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Comparative Study of Piperacillin, Ticarcillin, and Carbenicillin Pharmacokinetics

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Piperacillin, ticarcillin, and carbenicillin were administered intravenously to 10 healthy volunteers in a three-way, crossover study. The pharmacokinetics of the three drugs were in general quite similar. The peak serum concentration of piperacillin achieved at the end of a 30-min intravenous infusion was 63.5 ± 27.6 μg/ml. During the first 8 h, 67.5% of the dose of piperacillin was excreted in the urine, and the urinary concentration was extremely high. All three penicillins had high volumes of distribution. The serum half-life of the beta elimination phase of carbenicillin was lower than that of either piperacillin or ticarcillin. The volunteers experienced no adverse reactions from the administration of the drugs.

Carbenicillin, a carboxypenicillin derivative, was the first beta-lactam antimicrobial agent with antibacterial activity against *Pseudomonas aeruginosa* introduced into clinical use (1, 9, 11). Ticarcillin, an alpha carboxythienyl derivative of 6-aminopenicillanic acid, is two to four times as active against strains of *P. aeruginosa* as carbenicillin in vitro (13). Piperacillin {sodium 6-[D(−)-α-(4-ethyl-2,3-dioxo-1-piperazinylcarbonylamino)-α-phenylacetamido] penicillinate} is a new semisynthetic penicillin. In vitro studies have shown that piperacillin has greater activity than either carbenicillin or ticarcillin against a variety of gram-positive and gram-negative organisms, including *P. aeruginosa*, *Proteus* sp., and *Klebsiella* sp. (4, 5, 10, 12, 15-17).

We report the comparative pharmacokinetic properties of piperacillin, ticarcillin, and carbenicillin derived from a three-way crossover study of these compounds in normal human volunteers.

MATERIALS AND METHODS

Ten healthy volunteers, 25 to 64 years of age, six males and four females, were the subjects of these studies. The volunteers ranged in weight from 52.27 to 86.36 kg, with a mean weight of 70.85 ± 13.94 kg (standard deviation). The range of surface area was from 1.35 to 2 m^2, with a mean area of 1.82 ± 022 m^2. Informed consent was given by all volunteers according to institutional policy.

The studies were carried out according to a three-way crossover design. The volunteers received a 2-g dose each week of either piperacillin, ticarcillin, or carbenicillin, administered intravenously, during the successive three weeks of study, representing an average dose of 0.028 g of each compound per kg. The 2-g doses were dissolved in 250 ml of 5% dextrose-water and administered intravenously over a 30-min period. Blood samples were collected just before injection, at 15 min into the infusion, and at 30 min, marking the end of the infusion. Further blood samples were then collected at 5, 10, 30, 45, 60, and 90 min and 2, 3, 4, 5, 8, and 24 h after the end of the infusion. Specimens were immediately centrifuged at 10°C, and the serum was frozen at −70°C. Urine was collected for the first 8 h and then for the next 8 to 24 h.

Serum and urine concentrations of piperacillin, ticarcillin, and carbenicillin were determined by the cup-plate assay method, using *Bacillus subtilis* as the test organism (3).

All volunteers fasted and were voided before the administration of the compounds. Food and fluid intake resumed 2 h after injection. Volunteers remained sedentary during the study period. The following laboratory studies were made before and after administration of the compound: hemogram, urinalysis, blood urea nitrogen, serum creatinine, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, bilirubin, phosphorous, sodium, potassium chloride, calcium, albumin, globulin, cholesterol, triglycerides, and total serum lipids.

The data were analyzed with a program written for a Wang 700 B programmable calculator to derive the pharmacokinetic parameters. The data were fitted to two regression lines, and the following pharmacokinetic parameters based on a two-compartment model (6) were calculated: elimination constant, K_e (per hour); transfer rate constants between the central (V_1) and peripheral (V_2) compartments, K_{12} and K_{21} (per hour); "concentration × time," area below the curve, A micrograms per milliliter per hour; the total apparent volume of distribution (by the area method), V_d (liters per 100 kg); the total volume of distribution in the steady state, $V_{d_{ss}}$ (liters per 100 kg); the plasma clearance, C (liters per hour 1.73 m^2); and the half-life of the beta elimination phase, $t_{1/2}\beta$ (hours). The corrections developed by Loo and Riegelman (8) for the period of the intravenous infusion were applied to the data.

