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# Clinical Pharmacology of Ticarcillin (α-Carboxyl-3-Thienylmethyl Penicillin, BRL-~~2228~~ 2288)

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Clinical pharmacological studies of ticarcillin (α-carboxyl-3-thienylmethyl penicillin, BRL-2288) were conducted in patients with metastatic cancer and leukemia. After administration of 0.5 g intramuscularly, 1 g intramuscularly, and 1 g intravenously, the mean peak concentrations in serum were 18, 35, and 106 μg/ml, respectively. Greater than 80% of ticarcillin was excreted in the urine during the subsequent 6-h period. The mean concentrations in the serum of patients 15 min after they received an intravenous injection of 4 g of ticarcillin with and without probenecid were 508 and 519 μg/ml, respectively. Serum levels were determined in patients who received ticarcillin for therapy of infection in doses of 5 g every 6 h. The mean drug concentration in serum 15 min after the rapid administration of the first dose was 433 μg/ml. Subsequent doses were given during a 2-h infusion and the study was repeated 2 days later. The average initial serum level (4 h after the completion of the preceding dose) was 19 μg/ml, and the mean serum level at 15 min was 213 μg/ml. Drug concentrations in the serum of patients receiving ticarcillin by infusion in doses of 3.5 g every 4 h were also determined. In patients with normal renal function, the average initial serum level (2 h after completion of the preceding dose) was 49 μg/ml and the mean level at 15 min was 210 μg/ml. Drug concentrations in the serum of patients with impaired renal function were considerably higher. No detectable levels of ticarcillin were found in the cerebrospinal fluid.

Ticarcillin (α-carboxyl-3-thienylmethyl penicillin, BRL-2288) is a new semisynthetic penicillin (Fig. 1) which is a disodium salt soluble in water. Refrigerated aqueous solutions are stable for about 1 week. Like carbenicillin, ticarcillin has in vitro activity against most *Proteus* spp., *Pseudomonas* spp., and some strains of *Escherichia coli* and *Enterobacter* spp. (1, 6). However, it is more active in vitro against *Pseudomonas* spp. than carbenicillin (1). At concentrations of 50 μg/ml, ticarcillin inhibits over 80% of isolates of *Pseudomonas* spp. Carbenicillin concentrations of 200 μg/ml or greater are needed to inhibit the same proportion of organisms (1, 2).

Because of its spectrum of activity, ticarcillin appears to be a valuable antibiotic for the therapy of infections in cancer patients. These patients have a high incidence of infections caused by those organisms susceptible to carbenicillin and ticarcillin. The recovery rate from these infections has improved subtantially since the introduction of carbenicillin (3). However, large doses of carbenicillin are required for adequate therapy of systemic infections, which may result in excessive sodium intake and fluid overload (5). Since ticarcillin appears to be more active in vitro, it should be possible to administer lower doses of this drug. The present study was conducted to determine the drug concentrations in serum that can be attained after parenteral administration of ticarcillin to cancer patients.

## MATERIALS AND METHODS

Studies of ticarcillin (α-carboxyl-3-thienylmethyl penicillin, BRL-2288) were conducted in 38 patients with metastatic cancer and leukemia who were not severely debilitated. Their ages ranged from 15 to 81 years and their weight from 45 to 95 kg. Informed consent was obtained from each patient according to institutional policies. The drug was supplied by

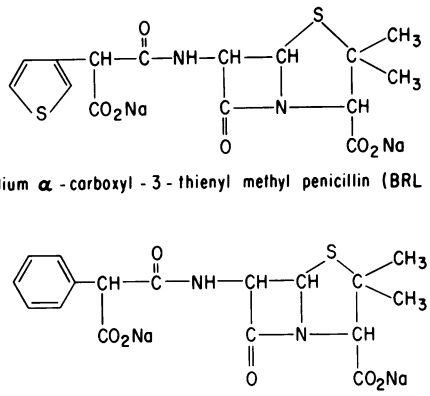


FIG. 1. *Chemical structure of disodium α-carboxyl-3-thienylmethyl penicillin and its resemblance to carbenicillin.*

Beecham-Massengil Pharmaceuticals, Division of Beecham Inc., Bristol, Tenn., as 1-g vials which were reconstituted in 2 ml of normal saline.

Seven patients who had normal renal and liver function received a 0.5-g dose intramuscularly (im). The same patients received a 1.0-g dose im and a 1-g dose by rapid intraveous (iv) injection, at intervals of no less than 2 days. Serum specimens were obtained at 0, 0.25, 0.5, 1, 2, 3, 4, and 6 h after the parenteral administration of ticarcillin. Urine specimens were collected immediately prior to and during the 6-h period of each study.

