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Renal function in premature infants during aminoglycoside therapy

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Abstract. The effect of three different aminoglycosides on renal function was evaluated in 30 premature infants of similar gestational age who were treated within 24 h of birth with either amikacin (10 infants, group A), gentamicin (10 infants, group B) or netilmicin (10 infants, group C), for a period of 7 days. Ten infection-free premature infants of similar post-conceptional age were used as controls. Serial determinations of plasma creatinine concentration (PCr), as well as the fractional excretion of sodium (FENa), potassium, magnesium (FEMg), phosphate (FEP) and uric acid (FEUA), and the urinary excretion of calcium (UCa/UCr ratio) were assessed before, during and after treatment. During the treatment period a significant increase in FENa, FEMg and UCa/UCr was observed in group B ($P < 0.05$ and $P < 0.01$, respectively) and an increase in FENa and UCa/UCr in group C ($P < 0.01$) compared with controls. These disturbances were observed with trough concentrations of aminoglycosides but were accentuated at peak serum concentrations and were restored to normal 2 days after stopping therapy. In addition, a significant correlation was demonstrated between FENa, FEMg and UCa/UCr ratio in treated patients. PCr levels decreased similarly in all patient groups, but in 8 of 30 infants (27%) they remained elevated and returned to control values only 10 days after stopping therapy. Such renal functional disturbances, although transient, may result in significant electrolyte and mineral imbalance in the sick premature infant.

Key words: Prematurity – Aminoglycoside toxicity – Renal tubular dysfunction

Introduction

Aminoglycosides are valuable broad-spectrum antibiotics which are used extensively for the treatment of suspected or documented infections in premature and full-term infants. Data on aminoglycoside nephrotoxicity in premature infants are both limited and contradictory and are also inconsistent as to the post-conceptional age at which therapy was instituted [1–7]. Furthermore, the use of certain tubular markers for the assessment of aminoglycoside toxicity, such as *N*-acetyl-β-glycosaminidase (NAG), may be of limited value, especially since the urinary activity of NAG is often elevated with serious infections, even prior to initiation of antibiotic therapy [8, 9].

The present controlled study was designed to assess the potential nephrotoxicity of amikacin, gentamicin or netilmicin administered to premature neonates of similar post-conceptional age during the first 24 h of life. The renal functional parameters studied included serial determinations of plasma creatinine (PCr), the fractional excretion of sodium (FENa), potassium (FEK), magnesium (FEMg), phosphorus (FEP) and uric acid (FEUA) and the excretion of calcium (UCa/UCr ratio); these were compared with values obtained from control infants of similar post-conceptional age.

Patients and methods

Forty preterm infants of similar mean gestational age (GA), as determined by the criteria of Dubowitz et al. [10], and similar birth weight were enrolled in the study within 24 h of birth. Stable metabolic and respiratory parameters (pH = 7.25–7.45, PO_2 = 50–70 mmHg, PCO_2 55 mmHg) were required for acceptance into the study. Infants small for GA, those receiving drugs that may affect renal function (frusemide, indomethacin, vancomycin or tolazoline), those with perinatal asphyxia and with moderate to severe respiratory distress syndrome, hyperbilirubinaemia and polycythaemia were excluded. We also excluded those infants whose clinical condition was serious at the onset of the study, or subsequently deteriorated, or infants who developed electrolyte disturbances during the course of the study. Informed consent was obtained from the parents. The study protocol was approved by the Research Committee of the University of Ioannina Medical School.

Of the 40 infants, 30 were treated IV for 7 days with one of three different aminoglycosides, in combination with cefotaxime, for suspected or proven sepsis, as defined by the criteria of Rodwell et al.

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Table 1. Mean serum concentrations of aminoglycosides (trough and peak) on the 3rd and 7th day of treatment and the corresponding therapeutic range of the drugs[a]

Group	3rd day of treatment		7th day of treatment		Therapeutic range	
	trough	peak	trough	peak	trough	peak
A (Amikacin)	9.6±3.7	27.6±6.9	8.8±4.7	25.7±9.0	5–10	20–30
B (Gentamicin)	1.7±0.6	6.8±1.8	2.2±1.5	8.0±1.4	0.5– 2.0	4–12
C (Netilmicin)	1.8±0.9	6.2±2.0	2.2±1.7	7.3±1.9	0.5– 3.0	4–12

