

## Amikacin in Newborn Infants: Comparative Pharmacology with Kanamycin and Clinical Efficacy in 45 Neonates with Bacterial Diseases

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The pharmacokinetic properties of amikacin (BBK8) were similar to those of kanamycin in newborn infants. Peak serum concentrations of both drugs were in the range of 15 to 25  $\mu\text{g/ml}$  with the exception of kanamycin in babies weighing greater than 2,000 g at birth where peak levels were 12.5 to 15  $\mu\text{g/ml}$ . Volumes of distribution, plasma clearances, and serum half-life values were comparable for the two drugs. The clinical and bacteriological responses to amikacin therapy were assessed in 45 neonates with bacterial diseases. A case fatality rate of 26% was observed in infants with septicemia and/or meningitis, whereas no deaths occurred among 22 infants with urinary tract and mucocutaneous infections. Cultures from infected sites were sterile within 72 h of initiating amikacin therapy in 47% of the infants, continued positive for greater than 72 h in 31%, and were not reevaluated during therapy in 22%. The clinical response was judged to be satisfactory in 92% of the surviving infants. The efficacy of amikacin was comparable to that of kanamycin or gentamicin in neonatal bacterial diseases.

Aminoglycosides are frequently administered to neonates to prevent or treat gram-negative bacterial infections. As a result, emergence of coliforms resistant to these drugs has developed in some nurseries. For example, streptomycin resistance was noted in the early 1960s, and kanamycin-resistant *Escherichia coli* and *Klebsiella* strains were observed within the past 5 years (5-8). Gentamicin has been used in many neonatal units. Significant resistance to this agent has been demonstrated recently in an infant intensive care unit (5) and can be anticipated in other centers where the antibiotic is used extensively. Therefore, it is imperative that the pharmacology, efficacy, and safety of new aminoglycosidic drugs which offer promise for treatment of neonatal bacterial diseases be evaluated.

The purpose of the present communication is to review our experience in newborn infants with a new aminoglycoside, amikacin (BBK8). Previously published data from our laboratory showed that amikacin susceptibilities of gram-negative bacilli and *Staphylococcus aureus* were comparable to those for kanamycin, with the exception that over 90% of *Pseudomonas aeruginosa* were susceptible to 15  $\mu\text{g}$  or less of amikacin per ml (6). Five kanamycin-resistant

*E. coli* strains isolated from cerebrospinal fluid (CSF) of neonates with meningitis were inhibited and killed by 5  $\mu\text{g}$  or less of amikacin per ml.

Pharmacological studies in 48 babies demonstrated mean serum levels of 17 to 20  $\mu\text{g/ml}$  at 30 min and of 3.3 to 5.3  $\mu\text{g/ml}$  at 12 h after a 7.5-mg/kg amikacin dose (6). Accumulation of drug in serum and acute renal or hematological toxicity were not observed after repeated doses for 5 to 7 days. Urinary amikacin concentrations were 50 to 650  $\mu\text{g/ml}$ , and the average 12-h urinary excretion of drug was 30 to 50% of the administered dose. Serum half-life values were inversely correlated with postnatal age and ranged from 3 to 9 h.

In this paper we present the comparative pharmacokinetic properties of amikacin and kanamycin in neonates and the clinical efficacy of amikacin in 45 infants with bacterial infections. The pharmacological data are based in part on our previously published studies of amikacin (6) and kanamycin (7).

### MATERIALS AND METHODS

**Antimicrobial assay.** Concentrations of amikacin and kanamycin in serum and CSF were assayed by a modification of the micromethod of Simon and Yin

(13) using *Bacillus subtilis* as the test organism. Standard antibiotic curves were prepared in an identical fashion to test samples.

**Serum half-life determinations.** The equation for the regression line of the log of serum antibiotic concentrations was calculated by the method of the least mean squares. The half-life was determined by dividing the  $\log_{10}2$  by the slope of the line.