RESULTS

In general, the pharmacokinetic properties of piperacillin, ticarcillin, and carbenicillin were quite similar. The mean serum concentrations of the three compounds after infusion of 2-g doses over a period of 30 min are given in Table 1. The mean peak serum concentrations achieved at the end of the infusions were 63.5, 60.9, and 53 μg/ml for piperacillin, ticarcillin, and carbenicillin, respectively. The serum concentrations observed for the three compounds were not statistically different. At 3 h after the infusion of 2-g doses of piperacillin, an average concentration of 4.3 μg/ml was still present in serum. By 4 h, the mean concentration had fallen to 1.8 μg/ml. Only very small amounts of piperacillin were detectable at 8 h after the completion of the infusion.

The pharmacokinetic parameters derived for the three drugs from the mean serum concentrations are given in Table 2. The elimination constants (K_e) and the compartmental transfer constants (K_{21} and K_{12}) were similar for the three drugs. The areas under the curve (A) found for piperacillin and ticarcillin were almost identical and were larger than that derived for carbenicillin. This was paralleled by the greater half-lives of the beta phase ($t_{1/2}\beta$) for piperacillin and ticarcillin than for carbenicillin. Piperacillin had the largest total apparent volume of distribution of the three drugs. However, the volumes of distribution in the steady state were similar for all three drugs. These volumes were quite large and indicate that the drugs are widely distributed in the body. As expected, the plasma clearances of all three drugs were similar.

The urinary concentrations of the three compounds were quite high (Table 3). The mean concentration of piperacillin in urine during the

TABLE 1. *Comparative serum concentrations of piperacillin, ticarcillin, and carbenicillin after 2-g doses infused over 30 min*

Time of sample	Serum concn (μg/ml)		
	Piperacillin	Ticarcillin	Carbenicillin
During infusion			
15 min	56.7 ± 19.9[a]	54.4 ± 20.5	34.1 ± 5.4
30 min	63.5 ± 27.6	60.9 ± 14.5	53 ± 12.7
Postinfusion			
5 min	58.3 ± 26.5	54.3 ± 14	39.2 ± 6.4
10 min	39.6 ± 13.5	40.1 ± 15.3	32.3 ± 7.3
30 min	30.8 ± 10.6	29.3 ± 9.7	30.6 ± 10.4
45 min	25.5 ± 13.4	25.6 ± 7.6	26.3 ± 9.4
60 min	17.5 ± 7.5	19.9 ± 8.7	19.5 ± 6.2
90 min	14.7 ± 5	14.6 ± 4.9	14.9 ± 6.2
2 h	8.7 ± 3.2	8.9 ± 3.3	8.6 ± 3.3
3 h	4.3 ± 2.7	5.2 ± 3	3.5 ± 1.4
4 h	1.8 ± 2	2.3 ± 1.6	1.4 ± 0.7
5 h	1.2 ± 0.6	1.1 ± 0.8	0.68 ± 0.66
8 h	0.14 ± 0.25	0.8 ± 0.25	0

[a] Mean ± standard deviation.

TABLE 2. *Comparative pharmacokinetic parameters of piperacillin, ticarcillin, and carbenicillin*

Drug	K_e (per h)	K_{21} (per h)	K_{12} (per h)	A (μg/ml per h)	$t_{1/2}\beta$ (h)	V_d (liters/100 kg)	$V_{d_{ss}}$ (liters/100 kg)	Clearance (liters/h per 1.73 m^2)
Piperacillin	1.346	1.683	0.604	92.77	0.867	47.62	30.72	20.48
Ticarcillin	1.182	1.537	0.513	93.28	0.956	41.76	34.14	20.37
Carbenicillin	1.207	2.19	0.46	82.78	0.777	38.25	34.19	22.97

TABLE 3. *Comparative urinary excretion of piperacillin, ticarcillin, and carbenicillin*

Drug	Concn (μg/ml)	Total excreted (mg)
Piperacillin	13,062 ± 7,867[a]	1,350 ± 676 (67.5)[b]
Ticarcillin	5,971 ± 4,949	803 ± 344 (40)
Carbenicillin	11,972 ± 4,666	1,585 ± 472 (79.2)

[a] Mean ± standard deviation.

