Aminoglycoside-associated nephrotoxicity in extrahepatic obstructive jaundice

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Experimental data demonstrate that biliary obstruction increases renal sensitivity to gentamicin. In the present study the incidence of and risk factors for aminoglycoside nephrotoxicity were prospectively studied in patients with extrahepatic obstructive jaundice. Two hundred and thirty-seven hospitalized adult patients were classified into three groups. Group I consisted of 84 patients with extrahepatic obstructive jaundice, who received aminoglycoside (gentamicin or tobramycin). Group II consisted of 81 patients with extrahepatic obstructive jaundice, who received either antibiotics other than aminoglycoside or no antimicrobial therapy. Group III consisted of 72 noncholestatic patients receiving aminoglycosides for different disorders. Nephrotoxicity developed in 27 patients (32%) in group I vs 9 patients (11%) in group II and 4 patients (5.6%) in group III ($p<0.00001$). In group I, a comparison of patients with and without nephrotoxicity revealed significantly higher values in the former for mean serum bilirubin concentration, initial steady-state trough aminoglycoside concentration and estimated half-life. Stepwise multivariate analysis with nephrotoxicity status as the dependent variable determined that the most significant variable for predicting nephrotoxicity was serum total bilirubin level. In extrahepatic cholestasis a high serum bilirubin level is a distinct factor predisposing to aminoglycoside nephrotoxicity.

Key words: Aminoglycoside nephrotoxicity; Extrahepatic obstructive jaundice; Risk factors.

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jaundice, and to identify the factors associated with the development of this complication.

Patients and Methods
Adult medical or surgical patients (age ≥18 years) admitted to the University Hospital over the 18-month period from March 1991 through September 1992 were studied prospectively. All patients diagnosed with either extrahepatic obstructive jaundice or cholangitis, and with a length of stay greater than 24 h were followed. Group I consisted of patients with extrahepatic obstructive jaundice who received at least four consecutive doses of an aminoglycoside (gentamicin or tobramycin). Group II consisted of patients with extrahepatic obstructive jaundice who received either antibiotic agents other than aminoglycosides or no antimicrobial therapy.

The diagnosis of extrahepatic obstructive jaundice was based on clinical history and specific laboratory tests, and was confirmed when a definitive cause of obstruction could be documented by echography, computerized axial tomography or cholangiography (transhepatic, endoscopic retrograde or intraoperative), ruling out, then, an intrahepatic cholestasis.

Patients seen by the Clinical Pharmacology Service for pharmacokinetic evaluation and dose adjustment of aminoglycoside therapy, and who did not have hepatobiliary disorders, were also prospectively followed and designated as the control study population (Group III). The diagnoses were heterogeneous and included acute pancreatitis, pyelonephritis, diverticulitis, pneumonia, exacerbations of chronic bronchitis, wound infections, septic arthritis and miscellaneous disorders.

The protocol was designed in accordance with the guidelines of the Declaration of Helsinki, and was approved by our center's ethical committee.

The decision to start antimicrobial therapy and choice of drug were made by the patient's physician, who was not informed of the study. In our clinical setting an aminoglycoside in combination with ampicillin or a cephalosporin are the most widely used antibiotic regimens for cholangitis. Concomitant antibiotic therapy was administered as clinically indicated in all groups. Agents taken into account as potential risk factors were cephalosporins, penicillins, clindamycin and vancomycin (11).

Excluded were patients with parenchymal liver disease, shock, pre-existing renal dysfunction, heart failure or previous exposure to intravenous contrast medium or prostaglandin synthesis inhibitors.

Renal dysfunction was defined as an increase in serum creatinine greater than or equal to 0.5 mg/dl. The change in serum creatinine level was determined by subtracting the initial level from the highest level during therapy or within 2-4 days after discontinuation of therapy. Patients in group II were evaluated from admission until discharge. This definition is consistent with that used in many other studies of aminoglycoside-induced nephrotoxicity (2, 12-14).

