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Pharmacokinetics of Ticarcillin and Clavulanic Acid (Timentin) in Relation to Renal Function

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The disposition of coadministered ticarcillin (3 g/1.73 m^2) and clavulanic acid (100 mg/1.73 m^2) was examined after a 30-min infusion in 24 noninfected subjects with various degrees of renal function. Noncompartmental pharmacokinetic parameters for the individual compounds were determined from plasma concentrations and urinary excretion rates. All clearances (total, renal, and nonrenal) and urinary recoveries of unchanged drug were found to be linearly related to creatinine clearance (CL_{CR}). The steady-state volume of distribution (9.9 and 12.9 liters for ticarcillin and clavulanic acid) approximated the extracellular fluid space and was not related to CL_{CR}. The half-lives increased with reduced renal function and ranged from 56 to 392 min for ticarcillin and 26 to 266 min for clavulanic acid. The clearances of both drugs decreased proportionately with reduction in renal function, facilitating dosing adjustments based on CL_{CR}. Calculations of expected steady-state maximum and minimum concentrations in plasma using constant doses and an extended dosing interval related to CL_{CR} further rationalized use of the 30:1 drug combination ratio for all patients.

Ticarcillin is a wide-spectrum penicillin which can be hydrolyzed by a number of beta-lactamases. Clavulanic acid is a potent inhibitor of these enzymes, and a synergistic effect is exhibited when the two agents are coadministered (5, 18, 20). A ticarcillin:clavulanic acid combination of 30:1 is used clinically, partly on the basis of pharmacokinetic matching in subjects with normal renal function (1).

Previous studies evaluated the pharmacokinetics of ticarcillin and clavulanic acid when administered separately (3, 4) or in combination (1, 2, 6) in subjects with normal renal function, but the disposition of the combination has not been assessed in relation to renal impairment. The purpose of this study was to evaluate the pharmacokinetics of ticarcillin-clavulanic acid in subjects with various degrees of renal impairment to evolve dosage guidelines and to determine whether the dosing ratio of 30:1 remains suitable in the presence of severe renal dysfunction.

MATERIALS AND METHODS

Subjects. A total of 24 adult subjects, aged 18 to 61 years, who gave informed written consent for the study were divided into four groups based on renal function (creatinine clearances [CL_{CR}], 10 to 30, 30 to 60, 60 to 80, and >100 ml min^{-1}). By chance, there were no subjects available with CL_{CR} between 80 and 100 ml min^{-1}. Individuals with a history of hypersensitivity to penicillins or cephalosporins, females with known or suspected pregnancy, and individuals on hemodialysis or peritoneal dialysis, with an infection, or with major cardiovascular or hepatobiliary dysfunction were excluded from the study. CL_{CR} for each subject was determined over 24 h within 7 days before the study. Complete blood counts and blood chemistries were also performed within 7 days before the start of the study and 10 days after the study. The subjects were also monitored for possible adverse effects throughout the study.

Drug administration. Ticarcillin-clavulanic acid (Timentin) was supplied by Beecham Pharmaceuticals (batch CT12846) as vials of 3 g of ticarcillin free acid as the disodium salt and 100 mg of clavulanic acid as the potassium salt. Each vial was reconstituted with 100 ml of sterile water for injection and used within 45 min. Each subject received a dose of 3.1 g/1.73 m^2 by intravenous infusion over 30 min.

Samples. Venous blood samples (3 to 5 ml) were drawn into lithium heparin tubes from the arm contralateral to that used for drug administration. Samples were taken before drug infusion and at 5, 10, 15, 20, 30, and 40 min and 1, 2, 3, 4, 6, 8, and 12 h after infusion from subjects with CL_{CR} of >60 ml min^{-1}. Additional samples were taken at 10, 24, and 36 h (excluding the 12-h sample) from subjects with CL_{CR} of <60 ml min^{-1}. The blood samples were centrifuged, and the plasma was separated within 30 min and frozen at −70°C until assayed.

Urine samples were obtained before drug infusion and at 0 to 2, 2 to 4, 4 to 8, and 8 to 12 h from subjects with CL_{CR} of >60 ml min^{-1}. Urine was also obtained at 8 to 24 and 24 to 36 h from subjects with CL_{CR} of <60 ml min^{-1}. Urine volumes were measured, and 10-ml samples were frozen at −70°C until assayed.

