Tobramycin population pharmacokinetics in neonates

Objective: To establish a tobramycin dosing schedule for neonates of various gestational ages.
Methods: This was a retrospective study with prospective validation. A retrospective study in 470 neonates, with suspected septicemia in the first week of life, was performed. All patients received tobramycin according to the following scheme: neonates with a gestational age of less than 28 weeks received 3.5 mg/kg every 24 hours, neonates from 28 to 36 weeks received 2.5 mg/kg every 18 hours, neonates older than 36 weeks received 2.5 mg/kg every 12 hours. Trough and peak tobramycin serum levels were determined before drug administration and 30 minutes after the fourth dose. Tobramycin data were analyzed according to a one-compartment open model with use of NONMEM population pharmacokinetic software. Individual empirical Bayes estimates were generated on the basis of the population estimates and used to calculate predicted peak and trough levels for different doses and dosing intervals. To establish an optimal dosing regimen, target trough levels were set at below 2 mg/L and target peak levels were set above 5 to 10 mg/L. The dosing regimen was prospectively evaluated in 23 patients.
Results: Of the 470 patients, 19.1% of measured peak and 32.8% of measured trough tobramycin serum levels were outside the desired therapeutic range, and 48.8% of neonates with a gestational age of less than 28 weeks had an aberrant trough level. With use of population estimates, the following dosing regimen was recommended: gestational age below 32 weeks, 4 mg/kg every 48 hours; gestational age between 32 and 37 weeks, 4 mg/kg every 36 hours, gestational age above 37 weeks, 4 mg/kg every 24 hours. With this dosing schedule, predicted peak levels were higher than 5 mg/L in 95.1% of the neonates. Predicted trough levels were higher than 2 mg/L in 1.9% of the neonates and higher than 1 mg/L in 7.6%. Prospectively measured peak levels were higher than 5 mg/L in all but one infant. Measured trough levels were higher than 2 mg/L in three patients and marginally higher than 1 mg/L in four patients.
Conclusions: With the use of this proposed schedule, taking into account differences in gestational ages, predicted peak levels will be therapeutic, whereas predicted trough levels will minimize toxicity. (Clin Pharmacol Ther 1997;62:392-9.)

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During recent years there has been much debate about the optimal dosing interval and required serum concentrations of aminoglycosides to maximize efficacy and minimize toxicity in adults.[1-5] Efficacy of aminoglycosides is related to the ratio of peak serum concentration to the minimal inhibitory concentration (MIC) of the infecting microorganism and the area under the time versus concentration curve (AUC),[1,5] whereas toxicity of these drugs seems to be related to high trough levels.[1,5] On the basis of these pharmacodynamic characteristics and the results of clinical trials, it was recently advocated in three meta-analytic studies[2,4,5] that aminoglycosides be administered once daily to adults.

Aminoglycosides also play an important role in the initial empiric treatment of neonatal septicemia.[6] Various regimens for dose, dosing interval, and monitoring have been suggested and imple-

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mented over the last two decades.[7-14] A significant relation between gestational age and the need for prolonged dosing intervals was established, and the more recent dosing regimens propose once daily dosing of aminoglycosides in very low birth weight infants.[11-15] However, we had the impression that high trough levels were frequently encountered in these infants even with once daily administration of aminoglycosides. We therefore performed this study to investigate the results of the dosing schedule we currently use to find a more appropriate dosing schedule to administer aminoglycosides to newborns of different gestational ages during the first week of life. Using population pharmacokinetics on our own data over the last few years, we established a dosing regimen that combined optimal efficacy with minimal toxicity. To validate this regimen, we prospectively tested it in our patient group.

PATIENTS AND METHODS

Patients. This retrospective study with prospective validation comprised all neonates in the first week of life who were treated with tobramycin as part of their empiric treatment for suspected neonatal sepsis in the neonatal intensive care unit of the Sophia Children's Hospital between August 1992 and December 1994. Only neonates whose paired peak and trough serum tobramycin levels were available were included. In the period between February and April 1997, additional patients were studied for validation.

