK-791 are not yet available and will not be included in this report.

Pharmacokinetic analyses. The area under the plasma concentration-time curve (AUC) was estimated by the trapezoid method. Pharmacokinetic parameters were estimated under the assumption that a two-compartment open model adequately describes the *N*-formimidoyl thienamycin disposition after intravenous administration. A general curve-stripping technique was used for making these estimates. The renal clear-

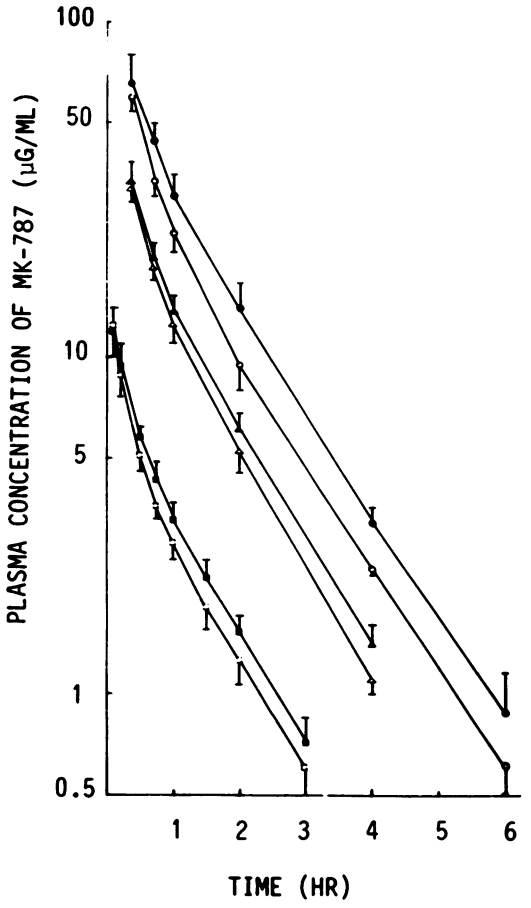

FIG. 1. Mean plasma concentration of *N*-formimidoyl thienamycin administered intravenously in doses of 150 mg (□), 500 mg (△), or 1,000 mg (○) alone (open symbols) or combined with equal doses of dehydropeptidase inhibitors (MK-789, MK-791; filled symbols). The standard deviations are indicated by bars.

ance of *N*-formimidoyl thienamycin was estimated as the quotient between renal excretion and the AUC.

Statistical analyses. All statistical analyses were performed with Student's *t* test for paired differences.

RESULTS

Safety and tolerance. One subject reported nausea during the infusions of *N*-formimidoyl thienamycin with or without MK-791. He did not vomit and maintained a normal blood pressure. No other clinical or laboratory adverse reactions related to *N*-formimidoyl thienamycin, MK-789, or MK-791 were noted. Renal function was not affected by any of the drugs tested as judged by repeated serum creatinine samples and by the determination of creatinine clearance before and during each test dose. No local reactions at the sites of infusions were observed.

Plasma kinetics of *N*-formimidoyl thienamycin. Plasma concentrations were directly proportional to the doses within the dose range of 150 to 1,000 mg (Fig. 1). The coadministration of *N*-formimidoyl thienamycin with either of the two dehydropeptidase inhibitors tested resulted in slightly increased plasma levels. That increase was more pronounced at all *N*-formimidoyl thienamycin/MK-791 dose ranges at a ratio of 1:1 than at a ratio of 1:0.25. The half-life of *N*-formimidoyl thienamycin was consistently about 1 h, irrespective of whether a dehydropeptidase inhibitor was given (Table 1). The AUC increased about 20%, and the plasma clearance of *N*-formimidoyl thienamycin decreased proportionally when the antibiotic was combined with MK-789 or MK-791. The increase in the AUC was significant ($P < 0.025$) at all dose levels of the inhibitors. Comparing the *N*-formimidoyl thienamycin/MK-791 ratios of 1:0.25 and 1:1 (i.e., 1,000 mg of *N*-formimidoyl thienamycin plus 250 or 1,000 mg of MK-791), the further increase in the AUC was slight but significant ($P < 0.025$), indicating a dose dependency. Such dose responses could not be demonstrated for the other ratios, indicating that the maximum effect on the plasma kinetics of *N*-formimidoyl thienamycin is achieved at a ratio between 1:0.25 and 1:0.5.

