Pharmacology of a New 1-Oxa- β -lactam (LY127935) in Normal Volunteers

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The pharmacokinetics of 1-oxa- β -lactam (LY127935), a new semisynthetic β -lactam antibiotic, was studied in four healthy adult volunteers (mean age of 27 years, mean body surface area $\pm$ standard error [SE] of 1.87 ± 0.08 m², and mean creatinine clearance $\pm$ SE of 116 ± 12 ml/min per 1.73 m²). Immediately after completion of a 1-g, 20-min intravenous (i.v.) infusion, the mean serum level $\pm$ SE was 70.7 ± 8.5 μ g/ml. After a 1-g intramuscular (i.m.) injection, peak serum levels occurred from 30 min to 1 h, and the mean peak serum level $\pm$ SE was 52.3 ± 1.6 μ g/ml. Beginning at 1 h, the serum concentrations after i.m. administration were higher than those after i.v. administration. At 8 h, the mean serum level $\pm$ SE was 3.8 ± 0.6 μ g/ml after completion of the i.v. infusion and 4.8 ± 0.7 μ g/ml after the i.m. injection. The mean serum half-lives for the β phase i.v. and i.m. administration were similar (2.3 ± 0.7 h and 2.4 ± 0.2 h, respectively). The mean apparent volume of distribution $\pm$ SE was 16.6 ± 1.9 liters per 1.73 m². The mean serum clearance $\pm$ SE of LY127935 was 85.4 ± 12.7 ml/min per 1.73 m², and the mean renal clearance $\pm$ SE was 54.5 ± 4.4 ml/min per 1.73 m². Urine concentrations of LY127935 were at least 140 μ g/ml in each volunteer during the first 12 h after i.m. or i.v. administration. The mean percentages of the dose recovered in the urine $\pm$ SE within 2 h after i.v. or i.m. administration were similar (30 ± 4 and 34 ± 11 , respectively). Only $67 \pm 3\%$ and $75 \pm 13\%$ were recovered in the urine within 24 h after i.v. and i.m. administration, respectively.

1-Oxa- β -lactam (LY127935) (6059-S) is a new semisynthetic β -lactam antibiotic in which sulfur is in place of oxygen in the six-membered ring of the conventional cephem nucleus (1-oxadethiacephalosporin). In addition, LY127935 has a 7amethoxy group on the altered cephem nucleus (Fig. 1). The in vitro activity is superior to that of cephalosporins and penicillins. LY127935 inhibits most *Enterobacteriaceae* in concentrations of <1 μ g/ml, *Bacteroides fragilis* and *Staphylococcus aureus* in concentrations of ≤ 6.3 μ g/ml, and *Pseudomonas aeruginosa* in concentrations of ≤ 12.5 μ g/ml (Parsons and Levison, unpublished data; T. Yoshida, M. Narisada, S. Matsuura, W. Nagata, and S. Kuwahara, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 18th, Atlanta, Ga., abstr. no. 151, 1978). The purpose of this study was to define the pharmacokinetics of LY127935 after intravenous (i.v.) and intramuscular (i.m.) administration in healthy adult volunteers.

MATERIALS AND METHODS

Four healthy adult male volunteers (average age of 27 years, range 23 to 32, average body surface area $\pm$ standard error (SE) of 1.87 ± 0.08 m², and mean creatinine clearance $\pm$ SE of 116 ± 12 ml/min per 1.73 m²) were studied. Each received a 20-min i.v. infusion of 1 g of LY127935 diluted in 50 ml of 5% dextrose in

water. Specimens of blood were drawn from the opposite arm at 20 (end of i.v. infusion), 25, 35, 50, 65, and 80 min and then at hourly intervals for another 11 h. Urine was collected from 0 to 2, 2 to 6, and 6 to 24 h.

One gram of LY127935 was injected intragluteally in the same four volunteers 48 h later. Blood was collected at 30, 45, and 60 min and then hourly for another 11 h. Urine was collected from 0 to 2, 2 to 6, and 6 to 24 h.

