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Renal Disposition of Gentamicin, Dibekacin, Tobramycin, Netilmicin, and Amikacin in Humans

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The tubular disposition of five aminoglycosides was studied in humans to establish a possible relationship between tubular reabsorption and the nephrotoxicity that has been described in the literature. Thirty-three healthy male volunteers received a continuous intravenous infusion of isotonic saline with inulin, followed 1 h later by inulin plus gentamicin, dibekacin, tobramycin, netilmicin, or amikacin (1 mg/kg per h) or amikacin (4 mg/kg per h) over a period of 2 h. Brain-stem-evoked response audiometry was performed both before and at the end of each infusion. The latency of wave V remained constant whichever antibiotic was considered. The glomerular filtration rate did not vary significantly during the infusion of each drug. The percent fractional excretion was 79 ± 6, 81 ± 22, 85 ± 5, and 99 ± 9 for gentamicin, dibekacin, tobramycin, and netilmicin, respectively, and 83 ± 4 and 124 ± 13 for amikacin at concentrations of 1 and 4 mg/kg per h, respectively. Net balance and renal clearance were similar for the five aminoglycosides when administered at a rate of 1 mg/kg per h. With gentamicin only, fractional excretion was correlated with the urinary flow rate. We can conclude that (i) gentamicin, generally considered the most nephrotoxic agent, had the highest degree of net reabsorption; (ii) netilmicin exhibited a net zero tubular balance; (iii) amikacin had different patterns of tubular disposition according to the dose, i.e., reabsorption at 1 mg/kg per h and secretion at 4 mg/kg per h, raising the hypothesis of a saturable process of reabsorption; and (iv) these differences in tubular reabsorption could account at least in part for the known different nephrotoxic potentials of these five aminoglycosides in humans.

In a previous study with rabbits (4), Brion et al. demonstrated that four aminoglycosides exhibited three different degrees of tubular reabsorption: gentamicin had the highest, netilmicin had the lowest, and dibekacin and amikacin, given at the same dose as the other drugs, had intermediate degrees of reabsorption. Except for amikacin, which appeared to exhibit the lowest intrinsic renal toxicity, nephrotoxicity was correlated with the tubular reabsorption of each aminoglycoside.

Aminoglycoside nephrotoxicity has been the subject of many clinical (9, 11, 14, 22–24), biochemical, and pharmacological (1, 7, 12, 13, 18) studies. Although the nephrotoxic potential of these antibiotics varies from one species to another, similar pathological patterns have generally been observed in both humans and animals.

Current knowledge of the renal disposition of aminoglycosides is derived primarily from studies of the tubular transport of gentamicin in animals (12, 20, 28) or in vitro (15, 26, 27). To our knowledge, no study so far has compared in humans the tubular disposition of the aminoglycosides most often used in clinical situations.

The purpose of the present work was to investigate the renal tubular disposition of five aminoglycosides and thus to draw a comparison with data previously obtained with rabbits as well as with data reported in the literature concerning the nephrotoxic potential of these antibiotics in humans.

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MATERIALS AND METHODS

Subjects. Thirty-three healthy male volunteers with a mean age of 23 years (range, 21 to 28 years) and a mean body weight of 69 kg (range, 61 to 94 kg) participated in the study after providing informed written consent. None was on medication for the 72 h before the study started. None had a known antecedent of renal or auditory disease or had received previous treatment by aminoglycosides or other potentially nephrotoxic drugs. In all subjects, the calculated glomerular filtration rate (GFR) was normal, i.e., above 90 ml/min. Before the experiment, each volunteer had a standard lunch and beverage.

Procedure. Each subject received a continuous intravenous infusion of isotonic saline (2 ml/kg per h) and inulin (20 mg/kg as the initial bolus dose and then 900 mg × [body surface/1.73 m^2] per h). The inulin steady state was not attained until 30 min later. A control period of 30 min was then observed. Each volunteer was randomly assigned to one of five groups of six subjects each, receiving a continuous intravenous infusion of gentamicin, dibekacin, tobramycin, netilmicin (1 mg/kg per h), or amikacin (4 mg/kg per h). The evaluated dose of amikacin was used in keeping with the current ratio of dosage between amikacin and the other aminoglycosides. Another group of three volunteers received amikacin at a dose of 1 mg/kg per h. For ethical

reasons we did not give loading doses, and 1 h of aminoglycoside infusion was considered sufficient to attain a state close to the steady state with a minimal toxic risk. Two experimental periods of 30 min each were then observed. Two venous catheters in the forearms were used for infusion and sampling. One blood sample was taken during each of these periods. Urine was collected by spontaneous micturition. The subjects were seated during the experiment. At the end of each 30-min period they were required to drink 1 ml of water per kg of body weight. Blood samples for antibiotic and biochemical assays were allowed to clot before centrifugation at 1,200 × *g* for 15 min for the collection of serum. Blood samples were heparinized only for inulin assays and centrifuged for the collection of plasma. Urine, serum, and plasma samples were analyzed within a few hours after collection.