Assays. Similar to a previously published procedure (2), ticarcillin concentrations in plasma and urine were determined by microbiological assay by using *Pseudomonas aeruginosa* ATCC 29336 as the test organism. Standards were prepared in antibiotic-free serum or in pH 6.0 phosphate buffer (for urine) in concentrations ranging from 4 to 64 μg ml^{-1}. Samples with concentrations greater than 64 μg ml^{-1} were diluted with serum or buffer, as appropriate. The plates were incubated at 37°C for 18 to 20 h, and triplicate zone diameters were averaged. Clavulanic acid concentrations were determined by an agar diffusion beta-lactamase inhibition method with *Klebsiella pneumoniae* ATCC 29665 as the test organism. Standard concentrations ranged from 0.156 to 2.5 μg ml^{-1}. The coefficients of variation for both compounds averaged less than 10% over the standard curve

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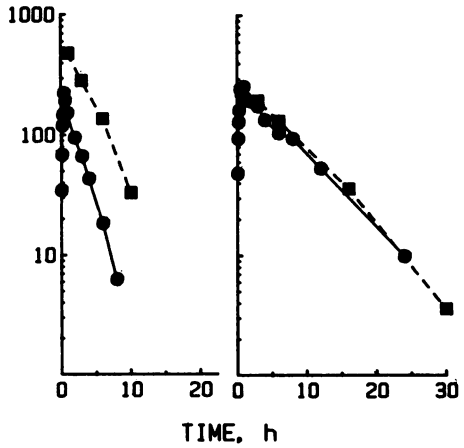

FIG. 1. Ticarcillin serum concentrations (● [mg liter^{-1}]) and urinary excretion rates (■ [mg h^{-1}]) in subject 11 (left; CL_{CR} = 146 ml min^{-1}) and subject 16 (right; CL_{CR} = 26 ml min^{-1}).

range. The use of two microorganisms provided specificity for each drug.

Pharmacokinetics. The disposition of ticarcillin and clavulanic acid was described using the basic noncompartmental pharmacokinetic parameters of total plasma clearance (CL = D/AUC), renal clearance (CL_R = A_u/AUC), nonrenal clearance (CL_{NR} = CL − CL_R), steady-state volume of distribution (V_{ss} = [(AUMC/AUC) − T/2]CL), and terminal-phase half-life ($t_{1/2}$ = ln 2/λ_z). The symbols include: D, dose; AUC, area under the plasma concentration-time curve; AUMC, area under the moment curve calculated as the area under the time multiplied by concentration versus time curve; A_u, amount of unchanged drug excreted in the urine; T, duration of infusion; and λ_z, slope of the terminal phase. The AUC and AUMC values were calculated by Lagrange polynomial interpolation and integration (17). Simultaneous nonlinear least-squares regression (12) of the terminal portion of the plasma-concentration-versus-time curve and the urinary-excretion-rate-versus-time curve was used to obtain λ_z. These values in turn were used to estimate residual AUC, AUMC, and A_u values from the last datum point to infinity.

Statistics. The relationships between the various clearances and the percent renally excreted versus CL_{CR} were examined by using the weighted perpendicular least-squares method for fitting data when both values are subject to error (16).

RESULTS

The ticarcillin-clavulanic acid combination was well tolerated by all 24 subjects in the study. No adverse effects or changes in the evaluated laboratory values attributable to the drug were reported.

Representative disposition profiles for ticarcillin and clavulanic acid serum concentration versus time and urinary excretion rates for a subject with normal renal function (subject 11) and a subject with severely impaired renal function (subject 16) are shown in Fig. 1 and 2. The plasma concentration (C_p) profiles displayed an upcurve owing to the infusion process and then declined in a mono- or biexponential manner. The profiles of amount of drug excreted in the urine over a time interval versus time usually paralleled the terminal portion of the plasma curve. However, the initial excretion rate point often did not fall on the line. A number of factors, namely that urine collection time intervals are not instantaneous, residual urine in the bladder after voiding may give an incomplete urine collection, and the time lag between when the drug is filtered and when it appears in the urine, can affect the accuracy of urinary excretion rate determinations. These factors, coupled with the fact that during the drug infusion there is simultaneous administration, distribution, and elimination of drug, can produce initial urinary excretion rate points which do not parallel the plasma curve. Thus, many of the first urinary excretion rate points could not be used in the datum fitting. In addition, as the degree of renal impairment increased, the urinary excretion rates decreased and the C_ps increased.