Concentrations of LY127935 were determined by an agar-diffusion method by using paper disks (7). A strain of *Escherichia coli* (5) was the indicator organism. Standards of LY127935 in serum for assay of serum samples and in Mueller-Hinton broth for assay of urine samples were prepared on the same day and stored at -70°C along with the unknown samples until assayed. The assay was done within 1 week of collection. The serum samples which had been collected 20 min to 4 h after dosing were diluted with normal human serum, and urine samples were diluted with Mueller-Hinton broth to an approximate concentration of 10 μ g/ml for assay. Each specimen was assayed in quadruplicate.

The semilogarithmic plot of the serum concentrations of LY127935 versus time after i.v. infusion conformed to a biexponential curve with an initial α (distribution) phase and a subsequent β (elimination) phase.

The serum half-life for the α phase ($T_{1/2\alpha}$) was defined as $T_{1/2\alpha} = \ln 2/\text{slope of } \alpha$, and the serum half-life for the β phase ($T_{1/2\beta}$) was $T_{1/2\beta} = \ln 2/\text{slope of } \beta$.

FIG. 1. Schematic diagram of the structure of LY127935.

The slope of the α phase (α) was determined from the five serum levels at 20, 25, 35, 50, and 65 min after i.v. infusion by the method of least squares, and the slope of the β phase (β) was determined from eight serum level determinations beginning 1.3 h after i.v. infusion or 1 h after i.m. injection. The area under the serum level curve (AUC) after the 20-min i.v. infusion was determined by Simpson's rule (1). The serum clearance (C_s) in milliliters per minute per 1.73 m² was calculated from the formula (3)

$$C_s = \frac{\text{Dose}}{\text{AUC} \times 60} \times \frac{1.73}{\text{BSA}}$$

where the dose is in micrograms and BSA is the body surface area. The renal clearance (C_r) in milliliters per minute per 1.73 m² was determined 2 to 6 h after i.v. infusion from the formula

$$C_r = \frac{U \times V}{C} \times \frac{1.73}{\text{BSA}}$$

where U is the LY127935 concentration in the urine (in micrograms per milliliter), V is the timed urine volume (in milliliters per minute), and C is the LY127935 serum concentration (in micrograms per milliliter). The apparent volume of distribution (AVD) in liters per 1.73 m² was calculated from the formula (3)

$$\text{AVD} = \frac{\text{Dose}}{\beta \times \text{AUC} \times 1,000} \times \frac{1.73}{\text{BSA}}$$

RESULTS

The mean serum concentrations $\pm$ SE of LY127935 after a 1-g, 20-min i.v. infusion are shown in Fig. 2 and after a 1-g i.m. injection in Fig. 3. The mean serum level $\pm$ SE immediately after the i.v. infusion was 70.7 $\pm$ 8.5 μ g/ml. After the 1-g i.m. injection, peak serum levels occurred from 30 min to 1 h, and the mean peak serum level $\pm$ SE was 52.3 $\pm$ 1.6 μ g/ml. Beginning at 1 h, the serum concentrations after i.m. administration were higher than those after i.v. administration. At 8 h, the mean serum level $\pm$ SE was 3.8 $\pm$ 0.6 μ g/ml after completion of the i.v. infusion and 4.8 $\pm$ 0.7 μ g/ml after the i.m. injection. The mean $T_{1/2\alpha}$ $\pm$ SE was 0.9 $\pm$ 0.1 h after i.v. administration. The mean $T_{1/2\beta}$ after i.v. and i.m. administration were similar, 2.3 $\pm$ 0.7 h and 2.4 $\pm$ 0.2 h, respectively. The mean apparent volume of distribution $\pm$ SE was 16.6 $\pm$ 1.9 liters per 1.73 m². The mean serum clearance $\pm$ SE of LY127935 was 85.4 $\pm$ 12.7 ml/min per 1.73 m², and the mean renal clearance $\pm$ SE was 54.5 $\pm$

FIG. 2. Average serum concentrations $\pm$ SE of LY127935 in four volunteers beginning immediately after a 1-g i.v. infusion given in 20 min.

FIG. 3. Average serum levels of LY127935 in four volunteers after 1-g i.m. injections.