[b] Percentage of 2-g dose excreted in 8 h.

first 8 h after infusion of a 2-g dose was 13,062 ± 7,867 μg/ml. As is generally found with penicillins, most of the dose was excreted in the urine during the first 8 h (Table 3). However, the amount excreted during the first 8 h for ticarcillin (40%) was lower than that excreted for either piperacillin (67.5%) or carbenicillin (79.2%).

Volunteers did not complain of pain at the site of infusion, and no adverse reactions to the drugs occurred. Laboratory tests performed before and after administration of the drugs remained normal.

DISCUSSION

The data presented here from the three-way crossover study of the three penicillins, piperacillin, ticarcillin, and carbenicillin, show that the pharmacokinetic behavior of the three drugs is nearly identical. Our results for ticarcillin and carbenicillin generally agree with those previously reported by other workers (7, 13, 14). Our data for piperacillin are in accord with those recently presented by Evans and co-workers (3). However, we caution that our study cannot be directly compared with previous studies of carbenicillin and ticarcillin, or the recent pharmacological study of piperacillin, because the dosages, methods of infusion, methods of calculation, and patient selection within them are different.

We found a shorter half-life for carbenicillin, compared with ticarcillin, as had been previously reported (13). The half-lives of the beta phase of piperacillin and ticarcillin were almost the same. The renal elimination of ticarcillin was lower than that found for carbenicillin and has also been previously noted (13). Cole et al. (2) attributed this to the increased conversion of ticarcillin to penicilloic acid.

Interestingly, Evans and co-workers (3) found that both the volume of distribution and the urinary excretion of piperacillin varied with the dose. At lower doses of piperacillin urinary excretion was lower but the volume of distribution was higher. It was suggested that the higher values for the volume of distribution at lower dosages may indicate a tendency to saturate particular tissues, so that increasing the dose is not paralleled by an increase in tissue concentration. The area under the curve increased with larger doses of piperacillin but did not change with the duration of the infusion.

Since the pharmacokinetic properties of piperacillin, ticarcillin, and carbenicillin are so similar, the antibacterial properties of the three drugs must be examined in an attempt to detect possible advantages of piperacillin over the two older penicillins. Clearly, piperacillin has a greater specific activity against most gram-negative strains when compared with carbenicillin and ticarcillin (4, 10, 12, 15–17). Piperacillin is as active as ampicillin against *Streptococcus faecalis* and inhibits 70% of the strains of *Bacteroides fragilis* at a concentration of 12.5 μg/ml (4). More importantly, piperacillin is by far the most active penicillin against *P. aeruginosa*. At least 90% of the strains of *P. aeruginosa* are inhibited at a concentration of 12.5 μg of piperacillin per ml (4, 17). Fifty percent of the strains of *P. aeruginosa* were inhibited at a concentration of 2 μg/ml, and 83% were inhibited at a concentration of 4 μg/ml. Piperacillin is slightly more active against *Neisseria* and *Haemophilus influenzae* than is ampicillin. Fortunately, in most instances the minimum bactericidal concentration is very close to the minimum inhibitory concentration. However, Evans et al. (3) found much higher values for the minimum bactericidal concentrations of piperacillin than for the minimum inhibitory concentrations for strains of *P. aeruginosa*.

In general, the specific activity of piperacillin is 8 to 16 times that of carbenicillin against strains of *P. aeruginosa* (4, 16, 17). This raises the possibility that smaller doses of piperacillin may be used effectively to treat infection due to *P. aeruginosa* than those required for carbenicillin or ticarcillin. Based on our pharmacokinetic studies, doses of piperacillin of 30 to 50 mg/kg administered every 4 h for a total dose range of 180 to 300 mg/kg per day should be sufficient to treat most patients with infections due to *P. aeruginosa*. Furthermore, because of the very high activity of piperacillin against many strains of *P. aeruginosa*, the concomitant administration of an aminocyclitol aminoglycoside may be unnecessary. Indeed, in an ongoing clinical study (unpublished data) we have found piperacillin to be an effective drug in the treatment of various life-threatening infections due to *P. aeruginosa* when used alone. To date, we have not observed the emergence of resistant strains. Extensive clinical studies are certainly warranted to determine whether piperacillin does live up to the clinical promise suggested by the in vitro studies.

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