The AUC and terminal $t_{1/2}$ of both ticarcillin and clavulanic acid increased with decreasing CL_{CR}. The $t_{1/2}$ for ticarcillin ranged from 56 to 392 min in severe impairment, and the clavulanic acid $t_{1/2}$ ranged from 26 to 266 min. The V_{ss} was not affected by renal function (V_{ss} = 9.9 ± 2.8 and 12.9 ± 4.1 liters for ticarcillin and clavulanic acid). The CL decreased in proportion to decreasing CL_{CR} (Fig. 3 and 4) with good linear correlations (r = 0.77 and 0.68 for ticarcillin and clavulanic acid). The CL_R, CL_{NR}, and percentage of dose renally excreted as unchanged drug also exhibited a similar linear proportionality to CL_{CR} (Fig. 3, 4, and 5). Subjects with normal CL_{CR} (>100 ml min^{-1}) exhibited more variation in CLs than did subjects with lower CL_{CR}.

DISCUSSION

This study examined the disposition of intravenously coadministered ticarcillin and clavulanic acid with respect to renal function. Because of a lack of sufficient datum points in the distribution phase after infusion, the variability in the number of well-defined exponential phases in the C_p versus time curve, and a few cases of the excretion rate not closely paralleling the C_p decline, pharmacokinetic datum analysis by noncompartmental methods was chosen over more traditional compartmental calculations.

In subjects with normal renal function, clavulanic acid is about 40% renally eliminated, suggesting an important CL_{NR} component (3). The unbound fraction (f_u) of clavulanic acid in serum has been reported to be 0.78 (7). Considering that probenecid has no effect on the CL_R of clavulanic acid (Med. Lett. 27:69–70, 1985) and that CL_{CR} approximates CL_R/f_u, active tubular secretion does not appear to be an important excretion mechanism. However ticarcillin (f_u = 0.35 [9]) is approximately 80% renally excreted with some metabolic

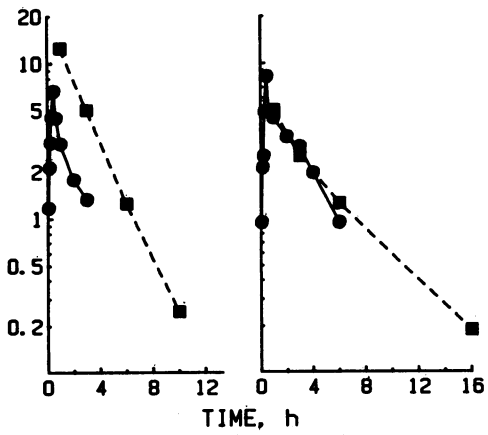

FIG. 2. Clavulanic acid serum concentrations (● [mg liter^{-1}]) and urinary excretion rates (■ [mg h^{-1}]) in subject 11 (left) and subject 16 (right).

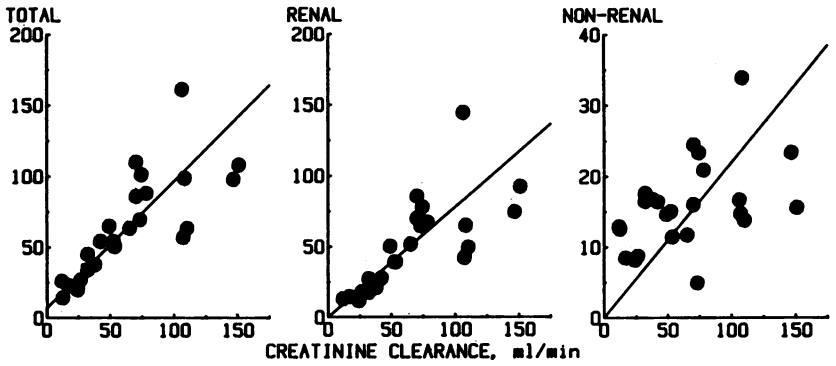

FIG. 3. Relationship between ticarcillin CL, CL_R, and CL_{NR} (ml min^{-1}) and CL_{CR}. Regression lines: $m = 0.90$, $b = 7.0$, $r = 0.77$; $m = 0.78$, $b = 0$, $r = 0.74$; and $m = 0.22$, $b = 0$, $r = 0.45$, respectively.

