Effect of Piperacillin on Tobramycin Pharmacokinetics in Patients with Normal Renal Function

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Received 21 March 1983/Accepted 25 July 1983

Aminoglycosides are inactivated by extended-spectrum penicillins in vitro and in patients with end-stage renal failure. In this prospective controlled study, we determined the effect of piperacillin on tobramycin pharmacokinetics. In 10 clinically stable male patients with calculated creatinine clearances of ≥60 ml/min, serial levels in serum of tobramycin alone and after single 4-g intravenous doses of piperacillin were determined. No statistically significant changes in the concentration of drug in serum, the half-life (t1/2), the elimination rate constant (K2), the volume of distribution (Vd), or the area under the serum concentration-time curve (AUC) occurred when tobramycin was used concurrently with piperacillin. Therefore, this antibiotic combination will not result in a clinically significant interaction in patients with normal renal function.

Piperacillin, a ureidopenicillin, is the most potent of the commercially available extended-spectrum penicillins with respect to in vitro antipseudomonas activity. In single-drug regimens for infection with susceptible gram-negative bacilli, it has potential safety advantages over aminoglycosides. In combination with aminoglycosides, piperacillin exhibits synergistic bactericidal activity, which is particularly useful in febrile, neutropenic patients (12). It has been postulated, however, that piperacillin, like other penicillins, inactivates aminoglycoside antibiotics by converting them to microbiologically inert amides (22). In vitro, piperacillin concentrations of ≥250 μg/ml have been shown to diminish the activity of gentamicin, tobramycin, and amikacin (7). To date, the in vivo significance of this interaction has been examined only between piperacillin and gentamicin. In six patients with end-stage renal disease, piperacillin decreased the mean half-life of gentamicin from 53.9 to 37.7 h (22). In the face of such limited published data, we undertook this clinical evaluation of the action of piperacillin on tobramycin, which appears to be the aminoglycoside most susceptible to inactivation (7). Tobramycin concentrations were determined by radioimmunoassay, which minimizes potential aminoglycoside inactivation during analysis (16). Our aim was to determine the clinical significance of this interaction and whether tobramycin dosing adjustments would be warranted in patients with normal renal function who are also receiving piperacillin.

MATERIALS AND METHODS

Informed consent was obtained from each patient who participated in this study, which was approved by the University of Illinois Institutional Review Committee. Ten clinically stable male subjects admitted to our Urology Service for transrectal prostatic needle biopsy received tobramycin for infection prophylaxis. The mean (± standard deviation [SD]) age of the subjects was 60 ± 18.0 years. All subjects had a calculated creatinine clearance of ≥60 ml/min, based on the method of Cockcroft and Gault (4), and a serum creatinine level of ≤1.2 mg/100 ml (Table 1). Subjects with unstable renal function, as defined by serum creatinine concentration fluctuations of >0.3 mg/100 ml during the study period, were excluded. Other exclusion criteria included hypersensitivity to piperacillin or tobramycin, presence of infected indwelling devices that could not be removed or replaced, and concurrent liver disease, as defined by alterations in liver function tests by more than twice the normal values.

Tobramycin sulfate (Nebcin; Eli Lilly & Co., Indianapolis, Ind.) was administered intravenously to each patient as a 1.5 mg/kg loading dose at 0600 on the morning of the biopsy. Two maintenance doses, as determined by the Sarubbi and Hull nomogram (19) were administered sequentially at 6-h intervals after the loading dose. Immediately after the third tobramycin dose, 4 g of piperacillin (Pipracil; Lederle Laboratories, Pearl River, N.Y.) was administered intravenously. This piperacillin dose was selected to simulate concentrations in serum at steady state associated with doses of 2 or 3 g every 4 h. Each dose of antibiotic was administered over 15 min as an intravenous infusion in 50 ml of 5% glucose.

Venous blood samples were obtained from a heparin lock placed in the arm contralateral to that in which
the antibiotics were being infused. During blood drawing, the first 1.5 ml of blood was discarded before a sample was obtained for antibiotic assay. After each specimen was obtained, 1.5 ml of heparin lock flush solution (100 U/ml) was injected to maintain patency. After the first tobramycin maintenance dose, serum samples were obtained immediately before and at 0.50, 1.25, 2.50, 3.75, and 5.67 h after completion of infusion. After the second tobramycin maintenance dose after piperacillin was administered, serum samples were obtained immediately before and at 0.50, 0.75, 1.25, 2.50, 3.75, 5.67 h after the completion of the tobramycin infusion. The level of tobramycin in serum at 5.67 h after the first maintenance dose represents the predose specimen for the second maintenance dose. The exact times of infusion and venous sampling were recorded and used for pharmacokinetic calculations.