Parameters. All parameters were abstracted from the patient files. Gestational ages and birth weights were recorded. Gestational age was determined on the basis of the mother's menstrual history, confirmed by early ultrasound examinations if available, and by physical examination with the use of the criteria of Dubowitz et al.[16]

Administration and dosage regimen of tobramycin. Tobramycin was given in combination with 50 to 100 mg/kg/day amoxicillin (INN, amoxicilline) as empiric treatment for suspected neonatal sepsis. Patients with documented invasive bacterial infection received intravenous therapy for at least 10 days. Patients with sterile cultures and without a focus of infection received therapy for a total of 72 hours. Administration of tobramycin was done in a 30-minute intravenous infusion with the following dosing regimen: gestational age <28 weeks, 3.5 mg/kg/24 hours; gestational age from 28 to 36 weeks, 2.5 mg/kg/18 hours; gestational age >36 weeks, 2.5 mg/kg/12 hours.

All doses and times of administration were recorded routinely. Trough and peak blood samples were taken before and 30 minutes after the fourth dose. Dosage adjustments were made according to the outcome, with the intention to keep trough levels below 2 mg/L and peaks between 4 and 10 mg/L.

Analytical techniques. Concentrations of tobramycin were measured by a Fluorescence Polarization Assay with use of a TDxFLx (Abbott Diagnostic Division, Amstelveen, The Netherlands).

Data analysis, dosage recommendations, and simulations. Tobramycin data were analyzed according to a one-compartment open model, assuming the data were attributable to the fourth dose after birth, with use of NONMEM population pharmacokinetics software (NONMEM version IV, NONMEM project group, University of California, San Francisco, Calif.). On the basis of the population estimates, individual empirical Bayes estimates were generated. Scatterplots against weight and age indicated that both clearance and volume of distribution were related to age and weight. After estimation of clearance per kilogram for birth weights, only a correlation between volume of distribution and age or weight remained (age and weight are naturally highly correlated in this group). The empirical Bayes estimates were used to calculate predicted peak and trough levels at steady state for different dose and dose interval combinations, and scatterplots against gestational age were constructed.

Target serum tobramycin levels were set. The target trough level was below 2 mg/L (generally accepted as trough when administering a drug more than once daily) and preferably below 1 mg/L.[4,17] Target peak levels were set at a minimum of 5 mg/L daily[18-21] and preferably 10 times the MIC of the infecting microorganism because of the possibility of emergence of aminoglycoside-resistant pathogens at lower ratios.[21,22] The MIC of the most important gram-negative pathogen, *Escherichia coli*, is 1 mg/L in the Dutch population,[23] so target peak levels were 5 to 10 mg/L.

Prospective study. The predictive performance of the dosing regimen was evaluated prospectively in patients receiving tobramycin according to the dosing recommendation mentioned in the results:

- Gestational age ≤32 weeks: 4 mg/kg every 48 hours
- Gestational age >32 weeks but <37 weeks: 4 mg/kg every 36 hours
- Gestational age >37 weeks: 4 mg/kg every 24 hours

Table I. Measured tobramycin concentrations

Tobramycin (mg/L)	*Gestational age groups (wk)*				
	GA < 28	*28 ≤ GA < 32*	*32 ≤ GA < 37*	*GA > 37*	*Total*
Trough ≤ 2	42 (51.3%)	103 (61.7%)	104 (81.2%)	67 (72.1%)	316 (67.2%)
Trough > 2	40 (48.8%)	64 (38.3%)	24 (18.8%)	26 (28.0%)	154 (32.8%)
Peak < 5	4 (4.9%)	37 (22.2%)	32 (25.0%)	17 (18.3%)	90 (19.1%)
5 ≤ Peak ≤ 10	75 (91.5%)	128 (76.6%)	96 (75.0%)	74 (79.6%)	373 (79.4%)
Peak > 10	3 (3.7%)	2 (1.2%)	0 (0%)	2 (2.2%)	7 (1.5%)
TOTAL	82 (17.4%)	167 (35.5%)	128 (27.2%)	93 (19.8%)	470 (100%)

GA, Gestational age.
Numbers are the number of patients; numbers in parentheses are the percentages of the total in the group.

Tobramycin peak and trough serum levels were determined 30 minutes after the first dose and just before the second dose and were analyzed as described in the retrospective study.

