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Effect of Furosemide on Aminoglycoside-Induced Nephrotoxicity and Auditory Toxicity in Humans

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We analyzed data from three prospective, controlled, randomized, double-blind clinical trails to determine whether furosemide increases the nephrotoxicity and auditory toxicity of aminoglycosides. All patients who received at least 72 h of treatment and who had no other cause for nephrotoxicity or auditory toxicity were included in the analysis. Nephrotoxicity developed in 10 of 50 (20.0%) patients given furosemide and in 38 of 222 (17.1%) patients not given furosemide ($P > 0.3$). Auditory toxicity developed in 5 of 23 patients (21.7%) given furosemide and in 28 of 119 patients (23.5%) not given furosemide ($P > 0.3$). In each case, the groups receiving and not receiving furosemide did not differ in mean age, initial creatinine, duration of aminoglycoside therapy, mean change in auditory acuity or creatinine, mean number of days to the development of toxicity, the frequency with which gentamicin, tobramycin, amikacin, or cephalothin was administered, or the mean predose and 1-h postdose plasma aminoglycoside levels. We conclude that furosemide use should not be considered a major risk factor for the development of aminoglycoside-induced nephrotoxicity or auditory toxicity.

In experimental animals, administration of furosemide increases the nephrotoxicity and auditory toxicity of aminoglycosides (1, 4, 10, 13, 15, 16, 23). Only one clinical study evaluating aminoglycoside-induced nephrotoxicity has found that furosemide increases renal damage, whereas two studies have failed to find an interaction. None of these studies evaluated auditory toxicity (5, 17, 21). A few clinical reports have supported the association with auditory toxicity, but these studies have not included a control group and have reported small numbers of patients (8, 9, 11, 12, 14).

We have conducted several clinical trials evaluating the nephrotoxicity and auditory toxicity of gentamicin, tobramycin, and amikacin (19, 20, 22). The data obtained from these prospective, controlled, randomized, double-blind trails have been used to evaluate the effect of furosemide on the nephrotoxicity and auditory toxicity of these aminoglycosides.

MATERIALS AND METHODS

Patients with suspected sepsis were candidates for entry into these studies. Patients were assigned to treatment groups by a table of random numbers and received gentamicin, tobramycin, or amikacin. Patients with meningitis, an allergy to penicillin, an infection due to an organism known to be resistant to gentamicin, tobramycin, or amikacin, or antibiotic treatment within the previous 48 h were not entered into the study. The initial aminoglycoside dosage was 2 mg of gentamicin or tobramycin per kg or 8 mg of amikacin per kg given intravenously over 20 to 30 min. Doses were then given every 8 h and initially adjusted for renal function with nomograms (6, 18). Pre- and 1-h postdose plasma aminoglycoside concentrations were determined with a radioenzymatic assay within 24 h. Subsequent doses were adjusted to maintain the 1-h postdose plasma level between 5 and 10 μg/ml for gentamicin and tobramycin and between 20 and 40 μg/ml for amikacin. Pre- and 1-h postdose plasma aminoglycoside levels were measured on days 1 and 3 and every alternate day during therapy. Levels were also measured after each dosage change. Patients also received penicillin (19), methicillin (20, 22), cephalothin (22), or nafcillin (20). The dose of penicillin was 20 $\times 10^6$ U/day, the dose of methicillin was 12 g/day, and the doses of nafcillin and cephalothin were 9 g/day. The dose of these beta-lactam antibiotics was not adjusted for renal dysfunction. Clindamycin, 2.4 g/day, was added when a pelvic or gastrointestinal source of infection was suspected and was the only other concurrent antibiotic administered. Non-antibiotic therapy was not controlled. Serum creatinine was measured before therapy, on days 2, 3, and 4 and every third day of therapy, and 2 days after therapy. Audiograms were measured at the bedside at 250, 500, 1,000, 2,000, 4,000, and 8,000 Hz on days 1 or 2 and 7 of therapy and 2 days after therapy. Patients receiving at least nine doses of aminoglycoside and with no other cause of acute renal failure in the previous 72 h were evaluated for nephrotoxicity. Nephrotoxicity

