

## Pharmacokinetics of Azlocillin in Subjects with Normal and Impaired Renal Function

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The pharmacokinetics of azlocillin were investigated in five healthy subjects and in 16 subjects with chronic renal failure. After intravenous bolus injection of a single dose of 30 mg/kg in normal subjects, pharmacokinetic data were calculated, using a two-compartment open body model. The mean distribution serum half-life ( $T_{1/2\alpha}$ ) was 0.11 h, and the mean elimination serum half-life ( $T_{1/2\beta}$ ) was 0.89 h. The volume of the central compartment ( $V_C$ ) was 7.36 liters/1.73 m<sup>2</sup>, and the apparent volume of distribution ( $V_{\text{dis}}$ ) was 14.15 liters/1.73 m<sup>2</sup>, i.e., 21.9% of body weight. The  $T_{1/2\beta}$  after a 30-min intravenous infusion of 80 mg/kg to the same healthy subjects was 1.11 h. Serum clearances ( $C_S$ ) for the 30- and 80-mg/kg doses were 215.0 and 152.9 ml/min per 1.73 m<sup>2</sup>. The mean renal clearances ( $C_R$ ) were 145.2 and 94.1 ml/min per 1.73 m<sup>2</sup> for the respective doses. Between 61.8 and 69.6% of the injected dose was recovered in urine during the first 24 h. The elimination half-life in subjects with chronic renal impairment increased with the degree of renal insufficiency. After a 30-min intravenous infusion of 80 mg/kg the  $T_{1/2\beta}$  values were 2.03, 4.01, and 5.66 h with creatinine clearances ( $C_{\text{cr}}$ ) within 30 to 50, 10 to 30, and <10 ml/min per 1.73 m<sup>2</sup>, respectively. Urinary elimination was inversely related to the degree of renal impairment. In four patients out of and on a 6-h hemodialysis session mean elimination half-life values were 6.53 and 2.81 h, respectively. The fraction of drug removed by dialysis was 45.8%. The linear relationships between the elimination of half-life ( $T_{1/2\beta}$ ) and serum creatinine and the elimination rate constant ( $\beta$ ) and creatinine clearance ( $C_{\text{cr}}$ ) provided a basis for adjustment of dosage in renal failure.

Azlocillin, a parenteral semisynthetic penicillin, one of a group of acylureidopenicillins, has a broad spectrum of activity covering non- $\beta$ -lactamase-producing cocci and gram-negative bacilli such as *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Proteus*, *Serratia*, and *Bacteroides fragilis*. Azlocillin is particularly effective against *Pseudomonas* spp., being four- to eightfold more active than carbenicillin in vitro against *Pseudomonas aeruginosa* and retaining activity against strains resistant to carbenicillin and gentamicin (9, 14). The purpose of this study was to define the pharmacokinetic properties of azlocillin in subjects with normal function and in patients with varying degrees of chronic renal insufficiency.

### MATERIALS AND METHODS

**Subjects.** Twenty-one subjects were selected for study after informed consent was obtained; 5 had normal renal function and 16 had chronic renal impairment of various etiologies.

(i) **Subjects with normal renal function.** After an overnight fast, five subjects without renal, hepatic, or hematological diseases, ranging in age from 22 to 28 years (mean, 23.6  $\pm$  2.6 years) and in weight from 59

to 83 kg (mean, 68.2  $\pm$  10.6 kg), were given a single i.v. dose of 30 mg/kg as a bolus injection (3 min). After 1 week, they received a 30-min infusion of 80 mg/kg. Blood samples were obtained 0, 1, 2, 5, 10, 15, 20, 30, 45, and 60 min and 1.5, 2, 3, 4, 6, and 8 h after the bolus injection and 0, 0.25, 0.50, 0.58, 0.75, 0.83, 1, 1.5, 2, 3, 4, 6, and 8 h during and after i.v. infusion. Urine samples were collected 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h after dosage.