To minimize inactivation of tobramycin by piperacillin during sample handling, each venous blood sample was placed in an ice bath immediately after collection and allowed to clot. The samples were then centrifuged for 5 min, and the sera were separated and stored at −70°C until they were assessed. Previous studies by Pickering and Gearhart (14) and in our own laboratory (unpublished data) have demonstrated that storage of serum specimens at −70°C for 1 month will not result in further aminoglycoside inactivation despite the continuing presence of various penicillins. In selected serum samples, penicillinase (10,000 U/ml of sample) was added as an additional measure to prevent the inactivation of tobramycin by piperacillin during handling. However, this procedure did not result in differences in tobramycin concentrations when compared with identical samples without penicillinase.

Within 72 h of sampling, tobramycin concentrations were determined by a radioimmunoassay technique (New England Nuclear Corp., Boston, Mass.). Within 1 month of sampling, piperacillin concentrations were measured by high-pressure liquid chromatography (D. T. Jung and N. Mahajan, submitted for publication).

Pharmacokinetic parameters were calculated by a one-compartment model with first-order kinetics. Linear regression analysis by the method of least squares was performed to determine the elimination rate constant (Kₑ). Half-life (t₁/₂) was calculated by the relationship $t₁/₂ = \log 2/Kₑ$. The volume of distribution (Vd) and the extrapolated peak serum concentration were calculated by the method of Sawchuk and Zaske (20) and Sawchuk et al. (21). The area under the serum concentration-time curve (AUC₀–∞) was estimated by using the logarithmic trapezoidal rule and extrapolating to infinity.

Statistical analysis was performed by using a paired t test to compare $t₁/₂$, $Kₑ$, $Vd$, and AUC₀–∞ between the tobramycin and tobramycin-piperacillin combination groups.

### RESULTS

The mean tobramycin concentrations in serum in 10 patients are shown in Table 2. The data compare the tobramycin concentrations when the aminoglycoside antibiotic was administered alone and in combination with piperacillin. The mean concentrations in serum are lower at all points of sampling for the tobramycin-piperacillin combination; however, the difference was not statistically significant ($P > 0.05$).

The mean ±SD half-life ($t₁/₂$) of tobramycin when administered alone was 2.9 ± 1.4 and 2.8 ± 0.9 h during combination treatment (Table 3). The mean ±SD elimination constant ($Kₑ$) was 0.29 ± 0.09 h⁻¹ when tobramycin was given alone and 0.27 ± 0.07 h⁻¹ when tobramycin-piperacillin was administered. The mean ±SD volume of distribution ($Vd$) was 0.27 ± 0.14 liter/kg in the tobramycin only group and 0.30 ± 0.11 liter/kg in the tobramycin-piperacillin group. AUC₀–∞ was 21.35 ± 8.33 μg/min per ml for tobramycin alone and 20.52 ± 11.02 μg/min per ml for combination treatment. Therefore, for each of the above parameters $t₁/₂$, $Kₑ$, $Vd$, and AUC₀–∞, paired t testing did not show any statistically significant differences between the two patient groups ($P > 0.05$).

The ratios of piperacillin to tobramycin concentration in serum were as follows for the indicated times: 0.50 h, 26.4 ± 9.0; 0.75 h, 23.9 ± 8.3; 1.25 h, 19.7 ± 7.5; 2.50 h, 12.6 ± 6.1; 3.75 h, 8.3 ± 5.1; and 5.67 h, 4.2 ± 3.5. The serum drug concentrations of piperacillin achieved were similar to those observed during typical treatment courses.

### DISCUSSION

Piperacillin, a ureidopenicillin, is bactericidal for *Pseudomonas* species. When used with aminoglycoside antibiotics, piperacillin exerts synergistic activity against most members of the family *Enterobacteriaceae*. The efficacy of this
antibiotic combination, which is particularly advantageous in febrile neutropenic or immunocompromised patients (12), is potentially limited by the degree of aminoglycoside inactivation that occurs. Without close monitoring of concentrations of the drug in serum and antibiotic dosage adjustments in some patients, ineffective aminoglycoside concentrations in serum could result in treatment failure.

