Prevalence and Risk Factors for Aminoglycoside Nephrotoxicity in Intensive Care Units[▽]

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In order to assess the prevalence of and risk factors for aminoglycoside-associated nephrotoxicity in intensive care units (ICUs), we evaluated 360 consecutive patients starting aminoglycoside therapy in an ICU. The patients had a baseline calculated glomerular filtration rate (cGFR) of ≥30 ml/min/1.73 m². Among these patients, 209 (58%) developed aminoglycoside-associated nephrotoxicity (the acute kidney injury [AKI] group, which consisted of individuals with a decrease in cGFR of >20% from the baseline cGFR), while 151 did not (non-AKI group). Both groups had similar baseline cGFRs. The AKI group developed a lower cGFR nadir (45 ± 27 versus 79 ± 39 ml/min/1.73 m² for the non-AKI group; $P < 0.001$); was older (56 ± 18 years versus 52 ± 19 years for the non-AKI group; $P = 0.033$); had a higher prevalence of diabetes (19.6% versus 9.3% for the non-AKI group; $P = 0.007$); was more frequently treated with other nephrotoxic drugs (51% versus 38% for the non-AKI group; $P = 0.024$); used iodinated contrast more frequently (18% versus 8% for the non-AKI group; $P = 0.0054$); and showed a higher prevalence of hypotension (63% versus 44% for the non-AKI group; $P = 0.0003$), shock (56% versus 31% for the non-AKI group; $P < 0.0001$), and jaundice (19% versus 8% for the non-AKI group; $P = 0.0036$). The mortality rate was 44.5% for the AKI group and 29.1% for the non-AKI group ($P = 0.0031$). A logistic regression model identified as significant ($P < 0.05$) the following independent factors that affected aminoglycoside-associated nephrotoxicity: a baseline cGFR of <60 ml/min/1.73 m² (odds ratio [OR], 0.42), diabetes (OR, 2.13), treatment with other nephrotoxins (OR, 1.61) or iodinated contrast (OR, 2.13), and hypotension (OR, 1.83). In conclusion, AKI was frequent among ICU patients receiving an aminoglycoside, and it was associated with a high rate of mortality. The presence of diabetes or hypotension and the use of other nephrotoxic drugs and iodinated contrast were independent risk factors for the development of aminoglycoside-associated nephrotoxicity.

Aminoglycosides are potent bactericidal antibiotics that are highly effective against gram-negative bacterial infections. They have increasingly been used as gram-negative organisms have become progressively more resistant to beta-lactam antibiotics and fluoroquinolones (8). In fact, they were recently found to be prescribed in 12.1% of the cases in which an antibiotic was necessary in the intensive care unit (ICU) (10). Aminoglycosides are administered by the parenteral route, have low albumin plasma binding levels, and are freely eliminated by glomerular filtration and reabsorbed by the proximal tubule (26). A fraction of the filtered load of the antibiotic binds to megalin, a receptor from the brush border of proximal tubule segments S1 and S2, which then transports it to the interior of the tubule cells (25). Their half-life in the renal cortex is estimated to range from 30 to 700 h (1).

The most important adverse effects of aminoglycosides are nephrotoxicity, ototoxicity, and, more rarely, neuromuscular blockade. Renal injury can occur in a substantial number of patients receiving an aminoglycoside, and whether it occurs depends on the patient's clinical condition and interactions with other nephrotoxic drugs (26). The most usual clinical presentation for aminoglycoside-associated nephrotoxicity is nonoliguric acute kidney injury (AKI), which occurs following 7 to 10 days of therapy (1, 26). Aminoglycoside-associated kidney injury may manifest as a decrease in the glomerular filtration rate (GFR), enzymuria, aminoaciduria, glycosuria, hypomagnesemia, hypocalcemia, and hypokalemia. Fanconi-like and Bartter-like syndromes, as well as impaired renal concentrating mechanisms, have also been described (15, 19, 26).