(ii) **Subjects with chronic renal insufficiency.** Sixteen patients with chronic renal failure, 18 to 74 years of age and weighing 56.5 to 90.4 kg, were given a single i.v. infusion of 80 mg of azlocillin per kg over 30 min. Four of these patients, requiring hemodialysis, were studied out of and on a 6-h hemodialysis session. Renal function data for these and all other subjects are listed in Table 1.

Blood specimens were taken at 0, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, and 24 h after infusion from subjects with creatinine clearance ( $C_{\text{cr}}$ ) of between 30 and 50 ml/min per 1.73 m<sup>2</sup>. Further samples (36 and 48 h) were drawn according to the severity of renal insufficiency. Urine samples were collected 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, and 36 to 48 h after dosage. The four subjects requiring hemodialysis received a single 30-min i.v. infusion of 80 mg/kg just before the beginning of dialysis. Blood samples were taken at 0 (end of perfusion, beginning of dialysis), 0.5, and 1 h and at

TABLE 1. Pharmacokinetic data on normal subjects (1 through 5) and uremic patients (6 through 21) after 30-min i.v. infusion of 80 mg of azlocillin per kg of body weight<sup>a</sup>

Subject no.	Creatinine				Azlocillin						
	Clearance <sup>b</sup> (ml/min per 1.73 m <sup>2</sup> )	Serum (mg/100 ml)	Maximum serum level (μg/ml)	T <sub>1/2β</sub> (h)	$\beta$ (h <sup>-1</sup> ) = ln <sup>2</sup> /T <sub>1/2β</sub>	V <sub>d,area</sub> (liters/kg)	AUC (μg/ml·h)	C <sub>s</sub> (ml/min per 1.73 m <sup>2</sup> )	% Excreted in urine (0-24 h)	C <sub>r</sub> <sup>b</sup> (ml/min per 1.73 m <sup>2</sup> )	
1	142.8	0.85	335	0.89	0.78	0.20	503	174.5	47.5	76.1	
2	132.3	0.79	460	1.19	0.58	0.17	801	101.1	68.8	96.4	
3	125.6	1.02	500	1.23	0.56	0.30	479	170.6	52.3	85.0	
4	124.9	0.90	415	1.27	0.55	0.25	586	161.8	57.6	88.9	
5	115.8	1.13	335	0.96	0.72	0.22	513	156.7	83.0	125.0	
6	52.2	1.41	265	2.08	0.33	0.27	898	90.2	57.4	52.5	
7	47.0	2.60	240	2.89	0.24	0.31	1,083	97.7	31.0	33.2	
8	46.2	5.20	355	1.43	0.49	0.25	658	122.2	33.8	39.4	
9	36.5	1.70	380	1.72	0.40	0.21	941	97.1	35.4	33.2	
10	22.6	3.16	380	4.24	0.16	0.27	1,803	46.3	37.4	17.6	
11	22.5	4.29	280	4.86	0.14	0.27	2,117	40.6	26.3	11.8	
12	13.8	5.42	395	3.29	0.21	0.28	1,370	68.2	12.0	7.8	
13	13.2	4.75	260	3.65	0.19	0.47	901	96.2	7.3	6.7	
14	6.6	19.44	395	5.74	0.12	0.31	2,149	40.3	20.3	8.7	
15	5.4	11.19	460	5.61	0.12	0.20	3,301	30.3	13.9	4.8	
16	5.0	11.30	335	5.60	0.12	0.27	2,426	38.3	6.1	2.7	
17	4.3	14.13	235	5.67	0.12	0.59	1,119	74.4	4.0	4.0	
18	0		500	4.71	0.15	0.33	1,625	51.7			
19	0		365	7.41	0.09	0.29	2,944	29.0			
20	0		250	8.38	0.08	0.37	2,599	33.4			
21	0		500	5.61	0.13	0.30	2,167	34.6			

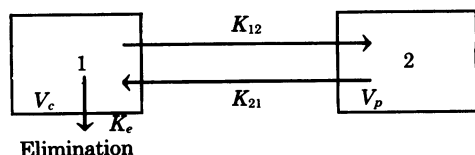
<sup>a</sup>AUC, area under the curve. See text for explanations of kinetic parameters.  
<sup>b</sup>C<sub>r</sub> and C<sub>s</sub> were calculated during the same time intervals of the study.

each hour thereafter throughout the hemodialysis session. Gambro multilayered dialyzers (1-m square) with a single-pass system were used. Blood flow was 200 to 250 ml/min, and dialysate flow was held constant at 800 ml/min.