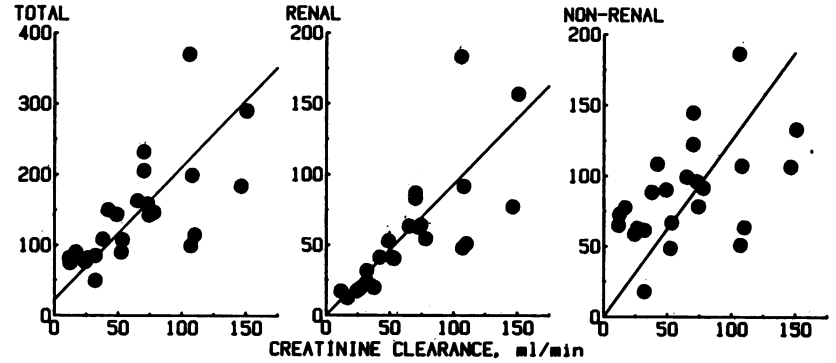

FIG. 4. Relationship between clavulanic acid CL, CL_R, and CL_{NR} (ml min^{-1}) and CL_{CR}. Regression lines: $m = 1.88$, $b = 22.2$, $r = 0.68$; $m = 0.93$, $b = 0$, $r = 0.75$; and $m = 1.25$, $b = 0$, $r = 0.49$, respectively.

conversion to its penicilloic acid (13). The facts that probenecid decreases CL_R of ticarcillin (4, 13) and $CL_R/f_u > CL_{CR}$ suggest that glomerular filtration and active tubular secretion are significant excretion mechanisms. As with most penicillins and cephalosporins, the V_{ss} for both drugs is relatively small, indicating that these drugs distribute primarily into the plasma and interstitial fluid.

Various pharmacokinetic parameters of ticarcillin and clavulanic acid determined in this study (Tables 1 and 2) were similar to values reported in subjects with normal or impaired renal function (1–3, 6, 14). When comparing ticarcillin and clavulanic acid administered alone and together, the pharmacokinetics of one compound does not appear to be significantly influenced by the presence of the other. Hoffken et al. (6) reported a somewhat reduced CL and CL_R for ticarcillin and CL_{NR} for clavulanic acid with coadministration as compared with single-compound dosage. However, these small changes are probably not clinically significant, considering the range of CL values reported in the literature.

The V_{ss} of both drugs was not altered in impaired renal function, but decreases in CL, CL_R, and the percentage of dose excreted unchanged in the urine were linearly related to CL_{CR}. Although the correlation was not as strong, there also was a tendency for CL_{NR} to be influenced by renal function. Similar observations have been reported for several antibiotics, including mezlocillin (10), aztreonam (8), cefotaxime (11), and amdinocillin (15). The reason for this is not known, but it may be the result of changes in hepatic or biliary function secondary to the presence of renal malfunction undetectable by typical nonspecific clinical evaluations of liver enzymes and blood chemistries.

The ratio of ticarcillin to clavulanic acid is important for the efficacy of the combination (1, 19). It is of considerable importance to note that similar decreases in CL for both drugs were observed in various degrees of renal impairment (Table 3). This nearly parallel decline in CL, with V_{ss} remaining relatively constant, suggests that the same ratio (3:0.1-g doses) of ticarcillin to clavulanic acid is appropriate regardless of renal function.