Serum creatinine concentration was measured before aminoglycoside treatment, every other day of therapy thereafter, and 3-5 days after therapy. The patient's maximum serum creatinine had to be >1.0 mg/dl to be considered nephrotoxic.

In each patient who met the nephrotoxicity criteria, the case was carefully reviewed to exclude other possible explanations before we considered nephrotoxicity as treatment-associated.

Creatinine clearance, reported as ml/min, was estimated by the method of Cockcroft & Gault (15) and adjusted for female sex by a factor of 0.85. Lean body weight was used in the calculation of creatinine clearance in obese subjects. Obesity was estimated using the body mass index.

Patients were followed daily, and data on demographic characteristics, height, weight, temperature, type, total dose and duration of aminoglycoside therapy, renal and hepatic function tests, hematology, urinalysis, clinical course, concomitant illness, medications and patient outcome were recorded at baseline and throughout the study, in addition to pharmacokinetic data. Serum levels used for biochemical analysis were those at the onset of therapy.

Aminoglycosides were administered by a 30-min intravenous infusion. Venous blood samples for aminoglycoside assays were collected into nonheparinized glass tubes (16), and were obtained at steady state (after at least 2 consecutive days of equal doses) before infusion of the dose and 30 min after the end of infusion. Exact infusion times, sampling times, the drug dose and duration of therapy were obtained for all patients.

Serum samples were assayed within 6 h after collection by an enzyme multiplied immunoassay technique (EMIT, Syva) using a Roche Cobas MIRA autoanalyzer. The coefficient of variation was <10% for gentamicin or tobramycin concentrations between 0 and 10 \( \mu \text{g/ml} \). Dose adjustment recommendations were calculated by the method of Sawchuk et al. (17). All pharmacokinetic calculations assumed a one-compartment model with first-order elimination kinetics. This method has been shown to provide reasonable estimates of pharmacokinetic parameters using two steady-state serum concentration-time points (18). Patients were not included in the analysis more than once.

Maintenance aminoglycoside doses were given in
Aminoglycoside nephrotoxicity in cholestasis

Three or two divided doses and were adjusted according to assay results, in an attempt both to achieve adequate peak serum concentrations (in the range of 5-10 μg/ml) and to keep pre-dose trough levels below 1.5 μg/ml.

Statistical methods

All data were analyzed using the Statistical Package for the Social Sciences (SPSSx) and SAS/Stat. The incidence of nephrotoxicity in the three groups was compared using Pearson’s chi-square analysis. Categorical variables were analyzed with Chi-square tests, and continuous data were analyzed with Student’s t-test for unpaired data or analysis of variance (ANOVA). When this indicated significant (p<0.05) differences, Tukey’s LSD test was used to determine the groups responsible for significance in ANOVA.

All of the factors were tested in a stepwise multivariate analysis, using a logistic regression model with nephrotoxicity as the dependent variable. A stepwise p-value of <0.05 for the chi-squared model was required for factors to be included in the final logistic model.

Regression coefficients estimated from multiple logistic regression were used to compute the probabilities of developing nephrotoxicity (P(NT)). The equation for the logistic approach is:

\[
P(NT) = \frac{1}{1 + e^{-(\beta_0 + \beta_1X_1 + \beta_2X_2 + \ldots + \beta_kX_k)}}
\]

\(X_1, X_2, \ldots X_k\) are independent variables or risk factors and \(\beta_0, \beta_1, \beta_2, \ldots \beta_k\) are the variable coefficients determined by logistic regression. This formula was used to calculate P(NT) for each patient in the study and to measure the fit of the model to the study population (19).

Results

Characteristics of the patients

One hundred and sixty-five patients with extrahepatic biliary obstruction were studied prospectively. Of these, 84 received more than four consecutive doses of an aminoglycoside (79 gentamicin; 5 tobramycin) (group I). An additional 81 patients (group II) received antibiotics other than aminoglycosides (39 patients) or no antimicrobial therapy (42 patients). Seventy-two control patients (group III) received aminoglycosides (69 gentamicin; 3 tobramycin).