**Antibiotic assay.** Serum and urine concentrations of azlocillin were determined by the agar diffusion method, using *Bacillus subtilis* ATCC 6633 as the test strain (3, 5). Assays were performed in triplicate. For all concentrations within the measured range (50 to 0.39  $\mu\text{g/ml}$ ), the 95% confidence limits did not exceed  $\pm 6\%$  of the determined values.

**Creatinine measurements.** Creatinine concentrations in urine and serum were measured by the colorimetric method of Jaffe (2).

**Pharmacokinetic analysis.** After i.v. bolus injection of 30 mg/kg in healthy subjects, the data were fitted to two regression lines (Fig. 1). Pharmacokinetic parameters were calculated by using a two-compartment open body model (10):



The following parameters were calculated: half-lives of the distribution phase ( $T_{1/2\alpha}$ ) and the elimination

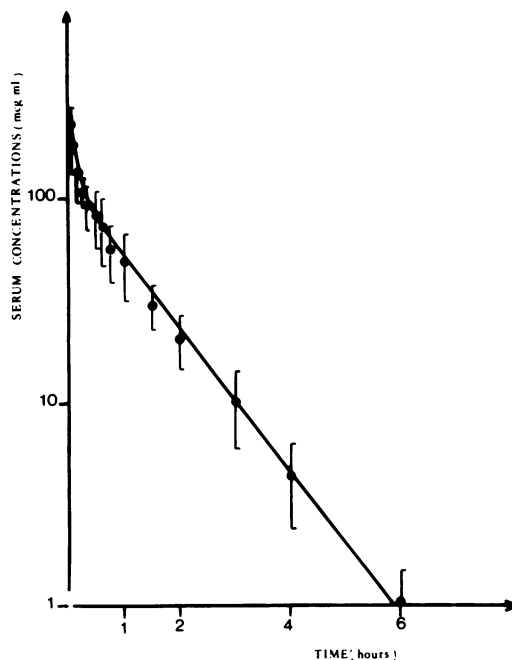


FIG. 1. Concentrations of azlocillin in serum of healthy subjects after bolus injection (3 min) of 30 mg/kg i.v.

phase ( $T_{1/2\beta}$ ) first-order rate constants ( $K_{12}$  and  $K_{21}$ ); overall elimination rate constant ( $K_e$ ); volume of the central ( $V_C$ ) and the peripheral ( $V_p$ ) compartments; apparent volume of distribution ( $V_{\text{diss}}$ ); and serum and renal clearances ( $C_S$  and  $C_R$ ). The elimination phase was measured after a 30-min i.v. infusion of 80 mg/kg using a one-compartment open body model. Programs written for a Hewlett-Packard (HP65) digital calculator were used to analyze these pharmacokinetic parameters.