A group of nine patients with normal renal and liver function were included in a study of 4 g of ticarcillin administered by rapid iv injection alone, compared to the same dose with probenecid, and to 4 g of carbenicillin administered by rapid iv injection. Studies were conducted in the same patients at intervals of at least 2 days. The antibiotic was administered in a fluid volume of 20 ml of normal saline. Probenecid was given orally in four doses of 0.5 g every 6 h, the last dose being given just prior to the study.

Studies were also performed in 22 patients who received ticarcillin by continuous iv infusion for therapy of infections. Five patients who had normal renal function received 5 g of ticarcillin in 20 ml of normal saline administered as a rapid iv injection within a 3-min period. Subsequent doses were given every 6 h as 5 g in 200 ml of 5% dextrose solution during a 2-h infusion. Drug concentrations in serum were determined at 0, 0.25, 0.5, 1, 2, 3, 4, and 6 h after the first dose. Two days later, serum samples were also obtained, immediately prior to administration of a dose (4 h after cessation of the preceding dose) and 0.25, 0.5, 1, 2, 3, 4, and 6 h after the beginning of the infusion. All of the ticarcillin had been infused by the end of the second hour. Seventeen patients received ticarcillin in doses of 3.5 g in 200 ml of dextrose solution infused over a 2-h period every 4 h. Serum levels were determined on the third day of infusion immediately prior to administration of a dose (2 h after cessation of the preceding dose) and at 0.25, 0.5, 1, 2, 3, and 4 h after the beginning of the infusion. Eleven of these patients had normal renal function; the remaining six had a creatinine clearance less than 75 ml/min (corrected to the patient's body surface area).

Cerebrospinal fluid was obtained from three patients who required a diagnostic lumbar puncture for other reasons. A dose of 4 g of ticarcillin was given in 20 ml of normal saline over 3 min, and 2 h later simultaneous serum and spinal fluid samples were obtained.

Serum specimens obtained (from eight of the nine patients) at 1 and 4 h after administration of 4 g of ticarcillin and 4 g of carbenicillin were used for in vitro studies against 10 isolates of *P. aeruginosa*. Serial dilutions of the serum specimen were made and inoculated with approximately $10^5$ colony-forming units of each isolate. The highest dilution of each drug completely inhibiting growth was determined.

Antibiotic concentrations in serum, urine, and cerebrospinal fluid were determined by using an agar well method with *P. aeruginosa* ATCC 23389 as the test organism. The organism was inoculated on a fresh slant of Trypticase soy agar (BBL), transferred after 24 h of incubation to freshly prepared (10 ml) Trypticase soy broth (BBL), and incubated at 37 C. A 1.4-ml amount of the overnight broth was added to 65 ml of Trypticase soy agar, and the medium was poured into plates. Wells (0.75 mm in diameter by 0.75 mm deep) were cut into the agar and filled with 0.1 ml of the specimens; the plates were incubated at 37 C for 18 h. Zones of inhibition were measured with a caliper and compared to a standard curve. The standard curve was determined by dissolving the antibiotic standard (ticarcillin or carbenicillin) in pooled human serum or urine to final concentrations of 40, 20, 10, and 5 μg/ml and measuring zones of inhibition after incubation at 37 C for 18 h. Serum specimens which required dilution for assay were diluted in pooled human serum. Urine specimens were diluted in human urine. The standard error of the mean was calculated according to the method of Mantel (4). The 95% confidence limits were determined as two times the standard of the mean.

## RESULTS

The average drug levels obtained in the serum of seven patients after administration of 0.5 and 1 g im and 1 g iv are shown in Fig. 2. The mean peak serum concentration after administration of 0.5 g occurred at 1 h and was 18 μg/ml. After administration of 1 g of ticarcillin im, the mean peak serum concentration occurred at 1 h and was 35 μg/ml. At 15 min after administration of 1 g of the drug iv the mean concentration in serum was 106 μg/ml. Serum levels 4 h after administration 1 g im and iv were 10 and 4 μg/ml, respectively.