**Drug distribution and plasma clearance.** The volumes of distribution ( $V_d$ ) of amikacin and kanamycin expressed in milliliters per kilogram were calculated using the formula:

$$V_d = \frac{\text{Dosage (mg/kg)}}{AUC \times K} \times 1,000$$

where ( $K$ ) is the elimination rate constant and  $AUC$  represents the area under the serum concentration-time curve which is formulated by successive trapezoidal approximation (4). Plasma clearance ( $C_p$ ) in ml/min per  $1.73 \text{ m}^2$  was determined using the formula:

$$C_p = \frac{\text{Total dosage}}{AUC} \times \frac{1,000 \mu\text{g}}{60 \text{ min}} \times \frac{1.73 \text{ m}^2}{SA}$$

where ( $SA$ ) is surface area in  $\text{m}^2$ .

**Study patients.** Pharmacological studies were performed in patients selected from the nurseries of Parkland Memorial Hospital, Dallas. Written informed parental consent was obtained for all infants. Serum samples for bioassay were collected by heel-stick technique. Eleven infants who were receiving amikacin intramuscularly were given one dose intravenously over a 20-min period and multiple serum samples after both routes of administration were obtained on successive days.

The clinical efficacy of amikacin was studied in 19 infants cared for at the Hospital Infantil San Vicente de Paul in Medellin, Columbia, in 17 infants at the Hospital Nacional de Ninos in San Jose, Costa

Rica, and in 9 infants at Parkland Memorial Hospital in Dallas. The parents of all patients were fully informed about the study and written consent was obtained before therapy. Penicillin G or ampicillin was given in combination with amikacin to 22 patients. It is customary to administer a penicillin and an aminoglycoside as initial therapy for neonatal infections until the pathogen has been identified. The clinical and bacteriological responses of these infants were evaluated and a complete blood count, urinalysis, blood urea nitrogen and/or serum creatinine were obtained at the beginning and completion of therapy.

## RESULTS

**Serum and CSF concentrations.** Complete serum concentration-time curves for amikacin and kanamycin have been presented elsewhere (6, 7). Mean serum amikacin levels 30 min after a 7.5-mg/kg dose were 17 to 20  $\mu\text{g/ml}$  for all infant groups irrespective of birth weight and age (Fig. 1). By contrast, average serum kanamycin concentrations 30 min after a 7.5-mg/kg dose were 17 to 22  $\mu\text{g/ml}$  in low-birth-weight (less than 2,000 g) infants and 12.5 to 15  $\mu\text{g/ml}$  in infants who weighed 2,000 g or greater at birth. Concentrations of both drugs were comparable 12 h after a dose with the exception of a higher mean kanamycin concentration in low-birth-weight infants who were 1 to 4 days of age.

Serum amikacin levels were measured in 11 infants after intravenous and intramuscular 7.5-mg/kg doses were administered on successive days (Fig. 2). Peak serum concentrations were 13.6 to 40  $\mu\text{g/ml}$  (mean, 21.1  $\mu\text{g/ml}$ ) after the intramuscular dose. By contrast, the peak

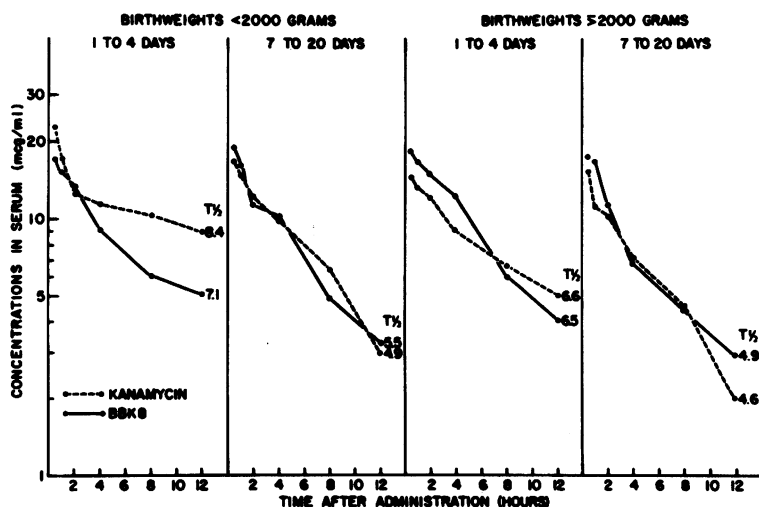


FIG. 1. Serum concentration-time curves for amikacin (BBK8) and kanamycin after 7.5-mg/kg doses administered intramuscularly to neonates according to birth weight and postnatal age.

