Impact of Gestational Age and Birth Weight on Amikacin Clearance on Day 1 of Life


Departments of *Pediatric Nephrology, †Pharmacy, ‡Neonatology, and §Pediatric Endocrinology, VU University Medical Center, Amsterdam, The Netherlands

Background and objectives: Intrauterine growth restriction (IUGR) and prematurity are associated with a low nephron endowment. It can therefore be expected that neonates who are born premature and/or after IUGR have a lower GFR. Measurement of GFR in neonates is difficult, but the clearance of amikacin has been proven to be a reliable marker. We hypothesized that amikacin clearance is lower after IUGR or premature birth as a marker of low nephron endowment.

Design, setting, participants, & measurements: Amikacin clearance was retrospectively analyzed in 161 neonates who received amikacin within the first 24 h of life. Using the MW/Pharm computer program, a population one-compartment model was calculated. The mean population pharmacokinetic parameters were individualized for each patient according to the maximum a posteriori Bayesian fitting method and provided the amikacin clearance.

Results: Our results show that birth weight z score and gestational age are correlated with the clearance of amikacin (partial correlation coefficient 0.159, \( P = 0.046 \), and 0.396, \( P < 0.001 \), respectively), after correction for other factors.

Conclusions: We conclude that renal clearance on the first day of life is lower in neonates with a lower gestational age and/or birth weight z score. This indicates that both prematurity and IUGR impair GFR on the first day of life.


Nephrogenesis in humans starts at approximately day 30 of gestation and ends before the 36th week of gestation (1). By a complex interaction between the metanephric mesenchyme and the ureteric bud (1), nephrons are formed to a total of 600,000 to 800,000 per kidney, with a wide interindividual range (2,3). Intrauterine growth restriction (IUGR) has been shown to lead to a low nephron number, both in humans (4–7) and in animal models (8–10). Premature birth (i.e., before completion of nephrogenesis) has also been shown to lead to fewer nephrons (11).

By hyperfiltration, the residual nephrons will compensate for this lower number (12). This leads to a normal GFR but is associated with glomerular sclerosis and hypertension in the long run (13,14). At the age of 6 to 12 yr, no difference between appropriate- and small-for-gestational-age children was found in GFR (15). Determination of GFR at these ages therefore does not reflect nephron endowment, whereas GFR before the onset of hyperfiltration (i.e., directly after birth) may be a marker of nephron number.

Unfortunately, measurement of GFR in neonates is difficult because urine collections are often unreliable and serum creatinine at birth is not a good marker of neonatal renal function but reflects maternal plasma concentration (16). Previously, the clearance of amikacin was used as a marker of GFR in neonates (17–20) because aminoglycoside clearance correlates well with GFR (21). Amikacin is often used in neonates in whom perinatal infection is suspected, and amikacin levels are routinely monitored. Because amikacin clearance is an indicator of GFR and GFR direct postnatally may be indicative of the renal mass present, we retrospectively analyzed amikacin clearances on the first day of life and studied the influence of gestational age (GA) and birth weight on GFR as a marker of nephron endowment.

Materials and Methods

Patients

At the neonatal intensive care unit of the VU University Medical Center, first-line treatment for (suspected) bacterial infection consists of amikacin (12 mg/kg intravenously in 30 min once every 36 h in infants <1500 g and once every 24 h in infants >1500 g) and benzylpenicillin (200,000 IU/kg every 24 h intravenously divided into four equal doses). After the first and before the second dose of amikacin, at least one blood sample was taken for therapeutic drug monitoring. Plasma was stored at 4°C until analysis, usually the same day.

Patients who were admitted to our neonatal intensive care unit with a first dose of amikacin administered within the first 24 h of life and at least one amikacin level were included. Exclusion criteria were perinatal asphyxia (defined as an Apgar score at 5 min \(<5; n = 15\)), use of inotropic drugs (dopamine and/or dobutamine; \( n = 12 \)) or prostaglandins, and congenital heart defects other than hemodynamically insig-
significant septum defects (either atrial or ventricular septal defects; n = 2). Another patient was excluded for the diagnosis of a teratoma with a weight equal to the weight of the neonate. The standard Dutch growth curves of fetuses that were used (22) do not provide information on birth weights in neonates with a GA <25 wk and 4 d. Because one neonate was born before this term, no z score could be calculated, and this neonate was excluded as well. After exclusion, 161 neonates who were treated with amikacin were studied. Patient characteristics are listed in Table 1.

Data were collected from chart review. All neonates were divided into four groups according to their birth weight z score quartile.

