ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 1975, p. 457-462

Vol. 8, No. 4
Printed in U.S.A.

Comparative In Vitro Activity and Clinical Pharmacology of Ticarcillin and Carbenicillin

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Received for publication 19 June 1975

The in vitro activity and human pharmacology of ticarcillin, a semisynthetic penicillin more active than carbenicillin against *Pseudomonas*, were compared. There has been no increase in resistance to ticarcillin of *Pseudomonas* strains over the past 5 years, but resistance of indole-positive *Proteus* and *Serratia* strains has been documented. After intramuscular (i.m.) injection of 1 g of ticarcillin, mean peak levels occurred at 1 h (26.9 μg/ml) with a decline over 6 h (6.8 μg/ml). Serum half-life was 84 min. Dilution of ticarcillin lidocaine reduced pain on i.m. injection but did not alter serum levels. Blood levels after 1 g i.m. are adequate to treat infections produced by *Escherichia coli*, *Proteus mirabilis*, and some *Enterobacter*, but not *Pseudomonas*. After rapid intravenous infusion of 3 and 5 g, mean peak serum levels of ticarcillin were slightly lower for 1 h than those achieved with carbenicillin. Probenecid administered before infusion produced increases in blood levels, half-lives, and volume of distribution. The biological half-life of ticarcillin was 72 min compared to 66 min with carbenicillin. There was a larger volume of distribution for ticarcillin than carbenicillin (15 liters versus 14 liters). The ticarcillin half-life when administered with probenecid was 108 min. Urinary recovery of ticarcillin was 77% against 95% of carbenicillin. However, approximately 10% of ticarcillin is recovered as penicilloic acid so that 95% of an intravenously administered dose is recovered.

Serious infections produced by members of the *Enterobacteriaceae* and *Pseudomonas aeruginosa* are a major cause of death in hospitalized patients (11). In spite of the development of aminoglycosides with broad activity against these species, mortality in patients with underlying disease remains high. Carbenicillin, an alpha carboxy benzyl penicillin derivative, was introduced in 1967. It has proved to be extremely useful in the treatment of infections due to *Pseudomonas*, *Enterobacter*, and indole-positive *Proteus* (7). Although a variety of acyl derivatives of 6-aminopenicillanic acid (6-APA) have had increased activity against *Pseudomonas* species (9), only an alpha carboxy thienyl derivative, ticarcillin, has been shown to be consistently more active in vitro at varying inoculum levels than has carbenicillin. We reported on the in vitro activity of ticarcillin in 1970 (8) and wished to compare its activity to our previous study at the present time since carbenicillin had been widely used in our institution. Furthermore, reports of increased resistance of *Pseudomonas* species to carbenicillin have been published (4). We also wished to report on the pharmacokinetics of ticarcillin after both intravenous (i.v.) and intramuscular (i.m.) administration in normal subjects.

MATERIALS AND METHODS

Ticarcillin was supplied as a powder and reconstituted fresh for each assay.

Bacteria tested were fresh isolates from patients hospitalized at the Columbia-Presbyterian Medical Center during 1973.

The minimal inhibitory activity of ticarcillin was determined by the agar dilution method using Mueller-Hinton medium. Agar plates containing twofold dilutions of ticarcillin were inoculated with 10^4 colony-forming units by using a replica plating apparatus.

Blood level studies were performed in healthy male physicians, students, or laboratory workers. Informed consent was obtained. Twenty-one healthy males received single i.m. injections of 1 g of ticarcillin diluted in water and 1 week later 1 g of ticarcillin diluted in 1% lidocaine. Serum samples were obtained at 0.5, 1, 2, 3, 4, and 6 h after injection. Twelve individuals subsequently received 1 g of carbenicillin i.m. diluted in water. Urine samples were collected for 0 to 6 h and for the 6- to 8-h period. Six volunteers received intravenously over 5 min 3 g of ticarcillin diluted in 20 ml of 5% glucose. On subsequent weeks the same volunteers received 5 g of ticarcillin in a

similar manner and the effect of probenecid was determined by administering 1 g orally 1 h before administration of 3 and 5 g of ticarcillin. Carbenicillin was administered at 3- and 5-g doses i.v. to three of the volunteers. All studies were performed with an interval of at least 1 week between doses. Serum samples were obtained at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, and 6 h after completion of the i.v. injection. Urine samples were collected in intervals up to 24 h.