4.4 ml/min per 1.73 m². Urine concentrations of LY127935 were at least 140 μ g/ml in each volunteer during the first 12 h after i.m. or i.v. administration. The mean percentage of the dose recovered in the urine $\pm$ SE (30 $\pm$ 4) within 2 h after i.v. administration was similar to that recovered (34 $\pm$ 11) within 2 h after i.m. administration. Only 53 $\pm$ 2% and 57 $\pm$ 14% were recovered within 6 h, and 67 $\pm$ 3% and 75 $\pm$ 13% were recovered within 24 h after i.v. and i.m. administration, respectively.

DISCUSSION

These results indicate that LY127935 has a pharmacological effect which in many respects

TABLE 1. Comparative pharmacokinetics of LY127935, cephalothin, cefamandole, and cefazolin

Variable	LY127935	Cephalothin	Cefamandole	Cefazolin
Peak serum concn ($\mu\text{g/ml}$)				
1 g i.v. ^a	70.7 $\pm$ 8.5 ^b	70	85	140
1 g i.m.	52.3 $\pm$ 1.6	20	20	59
Serum clearance (ml/min per 1.73 m ²)	85.4 $\pm$ 12.7	470	250	65
Renal clearance (ml/min per 1.73 m ²)	54.5 $\pm$ 4.4	275	250	65
Serum T _{1/2} β (h)	2.3 $\pm$ 0.7	0.6	0.9	1.9
AVD ^a (liters per 1.73 m ²)	16.6 $\pm$ 1.9	18	16	10
Renal excretion (% dose)				
0 to 2 h	32	68	66	50
0 to 24 h	71	66	80	95

^a Twenty- to 30-min i.v. infusion.^b Mean $\pm$ SE.

is similar to that of cefazolin (Table 1). The low renal clearance of LY127935 is similar to that reported for cefazolin (4, 6) and lower than that reported for cephalothin or cefamandole (2, 6). The renal clearance of LY127935 is similar to the serum clearance of LY127935, and approximately 70% of the dose is excreted in the urine in 24 h, suggesting that the kidney is the major route of elimination. The relatively low clearances probably account for the low urinary recovery of LY127935 within 2 h after dosing (about 30%) in comparison to that reported for either cephalothin or cefamandole (about 68%) and cefazolin (50%). The high 2-h urinary recovery for cefazolin (50%) compared to that of LY127935 (30%) can be explained by the higher serum levels of cefazolin since urinary recovery equals serum levels (*C*) times the renal clearance (*C_r*).

The prolonged T_{1/2} β of LY127935, which is slightly longer than that of cefazolin (2.3 h versus 1.9 h, respectively), is also possibly due to its low serum and renal clearances. LY127935 has an AVD (16.6 liters per 1.73 m²) larger than that of cefazolin (10 liters per 1.73 m²), which may be responsible in part for the lower peak serum levels of LY127935 after i.v. infusion. The differences in serum protein binding between LY127935, which is reported to be about 50% (personal communication, Robert Kammer, Eli Lilly & Co.), and cefazolin, which is 85%, may account in part for the larger apparent volume of distribution of LY127935. The peak serum concentration of LY127935 after i.v. administration was similar to that of cephalothin or cefamandole, each with similar volumes of distribution (2, 6). The peak serum level of LY127935 after i.m. administration was greater than peak serum levels reported after i.m. administration of cephalothin or cefamandole but was similar to that of cefazolin (Table 1).

The long T_{1/2} β , the high peak serum levels, and the reported low serum protein binding

combine to give LY127935 a prolonged duration of effective concentrations in serum, even against bacteria with a relatively high minimal inhibitory concentration, e.g., *P. aeruginosa*. Studies of clinical efficacy, however, are necessary for conclusive assessment.

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ADDENDUM

Compound LY127935 is described in this issue as an oxa- β -lactam. In past issues it was called 1-oxacephalosporin. The name cephem was proposed in 1962 (J. Am. Chem. Soc. 84: 3401) as a generic designation for the fused β -lactam dihydrothiazine ring system found in the cephalosporins. This system has been generally accepted. The oxa- β -lactam compound LY127935 has a β -lactam dihydrooxazine ring system and thus cannot qualify as a cephem or cephalosporin by definition. To avoid confusion, the nonspecific term oxa- β -lactam is used, pending approval of a generic name.

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