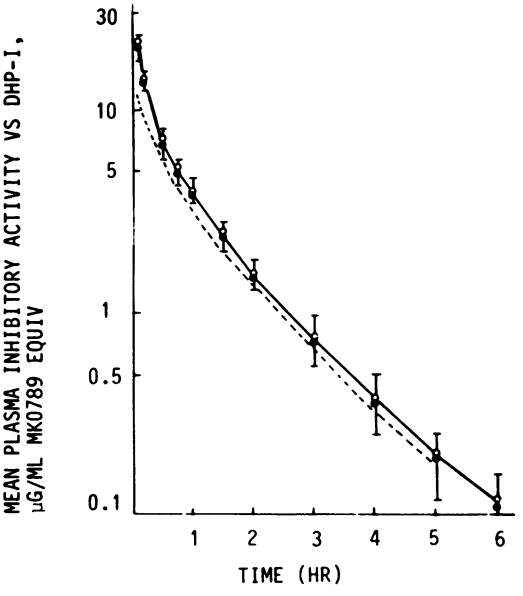

FIG. 2. Mean plasma concentrations of a dehydropeptidase inhibitor (MK-789) obtained after the intravenous administration of 150 mg alone (○) or together with 150 mg of *N*-formimidoyl thienamycin (●). The concentrations of *N*-formimidoyl thienamycin obtained with 150 mg of that drug alone are indicated by the dashed line. The standard deviations are indicated by bars.

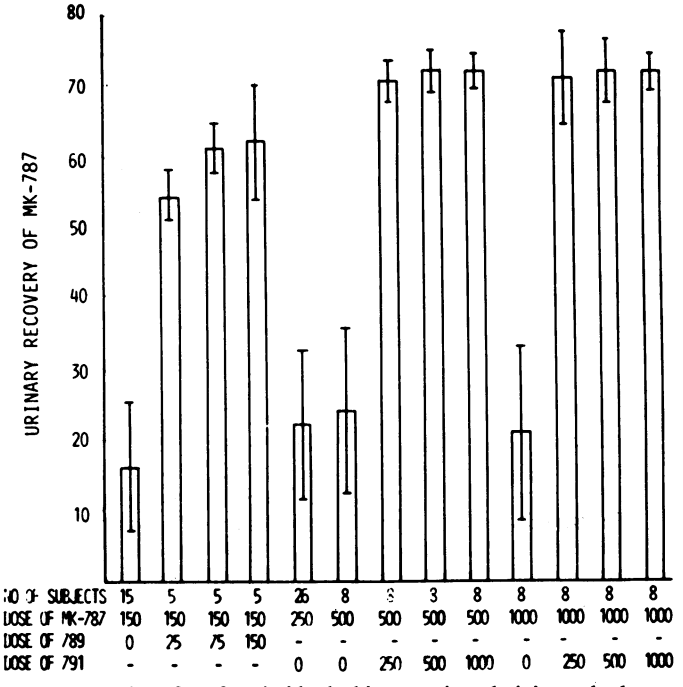

FIG. 3. Mean UR (0 to 10 h) of *N*-formimidoyl thienamycin administered alone or together with a dehydropeptidase inhibitor (MK-789 or MK-791). The standard deviations are indicated by bars.