[a] Values are μg/ml ± SD

[11]. Ten infants received amikacin (group A), 10 received gentamicin (group B) and 10 netilmicin (group C). The control group consisted of 10 infection-free infants of similar post-conceptional age, with or without mild respiratory problems or mild hyperbilirubinaemia, who were hospitalized over the same period and did not receive antibiotics. In order to ensure the randomized distribution of patients, the aminoglycosides were administered according to alphabetical order and over successive periods of 4 months each. The aminoglycosides were administered over 30 min, in a total volume of 5 ml of distilled water, at a dose of 10 mg/kg for amikacin and 2.5 mg/kg for gentamicin and netilmicin at the following time intervals: for infants with body weight <1,500 g the drugs were administered every 24 h, for those between 1,500 and 2,000 g every 18 h and for infants >2,000 g every 12 h. Trough and peak serum concentrations of the aminoglycosides were measured immediately before and 30 min after each dose.

The mean GA of the infants in group A was 33.6±1.8 weeks (range 31–36 weeks), in group B 33.2±1.5 weeks (range 29–36 weeks), in group C 32.5±1.9 weeks (range 28–35 weeks) and in the controls 33.2±1.5 weeks (range 30–35 weeks). All except 2 infants had a GA over 30 weeks. During the first 48 h after birth all infants received IV fluids (calculated on the basis of body weight, the rate of diuresis, the urine specific gravity, the blood pressure and the electrolyte balance) which contained 10% glucose with added calcium gluconate (4 ml/kg per 24 h), administered at a rate of 60–80 ml/kg per 24 h. On the 3rd day of life, the infants received either total parenteral nutrition (mixture of amino acids and lipids) or infant formula, depending on their clinical condition. Infants on parenteral nutrition also received supplemental calcium and/or phosphate, the doses of which were adjusted to maintain normal electrolyte balance. Blood and urine were obtained just prior to the start of therapy (zero time) and thereafter immediately before and after the infusion of the aminoglycosides on the 1st, 3rd, 4th and 7th days of treatment, as well as 48 h following discontinuation of therapy. Single-voided urine specimens were obtained over a 2- to 3-h period (using adhesive plastic bags) after ensuring complete emptying of the bladder by the Credé method of bladder compression. In the case of urine loss during the collection period the infant was excluded from the study. Complete urinalysis was performed on all urine specimens. Renal tubular function was assessed by examining FENa, FEK, FEP, FEMg and FEUA, as well as the urinary excretion of calcium (UCa/UCr ratio). Serial determinations of PCr were performed throughout the study to assess the maturational changes in glomerular function, and were compared with values obtained from the controls.

Measurements of Na, K, Ca, P, Mg, uric acid and creatinine in serum and urine specimens were performed with the automatic analyser RA-100 (Technicon). Serum concentrations of the aminoglycosides were determined using the polarized immunofluorescence assay (System TDX, Abbott). The inter- and intra-assay coefficients of variation were for amikacin 1.02% and 2.5%, for gentamicin 1.5% and 2.4% and for netilmicin 1.4% and 2%.

Statistical analysis. Data are expressed as mean plus or minus standard error of the mean. Intergroup comparison of the mean values of the various parameters was performed using the Mann Whitney U-test. The Spearman rank correlation coefficient was used to assess possible interdependency between those renal functional parameters (FENa, FEMg, UCa/UCr) which showed significant changes during the treatment period in each patient group.

Results

The mean trough and peak serum concentrations of the three aminoglycosides remained relatively constant and within the therapeutic range throughout the treatment period (Table 1). However, in 7 of 30 infants (4 in group A, 2 in group B and 1 in group C) the trough levels were above the recommended therapeutic range on the 3rd and the 7th days of therapy, while the corresponding peak levels were within the therapeutic range in groups B and C and elevated in group A. The mean values (±SEM) of the glomerular and tubular functional parameters are shown in Table 2.