Analysis of samples. Concentrations of aminoglycosides were determined by radio enzymatic assay, as previously described (2). Concentrations of inulin were measured by the method of Schreiner (19). Concentrations of sodium, potassium, phosphate, calcium, and magnesium were determined by standard methods with an Astra 8 multiparameter (Beckman Instruments, Inc., Fullerton, Calif.). Lactate dehydrogenase (LDH) activity was measured by optimized standard methods. Brain-stem-evoked response audiometry was performed on a RACIA EP3 apparatus. The stimuli were clicks of 40, 60, 80, and 100 decibels.

Serum protein binding. Protein binding in serum was investigated by equilibrium dialysis for 6 h at 37°C in 0.15 M phosphate buffer (pH 7.4) with a Dianorm System (Diachema A.G., Rüchlikon, Switzerland) with 0.2 ml of cells and cellulose dialysis membranes (Union Carbide Corp., Chicago, Ill.). Each antibiotic was tested at a concentration of 5 μg/ml (amikacin was also tested at 15 μg/ml) in pooled human sera in which Ca^{2+} and Mg^{2+} concentrations were similar to those measured in vivo during the experiment. Antibiotic concentrations were measured on each side of the dialysis membrane. Six hours of dialysis was enough to reach equilibrium. The stability of the molecules tested was verified after a 6-h incubation at 37°C in buffer and serum.

Analysis of data. For each control and experimental period, the following parameters were determined or calculated: urinary flow rate (UFR), GFR, and fractional excretion of sodium, potassium, phosphate, magnesium, calcium, and LDH. The T_m of phosphate, expressed in micromoles of glomerular filtrate per liter was calculated from fasting urinary phosphate per liter of glomerular filtrate and fasting phosphoremia using Bijvoët's diagram (3). For each experimental period and each aminoglycoside, the following parameters were calculated: (i) glomerular filtered load as the product of inulin renal clearance and aminoglycoside concentration in serum; (ii) fractional excretion, defined as the antibiotic-to-inulin clearance ratio; (iii) absolute rate of net aminoglycoside tubular secretion, defined as the rate of urinary excretion of antibiotic minus its glomerular filtered load; and (iv) aminoglycoside renal clearance.

The auditory brain-stem-evoked response was studied through the latency of wave V both before and just after each infusion. Data were analyzed for statistically significant differences among groups by analysis of variance. If significance was obtained, the means were tested two by two by the Student *t* test. Differences were considered significant when $P < 0.05$. Correlation coefficients were determined for antibiotic fractional excretion-UFR paired data, in each group of subjects.

TABLE 1. UFR and GFR[a] during intravenous infusion of aminoglycosides

Antibiotic	UFR (ml/min)		GFR (ml/min per kg)	
	Control	Expt	Control	Expt
Gentamicin	5.5 ± 3.7	6.0 ± 3.9	1.5 ± 0.4	1.6 ± 0.3
Dibekacin	6.7 ± 4.9	5.4 ± 4.6	1.6 ± 0.8	1.2 ± 0.4
Tobramycin	4.5 ± 3.8	4.8 ± 2.7	1.4 ± 0.5	1.4 ± 0.2
Netilmicin	6.5 ± 4.0	7.0 ± 3.0	1.4 ± 0.4	1.4 ± 0.5
Amikacin (4 mg/kg per h)	3.1 ± 4.6	6.2 ± 1.9	1.3 ± 0.4	1.2 ± 0.2
Amikacin (1 mg/kg per h)	3.3 ± 0.8	2.6 ± 1.5	1.5 ± 0.4	1.6 ± 0.4

[a] Each experimental value represents the mean ± standard deviation for the two experimental periods.

RESULTS

The UFR and GFR for control and experimental periods are reported in Table 1. No statistically significant variation of these parameters was observed.