Plasma kinetics of MK-789. The kinetics of MK-789 were studied in the group which received the highest *N*-formimidoyl thienamycin/MK-789 ratio, i.e., 150 mg of both drugs. The plasma concentrations of MK-789 were slightly higher than those achieved with the same dose of *N*-formimidoyl thienamycin. Almost identical plasma concentrations were found when that drug was administered alone and when it was given together with *N*-formimidoyl thienamycin (Fig. 2). The apparent distribution in the central compartment was 5.6 liters for

TABLE 2. Incremental UR of *N*-formimidoyl thienamycin combined with various doses of a dehydropeptidase inhibitor (MK-791)

Dose of *N*-formimidoyl thienamycin (mg)	No. of subjects	Sampling period (h)	Mean *N*-formimidoyl thienamycin UR (mg) with MK-791 dose (mg) of:				Significance (*P* value)[a] with doses of MK-791 of:		
			0	250	500	1,000	0 vs 250	250 vs 500	500 vs 1,000
500	8	0–1	65.4	179.2	174.8	166.6	<0.0005	NS	NS
500	8	1–2	25.6	75.3	74.7	79.4	<0.0005	NS	NS
500	8	2–3	2.19	7.43	7.33	8.41	<0.0005	NS	<0.025
500	8	3–4	1.08	3.63	3.72	4.38	<0.0005	NS	<0.01
500	8	4–5	0.54	1.64	1.81	2.08	<0.0005	NS	<0.025
500	8	5–6	0.35	0.82	0.93	1.00	<0.0005	<0.01	<0.01
500	8	6–8	0.27	0.56	0.64	0.71	<0.0005	NS	NS
500	8	8–10	0.08	0.14	0.18	0.23	<0.0005	<0.0005	<0.0005
1,000	8	0–1	119.3	361.1	346.2	373.6	<0.0005	NS	NS
1,000	8	1–2	39.8	146.1	150.9	146.1	<0.0005	NS	NS
1,000	8	2–3	1.97	6.91	7.28	7.49	<0.0005	NS	NS
1,000	8	3–4	1.03	3.36	4.24	3.97	<0.0005	<0.005	<0.005
1,000	8	4–5	0.51	1.56	1.91	1.87	<0.0005	<0.005	<0.005
1,000	8	5–6	0.24	0.73	0.94	1.06	<0.0005	<0.0025	<0.0005
1,000	8	6–8	0.22	0.52	0.71	0.80	<0.0005	<0.0025	<0.0025
1,000	8	8–10	0.07	0.13	0.18	0.19	<0.0005	<0.025	<0.025

[a] Statistical significances refer to Student's *t* test for paired differences. NS, Not significant ($P > 0.05$).

TABLE 3. Renal clearance of a 1,000-mg dose of *N*-formimidoyl thienamycin combined with various doses of a dehydropeptidase inhibitor (MK-791)

MK-791 dose (mg)	No. of subjects	Sampling period and *N*-formimidoyl thienamycin VCl_R[a] (ml/min 1.73 m^{-2})		Significance (*P* value)[b]
		0–3	5–10	
0	8	48.9 ± 28.1	49.9 ± 20.9	<0.35, NS
250	8	124.4 ± 10.3	87.2 ± 28.1	<0.0025
500	8	120.7 ± 10.9	107.5 ± 15.0	<0.0025
1,000	8	118.7 ± 10.0	115.6 ± 27.8	<0.40, NS

[a] VCl_R, Renal clearance; the mean ± the standard deviation are given.
[b] Statistical significances refer to Student's *t* test for paired differences. NS, Not significant.

MK-789 as opposed to 11.7 liters for *N*-formimidoyl thienamycin. The plasma clearance of MK-789 was about 160 ml/min per 1.73 m^2, and the half-life was about 1 h.

Renal excretion of *N*-formimidoyl thienamycin. When *N*-formimidoyl thienamycin was administered alone, the UR was highly variable and always below 43% of the dose administered (Fig. 3). Despite this pronounced inter-subject variability, very small within-subject variations were observed. Thus, in comparison with the screening phase of study no. 2, in which 250 mg of *N*-formimidoyl thienamycin was administered, with the 500- and 1,000-mg doses, the variations in the UR were between 0.1 and 5.8% of the dose (mean, 2.4%). The UR was not affected by the size of the *N*-formimidoyl thienamycin dose.

The coadministration of *N*-formimidoyl thienamycin with a dehydropeptidase inhibitor resulted in a dramatic increase in the UR (Fig. 3). When MK-789 was the inhibitor, there was a clear indication that the 25-mg dose did not give the full inhibition of the renal metabolism of *N*-formimidoyl thienamycin. An increase in the dose to 75 mg gave a UR of about 61% of the dose, which seemed to be the maximal effect that could be achieved with that inhibitor, since a further increase in the MK-789 dose did not increase the *N*-formimidoyl thienamycin UR.