FENa, FEMg and UCa/UCr ratio

Before initiation of therapy there was no statistical difference in the mean values for FENa, FEMg and the UCa/UCr ratio among the three treated patient groups and the controls. In the controls FENa, FEMg and UCa/UCr did not change significantly during the study period. During therapy a statistically significant increase was observed in FENa, FEMg and UCa/UCr ratio in group B and an increase in FENa and UCa/UCr ratio in group C patients. This increase was sustained throughout treatment, both at trough and, even more so, at peak serum concentrations of gentamicin and netilmicin. On the 4th day of therapy the mean values for FENa (at trough serum concentration of the drugs) increased to 2.0%±0.5% in group B ($P < 0.05$) and to 2.8%±1.0% in group C ($P < 0.01$), compared with a mean value of 0.9%±0.2% in the controls. Similarly the UCa/UCr ratio increased to a mean value of 0.23±0.07 in group B ($P < 0.05$) and 0.31±0.07 in group C ($P < 0.01$), compared with a mean value of 0.09±0.03 in controls. The FEMg increased significantly only in group B patients, reaching a mean value of 6.9%±2.7% on the 4th day of therapy, compared with 0.6%±0.3% in controls ($P < 0.05$). These disturbances were reversible and values tended to reach control levels 2 days following discontinuation of therapy.

The correlation between FENa, FEMg and UCa/UCr in each of the three patient groups and the controls is shown in Table 3. A significant correlation was found between FEMg and UCa/UCr ratio in all four groups ($P < 0.001$ and $P < 0.01$), between FENa and UCa/UCr ratio in patient groups A, B and C ($P < 0.001$) and between FENa and FEMg in patient groups A and B ($P < 0.001$ and $P < 0.0001$, respectively).

FEUA, FEK, FEP

There were no statistically significant changes in the mean values before treatment or during the study period between

Table 2. Mean values (±SEM) of renal functional parameters throughout the study period, both during the trough and peak plasma concentrations of aminoglycosides