Drug concentrations in the serum of nine patients who received a rapid iv injection of 4 g of ticarcillin with and without probenecid are shown in Fig. 3. At 15 min after the administra-

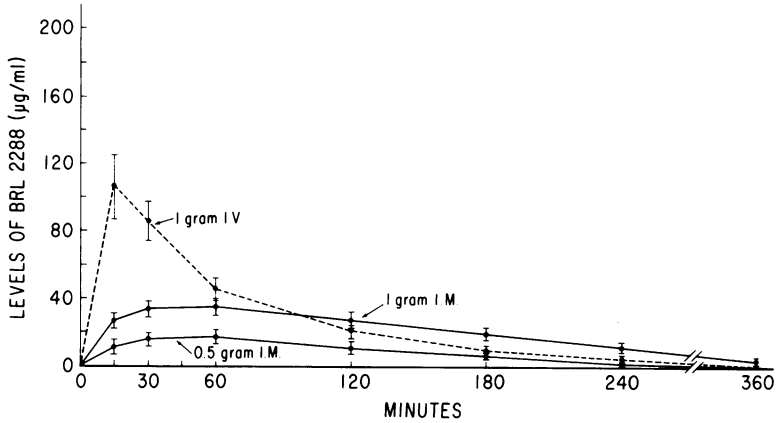


FIG. 2. *Concentrations of ticarcillin in serum after administration of 0.5 g im, 1 g im, and 1 g iv. The brackets represent ±2 standard errors.*

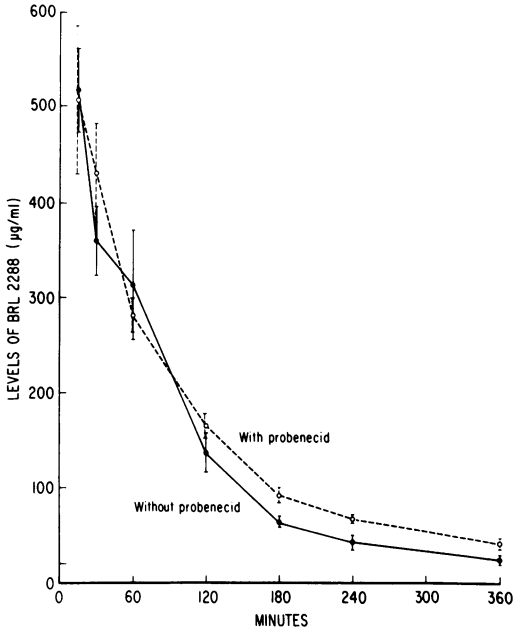


FIG. 3. *Concentrations of ticarcillin in serum after rapid intravenous administration of 4 g with and without probenecid. The brackets represent ±2 standard errors.*

tion, serum levels were 508 and 519 µg/ml, respectively. The administration of probenecid did not increase the mean serum levels of ticarcillin at this dose.

Drug concentrations after rapid iv infusion of 4 g of carbenicillin were determined and compared to 4 g of ticarcillin in the sera of the same nine patients (Fig. 4). At 15 min after drug administration, the mean serum level of carbenicillin (428 µg/ml) was lower than the mean serum level of ticarcillin (519 µg/ml). The mean serum levels of ticarcillin remained slightly higher during the subsequent 6 h. However, these differences were not significant.

Drug concentrations in the serum of five patients who received the antibiotic in doses of 5 g every 6 h for therapy of infections are shown in Fig. 5. The patients received the first dose as a rapid iv injection. Subsequent doses were given every 6 h as a 2-h infusion. The mean serum level 15 min after the rapid administration of the first dose was 433 µg/ml. Two days later, the study was repeated. The average initial serum level (4 h after completion of the preceding dose) was 19 µg/ml. The serum level rose during the 2 h of drug infusion to a mean peak of 213 µg/ml and then fell gradually until it reached the initial level at the end of the 6-h period.

Seventeen patients were studied after receiving ticarcillin by infusion in doses of 3.5 g every 4 h for at least 2 days (Fig. 6). The drug was administered over a 2-h period. Eleven patients (13 studies) had normal renal function (creatinine clearance > 80 ml/min). The mean serum level at the beginning of the study (2 h after completion of the preceding infusion) was 49 µg/ml; it then rose to a mean peak of 210 µg/ml at the end of the 2-h infusion and gradually decreased to the initial level at the end of the 6-h period.

The same study was performed in six patients with impaired renal function (creatinine clearance < 75 ml/min). The mean initial serum level (2 h after cessation of the preceding dose) was 173 µg/ml; it then rose to a mean peak of 423 µg/ml at the end of the infusion and remained greater than 170 µg/ml during the 4-h period.