Dosage guidelines for ticarcillin-clavulanic acid in subjects with various degrees of renal function have been constructed

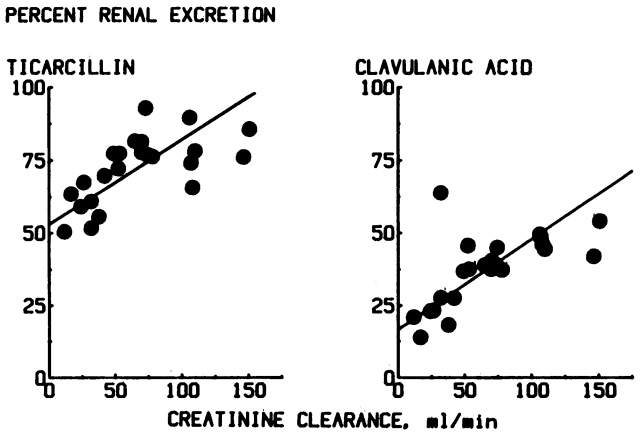

FIG. 5. Relationship between fraction of ticarcillin and clavulanic acid doses excreted in the urine and CL_{CR}. Regression lines: $m = 0.29$, $b = 52.8$, $r = 0.64$; and $m = 0.31$, $b = 16.6$, $r = 0.64$, respectively.

TABLE 1. Pharmacokinetic characteristics of ticarcillin[a]

Group (n)	CL_{CR} (ml min^{-1})	CL (ml min^{-1})	CL_R (ml min^{-1})	CL_{NR} (ml min^{-1})	V_{ss} (liters)	$t_{1/2}$ (min)	% Renally excreted
A (6)	121 (21)	97.8 (37.4)	78.2 (37.2)	19.7 (7.7)	9.7 (2.8)	79.3 (25.1)	78.2 (8.5)
B (6)	71.7 (4.4)	86.5 (17.9)	69.6 (11.6)	16.9 (7.6)	10.0 (1.8)	97.3 (26.1)	81.2 (6.2)
C (7)	42.6 (9.1)	48.8 (10.6)	33.3 (11.6)	12.5 (2.0)	9.5 (0.9)	143 (34)	66.4 (10.4)
D (5)	18.3 (6.7)	22.2 (5.2)	14.5 (2.8)	10.2 (2.3)	10.5 (5.4)	295 (68)	60.2 (7.3)

[a] Values are means (standard deviation).

TABLE 2. Pharmacokinetic characteristics of clavulanic acid[a]

Group (n)	CL_{CR} (ml min^{-1})	CL (ml min^{-1})	CL_R (ml min^{-1})	CL_{NR} (ml min^{-1})	V_{ss} (liters)	$t_{1/2}$ (min)	% Renally excreted
A (6)	121 (21)	210 (104)	102 (56)	108 (49)	13.0 (2.5)	56.7 (32.5)	47.5 (4.2)
B (6)	71.7 (4.4)	175 (36)	69.2 (13.0)	106 (24)	12.0 (3.1)	54.2 (17.4)	39.8 (2.8)
C (7)	42.6 (9.1)	105 (35)	35.9 (11.5)	68.9 (30.2)	11.3 (1.2)	91.2 (44.6)	36.8 (14.9)
D (5)	18.3 (6.7)	81.1 (6.1)	16.7 (2.8)	67.4 (7.7)	16.0 (7.6)	144 (71)	20.4 (4.4)

[a] Values are means (standard deviation).

(Table 4) based on providing equivalent ticarcillin AUC values and similar maximum C_p values and extending the dosing interval (τ) instead of decreasing the dose. These guidelines were determined by using the following relationships for ticarcillin and equations described previously (10).

(i) $CL = D/AUC = D/\bar{C} \cdot \tau$, where $\bar{C}$ is a time-averaged C_p which when multiplied by τ produces a given AUC value.

(ii) $CL = 0.9\ CL_{CR} + 7$ (as found in Fig. 3 for a 3-g dose of ticarcillin). With CL_{CR} in milliliters per minute and assuming a normal dosing interval of 3 g every 4 h, τ in hours can be determined by combining (i) and (ii), yielding:

(iii) $\tau = D/\bar{C}(0.9\ CL_{CR} + 7) = 388/(0.9\ CL_{CR} + 7)$.