It has been postulated that inactivation of the penicillin and formation of a biologically inert amide results from a nucleophilic reaction between the beta-lactam ring of the penicillin and the methylamino group on the aminoglycoside molecule (22). This interaction is affected by several factors, including the specific aminoglycoside antibiotic used, the renal function of the patient, and the concentration of penicillin in serum achieved. In a comparable study of the effect of carbenicillin on inactivation of aminoglycoside antibiotics in patients with end-stage renal failure on hemodialysis, Blair et al. (2) showed no changes in amikacin levels in serum or serum clearance with simultaneously administered carbenicillin. In contrast, carbenicillin decreased gentamicin half-life in serum and increased serum clearance by approximately 70 and 140%, respectively. These findings are similar to those from in vitro studies, which suggest that amikacin is most resistant, gentamicin is less resistant, and tobramycin is least resistant to inactivation by extended-spectrum penicillins (7, 14-16). Moreover, a clinically significant penicillin-aminoglycoside interaction appears to be more likely for patients with severe renal dysfunction, in whom high penicillin-aminoglycoside antibiotic ratios are achieved and maintained for prolonged time periods, thereby facilitating aminoglycoside inactivation. For patients with chronic renal failure, a decreased gentamicin concentration in serum and shorter gentamicin half-life have resulted from the concomitant administration of carbenicillin (2, 5, 6, 9, 10, 17, 22), ticarcillin (5, 6, 9, 18), and piperacillin (22). Similarly, ticarcillin has been reported to decrease the half-life of tobramycin in a patient with impaired renal dysfunction (3).

The deleterious effect of high penicillin concentrations and prolonged contact time on inactivation of aminoglycoside antibiotics has been supported by the results of numerous in vitro studies (7, 14, 15, 17, 23) and by a canine experimental model (16). Although there is one case report and one small study of gentamicin inactivation in patients with normal renal function by concurrent administration of carbenicillin (10) and ticarcillin (11), respectively, these findings are contrary to most other published clinical observations in patients with renal dysfunction.

Temperature and fluid environment are two
other factors which can affect the rate and extent of aminoglycoside inactivation in vitro during serum sample storage or processing before aminoglycoside assay or during preparation of intravenous admixtures. There appears to be a direct relationship between the temperature at which the antibiotic combination is incubated and the amount of aminoglycoside inactivation. Therefore, freezing temperatures inhibit (14, 15), whereas higher temperatures of 27 or 37°C enhance the loss of aminoglycoside activity (13, 17). As to the fluid environment, inactivation of aminoglycosides by extended-spectrum penicillins is most evident in aqueous solutions; however, the reaction is slowed in saline solutions or serum (8, 12, 16, 17).

Clinical investigation of the effect of piperacillin on aminoglycoside levels in serum has been limited to one published study of six patients with chronic renal failure undergoing hemodialysis three times per week. Piperacillin reduced the mean gentamicin half-life from 53.9 to 37.7 h (22). Our study is the first to determine the effect of piperacillin on tobramycin kinetics. Our interest in the latter combination stems from the use of tobramycin in patients infected with gentamicin-resistant members of the family Enterobacteriaceae, the preferential prescribing of this agent as a potentially less nephrotoxic aminoglycoside in selected patients (1), and the lack of published data about this drug interaction. Since tobramycin appears to be more susceptible than other aminoglycosides to inactivation by extended-spectrum penicillins, we sought to evaluate the effect of piperacillin on tobramycin pharmacokinetics to optimize antibiotic dosing when this antibiotic combination is used.

The results of our evaluation reveal no statistically significant changes in tobramycin concentration in serum, \( t^{1/2} \), \( K_{e1} \), \( V_d \), or AUC\( ^{0-\infty} \) when used concurrently with piperacillin. This antibiotic combination will not result in a clinically significant interaction in patients with normal renal function. Our results are consistent with speculations based on previous clinical studies of similar antibiotic combinations. That is, in patients with normal renal function, relatively rapid renal clearance limits the levels of antibiotics in serum achieved and the contact time between the drugs, thereby minimizing aminoglycoside inactivation (13, 17, 23). From our data on tobramycin, we suggest that gentamicin, amikacin, and netilmicin, which are generally less susceptible to inactivation by penicillins, are not affected by successive piperacillin administration in patients with normal renal function. In addition, staggered dose administration is probably unnecessary to minimize aminoglycoside inactivation when piperacillin is administered to such patients. Finally, no dosing

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<th>Subject no.</th>
<th>( K_r ) (h(^{-1}))</th>
<th>( t^{1/2} )</th>
<th>( V_d ) (liter ( \cdot ) kg(^{-1}))</th>
<th>AUC( ^{0-\infty} ) (μg/min per ml)</th>
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<td>Mean ± SD</td>
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<td>2.8 ± 0.9</td>
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adjustment of tobramycin, gentamicin, amikacin, or netilmicin is needed in patients with normal renal function who are also receiving piperacillin. Further evaluation of the piperacillin-tobramycin interaction in patients with chronic renal failure is in progress.

LITERATURE CITED