GFR has been reported to be affected by prenatal treatment with steroids or indomethacin (23,24) and by respiratory failure in the neonate in some (25,26) but not all studies (27). Data were therefore collected on prenatal drug use (antenatal betamethasone was scored when given within 8 d before birth), respiratory support during the first 24 h of life, and the use of surfactant. Urine production (ml/kg per h) during the first 24 h was calculated.

**Drug Analysis**

Plasma concentrations of amikacin were determined by fluorescence polarization immunoassay (TDx-FLx; Abbott Diagnostics, Abbott Park, IL).

**Pharmacokinetic Analysis**

Using the Kinpop module of the pharmacokinetic software package MW/Pharm 3.33 (Mediware, Groningen, The Netherlands), we calculated a population one-compartment model from the amikacin dosing and the plasma concentration values of the patients. This program uses an iterative two-stage Bayesian procedure and calculates means, medians, and SD of the pharmacokinetic parameters (28). During the iterative two-stage Bayesian procedure, pharmacokinetic parameters were set to be distributed log-normally. The calculated mean population pharmacokinetic parameters were individualized for each patient on the basis of his or her amikacin dosing and the measured blood concentrations according to the maximum a posteriori Bayesian fitting method (29), using the MW/Pharm computer program. By means of maximum a posteriori Bayesian fitting, any available information (a priori population parameters, drug dosage regimen, and measured plasma concentrations) can be used to estimate the a posteriori pharmacokinetic parameters of the individual patients. These a posteriori pharmacokinetic parameters of the individual patient are the maximum likelihood estimates obtained by maximum a posteriori Bayesian fitting, minimizing the deviations of measured and predicted concentrations and of population pharmacokinetic parameters and pharmacokinetic parameters of the individual patient (29). This approach is very flexible and ensures an optimal use of the information available, from both a population and the individual patient. From the individualized pharmacokinetic parameters, the distribution volume (L/kg) and amikacin clearance (ml/kg per min) were calculated.

**Statistical Analysis**

For parameters with a normal distribution, results are presented as mean (SD). For data with a non-normal distribution, results are presented as median (interquartile range [IQR]). When a difference between the groups existed, mean difference (95% confidence interval [CI] of the difference) is provided. Backward multiple regression was used to identify significant factors. Partial correlation coefficients of the significant factors were estimated. SPSS 11.0.1 for Windows (SPSS Inc., Chicago, IL) was used for statistical analysis. P < 0.05 was considered to be statistically significant.

**Results**

Amikacin pharmacokinetics were adequately described by a one-compartment model. Pharmacokinetic parameters as calculated by Kinpop are listed in Table 2. Comparing neonates in the lowest birth weight z score quartile with patients in the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>161</td>
</tr>
<tr>
<td>Male:female</td>
<td>95:66</td>
</tr>
<tr>
<td>Primigravida:multigravida</td>
<td>106:55</td>
</tr>
<tr>
<td>Singleton:twins:triplets</td>
<td>93:64:4</td>
</tr>
<tr>
<td>Prenatal steroids</td>
<td>34/111</td>
</tr>
<tr>
<td>Indomethacin tocolysis</td>
<td>11</td>
</tr>
<tr>
<td>Atosiban tocolysis</td>
<td></td>
</tr>
<tr>
<td>GA (wk; mean [SD])</td>
<td>52/157</td>
</tr>
<tr>
<td>Birth weight (g; median [IQR])</td>
<td>32.4 (3.9)</td>
</tr>
<tr>
<td>Birth weight z score (median [IQR])</td>
<td>1650 (1312 to 2187)</td>
</tr>
<tr>
<td>Body length at birth (cm; mean [SD])</td>
<td>41.1 (5.4)</td>
</tr>
<tr>
<td>Head circumference at birth (cm; mean [SD])</td>
<td>29.3 (3.4)</td>
</tr>
<tr>
<td>Apgar score at 5 min (median [IQR])</td>
<td>9 (8 to 9)</td>
</tr>
<tr>
<td>Umbilical artery pH (median [IQR])</td>
<td>7.27 (7.22 to 7.32)</td>
</tr>
<tr>
<td>Respiratory support</td>
<td>117</td>
</tr>
<tr>
<td>Ventilated</td>
<td>58</td>
</tr>
<tr>
<td>CPAP</td>
<td>59</td>
</tr>
<tr>
<td>Administration of surfactant</td>
<td>38/160</td>
</tr>
<tr>
<td>Urine production (ml/kg per h; mean [SD])</td>
<td>2.1 (1.2)</td>
</tr>
</tbody>
</table>

CPAP, continuous positive airway pressure.
highest birth weight z score quartile, the amikacin clearance (median 0.56 ml/kg per min [IQR 0.49 to 0.62] versus 0.64 ml/kg per min [IQR 0.54 to 0.75]; \(P = 0.032\)) was significantly lower in the lowest quartile group (mean difference \(0.11\) ml/kg per min [95% CI \(-0.21\) to \(-0.02\)]; Figure 1). Figure 2 shows the amikacin clearance per cluster of GA. In line with previous studies, a higher GA was correlated with a higher amikacin clearance.