Several risk factors for aminoglycoside-associated nephrotoxicity have been identified, including the presence of comorbidities, volume depletion, liver dysfunction, sepsis, renal dysfunction, hypokalemia, hypomagnesemia, advanced age, prolonged therapy, the type of aminoglycoside, the frequency of aminoglycoside dosing, an elevated serum aminoglycoside concentration, the timing of aminoglycoside administration, the simultaneous consumption of other medications, and interactions with other nephrotoxic drugs (5, 34). However, the majority of published studies (2, 5, 24, 27, 29, 30, 32) did not evaluate several of the most important risk factors simultaneously, had small sample sizes, or did not use appropriate statistical methods for risk factor assessment. In addition, few studies analyzed ICU patients.

Therefore, the aim of the present study was to assess the prevalence of aminoglycoside-associated nephrotoxicity in a large cohort of ICU patients and identify the independent risk factors associated with the development of renal injury.

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MATERIALS AND METHODS

This study was carried out through a retrospective cohort analysis of patients admitted to a clinical-surgical ICU (24 beds) of a tertiary-care university hospital over a period of three consecutive years. The study was approved by the local ethics committee (Sao Jose do Rio Preto Medical School, Sao Jose do Rio Preto, Brazil).

The ICU patients included in the study were ≥18 years old, they had begun the use of an aminoglycoside (amikacin or gentamicin) in the ICU, they had been taking the antibiotic for at least 4 days, and they had a calculated GFR (cGFR) of ≥30 ml/min/1.73 m² at the time that they began taking the aminoglycoside. The patients were treated with a single daily dose of aminoglycoside, and the initial doses were 3 to 5 mg/kg of body weight/day of gentamicin and 10 to 15 mg/kg/day of amikacin. Dose adjustments were performed by use of the cGFR. If the cGFR was <10 ml/min, gentamicin was given every 72 h, and if the cGFR was between 10 and 50 ml/min, gentamicin was given every 48 h. If the cGFR was <10 ml/min, 50% of the recommended amikacin dose was given every 48 h, and if the cGFR was between 10 and 50 ml/min, 50% of the recommended amikacin dose was given every 24 h.

The GFR was calculated by using the abbreviated modification of diet in renal disease (MDRD) formula, which includes sex, ethnicity, age, and serum creatinine level (17).

Nephrotoxicity was defined as a decrease in the cGFR of 20% or more from the baseline cGFR during aminoglycoside use. According to this definition, patients were divided into two groups: those with nephrotoxicity (the AKI group) and those without nephrotoxicity (the non-AKI group).

The following variables were assessed: sex; age; baseline cGFR (determined by use of the baseline serum creatinine level) and nadir cGFR (determined by use of the peak serum creatinine level); time of AKI diagnosis; the presence of oliguria (urine output, <400 ml/day); the presence of a previous renal disease (clinical report of renal calculi, glomerulonephritis, urinary tract infection, nephrotic syndrome, or nephritic syndrome); the presence of diabetes mellitus (clinical report); the presence of cardiovascular disease (clinical report of hypertension, coronary disease, or stroke); the presence of hypovolemia/dehydration (skin and mucosa appearance; heart rate, >120 beats per min; and at least one of the following: abundant vomiting, diarrhea, gastric tube drainage of >2 liters/day, or severe bleeding during the 24 h preceding aminoglycoside use)p occurrence of shock (a need for vasopressors); the occurrence of hypotension (systolic blood pressure of <80 mmHg or a 40% decrease in the customary blood pressure); jaundice (jaundice and/or a total bilirubin concentration of >2 mg/dl); the simultaneous use of other drugs, specifically, nephrotoxic drugs (nonsteroidal anti-inflammatory agents, vancomycin, cephalothin [cefalotin], amphotericin B, cisplatin, cyclosporine, tacrolimus), iodinated contrast, and furosemide; metabolic acidosis (pH < 7.30 and bicarbonate concentration of <20 meq/liter); hypokalemia (potassium concentration, <3.0 meq/liter); hepatic failure (on the basis of three of the following six criteria: serum glutamic oxalacetic transaminase level more than two times normal, total bilirubin concentration of >2.5 mg/dl, albumin concentration of <3.0 g/dl, increase in serum alkaline phosphatase level, prothrombin time of >15 s, and ascites); the duration of aminoglycoside use; and mortality.

Statistical analysis. The results are reported as a percentage or the mean ± standard deviation. Univariate analysis was performed by using a two-tail, nonpaired Student's t test, the Mann-Whitney test, or Fisher's test, as appropriate.