	Group	Before treatment	1st day		3rd day		4th day		7th day		2 days after treatment
			(trough)	(peak)	(trough)	(peak)	(trough)	(peak)	(trough)	(peak)	
FENa (%)	A	1.1 ±0.2	2.0 ±0.9	2.0 ±0.3**	2.2 ±0.8	3.5 ±1.3*	3.2 ±1.5*	4.1 ±2.0*	1.0 ±0.3	0.9 ±0.3	0.6 ±0.2
	B	0.9 ±0.2	1.4 ±0.4	1.8 ±0.5*	1.9 ±0.4*	3.5 ±0.9**	2.0 ±0.5*	3.3 ±0.6**	1.7 ±0.4*	3.4 ±1.3**	1.0 ±0.2
	C	1.2 ±0.1	1.9 ±0.4	2.6 ±0.6*	1.5 ±0.3*	2.6 ±0.6**	2.8 ±1.0**	3.8 ±1.2**	1.5 ±0.5**	2.2 ±0.7**	1.1 ±0.6
	Controls	1.0 ±0.1			0.9 ±0.2				0.5 ±0.1		0.7 ±0.2
FEMg (%)	A	0.4 ±0.1	1.0 ±0.5	0.6 ±0.1	1.4 ±0.8	2.0 ±0.9	2.6 ±1.4	2.8 ±1.6	1.1 ±0.5	1.5 ±0.3	2.0 ±1.0
	B	0.4 ±0.1	0.9 ±0.4	1.2 ±0.5	2.4 ±1.1*	5.7 ±1.9**	6.9 ±2.7*	8.1 ±3.7**	6.9 ±2.7*	8.1 ±3.7*	2.7 ±0.5*
	C	0.5 ±0.1	0.5 ±0.1	0.9 ±0.3	1.5 ±0.7	2.5 ±1.2	2.2 ±1.1	3.6 ±1.5*	2.7 ±0.9	3.2 ±1.0	2.8 ±0.7
	Controls	0.5 ±0.1			0.6 ±0.3				1.2 ±0.6		1.4 ±0.4
UCa/UCr (mg/mg)	A	0.08±0.01	0.11±0.06	0.14±0.02	0.12±0.05	0.24±0.07*	0.16±0.07	0.20±0.09	0.09±0.03	0.10±0.02	0.09±0.03
	B	0.11±0.02	0.11±0.03	0.19±0.04**	0.20±0.06*	0.64±0.35**	0.23±0.07*	0.50±0.07**	0.27±0.11	0.53±0.16**	0.15±0.03
	C	0.13±0.01	0.20±0.03**	0.24±0.04**	0.26±0.04**	0.37±0.08**	0.31±0.07**	0.43±0.11**	0.25±0.06*	0.35±0.05**	0.24±0.06*
	Controls	0.08±0.01			0.09±0.03				0.14±0.04		0.13±0.04
FEUA (%)	A	27.7 ±6.2	35.7 ±5.5	43.4 ±6.6	30.8 ±3.8	38.7 ±5.8	33.8 ±7.5	35.9 ±6.5	30.6 ±4.6	35.8 ±5.6	28.2 ±4.8
	B	40.1 ±2.8	54.3 ±6.6	46.1 ±6.3	46.5 ±8.4	49.2 ±7.1	42.5 ±8.7	41.1 ±6.2	31.1 ±5.4	38.7 ±8.0	29.6 ±4.7
	C	45.7 ±7.5	56.6 ±6.9	51.2 ±8.2	49.2 ±7.5	52.3 ±7.3	39.8 ±7.5	50.3 ±6.3	30.6 ±4.8	35.3 ±5.9	30.7 ±4.2
	Controls	39.3 ±8.5			32.9 ±5.8				24.1 ±3.5		32.1 ±7.0
FEK (%)	A	24.9 ±5.6	36.5 ±6.6	31.6 ±6.9	25.1 ±5.3	21.4 ±3.6	24.8 ±4.7	22.3 ±4.4	15.1 ±1.9	21.3 ±2.9	16.2 ±1.8
	B	21.2 ±3.0	34.2 ±8.2	28.1 ±4.0	21.5 ±4.3	24.4 ±4.7	12.8 ±1.5	17.1 ±2.4	10.3 ±1.6	17.4 ±5.1	9.7 ±1.1
	C	28.4 ±5.6	39.6 ±4.8	42.2 ±5.7	34.5 ±6.2	26.1 ±4.1	20.9 ±4.1	23.2 ±4.3	16.9 ±4.8	18.9 ±4.5	15.3 ±2.8
	Controls	25.5 ±3.0			16.2 ±4.4				14.3 ±2.5		13.1 ±1.5
FEP (%)	A	3.4 ±2.3	8.8 ±4.7	12.7 ±5.2	17.6 ±6.3	20.0 ±6.3	24.3 ±6.6	19.9 ±5.2	13.9 ±4.8	12.6 ±3.0	10.7 ±3.3
	B	3.4 ±1.7	11.5 ±5.2	6.6 ±3.1	15.3 ±6.7	11.1 ±4.9	13.8 ±5.7	11.3 ±4.6	6.7 ±3.3	13.3 ±7.1	12.5 ±3.5
	C	6.4 ±3.6	16.1 ±7.9	10.8 ±4.2	26.6 ±8.6	23.4 ±6.6	23.3 ±6.0	17.7 ±4.7	8.1 ±2.8	8.1 ±2.3	6.9 ±1.7
	Controls	4.8 ±2.4			10.4 ±3.5				9.9 ±2.6		11.1 ±2.8
Plasma creatinine (mg/dl)	A	0.94±0.04	1.10±0.09	1.04±0.05	1.06±0.10	1.07±0.10	1.04±0.12	1.05±0.13	0.90±0.12	0.92±0.12	0.84±0.12
	B	1.02±0.09	1.17±0.09	1.05±0.08	1.17±0.14	1.19±0.12	1.04±0.08	1.01±0.08	0.91±0.09	0.95±0.09	0.88±0.07
	C	1.01±0.07	1.17±0.04	1.11±0.08	1.09±0.04	1.08±0.04	1.02±0.04	1.01±0.04	0.94±0.06	0.94±0.06	0.93±0.09
	Controls	1.10±0.08			0.93±0.07				0.87±0.08		0.77±0.09

FENa, fractional excretion of sodium; FEMg, fractional excretion of magnesium; FEUA, fractional excretion of uric acid; FEK, fractional excretion of potassium; FEP, fractional excretion of phosphorus; UCa/UCr, urinary calcium/creatinine ratio
* $P < 0.05$ vs. controls; ** $P < 0.01$ vs. controls

Table 3. The significance of the correlation between FENa, FEMg and UCa/UCr during the study period in each one of the three treated patient groups and the controls

Group	*n*	FENa vs. FeMg	FENa vs. UCa/UCr	FEMg vs. UCa/UCr
A	89	$P < 0.001$	$P < 0.001$	$P < 0.001$
B	90	$P < 0.0001$	$P < 0.001$	$P < 0.001$
C	90	NS	$P < 0.001$	$P < 0.01$
Controls	40	NS	NS	$P < 0.001$

the controls and the three patient groups. The decrease in FEK that was observed during the treatment period ($P = 0.007$) was of a similar magnitude both in the controls and in patient groups A, B and C, and could reflect maturational changes.

