

Amikacin Pharmacokinetics and Suggested Dosage Modifications for the Preterm Infant

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The pharmacokinetics of amikacin administered intravenously at currently recommended doses (7.5 mg/kg every 12 h for infants with less than 7 days of life; 7.5 mg/kg every 8 h for infants with greater than 7 days of life) were studied in 28 preterm infants weighing less than 2,500 g (mean \pm standard deviation, 1.38 ± 0.47 kg; postconceptional age, 30.50 ± 2.86 weeks). The medication was infused over 45 min. Trough and peak serum samples as well as two additional samples were taken at steady state. The results showed a statistically significant inverse relationship between half-life (8.42 ± 2.55 h) and postconceptional age ($P = 0.002$) and a direct correlation between total body clearance (0.84 ± 0.28 ml/min per kg) and postconceptional age ($P = 0.02$). These pharmacokinetic data were used to calculate a new dosage schedule for preterm infants. The derived intravenous dosage of amikacin for infants of less than 30 weeks of postconceptional age was 9 mg/kg every 18 h. For infants of greater than 30 weeks of postconceptional age, the dosage was 9 mg/kg every 12 h. Peak and trough levels of amikacin in serum that fell within the therapeutic range were compared by using the currently recommended dosage schedule and the dosage schedule derived from our pharmacokinetic data. There was a reduction in the number of peak and trough levels that fell outside the accepted therapeutic range which was not statistically significant. Extension of the dosing interval and a further increase in the dosage may result in further improvement. Based on these data, the current recommendations are inadequate for the preterm infant. Our derived dosage schedule improved but did not eliminate high trough and low peak levels of amikacin in all infants. The current recommendations should be adjusted for the preterm infant. Ongoing therapeutic drug monitoring is essential to tailor the amikacin dosage to the individual patient.

Broad-spectrum antibiotic coverage for a neonate with suspected sepsis generally includes an aminoglycoside antibiotic and a penicillin derivative. While gentamicin has traditionally been used as the aminoglycoside of choice, other aminoglycosides must occasionally be considered for use in the neonate (5). For an 8-month period, amikacin was used as the aminoglycoside of choice in cases of suspected neonatal sepsis in our neonatal intensive care unit.

Reports of experience with the use of amikacin in the preterm infant population are limited (5, 9, 10). The current dosage recommendations for intravenous administration of amikacin are 7.5 mg/kg every 8 h for infants more than 7 days old and 7.5 mg/kg every 12 h for infants less than 7 days old (6, 11). These dosage recommendations appear to have been extrapolated from larger infants to extremely low birth weight infants (4, 6). The pharmacokinetics of amikacin have been studied previously, but these studies have included few infants with birth weights of less than 2,000 g. Therapeutic drug monitoring of amikacin levels in our center using the suggested dosage regimen showed that 50% of the extremely low birth weight infants (age, less than 30 weeks postconception) had unacceptably high trough levels (>10 μ g/ml). The more mature infants (age, greater than 30 weeks postconception) had acceptable trough levels but experienced a 37% incidence of subtherapeutic peak levels (<20 μ g/ml). This study was designed to clarify the pharmacokinetics of amikacin in extremely low birth weight infants and to develop a dosage schedule appropriate for these infants.

MATERIALS AND METHODS

This study was conducted in the Neonatal Intensive Care Unit at St. Joseph's Health Centre in London, Ontario, Canada, between January and May 1987. All infants less than 34 weeks gestational age in whom sepsis was considered in the differential diagnosis were eligible for inclusion in the study. Infants with severe growth restriction (birth weight less than the third percentile for the gestational age), perinatal asphyxia, or multiple congenital anomalies were not eligible for inclusion in the study. In addition, infants who received inotropes, indomethacin, diuretics, or other drugs known to affect renal function within 48 h of receiving amikacin were ineligible for the study. The study protocol was approved by the Committee on Human Research of the University of Western Ontario. Informed consent was obtained from the parents or guardians of all enrolled infants. The parents of two infants refused permission for inclusion of their infants in the study.

