Effects of Gestational Age, Birth Weight, and Hypoxemia on Pharmacokinetics of Amikacin in Serum of Infants

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The serum pharmacokinetics of amikacin were studied in 36 infants treated for suspected bacterial infection. A prolonged serum half-life was associated with the related variables of birth at an early gestational age, low birth weight, and hypoxemia. A postnatal age effect was not apparent when hypoxic infants were excluded.

Gram-negative bacilli represent a serious problem among hospitalized patients of all ages. The aminoglycosides have proven active against most strains of *Enterobacteriaceae*, and gentamicin has been found inhibitory for most strains of *Pseudomonas aeruginosa*. For this reason, an aminoglycoside, such as gentamicin, in combination with a penicillin, has formed the treatment basis for suspected septicemia in neonates. As a consequence, the emergence of gentamicin-resistant organisms has become increasingly more commonplace (7, 21, 27, 29, 30), and so the emergence of multiply resistant organisms in neonates at the University of Iowa Hospitals in 1975 was not surprising.

Amikacin is a new semisynthetic aminoglycoside antibiotic derived by acetylation from kanamycin A that is active in vitro against most strains of *Staphylococcus aureus*, *Enterobacteriaceae*, and *P. aeruginosa*, including strains resistant to gentamicin (14, 15, 19, 22, 23, 33). The serum pharmacokinetics of amikacin and kanamycin are very similar in both adults and children (2, 13). Mean peak serum levels of amikacin, which are approximately three times the minimal inhibitory concentrations of most commonly encountered pathogens, are achievable in adults (1, 2, 13, 32) and newborns (12, 13, 26). The present communication reports our experience with amikacin in newborn infants.

MATERIALS AND METHODS

Amikacin assay. Amikacin levels were determined by a radioenzymatic assay similar to that described by Haas and Davies (11). *Escherichia coli* 21218, from which the acetylating enzyme was derived, was kindly provided by A. L. Smith, Children's Hospital Medical Center, Boston. This assay requires small sample volumes and is unaffected by the presence of antibiotics other than aminoglyco-

sides. Ten freshly prepared amikacin standard solutions containing 0 to 25 $\mu\text{g/ml}$ in human serum were included in each assay procedure. A single lot of amikacin sulfate (Bristol Laboratories, 74-K 590) was used as a standard throughout the study. All samples were assayed in duplicate.

Study population. The study protocol was approved by the appropriate institutional research review committees, and written-informed parental consent was obtained for each study patient.

Thirty-seven newborns with suspected bacterial infection were selected from the neonatal intensive care unit of the University of Iowa Hospitals. One infant, treated for suspected septicemia, was excluded from analysis because of incomplete pharmacokinetic data. Sixteen had roentgenographic pneumonia (one meconium aspiration; in two, group B streptococcus and, in one, *Staphylococcus epidermidis* were cultured from the blood. No isolate was recovered from the blood or tracheal aspiration cultures in 13 patients). Ten had suspected septicemia from an unknown source (one group B streptococcus, one *E. coli*, one *S. epidermidis*, one *Pseudomonas maltophilia*, and six with no isolate). Four infants suffered chorioamnionitis (one bacteremic from *Peptostreptococcus* and no identified organism from three). Two had cellulitis at an intravenous site (one bacteremic from *Enterobacter agglomerans* and one with no isolate). Two children showed pustular eruptions (one containing gram-positive cocci on Gram stain, but both cultured no organisms). One patient had contracted a urinary tract infection due to *Streptococcus faecalis*, and one had intestinal perforation with peritonitis.

Except in one patient, with an organism known to be sensitive to amikacin prior to antibiotic therapy, initial treatment included 100 mg of ampicillin per kg every 12 h, administered intravenously, in addition to 7.5 mg of amikacin per kg every 12 h, administered by the intramuscular route. Fifteen infants also received a single dose of amikacin, given intravenously over a 30-min period by a constant rate infusion pump (Sage Instruments, Inc.). Intravenous antibiotics were not administered concurrently. Most infants received amikacin for 10 days,

and none took it for longer than 14 days. None of these infants had received prior antibiotic therapy, and none had evidence of renal functional impairment as judged by blood urea nitrogen, creatinine, and creatinine clearance determinations.

