Lack of Evidence for Interaction Between Tobramycin and Shock in Their Effect on Renal Function

RICHARD F. AMBINDER,* RICHARD D. MOORE, CRAIG R. SMITH, E. DAVID MELLITS, AND PAUL S. LIETMAN

Division of Clinical Pharmacology and Experimental Therapeutics and the Division of Internal Medicine of the Department of Medicine, and Department of Oncology, The Johns Hopkins University, Baltimore, Maryland, 21205

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We sought to determine whether there was an interaction between aminoglycoside use and shock in their effect on renal function among seriously ill patients suspected of having gram-negative sepsis. Serial serum creatinine determinations were used to estimate changes in creatinine clearance rates in 179 patients entered onto a prospective randomized trial of tobramycin-nafcillin versus cefotaxime. A 25% decline in estimated creatinine clearance was considered to be clinically important. Univariate chi-square analysis showed that both shock (P < 0.01) and tobramycin use (P < 0.001) were independently associated with decline in estimated creatinine clearance. A two-way analysis of variance showed that both shock (F = 10.44, P < 0.01) and tobramycin use (F = 42.6, P < 0.001) continued to be significantly associated with renal dysfunction in the presence of each other, but there was no significant interaction between shock and tobramycin in their effect (F = 0.62, P < 0.43). A multiple logistic regression with an interaction term representing the occurrence of shock and tobramycin use simultaneously yielded similar results. Our study provided no analytic evidence supporting the existence of an interaction between shock and aminoglycoside use in their effect on renal function.

Deterioration of renal function is a relatively common occurrence among patients having or suspected of having serious gram-negative infections. Such patients are often treated with regimens containing an aminoglycoside (8). The incidence of renal dysfunction attributable to aminoglycosides in this setting has been estimated at 10 to 25% (7). Shock is another cause of decline in renal function and also occurs frequently in this population.

Until recently, virtually all patients with suspected sepsis were treated with an aminoglycoside, so it was not possible to determine whether a decline in renal function was secondary to the aminoglycoside, to shock, or to an interaction between the two. With the advent of alternatives to aminoglycosides in the therapy of serious gram-negative infection, it has become possible to look for evidence of an interaction in a clinical setting.

In this paper we present the results of a two-way analysis of variance and multiple logistic regression analysis performed on data derived from a previously reported prospective double-blind, randomized, controlled trial of an aminoglycoside-containing regimen versus a non-aminoglycoside-containing regimen (6). These analyses were designed to determine whether an interaction between tobramycin and shock contributed to producing clinically significant deterioration of renal function in the seriously ill patient.

MATERIALS AND METHODS

Case report forms from the clinical trial were analyzed (6). In this trial, patients with suspected or proven serious infections were randomized to receive either cefotaxime alone or the combination of tobramycin and nafcillin and evaluated in a double-blind manner. All antibiotics were administered intravenously. The regimen for cefotaxime was 2 g every 4 h. Nafcillin was administered as 1.5 g every 4 h. Tobramycin administration was begun with a loading dose of 2 mg/kg. Subsequently doses were calculated from the Chan nomogram (modified so that the dose for normal renal function was 2 mg/kg) by using an estimate of creatinine clearance derived from the Kampmann nomogram (2, 5). Plasma levels at 1 h after a dose of tobramycin were obtained within 72 h in all patients, and the subsequent dosage of tobramycin was adjusted to maintain the 1-h level between 5 and 10 μg/ml. If tobramycin levels remained within the desired range, measurements were repeated every Monday, Wednesday, and Friday. If the dosage was altered or the estimated creatinine clearance changed substantially, measurements were made more frequently. Clindamycin was added to the regimen at a dose of 2.4 g/day when a pelvic or gastrointestinal source of infection was suspected. Patients did not receive any other antibiotics during the course of the study. Serum creatinine was measured by the Johns Hopkins Hospital Department of Laboratory Medicine immediately before therapy and every Monday, Wednesday, and Friday thereafter.

Shock was defined as the development of a systolic blood pressure less than or equal to 80 mmHg. For the purposes of this analysis, only those patients who met this criterion and had a repeat serum creatinine test at least 12 h afterwards were considered. Patients who became suddenly hypotensive and died were excluded.

A clinically significant decline in renal function was defined as a 25% or greater fall in the calculated creatinine clearance. Creatinine clearance was calculated from the serum creatinine, age, weight, and sex of the patient by the method of Cockroft and Gault (3). To calculate the change in renal function, the baseline was considered to be the highest calculated creatinine clearance during the first 24 h of therapy. The difference between the baseline value and the lowest value during the remainder of therapy or within 48 h after cessation of therapy was divided by the baseline value and the percent change determined.

* Corresponding author.
Univariate chi-square analyses were performed to define the relationships of tobramycin treatment and shock, each considered separately, to a clinically significant decline in renal function. To determine whether there was an interaction between shock and tobramycin use, the following two statistical approaches were utilized: (i) a two-way analysis of variance with interaction and (ii) a multiple logistic regression with an interaction term. For these analyses a P value of less than 0.05 for the interaction term was considered to be analytic evidence of an interaction between tobramycin and shock in producing a clinically significant decline in renal function. In the regression model, treatment with tobramycin was assigned a value of 1, and treatment with cefotaxime was assigned a value of 0. The occurrence of shock was assigned a value of 1, and the absence of shock was assigned a value of 0. The interaction term was the product of the tobramycin term and the shock term (i.e., the presence of the two simultaneously).