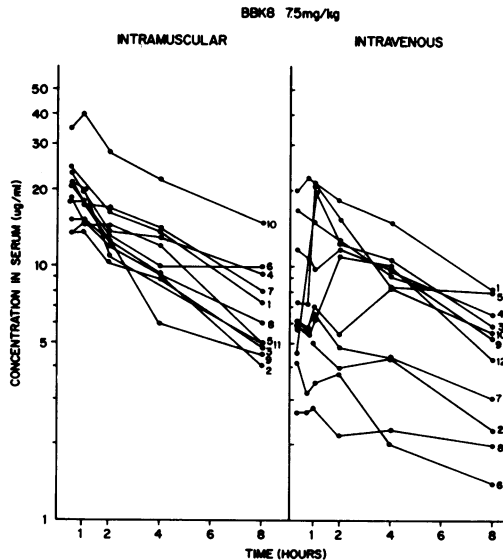


FIG. 2. Serum amikacin (BBK8) concentration-time curves after 7.5-mg/kg doses administered intramuscularly and intravenously to 11 neonates. Numbers in parentheses refer to individual patients and are shown so that the curves after both routes of administration in the same patient can be compared.

serum values in five infants who received amikacin intravenously over a 20-min period ranged from 2.8 to 7.0  $\mu\text{g/ml}$  (mean, 5.4  $\mu\text{g/ml}$ ), and the slopes of the serum concentration-time curves were less acute compared with those for the same infants after the intramuscular dose (Fig. 2). The curves after intravenous amikacin in the other six infants were comparable to those after intramuscular administration. Four of the five infants with low serum concentrations after the intravenous dose had birth weights of 1,920 g or less (1,080 to 1,920 g), whereas only two of the six infants with peak serum levels in the expected range had similar birth weights. The intravenous dose was administered in a peripheral vein by the same physician (J. Howard), and the time during which the drug was given and the actual mechanics of administering the drug were identical for all infants.

Fifteen ventricular fluid specimens were obtained from five infants with meningitis and ventriculitis who received amikacin intravenously as well as intramuscularly. Ventricular fluid amikacin concentrations 12 h after 1- or 2-mg intraventricular doses and 2 to 8 h after the intramuscular doses were 4.5 to 11.6  $\mu\text{g/ml}$  (mean, 7.3  $\mu\text{g/ml}$ ). Five CSF specimens were obtained from the lumbar intrathecal space of three infants who received parenteral therapy only. Amikacin concentrations 1 to 12

h after a 7.5-mg/kg intramuscular dose ranged from 0.8 to 9.2  $\mu\text{g/ml}$  (mean, 4.4  $\mu\text{g/ml}$ ).

**Serum half-life.** The serum half-life values for amikacin and kanamycin were inversely correlated with gestational and chronological ages and ranged from 7 to 8 h in low-birth-weight babies who were under 4 days of age to 4 to 5 h in the larger babies who were greater than 7 days of age (Fig. 1 and Table 1).

**Volume of distribution and plasma clearance.** The calculated distribution volumes of the two aminoglycosides were similar with exception of the larger kanamycin values in newborn infants 1 to 4 days of age (Table 1). The plasma clearance values were similar for amikacin and kanamycin throughout the neonatal period and correlated inversely with the serum half-life values.

**Clinical efficacy.** Clinical and bacteriological responses were evaluated in 45 neonates with documented bacterial diseases. The bacterial pathogens associated with these illnesses are shown in Table 2. Miscellaneous pathogens included one each of the following: *Proteus mirabilis*, *Haemophilus influenzae* type b, *Staphylococcus epidermidis*, and a gram-negative rod that was not identified. Two patients had mixed cultures with two organisms: *E. coli* and *Klebsiella* species from the urine of one infant and *S. aureus* and *E. coli* from an abscess cavity of a second baby.