The infectious processes under treatment in group III were intraabdominal in 34, urinary tract in eight, wound in eight, pneumonia in five, bone and joint in five, bacteremia in four, skin/soft tissue in three, neutropenic fever in one, and endocarditis in one patient.

The three groups were compared for demographic characteristics, baseline laboratory values, aminoglycoside treatment and clinical characteristics (Table 1). A significant difference existed for sex, women being more frequent in the groups with extrahepatic obstructive jaundice. Baseline hepatic function was similar in the groups with extrahepatic obstructive jaundice, but significantly different from controls. There were no differences in duration of therapy or in mean peak and trough concentration of aminoglycoside. No significant differences were found between the groups for any of the renal function tests or baseline clinical factors assessed (presence of fever, leukocytosis and blood pressure), and there was no clinical evidence that infections were more serious in one group than the other. A similar proportion of patients in each group had diabetes, and similar proportions received concomitant penicillin, other antibiotics or furosemide therapy; the only exception was cephalosporins, which were prescribed most frequently in group II.

Incidence of nephrotoxicity

Forty patients met the criteria for renal toxicity. The incidence of nephrotoxicity, defined as an increase in serum creatinine of more than 0.5 mg/dl, was 32% in jaundiced patients receiving aminoglycosides (27 out of 84), 11% in those not receiving aminoglycosides (9 of 81) and 5.6% (4 of 72) in the control group (p<0.00001).

No patient meeting the nephrotoxicity criteria had another clear reason (hypotension, volume contraction, arrhythmias) for the rise in serum creatinine. The mean increase in serum creatinine level above baseline in nephrotic patients was 1.8±1.9 mg/dl (range: 7.3 to 0.5 mg/dl, group I), 1.3±1.0 mg/dl (range: 3.6 to 0.5 mg/dl, group II) and 1.2±0.7 mg/dl (range: 2.2 to 0.5 mg/dl, group III). In patients with aminoglycoside-related nephrotoxicity, the rise in serum creatinine always occurred during therapy.

Only four patients with neoplastic biliary obstruction received aminoglycosides. Of these, three developed nephrotoxicity. Among cholestatic patients who did not receive aminoglycosides, there were nine in whom biliary obstruction was due to neoplastic disease. Of these, three developed renal dysfunction.

None of the patients who developed toxicity had a peak gentamicin level greater than 6.0 μg/ml. Two patients in whom toxicity developed in response to aminoglycoside had an initial trough level greater than 2.0 μg/ml.

Comparisons of patients with (40) or without (196) renal impairment showed that the factors significantly associated with decreased renal function were an in-
### TABLE 1
Comparison of demographic and clinical variables among groups