TABLE 1. Relationship of nephrotoxicity and auditory toxicity to furosemide administration

Drug administration	No. of patients with			
	Nephro-toxicity	No nephro-toxicity	Auditory toxicity	No auditory toxicity
Furosemide	10	40	5	18
No furosemide	38	184	28	91

was defined as a rise in serum creatinine of greater than or equal to 0.5 mg/100 ml if the initial level was less than 3 mg/100 ml or a rise of greater than or equal to 1 mg/100 ml if the initial creatinine was 3 mg/100 ml or above. The rise was determined by subtracting the initial creatinine from the highest creatinine during therapy or within 48 h after therapy. Patients who satisified the definition of nephrotoxicity but who had another cause for acute renal failure (hypotension or amphotericin B) were excluded from the analysis because the exact cause of the creatinine increase could not be determined.

Patients who received at least nine doses of an aminoglycoside and who were able to cooperate with serial audiograms were evaluated for auditory toxicity. Auditory toxicity was defined as a decrease in auditory threshold of greater than or equal to 15 decibels at any frequency in the range of 250 to 8,000 Hz.

All patients who met the above criteria were included in the analysis. Patients who received furosemide intravenously or orally during the administration of an aminoglycoside were included in the furosemide group; all other patients were included in the control group. Proportions were compared with the Fisher exact test, and means were compared with Student's *t* test. In both cases, a two-tailed analysis was used.

TABLE 2. Demographic characteristics of patients evaluated for nephrotoxicity: comparison of patients given furosemide and patients not given furosemide

Characteristic	Furosemide (n = 50)	No furosemide (n = 222)
Age (yr)	60.7 ± 2.9[a]	56.6 ± 2.4
Initial creatinine	2.7 ± 1.47	1.5 ± 0.23
Percent patients given:		
Gentamicin	50	49.5
Tobramycin	42	33.5
Amikacin	8	17
Cephalothin	20	15
Duration of aminoglycoside (days)	6.2 ± 0.65	6.6 ± 0.43
Total dose of gentamicin or tobramycin (g)	1.63 ± 0.71	2.27 ± 0.31
Gentamicin or tobramycin level (μg/ml)		
Predose	3.2 ± 0.42	2.9 ± 0.16
1-h postdose	5.8 ± 0.21	6.6 ± 0.22[b]
Creatinine increase (mg/100 ml)	0.46 ± 0.03	0.32 ± 0.10
Days to toxicity	7.0 ± 0.20	7.0 ± 0.44

[a] Mean ± standard error of the mean.
[b] $P < 0.05$.

TABLE 3. Demographic characteristics of patients evaluated for auditory toxicity: comparison of patients given furosemide and patients not given furosemide

Characteristic	Furosemide (n = 23)	No furosemide (n = 119)
Age	56.9 ± 4.1[a]	53 ± 1.8
Initial creatinine	2.65 ± 0.85	1.30 ± 0.15[b]
Percent patients given:		
Gentamicin	56.5	55.5
Tobramycin	34.8	34.5
Amikacin	8.7	10.0
Cephalothin	21.7	12.6
Duration of aminoglycoside (days)	6.2 ± 0.9	6.9 ± 0.3
Total dose of gentamicin or tobramycin (g)	1.84 ± 0.40	2.4 ± 0.66
Gentamicin or tobramycin level (μg/ml)		
Predose	3.0 ± 0.28	2.4 ± 0.13[b]
1-h postdose	5.8 ± 0.31	6.0 ± 0.16
Decrease in auditory threshold (decibels)	8.7 ± 1.7	10.7 ± 1.2
Days to toxicity	10.7 ± 1.90	7.9 ± 0.32[b]

[a] Mean ± standard error of the mean.
[b] $P < 0.05$.