The urinary excretion of ticarcillin and penicilloic acid was determined after the administration of 1 g i.v. Urine was collected for 12 h after injection. Penicilloic acid was prepared by the technique of Cole et al. (2) and thin-layer chromatography was performed as published.

Antibiotic assays. After clotting, blood samples were immediately centrifuged and the serum was divided into several samples to be frozen at −20 C. Known standards were prepared in pooled human serum obtained from the volunteers before the study. One lot of standards was used for the entire experiment with the standards kept frozen at −20 C. Urine samples were frozen and, when thawed, mixed and diluted in 0.05 M potassium phosphate, pH 7, buffer. Previously published agar-well diffusion techniques were used with *Pseudomonas aeruginosa* NCTC 10701 as indicator (1). The pharmacokinetics data were calculated by standard methods (3). The half-life calculated from the slope of the best-fitted line after equilibrium was considered to be established.

RESULTS

In vitro studies. A comparison of the ticarcillin MIC levels versus those obtained with carbenicillin and those obtained with ticarcillin 5 years previously are given in Table 1. Ticarcillin remains two- to fourfold more active than carbenicillin on a weight basis against *P. aeruginosa* isolates. Minimal superiority of ticarcillin over carbenicillin is noted for *Enterobacter*, *Serratia*, or indole-positive *Proteus* species. Nonetheless, at low antibiotic concentrations ticarcillin is also more active against some *Enterobacter* and *Serratia* isolates. It is of note that there has not been a marked increase in the resistance of *Pseudomonas* strains to either ticarcillin or carbenicillin in our institutions in the 5-year period that carbenicillin has been used. There is an increased resistance of indole-positive *Proteus* and *Serratia*. This is due to the presence of R factor-bearing strains which are also resistant to many of the currently available aminoglycosides, such as gentamicin and tobramycin (Neu, unpublished data).

Pharmacology. Peak serum levels occurred from 0.5 to 3 h, with the mean peak blood levels after i.m. injection at 1 h with a decline over the next 6 h (Table 2). There were no differences between the blood levels or half-life of the drug when it was diluted in lidocaine rather than water. The majority of the volunteers (16 of 21) felt that dilution in lidocaine significantly decreased the pain of injection. They did not note any difference in pain between i.m. ticarcillin and carbenicillin. The kinetics of carbenicillin removal were for the most part identical. Slightly higher peak levels are achieved with carbenicillin but the levels at 4 h are identical and ticarcillin achieves slightly higher levels at 6 h due to its slightly longer half-life. Some of the variation in blood levels is undoubtedly due to the weight variation of the subjects which ranged from 60 to 88.6 kg. The mean serum levels after the injection of 1 g of ticarcillin i.m. for all 21 subjects were the following: 0.5 h, 22.7 μg/ml; 1 h, 26.9 μg; 2 h, 21.1 μg; 3 h, 11.9 μg; 4 h, 7.9 μg; and 6 h, 6.8 μg, when diluted in water; when diluted in lidocaine, 0.5 h, 20.0 μg; 1 h, μg; 2 h, 20.7 μg; 3 h, 14.1 μg; 4 h, 84 μg; and 6 h, 24.7 μg; 2 h, 20.7 μg; 3 h, 14.1 μg; 4 h, 84

TABLE 1. *Comparison of ticarcillin and carbenicillin minimal inhibitory concentration levels*

Organism[a]	Compound	Date	% Inhibited								
			1.6[b]	3.2	6.4	12.5	25	50	100	200	>200
Pseudomonas	Ticarcillin	1969		6	14	14	36	72	89	92	100
	Ticarcillin	1974	1.5	1.5	7	20	50	70	91	93	100
	Carbenicillin	1974	1.5	1.5	5.4	8.6	22	48	70	92	100
Enterobacter	Ticarcillin	1966			52	65	87	87	91	96	100
	Ticarcillin	1974	26	51	58	65	70	77	80	81	100
	Carbenicillin	1974	7	23	51	60	74	77	81		100
Serratia	Ticarcillin	1969					16	23	30	33	100
	Ticarcillin	1974		24	34	38	48				100
	Carbenicillin	1974		14	28	34	38	41	45		100
Proteus morganii,	Ticarcillin	1969		57	80	100					
P. vulgaris,	Ticarcillin	1974	33	45	51	64	73	76			100
P. rettgeri	Carbenicillin	1974	42	45	57	67	78	85			100

[a] *Pseudomonas*, 128 isolates; *Enterobacter*, 43 isolates; *Serratia*, 29 isolates; *Proteus*, 33 isolates.
[b] Minimal inhibitory concentrations.