<table>
<thead>
<tr>
<th></th>
<th>Control + AMG</th>
<th>EOJ + AMG</th>
<th>EOJ</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55±19 (72)</td>
<td>61±15 (84)</td>
<td>63±16 (80)</td>
<td>ns</td>
</tr>
<tr>
<td>Female (%)</td>
<td>77 (38%)</td>
<td>50 (61%)</td>
<td>38 (48%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70±13</td>
<td>68±11</td>
<td>70±3</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Baseline serum levels</strong></td>
<td></td>
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</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.94±0.4 (72)</td>
<td>0.88±0.4 (84)</td>
<td>0.84±0.3 (80)</td>
<td>ns</td>
</tr>
<tr>
<td>Estimated creatinine clearance (ml/min)</td>
<td>101±36 (72)</td>
<td>105±47 (84)</td>
<td>107±68 (80)</td>
<td>ns</td>
</tr>
<tr>
<td>Prothrombin activity (%)</td>
<td>70±9 (56)</td>
<td>68±11 (70)</td>
<td>70±9 (69)</td>
<td>ns</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>0.6±0.3* (32)</td>
<td>7.2±7.1 (60)</td>
<td>9.1±7.4 (71)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l)</td>
<td>216.3±158.1* (29)</td>
<td>622.4±334.6 (56)</td>
<td>680.6±322.7 (69)</td>
<td>0.00001</td>
</tr>
<tr>
<td>GGT (U/l)</td>
<td>33.8±29.7* (39)</td>
<td>118.1±105.1 (69)</td>
<td>113.5±96.7 (74)</td>
<td>0.001</td>
</tr>
<tr>
<td>GPT (U/l)</td>
<td>34.7±27.4* (34)</td>
<td>155.7±177.3 (61)</td>
<td>146.3±186.2 (72)</td>
<td>0.001</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>34±0 (23)</td>
<td>34±7 (43)</td>
<td>56±8 (47)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>24 (33%)</td>
<td>31 (37%)</td>
<td>21 (26%)</td>
<td>ns</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>23 (32%)</td>
<td>33 (41%)</td>
<td>30 (37%)</td>
<td>ns</td>
</tr>
<tr>
<td>Penicillin</td>
<td>30 (42%)</td>
<td>34 (43%)</td>
<td>8 (21%)</td>
<td>0.045</td>
</tr>
<tr>
<td>Other antibiotics</td>
<td>16 (22%)</td>
<td>3 (10%)</td>
<td>5 (13%)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Total dose (mg)</strong></td>
<td>2158±1679 (72)</td>
<td>2041±1160 (83)</td>
<td>–</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Duration of therapy (days)</strong></td>
<td>9.8±5.8 (72)</td>
<td>10.0±5.4 (83)</td>
<td>–</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Trough level (µg/ml)</strong></td>
<td>0.6±0.7 (55)</td>
<td>0.9±0.9 (53)</td>
<td>–</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Peak level (µg/ml)</strong></td>
<td>3.6±1.5 (55)</td>
<td>4.1±1.7 (53)</td>
<td>–</td>
<td>ns</td>
</tr>
</tbody>
</table>

* Different from the other groups. AMG=aminoglycosides, EOJ=extrahepatic obstructive jaundice.

Mean±SD (n). GGT=gamma-glutamyl transpeptidase, GOT=glutamic-oxaloacetic transaminase, GPT=glutamic-pyruvic transaminase. To convert from U/l to µkat/l, multiply alkaline phosphatase, GGT, GOT and GPT by 0.01667.

### TABLE 2
Demographic and clinical information on nephrotoxic and non-nephrotoxic patients

<table>
<thead>
<tr>
<th></th>
<th>Nephrotoxicity</th>
<th>No nephrotoxicity</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64±14 (40)</td>
<td>60±17 (196)</td>
<td>ns</td>
</tr>
<tr>
<td>Female (%)</td>
<td>20 (54%)</td>
<td>90 (51%)</td>
<td>ns</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68±11 (22)</td>
<td>69±12 (95)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Baseline serum levels</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.66±0.4 (40)</td>
<td>0.88±0.4 (196)</td>
<td>ns</td>
</tr>
<tr>
<td>Estimated creatinine clearance (ml/min)</td>
<td>101±36 (40)</td>
<td>103±47 (196)</td>
<td>ns</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>11.4±9.2 (31)</td>
<td>5.6±6.2 (71)</td>
<td>0.002</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l)</td>
<td>699.7±316.9 (29)</td>
<td>554.9±341.3 (125)</td>
<td>ns</td>
</tr>
<tr>
<td>GGT (U/l)</td>
<td>484.6±353.8 (30)</td>
<td>304.6±306.5 (131)</td>
<td>0.00001</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>21 (52%)</td>
<td>51 (29%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Furosemide</td>
<td>3 (8%)</td>
<td>15 (9%)</td>
<td>ns</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>18 (51%)</td>
<td>88 (56%)</td>
<td>ns</td>
</tr>
<tr>
<td>Penicillin</td>
<td>13 (37%)</td>
<td>69 (44%)</td>
<td>ns</td>
</tr>
<tr>
<td>Other antibiotics</td>
<td>7 (20%)</td>
<td>22 (14%)</td>
<td>ns</td>
</tr>
<tr>
<td>Total dose (µg)</td>
<td>2054±1046 (31)</td>
<td>2106±1504 (124)</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of therapy (days)</td>
<td>10.7±5.5 (31)</td>
<td>9.7±5.7 (125)</td>
<td>ns</td>
</tr>
<tr>
<td>Estimated half-life (h)</td>
<td>7.2±5.9 (18)</td>
<td>3.9±2.6 (79)</td>
<td>0.03</td>
</tr>
<tr>
<td>Trough level (µg/ml)</td>
<td>1.4±1.0 (18)</td>
<td>0.8±0.8 (79)</td>
<td>0.006</td>
</tr>
<tr>
<td>Peak level (µg/ml)</td>
<td>4.2±1.2 (18)</td>
<td>3.9±1.7 (79)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Mean±SD (n). GGT=gamma-glutamyl transpeptidase, GOT=glutamic-oxaloacetic transaminase, GPT=glutamic-pyruvic transaminase. To convert from U/l to µmol/l, multiply bilirubin by 17.1 To convert from U/l to µkat/l, multiply alkaline phosphatase, GGT, GOT and GPT by 0.01667.