Prior to the initiation of antibiotic therapy, a complete blood count, serum glutamic oxaloacetic transaminase, bilirubin, urea nitrogen, and creatinine plus a chest roentgenogram, a urinalysis, and blood, urine, and cerebrospinal fluid cultures were obtained on each infant. When possible, creatinine clearance determinations were performed within the first several days of therapy. Response to 3,000 Hz at 88-deciBell sound pressure level was assessed by a Cribogram (Telesensory Equipment) during and after amikacin therapy and, at 90-deciBell sound pressure level, by a Neonatal Meter (Zenith) at the 6- and 12-month follow-up examinations. Estimation of gestational age, performed by the physician caring for the child, was by the Dubowitz method (4).

Blood for determination of PO_2 , PCO_2 , and pH (Instrument Laboratories, model 3013) was obtained from the radial or umbilical arteries and, on occasion, from arterialized capillary blood. Infants were considered hypoxemic if their P_aO_2 was less than 50 mm of Hg.

Capillary blood for serum amikacin levels was obtained by heel stick prior to antibiotic administration, at 15 min, 30 min, 1 h, 2 h, 4 h, and 8 h after the intramuscular injection of amikacin or after the completion of a timed 30-min intravenous infusion. Serum amikacin determinations were performed during the first two days, in the middle, and at the end of therapy in most infants. Comparative studies of intravenous and intramuscular administration were performed within 48 h of each other during the first 4 days of antibiotic therapy. Peak serum amikacin levels occurred 30 to 60 min after intramuscular injection or completion of intravenous infusion. The line of best fit, derived from a computerized linear regression analysis of the serial serum amikacin levels, was utilized to determine the serum half-life. Statistical analyses included the analysis of covariance and Student *t* tests (28).

RESULTS

The 36 study infants were 10 days of age or younger at the beginning of therapy; their mean age was 2.2 days. Their gestational age ranged from 30 to 42 weeks, with a mean of 36 weeks. Birth weights ranged from 780 to 4,495 g and the mean birth weight was 2,499 g. The amikacin serum half-life for the 36 newborns ranged from 1.0 to 13.5 h with a mean $\pm$ standard deviation (SD) of 5.4 ± 2.0 h, and the mean peak serum level $\pm$ SD was 17.7 ± 5.4 μ g/ml, with a range from 9.0 to 36.0 μ g/ml. The amikacin dosage was reduced for two infants whose peak serum levels exceeded 30 μ g/ml.

Fifteen infants had serum amikacin pharmacokinetics performed after intramuscular and intravenous administrations. These compara-

tive studies were performed within 2 days of each other. After intravenous administration, the mean peak serum level $\pm$ SD was 17.9 ± 3.7 μ g/ml, with a mean serum half-life $\pm$ SD of 5.7 ± 2.9 h. The mean peak serum level $\pm$ SD after intramuscular injection was 18.5 ± 3.3 μ g/ml, and the serum half-life $\pm$ SD was 5.7 ± 1.8 h. These mean peak serum and half-life values were not statistically different by the paired *t* test ($P > 0.10$).

While the hemoglobin concentrations in the 36 infants varied from 8.5 to 21.0 g/100 dl and the serum bilirubin varied from 1.5 to 12.5 mg/100 dl, no correlation could be made between the amikacin serum pharmacokinetics and either hemoglobin or serum bilirubin concentrations. Also, no effect of amikacin on either bilirubin or hemoglobin concentrations was apparent.