The statistical analyses were performed using the Statistical Package for the Social Sciences, Release 9 (10), and the Statistical Analysis System, 1982 edition (9).

RESULTS

Two hundred patients were enrolled in the study and randomized to receive therapy; 195 actually received the drug. Two or more creatinine determinations were measured in 179 of these. The mean duration of therapy in the group given cefotaxime and the group given nafcillin-tobramycin did not differ (4.0 ± 2.7 days). The distribution of a 25% or greater fall in calculated creatinine clearance by antibiotic treatment group and by the presence and absence of shock is shown in Table 1.

As an initial step, the univariate relationships between a clinically significant decline in renal function and shock and a clinically significant decline in renal function and tobramycin use were determined independently. An association was found with both treatment with tobramycin and shock, although treatment with tobramycin (P < 0.001) was more strongly associated than was the occurrence of shock (P < 0.01).

<table>
<thead>
<tr>
<th>TABLE 2. Two-way analysis of variance*</th>
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<tbody>
<tr>
<td>Source of variation</td>
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</tr>
<tr>
<td>Tobramycin use</td>
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<tr>
<td>Shock</td>
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<tr>
<td>Two-way interaction (type x shock)</td>
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<tr>
<td>Model</td>
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<tr>
<td>Residual</td>
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* Model $r^2 = 0.23$.

A two-way analysis of variance was also performed (Table 2). Both shock and tobramycin use continued to be significant factors associated with significant decline in renal function in the presence of one another, suggesting an additive effect. The interaction between tobramycin use and the occurrence of shock did not show a significant association. A multiple logistic regression was performed (Table 3). The interaction term again failed to achieve significance, although tobramycin use and shock were again significant associated factors in the presence of one another.

Finally, it has been demonstrated that several factors can increase the risk for a decline in renal function in patients receiving aminoglycosides (4). Among these are patient age, patient gender, initial creatinine clearance, and liver disease.

We added these factors along with furosemide use and underlying prognosis to the multiple logistic regression analysis of tobramycin use, shock, and the tobramycin-shock interaction term. Our results were not appreciably changed. Tobramycin and shock were again found to be predictors of a decline in renal function, but the interaction term did not have a significant association.

DISCUSSION

Univariate analysis showed that the use of tobramycin and the occurrence of shock are both risk factors for a decline in glomerular function. However, analysis of variance and multiple logistic regression analysis provided no analytic evidence to support an interaction; i.e., the effect of tobramycin on renal function is independent of the effect of shock on renal function and vice versa. Thus, the presence or absence of shock does not alter the effect of tobramycin, and the presence of tobramycin does not alter the effect of shock on renal function. An alternative approach with a continuous measure of calculated creatinine clearance in a multiple regression analysis also failed to suggest a correlation. The P values of >0.40 for the two-way analysis of variance and >0.80 for the multiple logistic regression are large enough that it is unlikely that a major interaction would have been missed.

Other investigators have addressed the question of interaction in experimental animals. One group reported the effect of gentamicin administration before surgically induced ischemia in rats and concluded that gentamicin caused increased renal susceptibility to ischemic injury (11). Another group studying a rabbit model concluded that neomycin and ischemia were not synergistic and, indeed, not even additive in their damaging effects on the kidney (1). These seemingly conflicting results have not yet been resolved.

The clinical situation we monitored differed in many ways from the animal model. First, our patients received various durations of aminoglycoside therapy. Second, we could not directly quantify the degree of ischemia. The occurrence of ischemia had to be inferred from patients' hypotensive episodes, which varied in time of occurrence, duration, and severity. Third, the temporal relationships between the occurrence of the hypotensive episode and tobramycin therapy were variable, with therapy occurring before, during, or

<table>
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<th>TABLE 3. Multiple logistic regression</th>
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<tr>
<td>Variable</td>
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<tr>
<td>Tobramycin use</td>
</tr>
<tr>
<td>Shock</td>
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<td>Interaction</td>
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* Numbers within parentheses indicate 95% confidence intervals.
after shock. Finally, the particular aminoglycoside used may be important, although this seems unlikely. It is possible that there is a subgroup of patients in whom aminoglycoside use and ischemic insult interact synergistically to bring about renal damage, but we were unable to demonstrate this by our analysis.

A cautionary note: in this trial aminoglycoside plasma levels were closely monitored. It seems likely that, in a setting where levels are less frequently monitored, shock would lead to a diminished glomerular filtration rate, which would lead to elevated aminoglycoside levels leading in turn to a further renal deterioration. This vicious cycle would lead to an apparent, but spurious, interaction between shock and aminoglycoside therapy in causing decline in renal function.

In conclusion, an analysis of data derived from this study has provided no evidence to suggest an interaction between aminoglycoside use and the occurrence of shock in their effects on renal function in a seriously ill general medical population in which plasma tobramycin levels are frequently monitored.

LITERATURE CITED