## RESULTS

**Subjects with normal renal function.** In subjects with normal renal function, mean peak serum concentrations were  $263 \pm 61.7 \mu\text{g/ml}$  after i.v. bolus injection of a 30-mg/kg dose. Serum levels decreased rapidly and were not detectable at 8 h (Fig. 1). The mean  $T_{1/2\beta}$  was  $0.89 \pm 0.08$  h and the rate constant ( $\beta$ ) was  $0.78 \pm 0.06 \text{ h}^{-1}$ . The  $T_{1/2\alpha}$  was  $0.11 \pm 0.06$  h and the rate constant ( $\alpha$ ) was  $8.46 \pm 5.84 \text{ h}^{-1}$ .  $K_{12}$ ,  $K_{21}$ , and  $K_e$  were 3.79, 3.71, and  $1.75 \text{ h}^{-1}$ , respectively. The value of the ratio  $K_e/K_{12}$ ,  $0.78 \pm 0.53$ , indicated that compartment 2 ( $V_p$ ) is a shallow distribution compartment. The  $V_C$  was  $7.4 \pm 1.8$  liters/1.73  $\text{m}^2$ , i.e.,  $0.11 \pm 0.03$  liter/kg. The apparent volume of distribution ( $V_{\text{diss}}$ ) was  $14.2 \pm 4.2$  liters/1.73  $\text{m}^2$ , i.e.,  $0.22 \pm 0.06$  liter/kg. The mean area under the serum concentration-versus-time curve was  $157 \pm 38 \mu\text{g/ml} \cdot \text{h}$ .  $C_S$  and  $C_R$  were  $215.0 \pm 50.5$  and  $145.2 \pm 48.5$  ml/min per 1.73  $\text{m}^2$ , respectively. A total of  $69.6 \pm 12.5\%$  of the injected dose was recovered in urine during 24 h. In the same healthy subjects, serum concentrations were  $409 \pm 73.9 \mu\text{g/ml}$  at the end of the 30-min infusion of 80 mg/kg. The  $T_{1/2\beta}$  was  $1.11 \pm 0.17$  h. The mean apparent volume of distribution ( $V_{\text{d-area}}$ ) was  $14.6 \pm 3.3$  liters/1.73  $\text{m}^2$ , i.e.,  $0.23 \pm 0.05$  liter/kg, a value very similar to that found in the i.v. bolus injection study. The  $C_S$  was  $152.9 \pm 29.8$  and the  $C_R$  was  $94.1 \pm 18.6$  ml/min per 1.73  $\text{m}^2$ . A total of  $61.8 \pm 14.2\%$  of the dose was found in urine during the first 24 h. These results are presented in Table 1.

**Subjects with chronic renal insufficiency.** The pharmacokinetic data on uremic patients receiving a single 30-min infusion of 80 mg/kg are given in Table 1 and Fig. 2. The maximum serum concentrations in these patients, obtained at the end of infusion, were similar to those found at the same dose in subjects with normal renal function. The increase in  $T_{1/2\beta}$  from 0.89 h (subject 1) to 8.38 h (subject 20) was pronounced only in patients with  $C_{\text{cr}}$  below 15 ml/min per 1.73  $\text{m}^2$  (Fig. 3). Renal insufficiency did not significantly modify the apparent volume of distribution ( $V_{\text{d-area}}$ ) except for hemodialysis patients; however, the  $V_{\text{d-area}}$  in these patients was higher than that of normal subjects ( $P < 0.01$ ).  $C_S$  and  $C_R$  decreased in relation to the degree of

renal failure. The difference,  $C_S - C_R$ , i.e., extra-renal clearance, remained constant in normal and uremic patients ( $P < 0.50$ ) ( $\approx 50$  to  $60$  ml/min per  $1.73$  m<sup>2</sup>). The ratio  $C_R/C_{cr}$  was  $0.74 \pm 0.20$  in healthy subjects and  $0.92 \pm 0.32$  in patients with renal impairment and  $C_{cr}$  below  $5$  ml/min per  $1.73$  m<sup>2</sup> ( $P < 0.50$ ). Urinary elimination accounted for  $60$  to  $70\%$  of the dose in healthy subjects and  $4.0\%$  in a patient (no. 17) with a  $C_{cr}$  below  $5$  ml/min per  $1.73$  m<sup>2</sup>. However, antibiotic urinary concentrations remained effective in 24-h urines for patients with  $C_{cr}$  higher than  $10$  ml/min per  $1.73$  m<sup>2</sup>. In hemodialysis patients, the elimination half-life was  $6.53 \pm 1.67$  h out of dialysis and  $2.81 \pm 1.08$  h on dialysis. The fraction of drug removed during a 6-h hemodialysis session, determined according to the formula of Gwilt and Perrier (6), was  $45.8 \pm 14.4\%$ .