Amikacin was administered at the currently recommended dose of 7.5 mg/kg every 12 h for infants less than or equal to 7 days old and 7.5 mg/kg every 8 h for infants more than 7 days old (6, 11). Amikacin (250 mg/ml; Amikin; Bristol Laboratories, Belleville, Ontario, Canada) was diluted to 25 mg/ml and supplied in unit-dose syringes by the pharmacy department. The drug was injected into a running intravenous solution of 5% glucose and water (neonate microinfusion pump; model IVAC 565; IVAC Corp., San Diego, Calif.). The infusion rate was set at 6 ml/h. Subsequent *in vitro* analysis by one of the research team (D.C.K.) replicating the method of administration showed that 95% of the amikacin dose was infused over 45 min. We assumed for

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practical purposes that the total dose was administered over 45 min.

The previously reported half-life of amikacin is 3 to 9 h (5, 10, 11). We assumed that steady-state kinetics were achieved by the fourth dose. Serum samples for monitoring amikacin levels were taken by heel prick or from an umbilical arterial catheter placed into the lower abdominal aorta through which no antibiotics were infused. The serum samples were collected immediately before the fourth dose and 15 min after the end of the 45-min infusion. Two additional serum samples were taken between the fourth and fifth doses. Concentrations of amikacin in serum were analyzed by a fluorescence polarization immunoassay (Abbott TDX; Diagnostic Division, Abbott Laboratories Ltd., Mississauga, Ontario, Canada). The coefficient of variation of this method is less than 4% over the entire therapeutic range at this center.

The concentration-time data were fitted to a one-compartment open model by using linear regression by least-squares analysis. A one-compartment open model is adequate for aminoglycoside pharmacokinetic data (3). The volume of distribution (V) of amikacin was determined by the method of Sawchuk et al. (12), as follows: $V = [K_o(1 - e^{-K_d t^i})]/[K_d(C_{max} - C_{min}e^{-K_d t^i})]$, where K_o is the infusion rate, K_d is the elimination rate constant, t^i is the duration of infusion, C_{max} is the concentration in serum at the end of the infusion, and C_{min} is the concentration in serum immediately before the next dose.

Total body clearance (CL) was determined by using the following equation: $CL = (K_d)(V)$. The half-life ($t_{1/2}$) was calculated by using the following standard equation (11): $t_{1/2} = 0.693/K_d$. The volume of distribution, half-life, and total body clearance were plotted against postconceptional age. A linear regression analysis was performed for each dependent variable against postconceptional age.

Based on the results of our pharmacokinetic data, revised dosage recommendations were calculated by using the following formulas (11): (i) $T_{max} = [\ln(C_{max}/C_{min})]/K_d$, where T_{max} is the maximum dosing interval, C_{max} is the maximum desired plasma concentration, and C_{min} is the minimum desired concentration in plasma; (ii) $C_{ave} = \text{dose}/(T_{max})(CL)$, where C_{ave} is the mean concentration in serum; and (iii) $\text{dose} = (C_{ave})(CL)$. Peak and trough amikacin levels obtained with the new dosage regimen were then compared with those obtained with the currently recommended schedule by chi-square analysis.

RESULTS

Twenty-eight neonates, including 15 male and 13 female infants, were included in the study of amikacin pharmacokinetics. Twenty of the infants were studied in the first week of life. The remaining eight infants were studied at a mean age of 31.25 ± 26.3 days of life. Nine infants (32%) weighed less than 1,000 g at the time of the study. At the time of

TABLE 1. Characteristics and mean amikacin pharmacokinetic parameters of the 28 infants in the study population

Parameter	Mean	Range	SD
Wt at time of study (kg)	1.38	0.61-2.31	± 0.47
Postconceptional age (wk)	30.50	26-36	± 2.86
Half-life (h)	8.42	4.45-15.64	± 2.55
Vol of distribution (liter/kg)	0.57	0.39-0.84	± 0.11
Total body clearance (ml/min per kg)	0.84	0.48-1.45	± 0.28

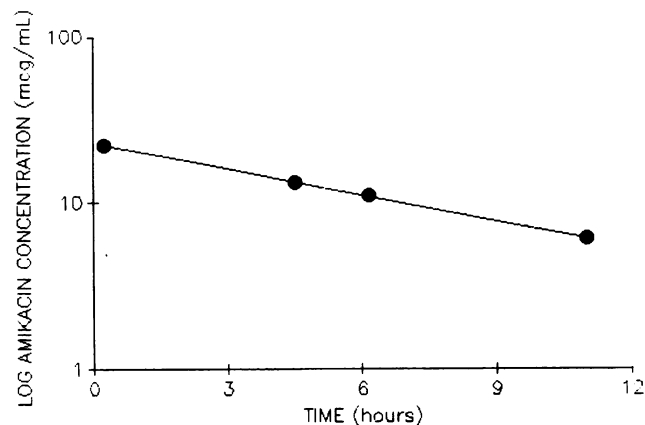


FIG. 1. Representative semilogarithmic concentration-time curve obtained from amikacin pharmacokinetic data.