A decrease in mean baseline serum total bilirubin level and gamma glutamyl transpeptidase, increased steady state trough aminoglycoside concentration and initial aminoglycoside half-life, and the presence of diabetes (Table 2).

A decrease in mean baseline initial calculated creati-
nine clearance was the only change associated (p≤0.048) with the development of aminoglycoside nephrotoxicity in the control group (67±27 ml/min vs 103±36 ml/min in non-nephrotoxic patients).

There were nine patients who developed renal dysfunction in group II (five received antibiotics other than aminoglycosides and four no antimicrobial therapy). Six out of nine had diabetes, a higher mean serum bilirubin level (13.5±10.9 mg/dl vs 8.6±6.7 mg/dl in non-renal impaired patients) and similar values for initial leukocyte count (×10⁹/mm³) (9.3±7.1 vs 9.7±4.1) and mean baseline serum creatinine concentration (0.86±0.4 mg/dl vs 0.83±0.3 mg/dl).

Comparisons of patients with extrahepatic obstructive jaundice in whom aminoglycoside nephrotoxicity did and did not develop, revealed significantly higher values in the former for mean serum bilirubin concentration (12.2±8.3 mg/dl (n=20) vs 4.7±4.8 mg/dl (n=40), p<0.001), initial steady state trough aminoglycoside concentration (1.3±0.9 µg/ml (n=17) vs 0.8±0.9 µg/ml (n=36), p<0.037) and initial estimated half-life (6.2±4.2 h vs 3.7±2.9 h, p<0.01). Renal dysfunction occurred in 16 of 30 patients (54%) with a serum bilirubin level greater than 5.0 mg/dl, and in 4 of 30 (13%) with a serum bilirubin level ≤5.0 mg/dl (p<0.001).

Thus, patients with basal serum bilirubin levels >5 mg/dl were four times more likely to have developed nephrotoxicity than those whose bilirubin levels were ≤5 mg/dl.

Predictors of nephrotoxicity
A multiple logistic regression model with nephrotoxicity status as the dependent variable was used to analyze the results in a population of 163 patients (60 group I, 71 group II and 32 group III; 74 patients deleted due to missing data). The most significant variable for predicting nephrotoxicity was basal serum total bilirubin level (odds ratio 1.14; 95% confidence interval, 1.07-1.21; p<0.0001).

The regression coefficient estimated from multiple logistic regression was used to compute the probabilities of renal dysfunction for each patient group, according to pretreatment serum total bilirubin levels. When we analyzed the probability of the appearance of renal impairment in the study population according to intervals of serum bilirubin concentration, we found a notable increase in the risk of renal dysfunction when serum bilirubin was ≥5 mg/dl. This probability increased from 0.13 (95% CI, 0.11-0.14) in patients with serum bilirubin levels between 3 and 5 mg/dl, to 0.18 (95% CI, 0.13-0.22), when serum bilirubin was from 5 to 10 mg/dl, and was greatest when bilirubin levels surpassed 15 mg/dl (probability 0.44, 95% CI, 0.24-0.63). According to these considerations serum bilirubin levels of 5 mg/dl were chosen as a cut-off point to compare the incidence of nephrotoxicity.