Twenty-three infants had amikacin serum pharmacokinetics performed on more than one occasion. In most of these infants, the peak amikacin serum level and the amikacin serum half-life were reproducible over time. However, two infants, who had severe respiratory distress with associated hypoxemia, experienced prolonged serum half-lives that subsequently shortened with the resolution of the hypoxic episode. In these two infants, the serum half-life decreased from 13.5 and 12 h to 5.0 and 3.5 h, respectively, as the hypoxic episodes resolved. Nine additional infants were identified as being hypoxemic at the time of pharmacokinetic testing, and seven of these had subsequent serum pharmacokinetics during periods of normoxemia. A prolonged serum amikacin half-life in association with hypoxemia was apparent in these infants (Table 1). The mean serum half-life $\pm$ SD for the 11 hypoxemic infants was 7.3 ± 3.4 h (range, 3.0 to 13.5 h) as compared with a mean serum half-life $\pm$ SD of 4.8 ± 1.8 h (range, 1.0 to 9.0 h) for the normoxemic infants. These mean half-lives differed significantly when examined by the group *t* test

TABLE 1. Hypoxia and serum amikacin pharmacokinetics

Condition of infant	Serum peak level (μ g/ml) ^a	Serum half-life (h) ^a	No. of infants
Normoxemic ($P_aO_2 > 50$ mm of Hg)	17.9 ± 5.7	4.8 ± 1.8^b	25
Hypoxemic ($P_aO_2 < 50$ mm of Hg)	16.6 ± 4.5	7.3 ± 3.4	11

^a Mean $\pm$ SD.

^b Significantly different from hypoxemic serum half-life value ($P < 0.01$).

($P < 0.01$). There was no difference between the mean peak serum levels for each group ($P > 0.10$). The normoxemic infants had a mean peak amikacin serum level $\pm$ SD of 17.9 ± 5.7 $\mu\text{g/ml}$, and the hypoxemic infants showed 16.6 ± 4.5 $\mu\text{g/ml}$.

The relationships between postnatal age, hypoxemia, and amikacin serum half-life are outlined in Table 2. Infants in each postnatal age category were evaluated by grouped t tests, and those infants on whom values were available for both postnatal age categories were compared by paired t tests. The mean gestational ages and birth weights of the 1 to 3 days and older infants were similar. A longer amikacin serum half-life was apparent when values from infants 1 to 3 days and more than 3 days of age were compared ($P < 0.05$, grouped and paired t tests). However, no postnatal age differences in serum half-lives were seen when values from hypoxemic infants were excluded. Examination of the data from infants more than 3 days of age showed no significant difference between the mean serum half-lives $\pm$ SD of 4.5 ± 2.1 and 5.2

± 1.9 for the 11 infants 4 to 7 days old and the 7 infants older than 7 days, respectively.

The mean serum half-life $\pm$ SD for low-birth-weight infants ($\leq 2,500$ g) was 5.9 ± 2.3 h as compared with 4.5 ± 1.6 h for term-birth-weight infants ($> 2,500$ g) (Table 3). Although the mean birth weights of these two groups of infants were significantly different ($P < 0.01$), there was no statistical difference between the respective serum half-lives when only normoxemic infants were considered ($P > 0.10$). The longest amikacin serum half-life occurred in hypoxemic infants of low birth weight ($P < 0.05$).

Preterm infants (< 37 -week gestation) had a longer mean serum amikacin half-life than full-term infants (≥ 37 -week gestation) ($P < 0.01$) (Table 4). The mean gestational ages as well as the respective mean birth weights were significantly different for the two groups ($P < 0.01$). The gestational age difference in serum amikacin half-life remained statistically significant ($P = 0.02$) even when hypoxemic infants were excluded.

All but 2 of the 37 infants improved clinically. No adverse effects, relatable to amikacin, were observed, and the drug appeared to be tolerated well in all 37 infants. Failures of therapy included one infant with suspected but undocumented septicemia, who continued to be symptomatic, and a second child whose cellulitis responded to therapy but who expired after a pulmonary hemorrhage on day 7. One infant with bacteremia due to *P. maltophilia* resistant