The urinary excretion of ticarcillin was deter-

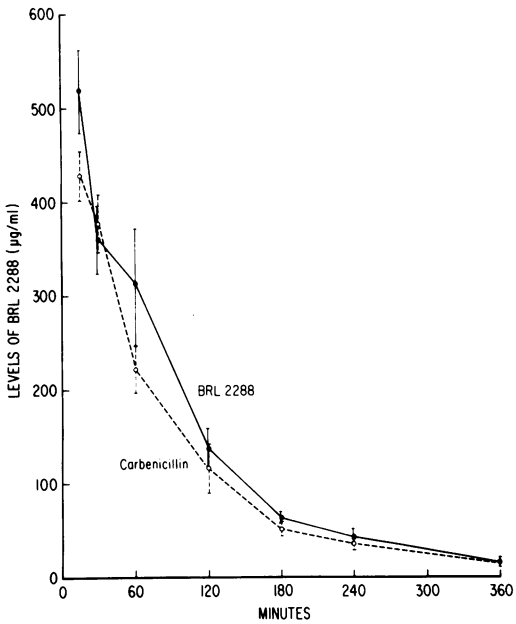


FIG. 4. *Concentrations of ticarcillin and carbenicillin in serum after rapid intravenous administration of 4 g. The brackets represent ±2 standard errors.*

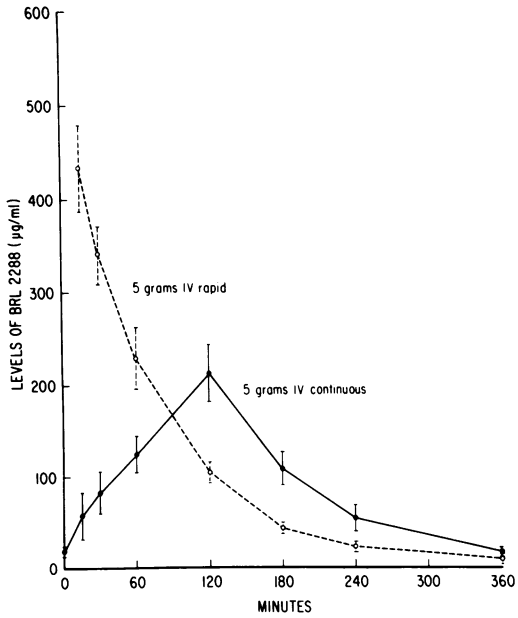


FIG. 5. *Concentrations of ticarcillin in serum after intravenous administration of 5 g. The broken line represents the levels obtained after the first rapid intravenous dose. The solid line represents values obtained 2 days later after continuous intravenous administration. The brackets represent ±2 standard errors.*

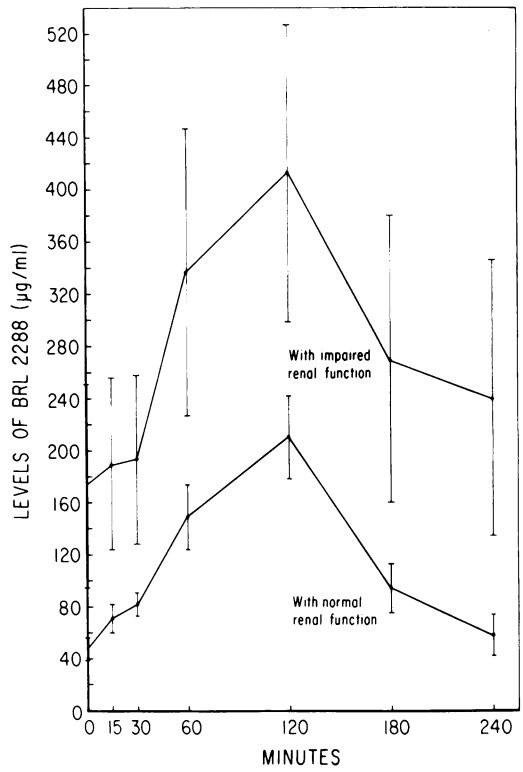


FIG. 6. *Concentrations of ticarcillin in the serum of patients with normal and impaired renal function after 2 days of intravenous administration. Dose: 3.5 g in a 2-h continuous infusion every 4 h. The brackets represent ±2 standard errors.*

mined in five patients who received 1 g im and five patients who received 1 g iv by rapid injection. During the first 6 h, the urinary excretion of ticarcillin was 82% of the administered dose in the patients who received the antibiotic im and 93% in the patients who received the antibiotic iv (Table 1).

Cerebrospinal fluid was obtained from three patients with acute leukemia who had no meningeal disease. Each sample was collected 2 h after a rapid intravenous injection of 4 g of ticarcillin, at which time the serum levels of the antibiotic were 105, 101, and 125 μg/ml. No detectable levels of the antibiotic were found in the cerebrospinal fluid of these three patients.

