Original article
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 (FEP), magnesium (FEMg), phosphate (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 (FEP), 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, PO2 = 50–70 mmHg, PCO2 35–55 mmHg) were required for acceptance into the study. Infants small for GA, those receiving drugs that may affect renal function (furosemide, 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.
A 9.6±3.7 27.6±6.9 8.8±4.7 25.7±9.0 5-10 20-30
rate of diuresis, the urine specific gravity, the blood pressure and the
between 1,500 and 2,000 g every 18 h and for infants >2,000 g every
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, 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 pe-
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.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>3rd day of treatment</th>
<th>7th day of treatment</th>
<th>Therapeutic range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>trough</td>
<td>peak</td>
<td>trough</td>
</tr>
<tr>
<td>A (Amikacin)</td>
<td>9.6±3.7</td>
<td>27.6±6.9</td>
<td>8.8±4.7</td>
</tr>
<tr>
<td>B (Gentamicin)</td>
<td>1.7±0.6</td>
<td>6.8±1.8</td>
<td>2.2±1.5</td>
</tr>
<tr>
<td>C (Netilmicin)</td>
<td>1.8±0.9</td>
<td>6.2±2.0</td>
<td>2.2±1.7</td>
</tr>
</tbody>
</table>

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.

FENa, FEMg and UCa/UCr ratio

Before initiation of therapy there was no statistical differ-
ence in the mean values for FENa, FEMg and the UCa/UCr
ratio among the three treated patient groups and the con-
trols. In the controls FENa, FEMg and UCa/UCr did not
change significantly during the study period. During ther-
apy a statistically significant increase was observed in
FENa, FEMg and UCa/UCr ratio in group B and an in-
crease 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