ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 1986, p. 359–360
0066-4804/86/090359-02$02.00/0

Vol. 30, No. 3

Comparative Pharmacokinetics of Low- and High-Dose Ticarcillin

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Received 18 February 1986/Accepted 13 June 1986

Certain antipseudomonal penicillins, such as mezlocillin, exhibit a nonlinear pharmacokinetic disposition with increasing doses. We evaluated the effect of a single low dose (50 mg/kg) compared with a high dose (80 mg/kg) on the pharmacokinetics of ticarcillin in a crossover trial of eight healthy volunteers. No significant alteration in plasma clearance (130.1 ± 36.5 versus 120.5 ± 38.0 ml/min), nonrenal clearance (36.5 ± 8.4 versus 33.4 ± 18.5 ml/min), or volume of distribution at steady state (12.8 ± 3.5 versus 12.3 ± 4.5 liters) was observed between the low- and high-dose regimens, respectively. The elimination half-life remained unchanged between the two doses (67.9 ± 14.3 versus 68.0 ± 12.2 min). Unlike other newer antipseudomonal penicillins, ticarcillin did not display dose-dependent pharmacokinetic behavior with the range of doses used in the clinical setting.

Mezlocillin, azlocillin, and piperacillin have been found to display nonlinear pharmacokinetic behavior with increasing doses (1, 2). In these investigations, significant differences in plasma clearance and the dose-normalized area under the curve have been observed. Specifically, there appears to be a decrease in nonrenal clearance (2) associated with increasing doses of mezlocillin. Compared with mezlocillin, ticarcillin is excreted to a larger extent via the kidney, with renal clearance accounting for greater than 75% of total plasma clearance (3, 4). Other investigators have studied the pharmacokinetics of ticarcillin in healthy volunteers by using 3.0- and 5.0-g doses (4). When the serum concentrations were plotted against time in this previous study, there appeared to be a disproportionate increase in the calculated area under the curve with increasing doses (4). This nonlinear increase suggests that ticarcillin displays a dose-dependent pharmacokinetic behavior. As a consequence, we attempted to characterize the effect of a single 50-mg/kg dose compared with an 80-mg/kg dose on ticarcillin disposition in a randomized, crossover trial of healthy volunteers.

MATERIALS AND METHODS

Volunteers. Eight healthy test subjects (five females and three males) with no known allergies to penicillin or other beta-lactam derivatives participated in the study. Informed written consent was obtained from all volunteers. The study was approved by the Committee on Human Research at the University of California. None of the females was known to be pregnant, and none of the volunteers had taken any other antimicrobial agents, probenecid, aspirin, or other inhibitors of active tubular secretion during the 2 weeks preceding the study. No caffeine or alcohol was taken by any subject during the study period. The mean age of the subjects was 24 years (range, 22 to 26 years).

Dosage. After an overnight fast, the subjects were randomly administered either 50 or 80 mg of ticarcillin per kg. After a 1-week washout period, the subjects were crossed over to the second dose of ticarcillin. Ticarcillin was infused in a 5% glucose solution (50 ml) over 25 min with a constant-rate Harvard infusion pump via a peripheral vein access. After infusion, intravenous lines were flushed with normal saline to maximize delivery of the antibiotic.

Sampling. Blood samples for the assay of antibiotic concentration in plasma were drawn from a contralateral vein before drug administration and at 25, 45, 60, 75, 90, 120, 150, 180, 240, 300, 360, and 480 min after the start of the ticarcillin infusion. Samples were immediately placed in ice, centrifuged, and stored at −20°C until assayed. Urine samples were collected before administration and from 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 8, 8 to 12, and 12 to 24 h after administration. No detectable ticarcillin was observed in the blood and urine samples collected before drug administration.

Ticarcillin assay. Concentrations of ticarcillin in plasma and urine were determined by high-pressure liquid chromatography (G. La Follette, E. T. Lin, and J. G. Gambertoglio, Abstr. 133rd Annu. Meet. Am. Pharm. Assoc., in press). Reproducibility measurements yielded intra- and interday variability of less than 7.5%. The lowest concentrations

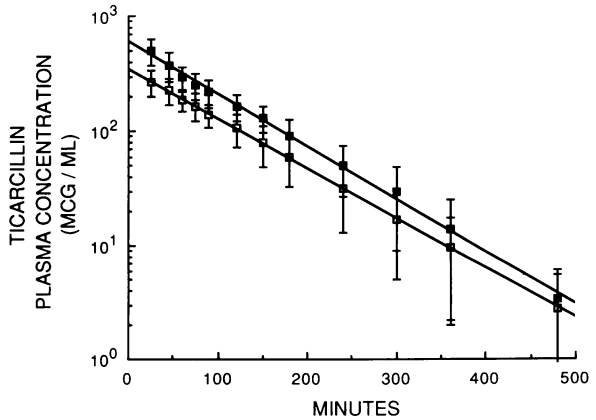

FIG. 1. Profile of plasma concentration versus time after single low dose (50 mg/kg; □) and high dose (80 mg/kg; ■) of ticarcillin administered intravenously to eight healthy subjects.