TABLE 2. Amikacin serum half-life related to postnatal age and hypoxia

Condition of infant	Postnatal age ^a			
	1-3 days		More than 3 days	
	Serum half-life (h) ^b	No. of infants	Serum half-life (h) ^b	No. of infants
Unpaired comparison				
All infants	6.4 ± 2.7^c	17	4.8 ± 1.8	19
Normoxemic infants	5.7 ± 2.5	10	4.3 ± 1.1	15
Hypoxemic infants	7.5 ± 2.7	7	7.5 ± 4.5	4
Paired comparison				
All infants ^d	7.1 ± 2.5	10	5.1 ± 2.3	10
Normoxemic infants	6.9 ± 2.0	4	6.1 ± 2.6	4
Hypoxemic infants	6.9 ± 1.5	4	6.0 ± 2.4	4

^a For the unpaired comparisons, the mean gestational ages $\pm$ SD were 36.7 ± 4.1 and 36.4 ± 3.7 weeks with mean birth weights $\pm$ SD of 2,565 and 2,417 g for 1- to 3-day and > 3 -day age groups, respectively.

^b Mean $\pm$ SD.

^c Significantly different from value for infants more than 3 days of age ($P < 0.05$).

^d Includes two infants initially hypoxemic who were normoxemic at the time of reevaluation.

TABLE 3. Amikacin serum half-life in relation to birth weight and hypoxemia

Condition of infant	Birth weight ^a			
	Low birth weight		Term birth weight	
	Half-life (h) ^b	No. of infants	Half-life (h) ^b	No. of infants
All infants	5.9 ± 2.3^c	19	4.5 ± 1.6	17
Normoxemic infants	5.0 ± 2.0	12	4.6 ± 1.7	13
Hypoxemic infants	9.0 ± 3.1^d	7	4.5 ± 1.5	4

^a Low-birth-weight infants ($\leq 2,500$ g) weighed $\pm$ SD $1,806 \pm 516$ g, whereas term-weight infants ($> 2,500$ g) weighed $3,248 \pm 476$ g ($P < 0.01$). The mean gestational ages $\pm$ SD were 34.1 ± 3.0 and 39.4 ± 2.6 weeks, respectively ($P < 0.01$).

^b Mean $\pm$ SD.

^c Significantly different than values from term-birth-weight infants ($P < 0.05$).

^d Significantly different from low-birth-weight normoxemic values ($P < 0.01$) and from term-birth-weight values of hypoxemic infants ($P < 0.05$).

TABLE 4. *Amikacin serum half-life in relation to gestational age and hypoxia*

Condition of infant	Gestational age ^a			
	Preterm		Full-term	
	Half-life (h) ^b	No. of infants	Half-life (h) ^b	No. of infants
All infants	6.2 ± 2.2 ^c	20	4.1 ± 1.2	16
Normoxemic infants	5.7 ± 2.1 ^d	12	4.0 ± 1.2	13
Hypoxemic infants	8.2 ± 3.5 ^e	8	5.0 ± 1.5	3

^a Preterm infants (<37-week gestation) had 33.7 ± 2.4 weeks of gestation as compared with full-term infants (≥37-week gestation) whose mean gestational age ± SD was 40.3 ± 1.5 ($P < 0.01$). The mean birth weights ± SD were 1,960 ± 661 g and 3,135 ± 667 g, respectively ($P < 0.01$).

^b Mean ± SD.

^c Significantly different from value for full term ($P < 0.01$).

^d Significantly different from value for full term ($P = 0.02$).

^e Not significantly different from value for full term ($p > 0.10$).

to 30 µg of amikacin per ml responded to removal of an umbilical arterial catheter. Ototoxicity during therapy was not apparent in any infant by Cribogram and has not been demonstrated by Neonatal Meter examination of the 20 infants available for reevaluation at 6 and 12 months of age.

DISCUSSION

The volume of aminoglycoside distribution appears to approximate the extracellular fluid volume (10). Excretion is almost entirely through the kidney by glomerular filtration, with the clearance of gentamicin (3), kanamycin (2), and amikacin (2, 17) paralleling that of creatinine. An age-related dose requirement for gentamicin has been reported (6), with children under 5 years of age requiring almost twice as much gentamicin as an adult to obtain similar peak serum concentrations.