enrollment in the study, the mean weight was 1.38 ± 0.47 kg and the mean postconceptional age was 30.50 ± 2.86 weeks. The characteristics of these 28 infants and the mean pharmacokinetic parameters for amikacin are shown in Table 1. There were no significant differences in the mean half-life, volume of distribution, or total body clearance of amikacin between male and female infants.

Figure 1 demonstrates a typical semilogarithmic concentration-time curve obtained from our pharmacokinetic data.

Figure 2 demonstrates the correlation between postconceptional age and total body clearance of amikacin. Total body clearance varied directly with postconceptional age (PC Age) ($y = 0.042 \text{ PC Age} - 0.45$; $r = 0.44$; $P = 0.02$). Figure 3 demonstrates the correlation between postconceptional age and amikacin half-life. There was an inverse correlation between postconceptional age and amikacin half-life ($y = 23.40 - 0.49 \text{ PC Age}$; $r = 0.55$; $P = 0.002$). There was no correlation between volume of distribution and postconceptional age.

There was no correlation between any of the dependent variables and body weight.

In the second phase of the study, peak and trough amikacin levels obtained for therapeutic drug monitoring were compared for two groups of infants. Group 1 included those patients who received amikacin prior to and during the study of amikacin pharmacokinetics. The dosage of amikacin was

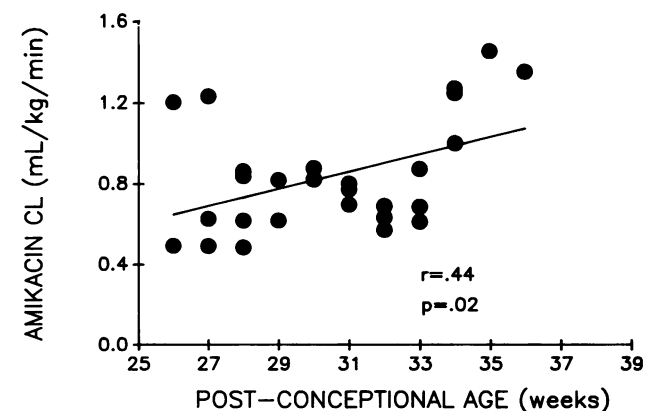


FIG. 2. Correlation between postconceptional age and total body clearance (CL) of amikacin.

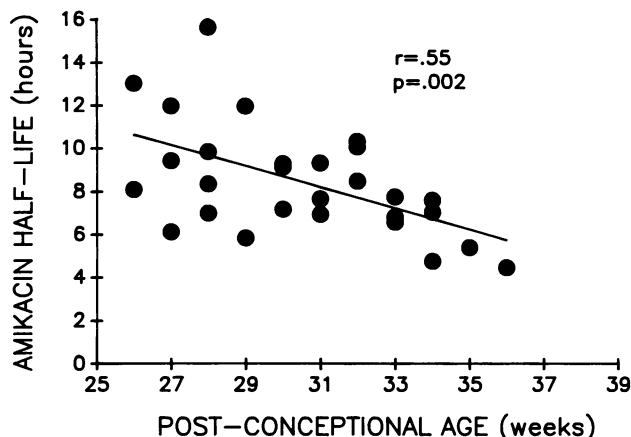


FIG. 3. Correlation between postconceptional age and amikacin half-life.

therefore the currently recommended dosage. Patients in group 2 received amikacin at the new dosage derived from our pharmacokinetic data and based on postconceptional age. We performed separate calculations for infants of less than 30 weeks of postconceptional age and infants of greater than 30 weeks of postconceptional age. The decision to calculate a separate dosage schedule for infants of greater and less than 30 weeks of gestational age was based on our therapeutic drug monitoring experience which suggested that infants of less than 30 weeks of postconceptional age had a high incidence of high trough levels and those of greater than 30 weeks of postconceptional age had low peak levels. The mean half-lives for these two groups were 9.48 and 7.35 h, respectively. For infants of less than 30 weeks of postconceptional age, the maximum dosing interval calculated was 19.74 h. For nursing convenience, this was reduced to 18 h, giving a calculated intravenous dosage of 9 mg/kg every 18 h. Performing the same calculations for infants of greater than 30 weeks of postconceptional age, we found a dosing interval of 14.97 h, which was reduced to 12 h. The calculated dosage was therefore 9 mg/kg every 12 h for infants of greater than 30 weeks of postconceptional age. Table 2 compares trough and peak levels of amikacin in group 1 infants who received the currently recommended amikacin dosage with those of amikacin in group 2 infants