TABLE 2. *Comparison of the blood levels of ticarcillin and carbenicillin after i.m. injection of 1 g*

Subject	Wt	Antibiotic	Diluent	Serum concn (μg/ml)					
				0.5 h	1 h	2 h	3 h	4 h	6 h
3	78.2	Ticarcillin	Water	7.8	9.8	16.0	15.5	13.5	6.0
		Ticarcillin	Lidocaine	6.8	11.5	16.0	14.0	10.5	6.0
		Carbenicillin	Water	12.2	20.0	22.0	12.0	7.5	3.7
5	84.5	Ticarcillin	Water	5.6	9.0	15.0	12.4	9.8	6.7
		Ticarcillin	Lidocaine	7.8	12.0	24.0	19.0	12.4	7.0
		Carbenicillin	Water	5.9	10.5	16.5	19.0	13.0	7.6
6	60.0	Ticarcillin	Water	8.0	10.0	9.2	5.0	6.2	6.4
		Ticarcillin	Lidocaine	7.8	12.0	21.0	15.1	8.8	6.2
		Carbenicillin	Water	39.0	33.0	25.0	15.0	7.8	4.5
8	61.4	Ticarcillin	Water	33.5	28.0	19.8	5.2	3.6	6.6
		Ticarcillin	Lidocaine	40.0	33.0	23.0	7.4	6.8	7.0
		Carbenicillin	Water	37.0	36.0	24.0	15.0	8.0	4.4
10	73.6	Ticarcillin	Water	17.5	20.0	10.0	8.0	5.0	7.2
		Ticarcillin	Lidocaine	16.2	19.0	15.5	4.4	4.4	5.2
		Carbenicillin	Water	29.0	22.0	15.2	9.6	3.6	3.2
11	76.4	Ticarcillin	Water	8.4	20.0	22.0	11.6	8.0	5.7
		Ticarcillin	Lidocaine	9.4	20.0	27.0	14.0	9.2	7.2
		Carbenicillin	Water	28.0	22.0	25.0	17.2	9.2	3.6
13	65.5	Ticarcillin	Water	31.0	33.0	22.2	16.4	9.8	7.2
		Ticarcillin	Lidocaine	44.0	42.0	20.5	20.5	7.0	6.5
		Carbenicillin	Water	12.0	25.0	20.2	4.5	2.5	3.2
15	68.2	Ticarcillin	Water	43.0	56.0	24.2	12.5	5.6	6.8
		Ticarcillin	Lidocaine	10.0	21.0	21.5	33.0	12.2	9.2
		Carbenicillin	Water	29.0	31.0	30.0	15.5	8.0	3.4
18	88.6	Ticarcillin	Water	9.0	11.5	16.8	17.5	12.2	7.6
		Ticarcillin	Lidocaine	6.8	15.0	14.5	15.0	12.0	5.2
		Carbenicillin	Water	6.2	14.0	20.2	14.0	11.9	4.2
Mean	72.9	Ticarcillin	Water	17.1	21.9	17.1	11.5	8.2	6.6
				(5.1)[a]	(5.6)	(2.0)	(1.5)	(1.1)	(0.2)
		Ticarcillin	Lidocaine	16.8	20.6	21.2	15.8	9.3	6.1
				(5.4)	(3.9)	(1.5)	(3.1)	(1.0)	(0.4)
		Carbenicillin	Water	14.8	23.7	22.0	13.5	7.9	4.2
				(4.4)	(2.9)	(1.7)	(1.6)	(1.3)	(0.6)

[a] Numbers in parentheses are standard error.