The variables that were statistically significant, on the basis of univariate analysis, or that were considered clinically important were analyzed by multivariate analysis by use of a logistic regression model. The initial model included the following variables (with the reference for each variable indicated in parentheses): age (<60 years); sex (male); baseline cGFR (≥60 ml/min/1.73 m²); time of aminoglycoside use (<10 days); type of aminoglycoside used (amikacin); and the presence of cardiovascular disease, diabetes, acidosis, hypovolemia, hypotension, or jaundice; furosemide use; iodinated contrast use; and the use of other nephrotoxic drugs (with the reference being the absence of these variables or nonuse of the drug). Shock was not included because it showed a strong correlation (0.76) with hypotension.

Two-way interactions between terms of interest were removed simultaneously from the initial model and were evaluated by the likelihood ratio test (the chunk test). As a group, the interaction terms were not statistically significant and were not included in the final model ($P = 0.97$).

Backward variable selection was used serially to remove nonsignificant factors. The variables that, when they were excluded, introduced a change in parameter

estimates greater than 10% were reintroduced into the model to account for confounding. The goodness of fit of the model was assessed by the Hosmer and Lemeshow test. The Wald test was used to assess the significance of variables in the model. The level of significance was established as a P value of <0.05.

The data were analyzed by using EPI-Info (version 6.04, 2001) software (CDC, Atlanta, GA) and BMDP (version PC90, 1990 IBM PC/MS-DOS) software (BMDPRL Statistical Software, Los Angeles, CA).

RESULTS

A total of 980 patients using an aminoglycoside were identified during the time period analyzed. Among these patients, all of the clinical information necessary for the study was available for 402 of them, and 360 fulfilled the inclusion criteria. Just over half (209 [58%]) of these 360 patients developed acute kidney dysfunction 6.7 ± 3.1 days after the beginning of aminoglycoside therapy. When the two aminoglycosides were analyzed separately, the prevalence rates of nephrotoxicity were similar: 60% for gentamicin and 56.7% for amikacin. Only 3 of these 209 patients (1.41%) presented with oliguria. The AKI group was older than the non-AKI group: 56 ± 18 years and 52 ± 19 years, respectively ($P < 0.003$). The frequencies of males were similar in the AKI group (58.3%) and the non-AKI group (52.3%).

The baseline cGFRs were similar in both groups (88.6 ± 42.4 ml/min/1.73 m² for the AKI group versus 84.0 ± 42.2 ml/min/1.73 m² for the non-AKI group). The cGFR nadir, as expected, was lower in the AKI group (44.6 ± 26.9 ml/min/1.73 m² versus 79.4 ± 38.7 ml/min/1.73 m² in the non-AKI group; $P < 0.001$). In the AKI group, the serum creatinine level increased from a baseline value of 1.0 ± 0.4 mg/dl to a peak value of 2.2 ± 1.3 mg/dl ($P < 0.001$).

When the patients were categorized by the baseline cGFR by using 60 ml/min/1.73 m² as the threshold, it was found that patients with a baseline cGFR of <60 ml/min/1.73 m² received a lower daily dose of amikacin than patients with a baseline cGFR of ≥60 ml/min/1.73 m²: 0.78 ± 0.27 g and 0.94 ± 0.24 g, respectively ($P = 0.0003$). Both groups categorized by different baseline cGFRs received similar daily amounts of gentamicin. Among the patients with a baseline cGFR of <60 ml/min/1.73 m², 49.5% developed AKI (50/101 patients), whereas 61% (159/259 patients) of the patients with a cGFR of ≥60 ml/min/1.73 m² developed AKI ($P = 0.0438$).

The AKI group received a smaller daily amount of amikacin (0.86 ± 0.25 g in the AKI group versus 0.95 ± 0.24 g in the non-AKI group; $P = 0.0467$), and both groups received similar daily amounts of gentamicin (0.22 ± 0.01 in the AKI group versus 0.21 ± 0.01 g in the non-AKI group).