Aminoglycosides can potentially cause nephrotoxicity; thus, an analysis of the interaction terms for the variables associated with nephrotoxicity designed as a guide in clinical decision-making – is summarized in Table 3. This analysis showed that interaction between bilirubin levels >5 mg/dl and aminoglycoside use was associated with an increased risk for the development of renal dysfunction.

Comparisons of the expected number of cases of nephrotoxicity for each interval of probability (P(NT)) with the observed number are shown in Table 4. The results demonstrate that the logistic model accurately fitted the study population.

Discussion
Aminoglycoside antibiotics remain an effective therapeutic modality in the treatment of gram-negative biliary tract infection in a general hospital setting. However, an important limitation in their use is the potential for adverse effects, most notably nephrotoxicity.

In the present study a 32% incidence of nephrotoxicity was found in jaundiced patients on aminoglycoside therapy, which is strikingly higher than the incidence
found in the control group (5.6%). This incidence is similar to the average incidence of aminoglycoside-associated nephrotoxicity, estimated to be 10% (11).

However, the 32% incidence of renal dysfunction in patients with obstructive jaundice is much higher than expected, and is similar to the reported incidence of 31.4% in patients with cirrhosis with features of portal hypertension and advanced liver failure (7). In a previous report of 42 episodes of biliary obstruction and/or cholangitis treated with aminoglycosides, eight patients (19%) developed nephrotoxicity (8).

Factors associated with aminoglycoside nephrotoxicity include hypotension, duration of therapy, associated liver disease, shock, advanced patient age, and coadministration of other nephrotoxic drugs (5,6,14,20). Nevertheless, none of these currently identified risk factors have been particularly sensitive in predicting nephrotoxicity in other patient populations, which suggests that other factors may be important (14,21). The model predicting aminoglycoside nephrotoxicity may be institution related (14), or may be more accurate for specific pathologies (22).

The nephrotoxic risk factors identified in this study by multiple logistic regression deserve attention. The interaction between elevated total bilirubin level at baseline and aminoglycoside use was associated with increased risk for the development of nephrotoxicity.

The high incidence of nephrotoxicity found in our group of patients was not due to differences in aminoglycoside dosing schedules. Furthermore, the three groups studied were similar with regard to the presence of underlying factors that could modify the risk of toxicity, and none of our patients had clinical evidence of dehydration or hemodynamic compromise at the onset of renal impairment. In addition, baseline liver function was not different in the two groups with obstructive jaundice.

In contrast with other studies (5,6,14,20) designed to investigate aminoglycoside nephrotoxicity, we included only patients with a "normal" basal serum creatinine level. However, it is well recognized that in the elderly, renal function can be overestimated from serum creatinine concentration because of reduced creatinine production, consequent to reduced muscle bulk.

This specific feature of liver disease as a risk factor for nephrotoxicity was first reported in a retrospective study including only patients with extrahepatic obstructive jaundice (8). This study lacked a control group of patients who were not receiving an aminoglycoside. An increased mean total bilirubin level was recently associated with development of nephrotoxicity in seriously ill, non-neutropenic patients (13). Thus, total serum bilirubin levels may become a key independent factor in identifying patients at risk for aminoglycoside nephrotoxicity.

It should be taken into account that obstructive jaundice itself induces renal impairment. This has also been related to elevated serum bilirubin levels, even after adjusting for postoperative sepsis and other complications (23,24). Therefore, the matched group of cholestatic patients not receiving aminoglycosides, in whom the incidence of nephrotoxicity was only 11%, and the stepwise multivariate analysis, provide further evidence that interaction between aminoglycoside use and serum bilirubin levels increase the probability of nephrotoxicity beyond what might be expected for each risk factor considered independently. Although our jaundiced patients were not randomly assigned to treatment groups, we think that the risk of selection bias is absent, since at the time of starting treatment the patient's physician was unaware of the study protocol, and baseline characteristics were similar in patients who did and did not receive aminoglycosides.