μg; and 6 h, 6.7 μg. The subjects ranged in weight from 53.2–88.6 kg. The mean half-life was 84 min. Grouping individuals by comparable weight did not reduce the variation in time of peak serum level achieved or the range of values. The standard error for peak levels at 1 h was 5.2 μg, and 1.1 μg for levels at 3 and 4 h.

The results of the rapid i.v. infusion of 3 and 5 g in five volunteers are given in Table 3. A rapid decline in blood level similar to that which occurs with other penicillins is demonstrated. After i.v. administration of 1 g, peak level at 0.25 h was 55 μg/ml with levels of 34 μg/ml at 1 h, 14 μg/ml at 2 h, and only 5.5 μg/ml at 3 h. Thus levels by 2 h are below those achieved with 1 g administered i.m. Comparison of the blood levels achieved when carbenicillin is given to the same subjects is shown in Table 4. After rapid infusion we did not see significant differences in the mean serum levels of the two compounds. Administration of probenecid did cause an increase in the peak serum levels and prolongation of higher blood levels.

Mean urinary recovery of ticarcillin was 77% for the 6-h period in contrast to almost complete (95%) recovery of carbenicillin (Table 5). Collection of urine for a 12-h period did not add an appreciable amount since the major recovery occurs in the first 3 h after rapid i.v. injection.

The data in Table 6 show that of a total dose approximately 10% is recovered as penicilloic acid and, if this is considered, approximately 95% of i.v. administered ticarcillin can be recovered in the urine in the 12-h period after injection.

The serum half-life was 72 ± 6 min for ticarcillin and 66 min for carbenicillin (Table 4). The apparent volume of distribution of ticarcillin after the 5-min infusion was 15 liters and the serum clearance was 132 ml/min; the

TABLE 3. *Serum levels after i.v. infusion of ticarcillin*

Subject	Dose (g)	Serum level (μg/ml)								
		0.25 h	0.5 h	0.75 h	1 h	1.5 h	2 h	3 h	4 h	6 h
1	3	215	230	130	105	75	60.5	30.9	25.5	4.9
2	3	210	230	105	97.5	90	60.0	30.9	25.5	7.1
4	3	219	160	132.5	135	67.5	70.0	46.0	36	12.0
5	3	420	308	172.5	145	117.5	90.1	47.5	34	9.0
6	3	220	160	132.5	111.5	118	69	43	31.5	10.0
Average		256.8 (54.4)[a]	217.6 (30.2)	136.5 (14.1)	119 (11.6)	93.6 (11.2)	69.9 (7.0)	39.7 (4.6)	30.5 (2.8)	8.6 (1.5)
1	5	440	325	280	240		152.5	87.5	58	17
2	5	470	255	230	190		172.5	72.5	66	8
4	5	520	340	285	28		155	97.5	68	33
5	5	660	460	370	370		210	125	86	35
6	5	430	350	250	210		210	152.5	80	28.5
Average		504 (48.7)	346 (92.6)	283 (29)	258 (38.1)		180 (13.3)	107 (11.5)	71.6 (5.9)	24.3 (6.5)

[a] Numbers in parentheses are standard error.

TABLE 4. *Comparison of mean blood levels of three subjects who received ticarcillin and carbenicillin by rapid i.v. infusion*

Compounds	Dose (g)	Mean blood levels (μg/ml)[a]							
		0.25 h	0.75 h	1 h	2 h	3 h	4 h	6 h	T 1/2
Ticarcillin	3	190 (35)	118 (29)	107 (20)	52 (9)	31 (0.5)	14 (0)	4 (0)	72
Ticarcillin Probenecid	3 1	223 (32)	139 (18.5)	123 (20)	78 (5)	54 (2)	35 (2.0)	17 (1.0)	108
Carbenicillin	3	223 (51)	171 (18)	99 (13)	59 (0.5)	34 (0.2)	20 (3.5)	7 (0.8)	66

[a] Numbers in parentheses are standard error.

renal clearance was 106 ml/min; the apparent volume of distribution of carbenicillin was 14 liters.