Newborn infants have longer serum half-lives than older infants, presumably because of less effective renal function in the early newborn period (12). Similarly, the mean serum amikacin half-life in our infants was approximately twice that reported in adults (1) and, when data from all infants were considered, was longer in the first several days of life than subsequently.

Effects of postnatal age on aminoglycoside pharmacokinetics have also been reported by

others (18, 26), including longer half-lives during the first week of life. These data are consistent with renal functional maturation, but other factors such as hypoxemia were not separately examined. Though an effect of postnatal age on amikacin clearance is suggested by both unpaired and paired data, this effect was not apparent when data from hypoxemic infants were excluded (Table 2). Similarly, a relationship of birth weight to amikacin serum half-life may, in part, be due to an inclusion of infants with hypoxemia (Table 3). Interestingly, while low birth weight appeared to have little effect on the amikacin pharmacokinetics of normoxemic infants, a prolongation of the amikacin serum half-life in hypoxemic infants of small birth weight seemed to occur. The amikacin serum half-life was consistently longer in early-gestational-age infants (Table 4). In early-gestational-age infants, hypoxemia was associated with the longest serum half-life.

The related variables of low birth weight, early gestational age, and hypoxemia appear from this data to be associated with prolonged amikacin serum half-lives. Adjusting for birth weight and gestational age, the effect of hypoxemia is not significant in infants less than 4 days of age when examined by analysis of covariance ($P = 0.33$), which may reflect the small sample size.

The renal blood flow in newborns is lower than in adults particularly if considered as a percentage of the cardiac output (31), and anoxic stimulation of the aortic chemoreceptors results in renal vasoconstriction (16). This response to anoxia seems independent of the reflex increase in systemic blood pressure associated with decreased apical heart rate and increased peripheral vascular resistance. For example, when a fetal lamb's umbilical cord is clamped, a momentary increase in renal blood flow associated with an increase in systemic blood pressure followed by a decrease in renal blood flow concomitant with a decrease in arterial PO_2 takes place (5). Guignard et al. (8) reported increases in the inulin and *para*-aminohippuric acid (PAH) clearances during the neonatal period. Subsequently, they showed that the inulin and PAH clearances were markedly depressed in neonates with idiopathic respiratory distress syndrome as compared with control infants (9). The impairment of inulin and PAH clearances correlated with the severity of pulmonary disease, and improvement in inulin and PAH clearances paralleled an improvement in respiratory distress.

The effect of hypoxemia upon newborns' amikacin serum pharmacokinetics and the similar effect observed in adult rats (20) may thus be

due to decreased renal blood flow in response to hypoxia, with a concomitant decrease in glomerular filtration rate. Though reported differences in intravenous and intramuscular pharmacokinetics (13) have not been reproducible by us or others (2), it is possible that a difference in absorption from intramuscular sites or alterations in tissue distribution might account for part of the serum half-life prolongation observed in hypoxemic infants. Additional studies will be necessary to clarify the mechanism for this effect.

Shorter aminoglycoside half-lives have been associated with fever and anemia (6); both are factors that may be associated with an increased glomerular filtration rate and could, therefore, affect the half-life of the aminoglycoside by increasing renal clearance. We, however, have been unable to demonstrate a variation in amikacin serum half-life in association with hemoglobin concentration in newborn infants. Since individual patients tend to be consistent in their aminoglycoside response over time (Table 2) (3, 6, 25), these data do not support the recommendation (12) for a loading dose of amikacin in newborn infants. Because multiple variables affect aminoglycoside pharmacokinetics in neonates, monitoring of serum levels is recommended.

A diminished *in vitro* antimicrobial activity of gentamicin has been demonstrated under anaerobic and hypercapnic conditions (24). That report together with the observations reported here point out the need to examine the effect of hypoxemia upon the pharmacokinetic and pharmacodynamic parameters of the aminoglycoside antibiotics. Such studies in animal models are currently under way in our laboratories.

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