Fifteen infants had septicemia documented by positive blood cultures on at least one occasion before antimicrobial therapy (Table 3). Four infants (27%) died; death occurred within 48 h of initiating amikacin therapy in two patients. The clinical response of the 11 surviving infants was assessed as satisfactory in 10 infants and unsatisfactory in the 11th patient. The bacteriological response was prompt (blood cultures sterile within 72 h of initiating amikacin) in seven (47%) of the 15 septic infants, delayed (cultures positive with the same pathogen for greater than 72 h) in one infant, and unknown in the remaining seven patients.

Meningitis was diagnosed in eight infants. Two infants died. The first infant's course was complicated by *E. coli* K1 ventriculitis, and despite intraventricular amikacin therapy the patient died on the 18th hospital day. The second patient had a meningomyelocele which became infected with *P. aeruginosa*. Parenteral carbenicillin and amikacin therapy combined with daily intraventricular administration of 1 mg of amikacin for 10 days were ineffective, and the infant died on the 26th hospital day. The bacteriological response to therapy was delayed in seven infants, and the

clinical response was satisfactory in five of six surviving patients.

Four infants had acute urinary tract infections that were diagnosed from culture of urine obtained from suprapubic bladder aspiration. The urine was sterile within 72 h of initiating amikacin in three infants; repeat culture from the fourth infant was not obtained during therapy. All four infants had satisfactory clinical courses.

Eighteen infants had mucocutaneous infections (Table 3). Sixteen of the neonates were from Medellin where purulent rhinitis and

omphalitis are frequently encountered. *E. coli* was the pathogen in 12 (71%) of these patients. Eleven of 18 (61%) infants showed prompt bacteriological responses, and the lesions responded satisfactorily to amikacin therapy in 17 babies. The single clinical failure was an infant with otitis media caused by *P. aeruginosa*.

**Safety of amikacin in neonates.** Amikacin was well tolerated in the 45 study patients. Complete blood counts, urinalyses, and blood urea nitrogen, and/or serum creatinine values were determined at the beginning and comple-

TABLE 1. Pharmacokinetic properties of kanamycin and amikacin in newborn infants

Infant groups		Vol of distribution (ml/kg)		Plasma clearance (ml/min/1.73 m <sup>2</sup> )		Serum half-life (h)	
Birth weight	Age (days)	Kanamycin	Amikacin	Kanamycin	Amikacin	Kanamycin	Amikacin
<2,000 g	1 to 4	715	563	23.0	21.3	8.6	7.1
	4 to 7	519	568	24.2	22.8	6.7	6.1
	>7	547	502	25.4	24.6	5.2	5.5
≥2,000 g	1 to 4	623	509	29.3	27.0	5.7	6.5
	4 to 7	460	567	36.3	29.8 <sup>a</sup>	5.0	5.1
	>7	497	594	45.5	36.4	3.8	4.9

TABLE 2. Bacteria isolated from 45 study patients

Organisms	No. of isolates	Septicemia	Meningitis	Urinary tract infection	Mucocutaneous infection
<i>Escherichia coli</i>	26	6	4	4	12
<i>Klebsiella-Enterobacter</i>	8	5	0	1	2
<i>Pseudomonas aeruginosa</i>	6	0	2	0	4
<i>Staphylococcus aureus</i>	2	1	0	0	1
Miscellaneous <sup>a</sup>	5	3	2	0	0
Total	47 <sup>b</sup>	15	8	5	19

<sup>a</sup> Includes *Salmonella* sp. (1), *Proteus mirabilis* (1), *H. influenzae* type b (1), *S. epidermidis* (1), and one gram-negative rod that was not identified.

<sup>b</sup> Two organisms were isolated from cultures of two patients.