The AKI and non-AKI groups were similar in terms of the number of days that they used the aminoglycosides (9.4 ± 4.6 days and 9.9 ± 4.5 days, respectively), the proportion of individuals who used furosemide (40% and 30%, respectively; $P = 0.059$), the furosemide dosage used (51 ± 20 mg and 51 ± 26 mg, respectively), and the frequencies of acidosis (49% and 40%, respectively) and hypokalemia (22% and 24%, respectively). The proportion of individuals using other nephrotoxic drugs (vancomycin, cyclosporine, cephalosporin, amphotericin B) was higher in the AKI group (51% versus 38% in the non-AKI group; $P = 0.024$), as was the proportion of individuals using iodinated contrast (18% versus 8% in the non-AKI group; $P = 0.005$).

The AKI group showed a higher frequency of comorbidities: diabetes (19% versus 9.3% in the non-AKI group; $P = 0.007$), jaundice (19% versus 9% in the non-AKI group; $P = 0.0036$), and liver dysfunction (7.6% versus 2% in the non-AKI group; $P = 0.0175$). Although previous cardiovascular disease was also more frequent among the patients in the AKI group (47% versus 37% in the non-AKI group), this result did not reach statistical significance ($P = 0.067$).

Patients in the AKI group had a higher frequency of hypovolemia (44% versus 27% in the non-AKI group; $P = 0.001$), hypotension (63% versus 44% in the non-AKI group; $P = 0.003$), and shock (56% versus 31% in the non-AKI group; $P < 0.001$).

The lengths of stay in the ICU were similar for both groups (16.1 ± 9.9 days and 15.5 ± 11 days for the AKI and non-AKI groups, respectively). The mortality rate was significantly higher in the AKI group (44.5% versus 29.1% in the non-AKI group; $P = 0.0031$).

Logistic regression. Logistic regression identified a baseline cGFR of <60 ml/min/1.73 m^2 to be an independent protective factor against AKI (odds ratio, [OR], 0.42; 95% confidence interval [CI], 0.24 to 0.72; $P = 0.02$). The independent risk factors for AKI were diabetes (OR, 2.13; 95% CI, 1.01 to 4.49; $P = 0.046$), the use of iodinated contrast (OR, 2.13; 95% CI, 1.02 to 4.43; $P = 0.043$), hypotension (OR, 1.83; 95% CI, 1.14 to 2.94, $P = 0.012$), and the simultaneous use of other nephrotoxic drugs (OR, 1.61; 95% CI, 1.00 to 2.59; $P = 0.048$).

DISCUSSION

The prevalence of aminoglycoside-associated nephrotoxicity reported in clinical studies varies widely, depending on the characteristics of the population analyzed and the criteria used to diagnose renal injury. Most of the published series estimate that it occurs in 10 to 20% of cases. The reliability of this estimate is hindered by the lack of uniform criteria for defining AKI in the various studies. Absolute increases (0.5 to 1.5 mg/dl) or relative increases (25 to 100%) in the serum creatinine level have been used for the diagnosis of AKI (3, 12, 18, 31, 35). When an increase in the serum creatinine level of 0.5 mg/dl or more was used as a diagnostic criterion, 29% of ICU patients were found to have aminoglycoside-associated nephrotoxicity (30). In the present study of critically ill patients, the use of a more sensitive definition of renal injury, i.e., a 20% decrease in cGFR, identified a much higher prevalence (58%) of aminoglycoside-associated nephrotoxicity. We should recognize, however, that the equations most widely used to measure GFR, like the MDRD and Cockroft-Gault equations, have not yet been validated for use with ICU patients. On the other hand, by using the most recent definitions for AKI, 90.91% of the 209 patients identified as having AKI in the current study will fit in the at-risk category or higher (50% increase in baseline creatinine level) for RIFLE (risk, injury, failure, loss, end-stage kidney disease) and 92.34% will fit in stage 1 or higher (an increase in the creatinine level of 0.3 mg/dl or higher from the baseline or a 50 to 100% increase in the creatinine level from the baseline) for AKIN (Acute Kidney Injury Network) classification (4, 21).