MK-791 increased the UR to about 70% (Fig. 3). The effects of MK-791 on the total UR (0 to 10 h) of *N*-formimidoyl thienamycin seemed to be similar irrespective of which dose of the inhibitor was used. However, the renal clearance for the various urine collection periods showed a dose-response relationship (see Table 3). The UR and the renal clearance of *N*-formimidoyl thienamycin increased with increasing doses of MK-791 when the individual sampling periods after the initial elimination phase were analyzed (Tables 2 and 3).

When we compared subjects with different degrees of metabolism of *N*-formimidoyl thienamycin, no differences were found in their response to various doses of MK-791 (Table 4). The coadministration of *N*-formimidoyl thienamycin with MK-791 resulted in a decrease in plasma clearance to about 80% of that observed when *N*-formimidoyl thienamycin was given

TABLE 4. Effect of a dehydropeptidase inhibitor (MK-791) on the creatinine clearance and the plasma and renal clearance of *N*-formimidoyl thienamycin[a]

Renal metabolism of *N*-formimidoyl thienamycin	No. of subjects	Dose of MK-791 (mg)	Cl_{Cr} (ml/min 1.73 m^{-2})	VCl_P (ml/min 1.73 m^{-2})	VCl_R (ml/min 1.73 m^{-2})
High	8	0	126.7 ± 10.8	195.1 ± 29.6	26.9 ± 8.3
		250	133.3 ± 18.8	169.1 ± 13.4	118.0 ± 9.3
		500	134.4 ± 16.0	167.3 ± 10.9	117.0 ± 8.1
		1,000	189.1 ± 10.8	158.1 ± 10.8	182.0 ± 6.2
Low	8	0	136.8 ± 11.2	226.1 ± 30.6	67.0 ± 19.0
		250	139.5 ± 12.3	177.3 ± 9.2	124.2 ± 11.5
		500	136.2 ± 22.6	180.0 ± 11.1	127.8 ± 10.2
		1,000	158.2 ± 27.7	176.5 ± 8.6	125.2 ± 8.0

[a] In subjects with varying degrees of renal metabolism of *N*-formimidoyl thienamycin when administered alone. The subjects received 500 or 1,000 mg of *N*-formimidoyl thienamycin at each dose. A high degree of metabolism of *N*-formimidoyl thienamycin indicates a UR of less than 16% of the dose, and a low degree of metabolism indicates a UR of more than 16%. All values are means ± standard deviations. Cl_{Cr}, Creatinine clearance; VCl_P, plasma clearance; VCl_R, renal clearance.

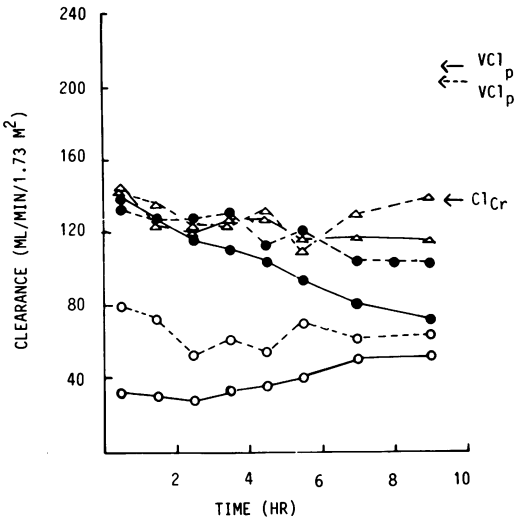

FIG. 4. Incremental renal clearance of *N*-formimidoyl thienamycin in subjects receiving 500 mg alone (○) or with 250 mg (●) or 500 mg (△) of dehydropeptidase inhibitor (MK-791). Values are the means for high metabolizers (<16% UR of *N*-formimidoyl thienamycin doses, solid lines) and low metabolizers (>16% UR of *N*-formimidoyl thienamycin doses, dashed lines). The mean plasma clearance (VCl_P) of *N*-formimidoyl thienamycin alone for the high (solid arrow) and the low (dashed arrow), as well as the mean, creatinine clearance (Cl_{Cr}) are indicated.