RESULTS

Three clinical trials comprise the data base for this retrospective analysis. During these studies, 272 patients had their renal function evaluated, and 142 patients had their auditory function evaluated. By using the definitions previously described, 48 (17.6%) patients met the criteria for nephrotoxicity, and 33 (23.3%) patients met the criteria for auditory toxicity. Of the 272 patients who had their renal function evaluated, 50 (18.4%) were given furosemide, and of the 142 patients who had their auditory function evaluated, 23 (16.2%) were given furosemide. Nephrotoxicity developed in 10 of 50 (20.0%) patients given furosemide and in 38 of 222 (17.1%) patients not given furosemide. Auditory toxicity developed in 5 of 23 patients (21.7%) given furosemide and in 28 of 119 patients (23.5%) not given furosemide (Table 1). These differences are not statistically significant. In each case, the groups receiving and not receiving furosemide did not differ in mean age, initial creatinine, duration of aminoglycoside therapy, mean change in auditory acuity, mean change in

TABLE 4. Relationship of furosemide dose and duration of therapy to nephrotoxicity and auditory toxicity

Toxicity	Furosemide dose (g)		Therapy (days)	
	Total	Range	Duration	Range
Nephrotoxicity				
Present (n = 10)	0.67 ± 0.25[a]	0.02–2.4	6 ± 1.6	2–15
Absent (n = 38)	0.44 ± 0.14	0.01–4.3	4.9 ± 0.7	2–11
Auditory toxicity				
Present (n = 5)	0.26 ± 0.14	0.04–0.68	4.5 ± 2.3	1–11
Absent (n = 28)	0.46 ± 0.12	0.01–2.4	4.1 ± 0.4	1–10

[a] Mean ± standard error of the mean.

creatinine, mean number of days to the development of toxicity, and the percentages of patients in each group who received gentamicin, tobramycin, amikacin, or cephalothin (Tables 2 and 3). Pre- and 1-h postdose plasma levels were similar in the groups receiving and not receiving furosemide. In patients evaluated for nephrotoxicity, the group not given furosemide had a small but significantly higher postdose level of gentamicin or tobramycin. In patients evaluated for auditory toxicity, the group not given furosemide had a small but significantly lower predose level. The total dose of furosemide and the duration of furosemide administration did not correlate with the development of nephrotoxicity or auditory toxicity (Table 4).

One patient received ethacrynic acid. He was treated for 5 days with gentamicin for *Klebsiella pneumoniae* bacteremia. During treatment, the "peak" serum levels ranged from 3.6 to 8.2 μg/ml, and the "valley" levels ranged from 3.1 to 6.9 μg/ml. The patient's serum creatinine was 3.6 mg/100 ml at the initiation of aminoglycoside therapy. During the first 4 days of aminoglycoside administration, the patient received four 300-mg intravenous doses of furosemide without any clinically apparent change in auditory function. The last dose of furosemide was given when the serum creatinine was 4.1 mg/100 ml. On day 6 of therapy, 24 h after the last dose of furosemide, the patient received a 100-mg intravenous dose of ethacrynic acid when the serum creatinine was 4.6 mg/100 ml. Within 1 h, the patient complained of tinnitus, and within 6 h decreased hearing was noted. The deficit rapidly progressed, resulting in deafness within 8 h. Despite discontinuing the aminoglycoside and ethacrynic acid, the deafness persisted for 2 days, until the patient suddenly expired. This was the only patient we treated who developed sudden deafness and the only patient who received concurrent ethacrynic acid.