An assessment of the reasonability of these dosage guidelines (Table 4) was done in the following manner. The first-dose maximum serum concentrations (C^1_{max}) of the two agents occur at the end of the infusion period. The first-dose minimum serum concentrations (C^1_{min}) at $t = \tau$, the end of each dosage interval, were obtained either by direct measurement or by extrapolation using the least-squares fitted slope (λ_z). Because subsequent multiple doses are designed to be given during the terminal elimination phase (λ_z), the expected steady-state C_{max} and C_{min} values (C^{ss}_{max} and C^{ss}_{min}) can be calculated by multiplying the first-dose values by the multiple-dosing function: $r = 1/(1 - e^{-\lambda_z \cdot \tau})$, where e is the base of the natural logarithm system. This calculation assumes that the pharmacokinetics of these compounds are linear with dose and stable with time.

The expected C^{ss}_{max} and C^{ss}_{min} values for the 24 patients of this study are shown in Fig. 6. The C^{ss}_{max} values of both ticarcillin and clavulanic acid exhibited a narrow range largely because of the consistency in dose and V_{ss} among the patients. The C^{ss}_{min} values showed greater variability because of the additional dependence of the terminal slope on renal and metabolic clearances. However, the C^{ss}_{max} and C^{ss}_{min} values were similar at all levels of renal function, confirming the suitability of the dosage recommendations based on extending τ to attain similar C_{max} and C_{min}, as well as equal AUC values. This also indicates that, to whatever extent the 30:1 ratio of ticarcillin:clavulanic acid is effective in patients with normal renal function, the same ratio will be maintained over the dosage interval as renal function lessens. It should be noted that the ticarcillin:clavulanic acid ratio in serum changes with time from 41.9 ± 7.7 at C^{ss}_{max} to 386 ± 360 at C^{ss}_{min}. However, the synergistic effectiveness of the combination is determined not only by this ratio but by

TABLE 3. Ratio of CL and V_{ss} values between subject groups

Groups[a]	Ticarcillin ratios		Clavulanic acid ratios	
	CL	V_{ss}	CL	V_{ss}
B/A	0.88	1.03	0.83	0.71
C/A	0.50	0.98	0.50	0.75
D/A	0.23	1.08	0.39	0.81

[a] As identified in Tables 1 and 2.

TABLE 4. Dosing intervals for 3.1-g doses of ticarcillin-clavulanic acid as a function of CL_{CR}

CL_{CR} (ml min^{-1})	τ (h)
>80	4
60–80	6
30–60	8
10–30	12
<10	24

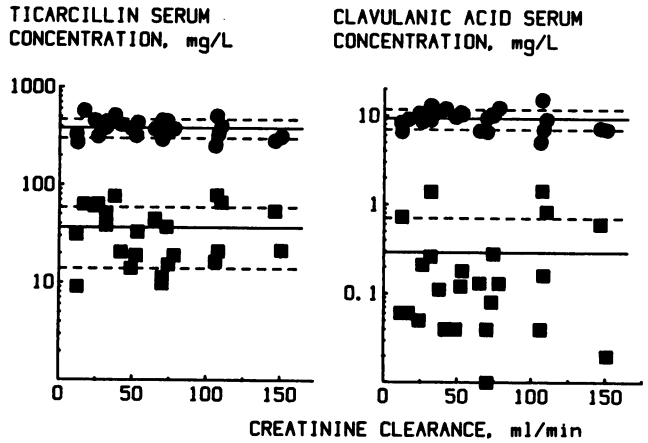

FIG. 6. Expected C^{ss}_{max} and C^{ss}_{min} of ticarcillin and clavulanic acid after multiple-dose infusions of 3.1 g of ticarcillin-clavulanic acid per 1.73 m^2 according to the dosage regimen shown in Table 4. Points are for the serum data from subjects of this study extrapolated to steady-state conditions, solid lines are the means, and dashed lines are standard deviations. ●, Maximum t = 0.5 h; ■, minimum $t = \tau$.

factors such as relative tissue distribution, postantibiotic effects, and regeneration rate of beta-lactamases at the infection site. These are only approximate guidelines based on the pharmacokinetic properties of ticarcillin observed in our subject population. Alternate dosing schemes may be warranted, depending on the hepatobiliary and cardiovascular function of the patient. More frequent and larger doses of ticarcillin-clavulanic acid will attain both higher C_p values and higher ratios in the event of treatment of severe infections or resistant organisms.

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