alone. The renal clearance of *N*-formimidoyl thienamycin increased to values slightly below the creatinine clearance when MK-791 was added. A further analysis of the incremental data demonstrated that the time during which the renal clearance approached the glomerular filtration rate varied with the dose of MK-791 and with the degree of metabolism of *N*-formimidoyl thienamycin. Both low and high metabolizers who received 500 mg of *N*-formimidoyl thienamycin maintained a high renal clearance of it for more than 8 h at an *N*-formimidoyl thienamycin/MK-791 ratio of 1:1 (Fig. 4). At a ratio of 1:0.5, that was the case only for the low metabolizers, whereas the high metabolizers showed a continuous decline from 5 h after the beginning of the administration. Similar results were obtained in the subjects receiving 1,000 mg of *N*-formimidoyl thienamycin. In all of the subjects, the renal clearances of *N*-formimidoyl thienamycin were considerably lower than the plasma clearances during the entire study period. When we studied the mean results, no effect could be demonstrated by an increase in the *N*-formimidoyl thienamycin/MK-791 ratio above 1:1. However, in the highest metabolizers, such effects were found, as exemplified by the data for a subject with a UR of 7.7% of the *N*-formimidoyl thienamycin dose (Fig. 5). The renal clearance during 8 to 10 h after administration was considerably higher at an *N*-formimidoyl thienamycin/MK-791 ratio of 1:2 than it was at 1:1 or 1:0.5.

Although increasing doses of MK-791 did not result in any obvious effects on the total UR of *N*-formimidoyl thienamycin, they did result in prolonged high levels of the antibiotic in the urine. The practical consequence of that is exemplified by Fig. 6, in which the urine concentrations have been recalculated according to a diuresis of 60 ml/h to eliminate the effects of the forced diuresis made necessary by the study design, which required frequent urine samples from the subjects. When we used this method for the calculation of urine concentrations, remarkably consistent results were obtained for each *N*-formimidoyl thienamycin/MK-791 ratio. The standard deviation was normally about 10% of the mean value and never exceeded 24%, with the exception of the 1:0 ratio when the interindividual variability affected the standard deviation. Rather marked differences in urine concentrations were obtained when the 1:0.25 ratio of *N*-formimidoyl thienamycin to MK-791 was compared with the 1:0.5, 1:1, and 1:2 ratios. Notably, higher mean urine concentrations were obtained with 500 mg of *N*-formimidoyl thienamycin plus 250 mg of MK-791 than with 1,000 mg of *N*-formimidoyl thienamycin alone.

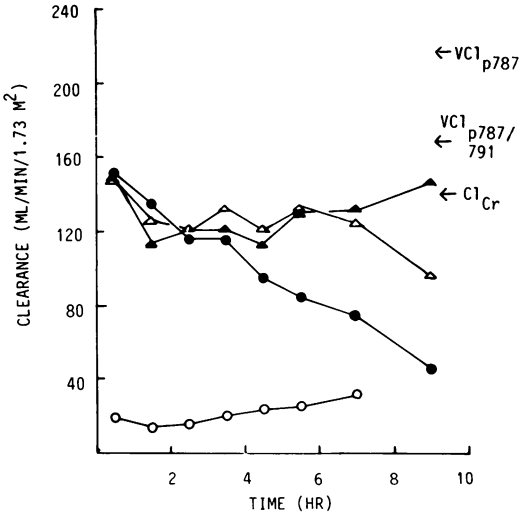

FIG. 5. Incremental renal clearance in a subject with 7.7% UR of *N*-formimidoyl thienamycin receiving 500 mg of *N*-formimidoyl thienamycin alone (○) or with 250 mg (●), 500 mg (△), or 1,000 mg (▲) of a dehydropeptidase inhibitor (MK-791). The arrows indicate the mean plasma clearance of *N*-formimidoyl thienamycin determined after the administration of *N*-formimidoyl thienamycin alone ($VCl_{P\text{-}787}$) or with MK-791 ($VCl_{P\text{-}787/791}$) and the mean creatinine clearance for the collection periods.