The data concerning the antibiotics are presented in Table 2. Inulin steady state was reached 30 min after the beginning of the infusion. A steady state of aminoglycosides was not completely obtained during the experimental periods, and the concentrations of antibiotic in serum were higher during the second experimental period than during the first, even if the differences observed were not statistically significant. The aminoglycoside levels in serum (in micrograms per milliliter) obtained during experimental periods 1 and 2 were, respectively, 5.1 ± 1.3 and 5.7 ± 1.4 for gentamicin, 4.6 ± 0.8 and 5.0 ± 0.9 for tobramycin, 5.1 ± 0.8 and 5.8 ± 1.1 for netilmicin, 4.6 ± 0.8 and 5.0 ± 0.7 for dibekacin, 5.8 ± 1.5 and 6.5 ± 1.8 for amikacin (1 mg/kg per h), and 15 ± 4 and 17 ± 5 for amikacin (4 mg/kg per h). During these two experimental periods, percent fractional excretions of the five aminoglycosides were similar: 78 ± 6 and 80 ± 5 for gentamicin, 87 ± 4 and 84 ± 8 for tobramycin, 102 ± 13 and 97 ± 15 for netilmicin, 83 ± 13 and 81 ± 10 for dibekacin, 80 ± 5 and 84 ± 9 for amikacin (1 mg/kg per h), and 128 ± 17 and 123 ± 10 for amikacin (4 mg/kg per h). For these reasons, each value in Table 2 represents the mean of the two experimental periods. Glomerular filtered load, absolute rate of net tubular secretion, ratio of excreted-to-infused antibiotic, plasma levels, and renal clearance were similar for all the aminoglycosides tested, except amikacin at 4 mg/kg per h. The fractional excretion of gentamicin was significantly lower than that of netilmicin. The fractional excretion of amikacin (4 mg/kg per h) was significantly higher than that of the other four drugs. Similar values of this parameter were noted with dibekacin, tobramycin, and amikacin (1 mg/kg per h). For gentamicin, significant correlation ($r = 0.71$) was noted between UFR and fractional excretion. This correlation was not found with the other drugs, despite similar interindividual variation of UFR within each group. The biochemical data are reported in Table 3. No significant variation of the fractional excretion of sodium, calcium, potassium, magnesium, or LDH was observed. An apparent, significant increase of the fractional excretion of phosphate was noted with gentamicin and netilmicin between control and experimental periods. However, the phosphate T_m remained unchanged, i.e., 1.05 ± 0.13 and 0.98 ± 0.13 with gentamicin and 0.18 ± 0.15 and 1.05 ± 0.15 with netilmicin for the control and experimental periods, respectively. The latency of the wave V measured

TABLE 2. Concentrations in human serum and urinary excretion of gentamicin, dibekacin, tobramycin, netilmicin, and amikacin[a]

Antibiotic	Concn in serum (μg/ml)	Glomerular filtered load (μg/min per kg)	Absolute rate of net tubular secretion (μg/min per kg)	Fractional excretion (%)	Excreted/infused ratio (%)	Antibiotic renal clearance (ml/min per kg)
Gentamicin	5.3 ± 1.3	8.7 ± 2.6	0	79 ± 6	38 ± 9	1.3 ± 0.2
Dibekacin	4.8 ± 0.4	5.3 ± 2.0	3 ± 6	81 ± 22	29 ± 20	0.9 ± 0.4
Tobramycin	4.8 ± 0.3	6.8 ± 1.2	0	85 ± 5	36 ± 12	1.2 ± 0.2
Netilmicin	5.4 ± 0.9	7.3 ± 1.7	27 ± 52	99 ± 19	32 ± 7	1.4 ± 0.4
Amikacin (4 mg/kg per h)	16.2 ± 4.6	18.8 ± 4.4	312 ± 258	124 ± 13	38 ± 7	1.5 ± 0.2
Amikacin (1 mg/kg per h)	6.2 ± 1.1	9.5 ± 2.0	0	83 ± 4	41 ± 3	1.3 ± 0.2

[a] The procedure is described in the text. Each value in the table represents the mean ± standard deviation of the two experimental periods.

by the auditory brain-stem-evoked response remained unchanged after the infusion of each drug.

Binding to serum proteins was zero for all five aminoglycosides at the concentrations tested in vitro.