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TABLE 1. Mean pharmacokinetic parameters of a single low dose (50 mg/kg) and a high dose (80 mg/kg) of ticarcillin in eight healthy volunteers[a]

Dose (mg/kg)	CL_T (ml/min)	CL_R (ml/min)	CL_{NR} (ml/min)	k_{el} (min^{-1})	$t_{1/2}$ (min)	V_{ss} (liters)	V_{area} (liters)
50	130.1 ± 36.5	93.6 ± 38.1	36.5 ± 8.4	0.0106 ± 0.0022	67.9 ± 14.3	12.8 ± 3.5	12.5 ± 3.4
80	120.5 ± 38.0	87.1 ± 23.1	33.4 ± 18.5	0.0105 ± 0.0021	68.0 ± 12.2	12.3 ± 4.5	11.9 ± 5.0

[a] Abbreviations: CL_T, total body clearance; CL_R, renal clearance; CL_{NR}, nonrenal clearance; k_{el}, elimination rate constant; $t_{1/2}$, half-life; V_{ss}, volume of distribution at steady state; V_{area}, volume of distribution at equilibrium.

measurable in plasma and urine were 0.5 and 1.0 μg/ml, respectively.

Pharmacokinetic analysis. Plasma concentration-time profiles were fitted to a one-compartment open model with zero-order input. The curve fitting was used primarily for estimation of the terminal elimination rate constant (k_{el}) and half-life. The area under the plasma concentration-time curve (AUC) was calculated by the log-trapezoidal rule with extrapolation to infinity. Total body clearance was derived by dividing the ticarcillin dose by the AUC. The apparent volume of distribution at equilibrium (V_{area}) and the volume of distribution at steady state (V_{ss}) were calculated with the following equations: $V_{area} = \text{dose}/k_{el} \times \text{AUC}$ and $V_{ss} = [\text{dose} \times (\text{AUMC})/(\text{AUC})^2] - [t' (\text{dose})/2(\text{AUC})]$, where t' is the infusion time and AUMC is the area under the first moment curve measured with the log-trapezoidal rule. Renal clearance was determined by dividing the amount of ticarcillin excreted in the urine by the AUC for the given collection period.

RESULTS

The plasma-concentration-versus-time-profile of a single low dose (50 mg/kg) and a high dose (80 mg/kg) of ticarcillin in a representative subject (subject 1) is shown in Fig. 1. The pharmacokinetic parameters are shown in Table 1. The terminal half-lives were 67.9 ± 14.3 and 68.0 ± 12.2 min for the low and high dose, respectively. Mean total body clearance for the low dose was 130.1 ± 36.5 ml/min compared with 120.5 ± 38.0 ml/min for the high dose. Mean renal clearances of 93.6 ± 38.1 and 87.1 ± 23.1 ml/min were observed for the low and high dose, respectively. Mean nonrenal clearances were 36.5 ± 8.4 and 33.4 ± 18.5 ml/min. None of the differences in total body, renal, and nonrenal clearances were statistically significant ($P > 0.05$, Student's t test).

Low- and high-dose ticarcillin regimens had mean V_{ss} values of 12.8 ± 3.5 and 12.3 ± 4.5 liters, respectively. These values were not statistically different.

DISCUSSION

Contrary to the data of a previous investigation (4), no alteration in ticarcillin pharmacokinetic behavior was observed with the administration of a single low dose compared with a high dose. The reasons for the differences between the studies are not clear, but they may have been due to a variety of factors. The earlier study administered ticarcillin as a 5-min bolus in fixed 3.0- and 5.0-g doses. We infused ticarcillin over 25 min and randomly gave 50- and 80-mg/kg doses. The previous investigation used a microbiologic assay, whereas the present study used high-pressure liquid chromatography analysis.

Our observations are in contrast to those previously reported with mezlocillin and other newer penicillins (1, 2). As increasing doses of mezlocillin are administered, there is a dose-dependent decrease in plasma clearance.

Unlike other antipseudomonal penicillins clearances, ticarcillin clearance is unchanged with increasing doses. The significance of saturable antibiotic clearance on dosage design remains to be determined by future comparative clinical trials.

ACKNOWLEDGMENT

This study was supported in part by a grant from Beecham Laboratories.

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