DISCUSSION

**Subjects with normal renal function.** Our pharmacokinetic data are quite similar to those

found by others (4, 11, 15). Results found for the two doses (30 and 80 mg/kg) show an increase in  $T_{1/2\beta}$  and a decrease in  $C_S$  and  $C_R$ , suggesting that azlocillin pharmacokinetics are dose dependent. The same phenomenon was found by Bergan (1) for mezlocillin. From 60 to 70% of the injected dose was recovered from urine during the first 24 h. The difference between serum and renal clearances suggests that azlocillin is eliminated by extrarenal processes, most likely by biliary excretion (13). After a single i.v. dose of 2 g ( $\approx 30$  mg/kg), the azlocillin  $T_{1/2\beta}$  lies in the same range as that of ampicillin (43.7 min) (7), but it is slightly shorter than that of carbenicillin (60 min) (8).

**Patients with chronic renal insufficiency.** In uremic patients, the  $T_{1/2\beta}$  increased with the degree of renal impairment, reaching 6.53 h in patients with chronic end-stage renal function. This increase is of moderate degree compared with the increase in half-life of carbenicillin. Our results are very similar to those found by Fiegel and Becker (4) after a single i.v. 2-g dose:  $47 \pm$

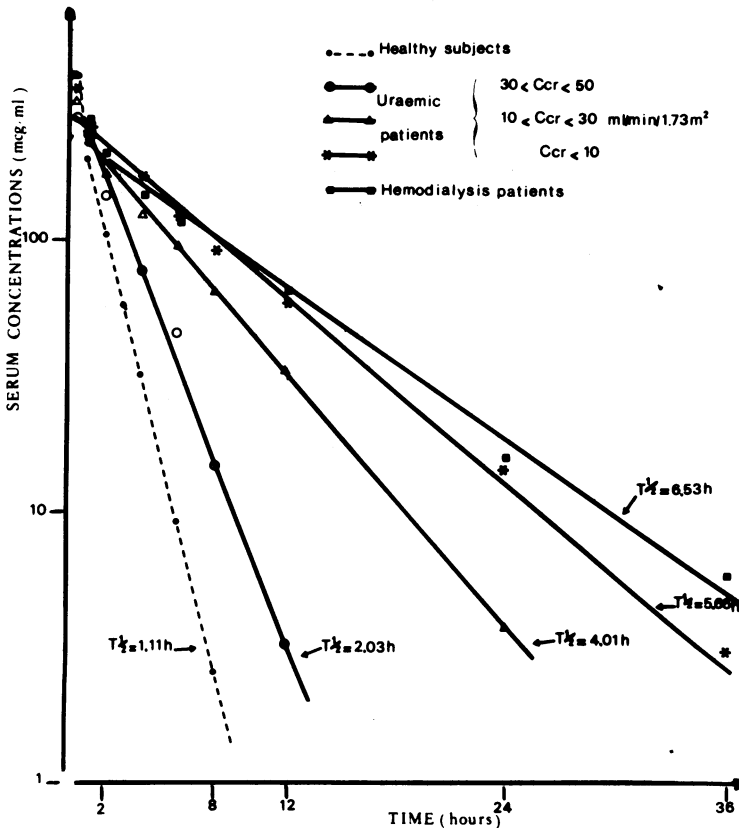


FIG. 2. Average serum levels of azlocillin in normal and uremic subjects after a 30-min i.v. infusion of 80 mg/kg.