DISCUSSION

During this study, no significant variation of either GFR or latency of wave V on the auditory brain-stem-evoked response was noted, nor did we observe any modification on the fractional excretion of various electrolytes. An increase in the fractional excretion of phosphate was noted during the infusion of each aminoglycoside, and a significant variation was observed with gentamicin and netilmicin. However, the phosphate T_m was normal, suggesting that the modifications we observed with the fractional excretion of phosphate were probably due to the experimental conditions and were independent of the antibiotics. In the same respect, a constant pattern of LDH excretion was noted. Thus, during this study the infusion of therapeutic doses of aminoglycosides (2 or 8 mg/kg for amikacin) produced no detectable toxic effect. These results indicate that the protocol used here can be safely applied to future studies of the renal behavior of aminoglycosides. The tubular disposition appeared somewhat different for the five aminoglycosides studied. Gentamicin exhibited the highest degree of reabsorption. Dibekacin, tobramycin, and amikacin (1 mg/kg per h) showed the same degree of tubular reabsorption. Netilmicin had a zero net tubular balance. These results indicate that all of these four aminoglycosides undergo tubular reabsorption. The significant difference between the tubular disposition of gentamicin and netilmicin was unpredictable in view of the similar pharmacokinetic characteristics of these two drugs (16).

These results, obtained with humans, are quite similar to those reported previously for rabbits (4). The same decreasing order of tubular reabsorption applied in both cases. However, reabsorption of each drug seemed to be greater in rabbits. It should be noted that for humans, drug levels in serum and glomerular filtered load for each of the five aminoglycosides (except for amikacin [4 mg/kg per h]) were similar, whereas for rabbits a significant difference was observed between the filtered loads of gentamicin and netilmicin. In spite of these species-related differences, the order of tubular reabsorption was similar in humans and rabbits, as were the net balances of the five drugs and their renal clearances.

In this study we found, as generally reported in the literature (16), that the five aminoglycosides tested were not bound to serum proteins. Thus, both the filtered load and the fractional excretion were calculated by using the total serum concentrations of each drug.

From our data we cannot draw any conclusions about the precise mechanisms of tubular reabsorption of aminoglycosides. However, it should be noted that amikacin exhibited a pattern of tubular disposition that was dependent on the dose, i.e., at a dose of 1 mg/kg per h it was reabsorbed, whereas at a dose of 4 mg/kg per h it was not, suggesting either a saturable process of reabsorption or a basolateral secretory pathway of the antibiotic which the higher dose uncovered. Pastoriza-Munoz et al. (17) reported that in rats, filtered netilmicin was absorbed along the proximal convoluted tubule and loop of Henle by a mechanism which at high filtered loads appeared to exhibit saturation kinetics. If the pattern observed in humans is a property only of amikacin and not of the other aminoglycosides, this might explain why the nephrotoxic potential of this drug is lower than that of gentamicin. This remains to be determined. Similarly, we noted that with gentamicin, the higher the UFR the lower the reabsorption rate. Although these results are not a demonstration of a causative relationship between excretion and urine flow, they might correspond to the fact that gentamicin was the most intensively reabsorbed aminoglycoside. In a previous study with rabbits, Carbon et al. (5) showed that furosemide enhanced the gentamicin urinary excretion through a tubular process, i.e., proximal reabsorption was decreased by a diuresis effect. All these results suggest that the duration of contact between the antibiotic and the brush border membrane of the tubular cells might play an important role in tubular absorption. They also suggest that gentamicin undergoes a bidirectional transport. In fact, this phenomenon has been reported for gentamicin by Senekjian et al. (20) and Sheth et al. (21) and for netilmicin by Pastoriza-Munoz et al. (17). These authors explained the higher fractional excretion and the lower accumulation of netilmicin than of gentamicin in tissue by the fact that the apical membrane transport rate of netilmicin was intrinsically lower than that of gentamicin. The second possible explanation was that netilmicin undergoes a transtubular secretory flux greater in magnitude than the flux of gentamicin. These hypotheses could explain the differences we noted between these two aminoglycosides in humans.

Previous data obtained with rabbits suggested that the nephrotoxic potential of aminoglycoside might be determined by two major factors: the extent to which the antibiotic is transported into proximal tubular cells and the damage done to intracellular organelles. The present data obtained with humans should be considered in light of biochemical and clinical studies comparing the nephrotoxicity of aminoglycosides.