Serum specimens obtained from eight of the nine patients who received 4 g of ticarcillin and 4 g of carbenicillin were tested against 10 isolates of *P. aeruginosa* to determine the serum inhibitory levels, 1 and 4 h after the administration of the antibiotic. Ticarcillin and carbenicillin were inhibitory at the same dilution against 26% of the 1-h samples. Ticarcillin was more

inhibitory than carbenicillin against 63% of these specimens, and carbenicillin was more inhibitory than ticarcillin against only 11%, usually with one tube difference (Table 2). In the 4-h specimens, ticarcillin and carbenicillin were equally inhibitory in 45% of the samples, ticarcillin was more inhibitory than carbenicillin in 40%, and carbenicillin was more inhibitory than ticarcillin in 15% (Table 3).

## DISCUSSION

The results of this study indicate that the intramuscular administration of ticarcillin in doses of 0.5 and 1 g would probably not be useful for the therapy of systemic infections since adequate serum levels cannot be maintained. Higher concentrations in the serum were obtained after the rapid iv administration of 1 g, but they were inadequate 2 h later. It is conceivable that these dosage schedules of the antibiotic may have clinical usefulness for the treatment of urinary tract infections, since very high concentrations can be achieved in the urine. Ticarcillin is excreted in the urine almost completely during the first 6 h after parenteral administration.

Serum levels of ticarcillin adequate to inhibit most susceptible gram-negative bacilli are obtained after rapid iv administration of 4 g. However, the antibiotic concentrations in serum rapidly decrease, and 3 to 4 h later they are below 50 μg/ml. The administration of probenecid did not increase the mean serum levels of ticarcillin significantly.

The administration of 5 g of ticarcillin every 6 h in a 2-h infusion produced high concentrations in serum, but was inadequate for systemic infections (V. Rodriguez et al., manuscript in preparation). Serum levels of 50 μg/ml or greater are not maintained beyond 4 h after administration. However, if ticarcillin is administered every 4 h in doses of 3.5 g, adequate serum levels are maintained. In patients with impaired renal function, these levels are about three times higher.

The results of this study indicate that concentrations of ticarcillin in serum achieved after parenteral administration are comparable to those obtained with carbenicillin. However, the serum inhibitory activity against *P. aeruginosa* in vitro is more effective with ticarcillin than with carbenicillin. Doses of 3.5 g administered during 2-h iv infusions every 4 h yield adequate serum levels. Clinical studies are in progress to determine whether a daily dose of 21 g used in this regimen produces therapeutic results comparable to that obtained with 30 g of carbenicillin.

TABLE 1. *Urinary excretion during 6 h after administration of 1 g of ticarcillin*[a]

| Route of administration | Mean urinary excretion | | Mean urinary concn (mg/ml) |
|---|---|---|---|
| | Amt (g) | Percent | |
| Intramuscular | 0.820 (0.382-1.350) | 82 | 1.722 (0.490-4.100) |
| Intravenous | 0.926 (0.627-1.292) | 93 | 1.956 (0.510-3.400) |

[a] Numbers in parentheses indicate ranges.

TABLE 2. *Comparison of serum inhibitory activity of ticarcillin and carbenicillin (1 h after injection)*

| Serial dilution of carbenicillin | Serial dilution of ticarcillin | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | None | 1:2 | 1:4 | 1:8 | 1:16 | 1:32 | 1:64 | 1:128 |
| None | 1 | 1 | 4 | 4 | 0 | 0 | 0 | 0 |
| 1:2 | 1 | 5 | 10 | 7 | 0 | 0 | 0 | 0 |
| 1:4 | 0 | 3 | 12 | 17 | 4 | 0 | 0 | 0 |
| 1:8 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 |
| 1:16 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| 1:32 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1:64 | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 0 |
| 1:128 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |

TABLE 3. *Comparison of serum inhibitory activity of ticarcillin and carbenicillin (4 h after injection)*

| Serial dilution of carbenicillin | Serial dilution of ticarcillin | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | None | 1:2 | 1:4 | 1:8 | 1:16 | 1:32 | 1:64 | 1:128 |
| None | 14 | 11 | 1 | 0 | 0 | 0 | 0 | 0 |
| 1:2 | 2 | 17 | 12 | 3 | 0 | 0 | 0 | 0 |
| 1:4 | 2 | 5 | 3 | 0 | 1 | 0 | 0 | 0 |
| 1:8 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 |
| 1:16 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| 1:32 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| 1:64 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| 1:128 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

### ACKNOWLEDGMENTS

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