Most patients who developed renal dysfunction in group II had diabetes. It is unclear whether it was a causal association, because this subgroup of patients also had a slightly higher mean serum bilirubin concentration. In fact, animal studies suggest that diabetes protects from gentamicin nephrotoxicity when renal function is not decreased (25).

Higher measured trough serum concentrations and prolonged half-life were variables identified by univariate analysis. It is unclear whether these were a result of or a cause of reduced renal function. Interestingly, bile-duct ligated rats that developed nephrotoxicity after gentamicin treatment had an increased trough gentamicin concentration even before the appearance of impaired renal function (9,10). Thus, although considerable overlap was observed in individual levels, elevated trough serum concentration may be of value in predicting nephrotoxic potential.

The mechanisms underlying increased susceptibility to aminoglycoside nephrotoxicity in jaundiced patients with extrahepatic biliary obstruction remain elusive, with several factors involved in the production of renal impairment. Bilirubin and bile acids have effects at the cellular level which might be additive to those of aminoglycoside, since gentamicin—like bilirubin and bile acids—uncouples mitochondrial oxidative phosphorylation, inhibits ATPase activity and disrupts plasma and lysosomal membranes (9).

Another factor that deserves examination is renal hemodynamics. Animal studies have shown that common bile-duct ligation is associated with normal glomerular filtration rate and diminished renal blood flow (26). Renal underperfusion enhances aminoglycoside
nephrotoxicity (27). However, some features of these models, such as the impaired response to renal vasodilators, have been described in the chronic cirrhotic phase of common bile duct ligation (28), and therefore, the findings cannot be extrapolated to patients with acute biliary obstruction.

A prostaglandin-mediated mechanism has been suggested to explain the greater susceptibility of patients with cirrhosis to aminoglycoside nephrotoxicity (6). In patients with liver failure and stable renal function, elevated serum prostanoylicin levels and increased levels of urinary prostaglandin E₂, a renal vasodilator, are hypothesized to be mechanisms by which the kidney compensates for the vasoconstrictive stimulus of angiotensin. Because aminoglycosides have been shown to inhibit renal phosphatidylinositol-specific phospholipase C—a enzyme important for the release of arachidonic acid, a prostaglandin precursor (29)—aminoglycosides may interfere with this compensatory mechanism to maintain cortical renal blood flow. In fact, a fall in levels of urinary prostaglandin E₂ has been reported during the development of aminoglycoside nephrotoxicity (6).

An increase in renal prostaglandin production in response to renal vasoconstriction was also found in animal models of bile-duct ligation (30,31). Nonetheless, it is unclear whether a similar mechanism operates in patients with acute biliary obstruction.

Finally, systemic endotoxemia is a common feature in cirrhosis and extrahepatic biliary obstruction (32). Endotoxia occurs in common bile-duct ligated rats (33) and in humans with extrahepatic cholestasis (32), and is a factor known to potentiate gentamicin nephrotoxicity (34). Endotoxins (bacterial lipopolysaccharides) are able to induce nitric oxide synthase; the resulting increase in nitric oxide production leads to vasorelaxation and decreased responsiveness to vasoconstrictors (35,36). Thus, systemic endotoxemia might also play a role in the susceptibility of patients with obstructive jaundice to aminoglycoside nephrotoxicity, through an impairment in renal perfusion.

In conclusion, patients with extrahepatic cholestasis are at increased risk for aminoglycoside nephrotoxicity. In this population, the elevated serum bilirubin concentration is a distinct factor predisposing to aminoglycoside nephrotoxicity. This conclusion is supported by experimental studies and a retrospective analysis, and should serve to stimulate the search for other less toxic antibiotic regimens.

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