DISCUSSION

The data we have gathered in our previous trials of aminoglycosides have afforded us the opportunity to retrospectively analyze the influence of furosemide on aminoglycoside-induced nephrotoxicity and auditory toxicity. We have been unable to demonstrate that furosemide increases the nephrotoxicity or auditory toxicity of gentamicin, tobramycin, and amikacin. With our sample sizes, we would have been able to detect an increase in nephrotoxicity or auditory toxicity of approximately 15 and 25%, respectively. Because these data were gathered in prospective, controlled, randomized, double-blind trials, bias in assessing renal and auditory function was minimized. However, these trials were not designed to specifically assess the interaction of furosemide with aminoglycosides, and there may be an unrecognized factor or bias that is masking an interaction in our analysis. The implications of these data are limited to the conditions under which furosemide and aminoglycosides were used in the treatment of our patients. It may be that other modes of administering furosemide that were not used in our patients (e.g., high-dose intravenous bolus infusion) are associated with an interaction.

The studies in experimental animals suggesting that furosemide increases the nephrotoxicity of aminoglycosides failed to control for sodium, potassium, and water losses due to furosemide. Sodium depletion has been shown to increase nephrotoxicity (2). When Chiu and Long controlled for water losses in rats, they failed to find that furosemide increased gentamicin nephrotoxicity (7). Our data are consistent with these observations and suggest that furosemide can be given to patients receiving aminoglycosides without increased risk of nephrotoxicity. We assume that our results were due to the avoidance of severe sodium, potassium, and water depletion in our patients.

Furosemide or ethacrynic acid may cause hearing loss in the absence of aminoglycoside administration (11, 21). This effect is dose dependent. Patients developing hearing loss usually have underlying congestive heart failure or severe renal disease and receive total doses in excess of 150 mg of ethacrynic acid or 200 mg of

furosemide. Furosemide administration is usually associated with tinnitus and transient hearing loss lasting less than 6 h (11). Ethacrynic acid, on the other hand, can cause more profound and lasting effects (21).

Brummett et al. studied the interaction of kanamycin and furosemide in guinea pigs and found a dose-dependent interaction (4). A dose of 50 mg of furosemide per kg produced a minimal effect, whereas doses greater than 100 mg/kg produced severe irreversible decreases in cochlear potential. Obtani et al. studied the interaction with kanamycin in rabbits given 30 mg of furosemide per kg for 5 to 60 days (15). All animals given the combination developed severe renal failure and severe loss of outer hair cells in the cochlea. Serum and perilymph kanamycin levels were twice as high with the combination as compared to a control group given kanamycin alone. Gentamicin did not interact with furosemide. Obtani et al. concluded that the interaction with kanamycin was due to increased serum and perilymph levels of kanamycin caused by renal failure. Nakai studied mice and guinea pigs given 3',4'-dideoxykanamycin B and 40 mg of furosemide or ethacrynic acid per kg (13). No interaction was found with furosemide, but severe damage was noted with ethacrynic acid. These studies suggest that the interaction of furosemide and aminoglycosides is dose dependent, differs among species and among aminoglycosides, and may be related to increased serum levels of aminoglycosides due to the development of renal failure. Our results suggest that the doses of furosemide usually given to patients concurrently receiving aminoglycosides do not produce renal failure and that gentamicin, tobramycin, and amikacin can be given with furosemide without increasing the risk of auditory toxicity.

Despite worsening renal failure, repeated large intravenous doses of furosemide failed to induce any clinically apparent changes in hearing in one patient who was given ethacrynic acid. However, the close temporal relationship between the concurrent administration of ethacrynic acid and the development of deafness suggests that ethacrynic acid may interact with gentamicin and may differ from furosemide in its ability to cause auditory toxicity during gentamicin administration. This observation is consistent with data obtained in experimental animals suggesting that ethacrynic acid is more likely than furosemide to potentiate aminoglycoside-induced auditory toxicity (3, 13). The greater auditory toxicity may be due to formation of a cysteine adduct of ethacrynic acid which may cause irreversible hearing loss when combined with an aminoglycoside (3).

Based on our observations, we believe furosemide administration should not be considered a major risk factor for the development of nephrotoxicity or auditory toxicity with aminoglycosides. The combination of ethacrynic acid and an aminoglycoside, however, may cause severe auditory toxicity.

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