A noteworthy finding of this study is that the rate of mortality was significantly higher among those patients developing nephrotoxicity than among patients with stable renal function. Indeed, emerging evidence suggests that even minor changes in the serum creatinine level are associated with increased rates of inpatient mortality (7, 21). Information on the influence of aminoglycoside-associated nephrotoxicity on patient mortality is scarce. A peak serum creatinine level of >1.2 mg/dl was associated with a higher rate of mortality (on the basis of univariate analysis) among febrile neutropenic patients receiving gentamicin (6). When cirrhotic septic patients were treated with ceftazidime or netilmicin plus mezlocillin in a prospective, randomized trial, renal failure was present at the time of death in 8% of the patients treated with ceftazidime, whereas it was present in 56% of the patients treated with netilmicin ($P < 0.05$) (20).

In the present study, the majority of risk factors potentially connected to aminoglycoside-associated nephrotoxicity were studied in a large cohort of patients by using an adequate statistical methodology. Diabetes as a comorbidity, the presence of hypotension, the simultaneous use of iodinated contrast, and the simultaneous use of other nephrotoxic drugs emerged as independent risk factors for the development of AKI. On the other hand, a baseline GFR of <60 ml/min/1.73 m^2 was identified as an independent protection factor. Although hypotension and the use of other nephrotoxic drugs might themselves be the cause of AKI in some of the patients studied, the timing of development of the renal injury and the fact that only 1.44% of the patients were oliguric are strongly indicative of aminoglycoside-associated renal injury.

Data on the influence of diabetes as a risk factor for AKI in patients treated with aminoglycoside are contradictory. Diabetic rats were protected against renal injury in an experimental model of aminoglycoside-associated nephrotoxicity (9, 33). This protection was attributed to osmotic diuresis, which decreased the tubular absorption of aminoglycosides and, consequently, their concentrations in the renal cortex (9, 33). When the hyperglycemic state was corrected by insulin, the animals lost their protection against aminoglycoside-associated nephrotoxicity (11). In a clinical study involving 86 elderly patients, diabetes was associated with an increased rate of aminoglycoside-associated nephrotoxicity. In that study, 9.3% of the patients receiving aminoglycosides developed nephrotoxicity, and diabetes mellitus was identified by logistic regression as a risk factor for aminoglycoside-associated kidney injury (2). On the other hand, a study of 249 elderly patients receiving amikacin or gentamicin did not find diabetes to be a risk factor for nephrotoxicity, based on logistic regression analysis (29). Similarly, stepwise discriminant analysis of 214 patients treated with gentamicin or tobramycin did not identify diabetes as a risk factor for aminoglycoside-associated nephrotoxicity (24). In the present study, diabetes was clearly identified as a risk factor for aminoglycoside-associated nephrotoxicity.

In contrast to the question of the association of diabetes, hypotension and shock have constantly been identified, both experimentally and clinically, as risk factors for aminoglycoside-associated AKI (24, 32, 36). These conditions cause renal hypoperfusion and ischemia. Aminoglycosides interfere with the synthesis of energy molecules, increasing the risk of kidney injury during an ischemic episode. Moreover, ischemia alters membrane lipids, thus enhancing the accumulation of aminoglycosides in the proximal tubular cells (23, 37). In the present

study, hypovolemia, hypotension, and shock occurred significantly more often in the AKI group, based on the univariate analysis, but only hypotension was an independent factor for nephrotoxicity in the logistic regression analysis.

Iodinated contrast is widely used, so it is likely to be administered to patients receiving an aminoglycoside. This combination of treatments is potentially synergistic, since contrast agents and aminoglycosides together harm renal hemodynamics and tubular cell function. In fact, it is recommended that an aminoglycoside not be used less than 24 h before iodinated contrast administration (14). In one of the few series analyzing iodinated contrast as a risk factor for aminoglycoside-associated nephrotoxicity, AKI was observed in 15% of the 88 patients studied, and univariate analysis did not identify the use of iodinated contrast as a risk factor for its development (27). On the other hand, the present study of a large cohort found that the use of iodinated contrast significantly increased the risk of AKI in patients treated with aminoglycosides.

The simultaneous use of aminoglycosides and other potentially nephrotoxic drugs has been shown to increase the risk of aminoglycoside-associated kidney injury. Indeed, this synergistic action has been demonstrated in patients and in animal studies. Clinical studies have implicated several drugs in this synergy, such as vancomycin, amphotericin B, piperacillin, cephalosporins, foscarnet, allopurinol, nonsteroidal anti-inflammatory agents, inhibitors of angiotensin-converting enzyme, cyclosporine, and cisplatin (5, 16, 27, 28, 34). Consistent with these results, the simultaneous use of an aminoglycoside with vancomycin, cyclosporine, cephalosporins, or amphotericin B significantly increased the risk of AKI.