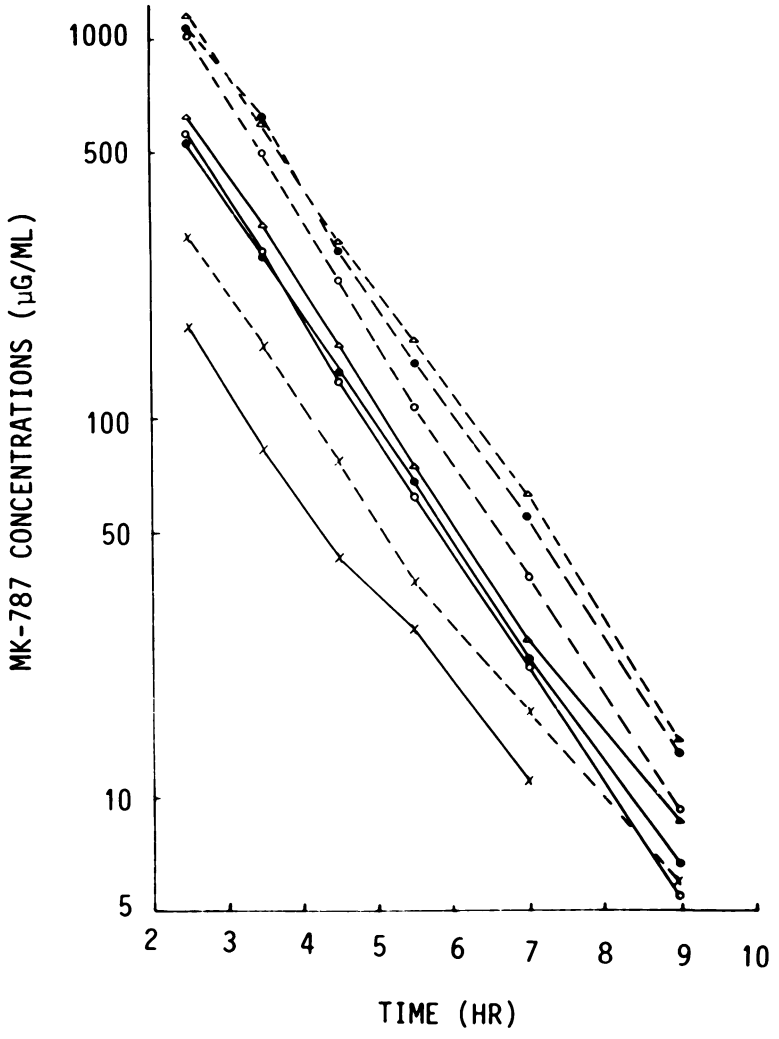

FIG. 6. Mean urine concentrations of *N*-formimidoyl thienamycin administered alone (×) or together with 250 mg (○), 500 mg (●), or 1,000 mg (△) of a dehydropeptidase inhibitor (MK-791). The solid lines indicate the results obtained with a 500-mg dose of *N*-formimidoyl thienamycin, and the dashed lines indicate the results obtained with 1,000 mg of *N*-formimidoyl thienamycin. The actual urine concentrations have been recalculated based on an assumed diuresis of 60 ml/h.

DISCUSSION

These and previous studies (3) show that the systemic disposition of *N*-formimidoyl thienamycin in healthy subjects is characterized by a half-life in plasma of about 1 h and by a volume of distribution in the central compartment of about 10 liters. This study, which included many volunteers, also confirmed the finding of extensive inter-subject variability and low intra-subject variation in the urinary excretion of *N*-formimidoyl thienamycin (3). It has previously been assumed that the low UR of *N*-formimidoyl thienamycin is caused by a dipeptidase, dehydropeptidase I, located at the brush border of the proximal tubular cells. Evidence in favor of this theory is the beneficial effect of each of two dehydropeptidase inhibitors, MK-789 and MK-791, on the UR of *N*-formimidoyl thienamycin. Both of these compounds increased the UR of *N*-formimidoyl thienamycin to above 50% of the dose administered. MK-789 was found to have pharmacokinetic characteristics different from those of *N*-formimidoyl thienamycin. The volume of distribution in the central compartment was 5 liters, which is explainable by the fact that the drug is lipid insoluble and highly bound to plasma proteins. Preliminary and unpublished data on MK-791 indicate that it has a low protein binding in plasma—about 25%—and that its