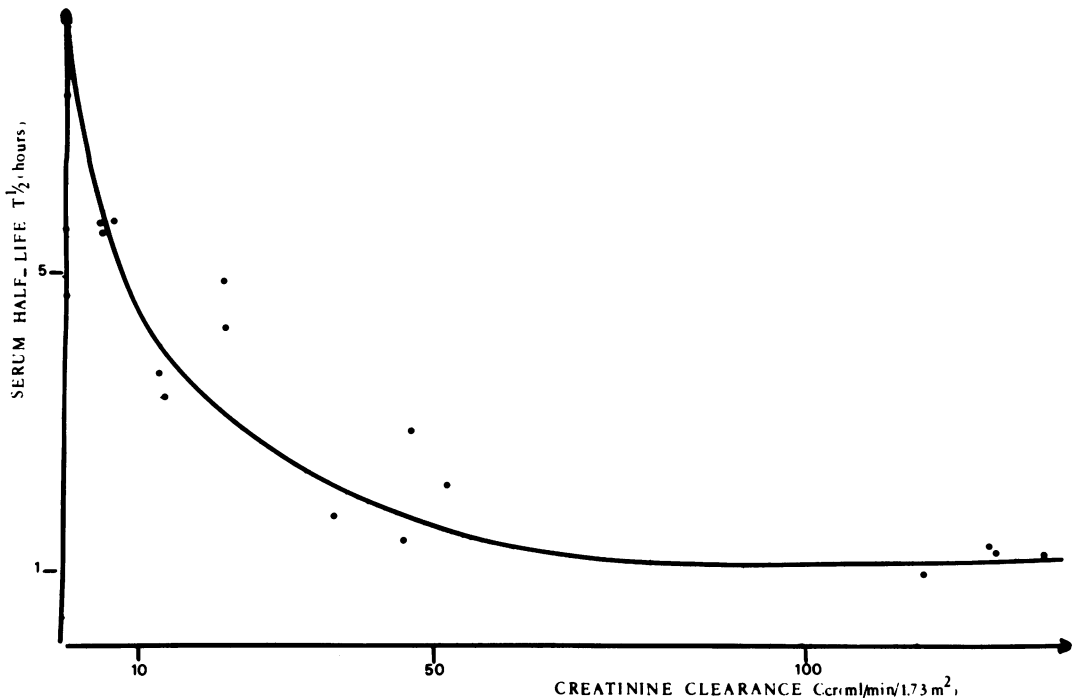


FIG. 3. Relationship between azlocillin elimination half-life ( $T_{1/2\beta}$ ) and creatinine clearance ( $C_{cr}$ ) in normal and uremic subjects.

8.8 min in normal subjects and 293.3 min in patients with severely impaired renal function. In our study, renal failure did not significantly change the apparent volume of distribution except for hemodialysis patients. The ratio  $C_R/C_{cr}$  was not statistically modified in uremic patients, and thus the capacity of renal excretion per nephron is not altered. The difference,  $C_S - C_R$ , remained constant in all our patients, indicating that extrarenal elimination did not change in uremic patients. By least-squares regression, linear relationships were found between pharmacokinetic data and biological parameters estimating glomerular filtration:  $T_{1/2\beta} = 0.29$  creatinine (milligrams per 100 ml) + 1.60 ( $n = 17$ ,  $r = 0.84$ ,  $P < 0.01$ );  $\beta = 0.004 C_{cr} + 0.12$  ( $n = 21$ ,  $r = 0.94$ ,  $P < 0.001$ ). The extrarenal elimination rate constant of azlocillin was found to be  $0.12 \text{ h}^{-1}$ , suggesting that azlocillin must be excreted by an extrarenal process. Based on these pharmacokinetic results, dosage schedules adapted to the degree of renal failure could be proposed. In subjects with normal renal function, an i.v. dose of 30 mg/kg ( $\approx 2 \text{ g}$ ) every 8 h seems to be sufficient in the treatment of urinary infections. For systemic infections, it is necessary to give a dose of 80 mg/kg i.v. every 8 h to maintain effective serum concentrations. In uremic pa-

tients whose  $C_{cr}$  remains higher than 30 ml/min per  $1.73 \text{ m}^2$ , a dose of 80 mg/kg i.v. can be administered every 8 h. In cases of severe renal impairment ( $C_{cr}$  within 10 to 30 ml/min), we suggest a dose of 80 mg/kg every 12 h. In patients with  $C_{cr}$  below 10 ml/min, we propose a loading dose of 80 mg/kg i.v. and a sustaining dose of 40 mg/kg i.v. every 12 h. In patients undergoing chronic hemodialysis, a dose of 80 mg/kg at the end of each extrarenal purification session and then a dose of 40 mg/kg every 12 h should be sufficient to maintain effective antibiotic serum concentrations between two sessions. The dosage schedules are approximate, and, especially in cases of very severe renal failure, azlocillin serum concentrations should be checked regularly to maintain effective and nontoxic serum levels.

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