TABLE 3. Clinical and bacteriological responses of 45 infants treated with amikacin

Condition	No. of patients	Died <sup>a</sup>		Bacteriological response			Clinical response of survivors	
		<48 h	>48 h	Prompt <72 h	Delayed >72 h	Unknown	Satisfactory	Unsatisfactory
Septicemia	15	2	2	7	1	7	10	1
Meningitis	8		2		7	1	5	1
Urinary tract infection	4			3		1	4	
Mucocutaneous infection <sup>b</sup>	18			11	6	1	17	1
Total	45	2	4	21	14	10	36	3

<sup>a</sup> Deaths recorded according to time after initiation of therapy.

<sup>b</sup> Includes purulent rhinitis (five patients), omphalitis (nine patients), wound infection (two patients), otitis media (one patient), and chest wall abscess (one patient).

tion of amikacin therapy in 39 infants. There was no evidence of acute hematological or renal toxicity after 5 to 24 days (mean, 10.6 days) of therapy; ototoxicity was not evaluated.

### DISCUSSION

As anticipated from studies in normal adult volunteers (3), the pharmacokinetic properties of amikacin were similar to those of kanamycin in newborn infants. Serum concentration-time curves after 7.5-mg/kg doses were comparable for the two aminoglycosides with the exception of lower peak serum kanamycin levels in the larger birth-weight babies. The distribution volumes of these two aminoglycosides were similar to the bromide spaces (2) and the ticarcillin volumes (11) measured in babies, suggesting that these antibiotics distribute within the calculated extracellular fluid space of neonates (1). Plasma clearances and serum half-life values were almost identical for the two drugs and most likely reflect the low but increasing glomerular filtration rates characteristic of the newborn period (14).

We are unable to explain why 5 of 11 infants achieved peak serum levels of only 3 to 7  $\mu\text{g/ml}$  after an intravenous amikacin dose and considerably higher concentrations (15 to 40  $\mu\text{g/ml}$ ) after intramuscular administration. It is unlikely that the peak serum values were missed because samples were obtained at zero time and at 10, 20, 45, 60, 120, and 480 min after initiation of the 20-min intravenous injection. It is possible that the distribution of amikacin after intravenous administration in these babies was different than that after an intramuscular dose.

The clinical and bacteriological efficacy of amikacin was comparable to that of kanamycin or gentamicin in neonatal bacterial diseases caused by susceptible pathogens. Two of the six deaths occurred within 48 h of admission to the hospital and both infants had evidence of disseminated intravascular coagulation before initiation of therapy. The case fatality rate of 26% (6 of 23 infants) in neonatal septicemia and meningitis caused principally by gram-negative organisms was less than the rates (40 to 60%) recorded in the literature (10, 12). The bacteriological response to amikacin therapy was prompt in 21 (47%) infants, delayed in 14 (31%), and indeterminate in 10 (22%) infants. Delayed sterilization of CSF cultures observed in seven of eight infants with meningitis was not unexpected in view of our previous experience with neonatal gram-negative enteric meningitis (9).

The clinical responses of the 39 survivors was judged to be satisfactory in 36 (92%) infants and unsatisfactory in three infants. Although the terms satisfactory and unsatisfactory are inexact, subjective descriptions, it is difficult to be more objective because most neonates with bacterial diseases have few distinctive signs that can be evaluated on a daily basis. Thus, pediatricians use poor feeding, diminished suck, lethargy, irritability, and other nonspecific findings to assess the clinical responses of neonates to antimicrobial therapy. In this context, we conclude that amikacin was as effective as kanamycin or gentamicin for therapy of neonatal bacterial diseases.

A dosage schedule of 10 mg of amikacin per kg given initially followed by 7.5-mg/kg doses administered intramuscularly every 12 h results in peak serum concentrations of 15 to 25  $\mu\text{g/ml}$  without accumulation of drug in serum. Intravenous amikacin should be used only when the intramuscular route is contraindicated such as in babies with bleeding disorders or sclerema. Serum concentrations must be monitored in such infants to be certain that peak values are within the therapeutic and safe range. Amikacin should not be used routinely in newborn and young infants until there are long-term follow-up studies establishing its safety with regard to cochlear and vestibular function.

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