TABLE 2. Characteristics of group 1 and group 2 patients and comparison of peak and trough amikacin levels falling within and outside the acceptable therapeutic range

Parameter	Group 1 (old dose)	Group 2 (new dose)
No. of patients	59	29
Mean postconceptional age (wk)	30.57 ± 3.46	31.45 ± 5.32
Mean wt (kg)	1.31 ± 0.5	1.73 ± 1.01
Mean trough concn (µg/ml)	9.10 ± 3.77	8.26 ± 2.99
Mean peak concn (µg/ml)	21.88 ± 4.88	23.90 ± 4.25
Trough concn, ≤10 µg/ml	39/58 (67) ^a	21/29 (72)
Trough concn, >10 µg/ml	19/58 (33)	8/29 (28)
Peak concn, 20–30 µg/ml	38/56 (68) ^b	22/28 (79)
Peak concn, <20 µg/ml	17/56 (30)	6/28 (21)

^a Values indicate the number of patients with the given parameter/total number of patients tested. Values in parentheses are percentages.

^b One additional patient had a peak level exceeding 30 µg/ml (31.90 µg/ml).

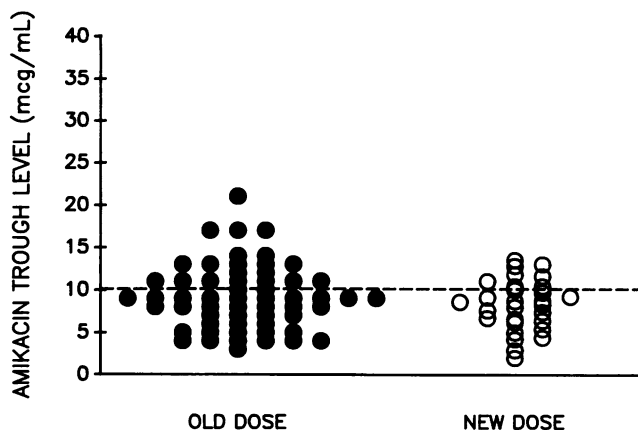


FIG. 4. Trough levels of amikacin at steady state in group 1 (old dose, 7.5 mg/kg every 8 or 12 h) and group 2 (new dose, 9 mg/kg every 12 or 18 h) patients.

who received the dosage regimen calculated by using our pharmacokinetic data. Although the results did not reach statistical significance, the trend was for improvement, with more levels falling within the accepted therapeutic range. This is demonstrated in Fig. 4 and 5.

DISCUSSION

Dosage recommendations for the use of amikacin in preterm neonates have been extrapolated from recommendations for larger infants, children, and adults. There is confusion in the literature concerning the validity of these recommendations. Prober et al. (9) found current dosage recommendations to produce adequate peak and trough levels in preterm infants. Other investigators (8, 13) found that the same dosage schedule produced levels considered toxic in 70% of infants with weights of less than 1,000 g and in 30% of larger infants. Our initial therapeutic drug monitoring of amikacin levels in extremely low birth weight infants also indicated a high incidence of levels of amikacin in serum considered to be potentially toxic. For this reason we felt that it was necessary to clarify the pharmacokinetics of amikacin in preterm infants.

Our results are in agreement with previously published

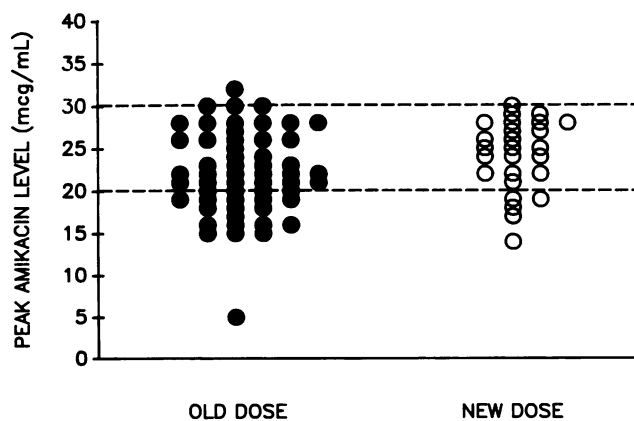


FIG. 5. Peak levels of amikacin at steady state in group 1 (old dose, 7.5 mg/kg every 8 or 12 h) and group 2 (new dose, 9 mg/kg every 12 or 18 h) patients.