Chronic kidney disease has been indicated to be a risk factor for aminoglycoside-associated nephrotoxicity. Patients with chronic kidney disease have a potentially higher risk of accidental aminoglycoside overdosing due to misestimation of the necessary dose correction. In addition, they have less renal reserve, and their ability to recover from renal injury is impaired. Nevertheless, published results are conflicting. Paterson et al. (27) found a baseline creatinine clearance rate of 39.6 ml/min in patients developing aminoglycoside-associated nephrotoxicity, whereas it was 46.7 ml/min in patients who did not develop kidney dysfunction. However, this difference was not statistically significant. In the same paper, a logistic regression model identified an elevated baseline serum creatinine level as a risk factor for aminoglycoside-associated nephrotoxicity (27). Another study examined the case records of 1,154 patients for whom pre- and posttreatment serum creatinine values were available from phase II and phase III studies with amikacin. The prevalence of nephrotoxicity (according to the change in the serum creatinine level) was 8.7%, and one of the factors related to nephrotoxicity was an elevated initial serum creatinine level (16). In an analysis of 1,489 patients treated with an aminoglycoside, baseline renal dysfunction was identified as a risk factor for nephrotoxicity in the univariate analysis, but this was not confirmed in the multiple logistic regression analysis (5). Two different studies assessing aminoglycoside-associated nephrotoxicity in 96 and 249 patients, respectively, did not recognize the initial serum creatinine level or a decreased GFR as a risk factor for kidney injury in the logistic regression analysis (13, 29). Finally, a higher initial creatinine clearance rate was associated with an increased risk of nephrotoxicity.

Moore and colleagues (24, 32) reviewed 214 case reports of two randomized clinical trials involving gentamicin or tobramycin. Patients who developed kidney failure were found to have a higher initial rate of creatinine clearance (70 ± 5 versus 58 ± 3 ml/min/1.73 m^2 for patients who did not develop kidney failure; $P = 0.04$), which was confirmed to be a risk factor by stepwise discriminant analysis (24, 32). The findings described in the last report are consistent with the results of the present study. Although the mean cGFR was similar for both groups, a baseline GFR of <60 ml/min/m^2 conferred significant protection against aminoglycoside-associated nephrotoxicity. It is possible that a moderate decrease in the GFR associated with an adequate antibiotic dose correction allowed a lower load of aminoglycoside to reach the tubular lumina, thus decreasing tubular reabsorption and the cortical accumulation of the antibiotic. One way to reconcile these contradictory results is to conclude that in previous studies reporting an increased risk of aminoglycoside-associated nephrotoxicity in patients with chronic kidney disease, the patients suffered more severe baseline renal injury, as reflected in lower baseline GFRs, and this made the kidneys more vulnerable to subsequent insults. It is also reasonable to assume that a decrease in the baseline GFR may urge the ICU team to prescribe a lower dose of aminoglycoside; this would protect the tubule cells against a high luminal concentration of antibiotic. In fact, when we analyzed the amikacin dose in terms of the baseline cGFR, we found that patients with a baseline cGFR of <60 ml/min/1.73 m^2 received a lower dose of antibiotic than patients with a baseline cGFR of $\geq$60 ml/min/1.73 m^2.

In conclusion, aminoglycoside-associated nephrotoxicity occurred frequently and was associated with a high rate of mortality in the ICU patients evaluated in this study. A baseline GFR of <60 ml/min/1.73 m^2 was an independent protective factor against aminoglycoside-associated nephrotoxicity, while diabetes, hypotension, the simultaneous use of iodinated contrast, and the simultaneous use of other nephrotoxic drugs were independent risk factors for the development of nephrotoxicity. These data indicate that if an appropriate correction of the dose of the drug delivered is used, a decreased baseline GFR it is not a risk factor for aminoglycoside-associated nephrotoxicity. Moreover, these results strongly suggest that aminoglycosides should be avoided or used with extreme caution in hypotensive and/or diabetic patients or patients receiving other nephrotoxic drugs, including iodinated contrast, in the ICU.

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