TABLE 3. Effects of infusing aminoglycosides on the fractional excretion of sodium, potassium, phosphate, magnesium, calcium, and LDH[a]

Antibiotic	Fractional excretions (%) of:											
	Sodium		Potassium		Phosphate		Magnesium		Calcium		LDH	
	Control	Expt	Control	Expt	Control	Expt	Control	Expt	Control	Expt	Control	Expt
Gentamicin	2.2 ± 0.5	2.2 ± 1.0	33 ± 18	21 ± 17	14 ± 5	22 ± 7	5.0 ± 1.2	5.0 ± 1.2	1.4 ± 0.4	1.7 ± 0.6	0.11 ± 0.08	0.06 ± 0.03
Dibekacin	1.9 ± 1.2	1.9 ± 0.7	16 ± 10	16 ± 7	15 ± 13	24 ± 19	5.2 ± 3.4	6.2 ± 2.6	2.3 ± 1.0	2.8 ± 1.6	0.13 ± 0.08	0.12 ± 0.04
Tobramycin	2.2 ± 1.2	2.0 ± 0.7	30 ± 10	19 ± 10	11 ± 4	19 ± 16	6.5 ± 1.5	4.7 ± 0.6	3.0 ± 1.0	2.2 ± 0.8	0.13 ± 0.06	0.12 ± 0.05
Netilmicin	3.2 ± 2.3	3.1 ± 1.4	27 ± 16	18 ± 4	11 ± 6	19 ± 6	5.4 ± 1.2	6.7 ± 2.7	3.4 ± 1.2	3.5 ± 1.2	0.13 ± 0.07	0.18 ± 0.08
Amikacin (4 mg/kg per h)	2.6 ± 0.4	3.8 ± 1.2	24 ± 13	29 ± 21	22 ± 9	28 ± 9	6.3 ± 3.6	5.7 ± 1.4	2.4 ± 0.9	3.0 ± 1.5	0.14 ± 0.09	0.09 ± 0.02

[a] Procedure is described in the text.

The relationship between the toxicity of aminoglycosides and their potency to inhibit enzymatic activities involved in the metabolism of phospholipids has been investigated recently (10, 25, 26). Marche et al. (13) used the erythrocyte membrane model to rank the capacity of the aminoglycosides to impair phosphoinositide metabolism as follows: neomycin > gentamicin > dibekacin > kanamycin > amikacin = streptomycin. The low intrinsic nephrotoxicity of amikacin reported by Marche et al. (13) is in agreement with the results obtained by Viotte et al. (27), who, on the basis of the ultrastructural and biochemical alterations observed in rat kidney cortices, gave the following decreasing order of toxicity: gentamacin > netilmicin > dibekacin = tobramycin > amikacin.

Using the recommended clinical dosages, De Broe et al. (7) reported that after four days of treatment, gentamicin and tobramycin in humans could not be distinguished on the basis of cortical accumulation, lysosomal overloading, or effect on lysosomal phospholipase A_1. Conversely, amikacin induced significantly less lysosomal overloading than these two drugs and no loss of phospholipase A_1 activity. These results were similar to those obtained by the same authors when using either cultured cells (25) or animals treated with therapeutic doses (26).

In evaluating clinical nephrotoxicity, the results of studies on humans are sometimes contradictory. For example, Smith et al. (23) reported that tobramycin was less nephrotoxic than gentamicin. Fong et al. (8), on the other hand, found no significant differences between the two drugs, and Moore et al. (14), reporting the results of a multifactorial analysis, also found that the nephrotoxic potential of these two aminoglycosides was similar, a result quite different from that published by the same authors a few years earlier (23). Daschner et al. (6) reported that for humans receiving either netilmicin plus ticarcillin or tobramycin plus ticarcillin, the group receiving netilmicin developed significantly less nephrotoxicity than the group receiving tobramycin (0 versus 15%). Holm et al. (9), in a study of 135 patients, reported that nephrotoxicity occurred significantly less frequently (6%) in the group receiving amikacin than in the group receiving gentamicin (20%). In a survey of aminoglycoside nephrotoxicity covering approximately 10,000 patients in clinical trials between 1975 and 1982, Kahlmeter and Dahlager (11) reported the following frequencies of nephrotoxicity: 14% for gentamicin, 12.9% for tobramycin, 9.4% for amikacin, and 8.7% for netilmicin. Thus, biochemical and clinical studies gave similar conclusions, i.e., gentamicin appears to have the highest nephrotoxic potential and netilmicin and amikacin appear to have the lowest. Tobramycin and dibekacin exhibit a pattern close to that of gentamicin. Amikacin seems to have the lowest intrinsic nephrotoxic potential. Our results on the renal disposition of aminoglycosides in humans suggest a possible correlation between the nephrotoxicity of these drugs and their tubular disposition. Consequently, we would suggest that new aminoglycosides be evaluated both for lesions caused on subcellular structures and for renal tubular disposition in vivo.

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