Backward multiple regression identified no factors to be significantly associated with the distribution volume. Analysis of contributing factors to the amikacin clearance showed three significant parameters: Distribution volume, GA, and birth weight z score. Both the distribution volume and amikacin clearance were derived from the same pharmacokinetic model, which explains the high correlation between the two (partial correlation coefficient \(0.595\), corrected for GA and birth weight z score). In a multiple regression model with these three factors, the adjusted \(R^2\) was 0.475. The partial correlation coefficient between amikacin clearance and birth weight z score was 0.159 (\(P = 0.046\), corrected for volume of distribution and GA) and between amikacin clearance and GA was 0.396 (\(P < 0.001\), corrected for volume of distribution and birth weight z score). No influence of gender, multiple pregnancy, prenatal use of steroids, indomethacin or atosiban, Apgar score at 5 min, umbilical artery pH, urine production, respiratory support, or use of surfactant was found on amikacin clearance.

### Discussion

Our results show that a lower birth weight z score and a lower GA are correlated with a lower clearance of amikacin, after correction for other factors. This indicates that both IUGR and prematurity impair GFR on the first day of life as a marker of nephron endowment.

IUGR has been shown to lead to a low nephron endowment (4–7). GFR is based on two factors: The number of nephrons multiplied by the single-nephron GFR (SNGFR). This implies that GFR is decreased when the nephron number is decreased, as long as SNGFR is constant. Compensatory hyperfiltration leads to an increase in SNGFR and consequently an increase in GFR. This explains the normal GFR in children after IUGR (15). In newborns, it is hypothesized that SNGFR is not yet increased after IUGR. GFR can therefore be used as an indication of the nephron number. Even if SNGFR is increased after IUGR or prematurity, this would suggest a more pronounced impairment of nephron endowment.

Previously, Robinson et al. (30) did not find a significantly lower GFR on day 1 of life in a small study. In contrast, neonates with IUGR have been shown to eliminate vancomycin more slowly in the first 4 wk of life (20,31). Because vancomycin elimination is largely through the kidney, these studies are consistent with the influence of birth weight z score on the clearance of amikacin in our study.

Another study in premature infants demonstrated that GFR and tubular functions are impaired at the age of 6 to 12 yr when compared with term control subjects (15); however, no differences between the groups born with low versus appropriate birth weight for GA were noted. The authors concluded that being born prematurely will impair nephrogenesis, with no additional unfavorable effect of the IUGR (15). In adolescents, studies that show the impact of birth weight on GFR (32) and studies that do not (33,34) are available, even though Kistner et
al. (34) did find more individuals with an impaired GFR (<90 ml/min per 1.73 m²) in the IUGR group.

We found a positive correlation between amikacin clearance and GA, as has been described for aminoglycosides (18,20,35–39). The absolute value of amikacin clearance (0.61 ml/kg per min) is comparable to previously reported values (0.52 to 0.6 ml/kg per min (17–19,40). Also, the distribution volume of amikacin was similar to previously reported values of 0.58 L/kg (18) and 0.59 L/kg (17). Aminoglycoside clearance increases with rising postnatal age (39–41), which is similar to the positive correlation between GFR and postnatal age (16,27). To eliminate the influence of postnatal maturation, we included only neonates who received the first dose of amikacin within 24 h after birth.

Aminoglycoside clearance has been suggested to be increased in girls (36) but was also reported to be equal among genders (41). Using multiple regression, we found no influence of gender on amikacin clearance (partial correlation coefficient = −0.076 corrected for volume of distribution, GA, and birth weight z score; P = 0.34).

Previously, a reduction in GFR on postnatal day 3 (23) and a reduced urine output and increased serum creatinine during the first 3 d of life (24) were reported in neonates whose mothers were treated with indomethacin. We found no correlation between prenatal use of indomethacin and amikacin clearance. This discrepancy may be explained by the duration and dosage of indomethacin: In our cohort, 10 of 11 mothers were treated with indomethacin. We found no correlation between weight at birth and the number and size of renal glomeruli in humans: A histomorphometric study. Kidney Int 58: 770–773, 2000

Hughson M, Farris AB, Douglas-Denton R, Hoy WE, Be-