Plasma creatinine

Before initiation of treatment there was no statistical difference in the mean values for PCr among the three groups of patients and the controls (Table 2). During the study period the PCr in the controls showed a downward trend ($P < 0.05$). The values obtained were not statistically different when compared with those in patient groups A, B and C. However, in 8 of 30 treated infants (27%) (3 infants in group A, 3 in group B and 2 in group C) PCr levels increased to a mean of 1.27±0.07 mg/dl on the 7th day of treatment, compared with 0.87±0.08 mg/dl in controls ($P < 0.01$), and remained elevated 2 days after discontinuation of therapy. On re-examination 10 days later, the PCr had decreased to control levels. Of the above 8 infants, 3 (37%) demonstrated proteinuria, haematuria and cylinduria, compared with only 2 of the 22 treated infants (9%) with normal PCr who had similar abnormalities on urinalysis.

Discussion

Our study shows that early exposure of premature infants of similar post-conceptional age to therapeutic doses of gentamicin and netilmicin is associated with a sustained elevation of FENa and calcium excretion and, in the case of gentamicin, also of FEMg, which was most evident on the 4th and 7th days of therapy. This disturbance in renal tubular function was transient and most values approached

those of the control infants within 2 days of stopping therapy. Our findings are in agreement with those of Rothberg and Andronikou [6] who showed that exposure of premature infants to tobramycin resulted in a sustained elevation of FENa, which subsequently decreased to normal 2 days posttherapy.

Our data also suggest that amikacin is less toxic than gentamicin or netilmicin despite the fact that high trough serum concentrations were observed in 4 of 10 amikacin-treated infants. Our findings are supported by studies in premature newborns [2], as well as experimental studies in rats [12] which have demonstrated that amikacin is less toxic than the other aminoglycosides; this has been attributed to its lower binding affinity to proximal tubular cells [13] and to its lower intrinsic potential to induce phospholipidosis [14]. Based on our findings we can postulate that the observed disturbances in FENa, UCa/UCr ratio and FEMg are most likely related to the specific effect of gentamicin and netilmicin on the proximal tubular cell rather than to the presence of sepsis or to the concomitant use of cefotaxime. Furthermore, the fact that the observed renal tubular disturbances were even more accentuated during the peak serum concentrations of gentamicin and netilmicin may support the above assumption.

Elinder and Aperia [5] observed a decrease in glomerular filtration rate (GFR) during gentamicin treatment in premature and full-term infants. We assessed changes in GFR by obtaining serial determinations of PCr concentrations in the same infants throughout the study period and comparing these with control infants [15–17]. The PCr levels in 22 of 30 premature infants (83%) on aminoglycoside therapy were not statistically different from controls. The rise in PCr concentration observed in 8 of 30 of our treated infants (27%) has also been reported by Feldman and Guignard [15] in 7 of 22 neonates (30%) and by Adelman et al. [8, 9] in 26% of infants on gentamicin therapy. In our study these infants exhibited more severe disturbances in FENa, UCa/UCr ratio and FEMg and also they had proteinuria, haematuria and cylinduria. The disturbance in PCr in these infants was transient and reversible following discontinuation of therapy.

The effect of aminoglycosides on the urinary excretion of calcium and magnesium in premature infants has not been examined by other investigators. Our data demonstrate that there is a significant correlation between the observed urinary losses of sodium and those of calcium and magnesium, as well as between the urinary excretion of calcium and magnesium. These findings are supported by animal studies that show that conditions which may increase the excretion of one of the cations may lead to a similar increase in the excretion of the others [18–20]. Furthermore, studies in the sick premature infant by Brown and Steranka [21] suggest that sodium excretion may be an important factor controlling calcium excretion. The clinical importance of our data lies in the fact that although the observed renal functional disturbances are transient and reversible they may render the sick premature infant more susceptible to early-onset neonatal hypocalcaemia and other electrolyte disturbances.

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