DISCUSSION

In the past 5 years, in spite of extensive use of carbenicillin to treat *Pseudomonas* and *Enterobacter* infections in our institution (7), we have not seen an appreciable increase in resistance either to carbenicillin or ticarcillin. This is in contrast to the situation in other institutions where use has been greater (4) and perhaps less closely regulated. Strains isolated from blood, urine, wounds, and sputum show a two- to fourfold greater susceptibility to ticarcillin compared with carbenicillin. In contrast, there has been a decline in our institution in the susceptibility of indole-positive *Proteus* and *Serratia* strains to beta-lactam antibiotics with an increased prevalence of strains that possess R factors mediating beta-lactamase production. Whether this is a phenomenon restricted to our institution or if it has occurred elsewhere has not been established.

Blood levels produced by i.m. injection of 1 g of ticarcillin would provide adequate blood levels to treat infections produced by susceptible strains of *E. coli*, *P. mirabilis*, and the majority of susceptible *Enterobacter* and indole-positive *Proteus* infections, but not for *Pseudomonas*. The urinary levels are more than adequate for all susceptible strains of both *Enterobacteriaceae* and *Pseudomonas*, even for 8 h after injection of 1 g. The use of lidocaine to decrease pain on i.m. injection does not alter the serum, urine levels, or half-life of the drug. The majority of subjects felt that use of lido-

TABLE 5. *Comparison of urinary recovery of ticarcillin and carbenicillin*

Compound	Subjects	Route	Dose (g)	% Recovered[a]				
				0–3 h	3–6 h	0–6 h	6–8 h	0–8 h
Ticarcillin	9	i.m.	1			60 (1.6)	12 (1.8)	72
Carbenicillin	9	i.m.	1			68 (8.7)	8 (1.8)	76
Ticarcillin	6	i.v.	3	57 (1.4)	20 (1.5)	77		
Ticarcillin	6	i.v.	5	59 (8.3)	17 (1.4)			
Ticarcillin + probenecid	3	i.v.	3	42 (1.2)	16 (1.6)	58		
Carbenicillin	3	i.v.	3	65	31	96		

[a] Numbers in parentheses are the standard error.

TABLE 6. *Recovery of ticarcillin and penicilloic acid after administration of 1 g i.v.*

Antibiotic	Amt recovered (mg)[a]
Penicilloic acid	124[b] (23)
Ticarcillin	831 (27)
Total recovery	95.5%

[a] Numbers in parentheses are the standard error.
[b] Mean of 10 subjects.

caine significantly lowered the pain of i.m. injection. In a comprehensive questionnaire to evaluate response to the injection most subjects concluded that pain rarely lasted more than 5 to 10 min after injection.

After a rapid 5-min i.v. infusion of the drug into a large vein we found higher average blood levels with ticarcillin than with carbenicillin. These results were similar to those of Rodriguez et al. (10), but in contrast to those of Libke et al. (5) who found a 28% lower initial level of ticarcillin. It is possible that the differences could have been due to different lots of drugs or the fact that we injected into the large veins, hence avoiding venous spasm which Libke et al. (5) said had occurred. The half-life of ticarcillin, 72 min, which we found is similar to that of Libke et al. (5), 72 min, as is our apparent volume of distribution, but we found a slightly lower serum clearance.

Renal elimination was less for ticarcillin than for carbenicillin, but this has been attributed by Cole et al. (2) to increased conversion of ticarcillin to penicilloic acid. The majoirty of the drug is cleared in the first 3 h after rapid infusion.

We found that pretreatment with probenecid increased both serum levels and half-life of ticarcillin as it does with carbenicillin. These increases are in contrast to results of Rodriguez et al. (10), but in line with those of Libke et al. (5). However, the increase provided would be of minor importance clinically since the levels in the period from 4 to 6 h after rapid injection would be lower than the inhibitory concentration needed to inhibit many *Pseudomonas* strains.

These studies indicate that the concentrations of ticarcillin in serum are similar to those achieved with carbenicillin. On the basis of these studies we have used a program of 3 g of ticarcillin administered every 4 h to treat systemic infections in 90 patients (Parry and Neu, manuscript in preparation). We have administered the drug over a 30-min period and achieved adequate serum concentrations.

ACKNOWLEDGMENTS

We wish to express our appreciation to Elaine Longo and Iris Rivera for help during this project and to B. P. Polt and F. S. Barr for penicilloic acid determinations.

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