amikacin pharmacokinetic data for larger infants (3–5, 7, 8, 13). As expected, the half-life was relatively prolonged and showed an inverse relationship with postconceptional age. Total body clearance increased rapidly with increasing postconceptional age.

The elimination of amikacin, as with other aminoglycosides, is almost entirely renal (8, 15). Although renal function was considered to be normal in our study infants and we excluded infants who received drugs known to affect renal function, we did not document creatinine clearance. Many of the patients in our study were less than 7 days old, and creatinine clearance would not be an accurate reflection of neonatal renal function (2). Renal functional maturation has been shown to correlate with the postconceptional age of the preterm infant and explains these pharmacokinetic data (2, 13, 14). As the half-life is dependent on the glomerular filtration rate, the relatively long half-life is expected to be due to the lower glomerular filtration rate of the preterm infant. The marked variability in half-life and total body clearance in preterm neonates compared with that in children and adults underlines the importance of accurate dosing recommendations for these infants (1, 8).

Because of the relatively large extracellular fluid volume of the preterm infant, the volume of distribution is increased and varies greatly from infant to infant (3, 4, 10). The lack of a relationship between postconceptional age or postnatal age and volume of distribution is expected and reflects the fluctuating state of hydration in the early days of life. Volume of distribution is considered a physiological indicator of extracellular fluid volume and can show wide variation between patients and in individual patients at different times (3, 4).

The derived dosages of amikacin based on our pharmacokinetic data indicate that preterm infants require a reduction in the total daily dose of amikacin and an increase in the dosing interval. Current recommendations suggest reducing the dosing interval from 12 to 8 h after 7 days of life. This recommendation has not been substantiated in very low birth weight infants. It is based on the assumption that the renal function matures rapidly in the first week of life, irrespective of gestational age at birth. Our current understanding of renal function maturation suggests that this assumption may not be valid in the extremely preterm infant population (1, 2). We performed a regression analysis on our data, using postnatal age as the independent variable, and found no correlation between postnatal age and half-life in serum. There was a weak correlation between total body clearance and postnatal age. However, because of the small number of neonates studied after the first week of life (eight patients), it was not valid to draw any conclusions from this information. It is more physiologically appropriate to base dosage recommendations on postconceptional age when treating extremely immature neonates.

Earlier reports on the use of amikacin in the treatment of gram-negative sepsis have shown these organisms to be very susceptible to amikacin (4, 9). To ensure adequate therapeutic levels of amikacin, we aimed for peak levels of 20 to 30 $\mu\text{g/ml}$ with trough levels of less than 10 $\mu\text{g/ml}$. The toxic effects of amikacin in adults have been associated with peak levels of greater than 38.5 $\mu\text{g/ml}$ and trough levels of greater than 10 $\mu\text{g/ml}$ (7, 13, 14). There is no documentation in the literature of toxic levels for infants; however, these levels have been adopted as safe guidelines. Cases of toxicity in infants at lower amikacin levels in serum than are considered toxic in adults have not been reported.

Our derived amikacin dosage schedule reduced the incidence of high trough levels and low peak levels in our

population of preterm neonates. This was not statistically significant, however. Individual dosage calculations with the equations for total body clearance and half-life derived from our data might further tailor dosages for individual patients but is impractical in the clinical setting. A further increase in the dosage and a lengthening of the dosage interval might further reduce the occurrence of unacceptable levels. However, taking into consideration the dramatic fluctuations in physiological parameters that can occur in sick preterm infants, it is unlikely that a schedule applicable to all infants can be derived.

Based on our experience, the currently recommended amikacin dosage schedule is inadequate for the very preterm infant and needs to be modified.

Therapeutic drug monitoring of amikacin levels should be available for every infant who receives this aminoglycoside. Even with additional modifications in dosage, many infants will have levels outside the therapeutic range. Modification of dosage guidelines cannot replace therapeutic drug monitoring for the individual patient.

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