pharmacokinetics are almost identical to those of *N*-formimidoyl thienamycin (F. M. Kahan, Merck, Sharp & Dohme Research Laboratories, personal communication).

In relation to the total UR of *N*-formimidoyl thienamycin, the maximal inhibition of renal metabolism was achieved at an *N*-formimidoyl thienamycin/MK-791 dose ratio of 1:0.25, the lowest ratio tested. Increasing the ratio caused no further increase in the total UR. However, when incremental UR and renal clearance were analyzed, it became obvious that a prolonged inhibition of the metabolism of *N*-formimidoyl thienamycin was obtained with *N*-formimidoyl thienamycin/MK-791 ratios above 1:0.25. The optimal ratio between *N*-formimidoyl thienamycin and MK-791 for the maintained inhibition of renal metabolism during a dose interval of 8 to 10 h seems to be 1:1.

The renal handling of *N*-formimidoyl thienamycin seems to be a combination of glomerular filtration and tubular secretion, the latter mechanism being responsible for about 20% of the renal excretion. Our data indicate that the dehydropeptidase inhibitors act through the competitive exclusion of the secreted fraction of *N*-formimidoyl thienamycin at the tubular level, thus shifting renal excretion primarily to glomerular filtration. A support for that hypothesis is the finding that MK-791 increased the renal clearance of *N*-formimidoyl thienamycin to levels close to the creatinine clearance values determined in the subjects. In view of the fact that creatinine clearance gives an estimate of the glomerular filtration rate, which in a healthy subject is at least 10% too high (1), our results demonstrate that with the coadministration of *N*-formimidoyl thienamycin and MK-791, a renal clearance of *N*-formimidoyl thienamycin close to or identical to the glomerular filtration rate is achieved. The theory that the dehydropeptidase inhibitors have a probenecid-like effect on the renal handling of *N*-formimidoyl thienamycin was also supported by the increase in the plasma levels of the antibiotic when coadministered with an inhibitor. The fact that the plasma half-life of *N*-formimidoyl thienamycin did not increase remains unexplained, as does the fact that the dehydropeptidase inhibitors did not reduce the UR as was observed when probenecid was coadministered with *N*-formimidoyl thienamycin (3).

When we compared the renal and plasma clearances of *N*-formimidoyl thienamycin when coadministered with a dehydropeptidase inhibitor, it was obvious that the renal clearance was about 70% of the plasma clearance. Interestingly, the highest UR which could be achieved was about 72%. Thus, 20 to 25% of the *N*-formimidoyl thienamycin dose was unaccounted for in our studies, indicating that a mechanism exists for the elimination of the antibiotic independent of the kidneys or of metabolism by dehydropeptidase I or both.

As mentioned above, the maximal degree of the inhibition of the dehydropeptidase metabolism of *N*-formimidoyl thienamycin was achieved at an *N*-formimidoyl thienamycin/MK-791 ratio of 1:0.5 or higher when the total UR was considered. However, when we studied the various sampling periods after the administration of the combination, a dose response became apparent. MK-791 at a dose equal to that of *N*-formimidoyl thienamycin maintained maximum inhibitory capacity throughout the study period, i.e., 8 to 10 h, whereas the lower ratios had a considerably shorter duration of activity and higher ratios added no obvious further benefit.

Further studies on the pharmacokinetics of *N*-formimidoyl thienamycin must be performed and include trials in which it is combined not only with MK-791 but also with probenecid to elicit the renal handling of the antibiotic. Other studies required are those in patients with decreased renal function and those in which radioisotope-labeled *N*-formimidoyl thienamycin is used.

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