RESULTS

Retrospective study. Four hundred seventy neonates were enrolled in the study. Their gestational ages and birth weights ranged from 23 to 42 weeks (median age, 31.5 weeks) and from 485 to 5245 gm (median weight, 1530 gm), respectively.

Table I summarizes the results of tobramycin peak and trough concentrations for the different gestational age groups. As shown in Table I, 19.1% of peak levels and 32.8% of trough levels were outside the desired therapeutic range. In the gestational age groups <28 weeks and between 28 and 32 weeks, the percentage of aberrant trough levels was particularly high—48.8% and 38.3%, respectively.

On the basis of the scatterplots and set target serum tobramycin levels, the dosing is recommended at 4 mg/kg with the following dosing intervals:

- Gestational age ≤32 weeks: 4 mg/kg every 48 hours
- Gestational age >32 but <37 weeks: 4 mg/kg every 36 hours
- Gestational age >37 weeks: 4 mg/kg every 24 hours

For illustrative purposes, the curves predicted with use of the advised dosing regimen and the empirical Bayes estimates were constructed and concentrations corresponding to the 5th, 50th, and 95th percentiles computed for the three dosing interval–age groups (Fig. 1). Calculations were performed with SPSS for Windows (version 6.1.2). Fig. 2 and Table II show the predicted peak and trough levels with these recommendations. Fig. 2 clearly shows that predicted peak levels rose with gestational age. Predicted peak levels ranged from 2.9 to 18.7 mg/L, with a median of 8.0 mg/L. Predicted peak levels were below 5 mg/L in 4.9% of the newborns and above 10 mg/L in 27.9% of the newborns. Median peak levels in the gestational age groups were 6.1 mg/L in the group <28 weeks old, 7.3 mg/L in the group aged between 28 and 32 weeks, 8.7 mg/L in the group aged between 32 and 37 weeks, and 13.2 in the term group. Insufficient peak levels were found in 11 of 82 (13.4%) of neonates with a gestational age <28 weeks. Of these 11 newborns, 10 had predicted peak levels between 4 and 5 mg/L. Predicted trough levels ranged from 0.01 to 8.1 mg/L (median, 0.36 mg/L). Trough levels were above 2 mg/L in 1.9% of all patients and between 1 and 2 mg/L in 5.7%. As Fig. 2 shows, there was no relation between gestational age and trough levels. Fig. 1 shows the predicted serum levels over time for the three gestational age groups. The 50th percentile line of tobramycin serum levels dropped below 1 mg/L at approximately 18, 24, and 32 hours in the groups that received tobramycin once every 24, 36, and 48 hours, respectively.

Prospective study. Prospective evaluation was performed in 23 neonates. Their gestational ages ranged from 24.4 to 42.1 weeks (median, 32.5 weeks). Table III summarizes the results of observed tobramycin peak and trough concentrations for the different gestational age groups with use of the recommended dosing regimen. Peak levels ranged from 2.9 to 13.5 mg/L, with a median of 7.9 mg/L. Only one peak level was below 5 mg/L. Median peak levels in the gestational age groups were 6.9 mg/L in the group <32 weeks old, 7.3 mg/L in the group aged between 32 and 37

weeks, and 9.0 in the term group. Trough levels were between 0.1 and 5.7 mg/L (median, 0.7 mg/L). High trough levels were found in seven patients. Of these, three patients had trough levels of 1.2 mg/L and one patient had a trough level of 1.3 mg/L. Median trough levels in the gestational age groups were 0.7 mg/L in the group <32 weeks old, 0.65 mg/L in the group aged between 32 and 37 weeks, and 0.95 mg/L in the term group.

DISCUSSION

Earlier investigations of the pharmacokinetics of aminoglycosides and other drugs in neonates have shown that elimination half-lives are longer in neonates, especially in preterm neonates.[8-11,24] This is primarily the result of a higher percentage of body water and thus a larger volume of distribution and reduced clearance.[25,26] Most dosing schedules for preterm and term neonates take this into account.[7-12,14] We had the clinical impression that our use of gestational age–related dosing still led to serum concentrations that were frequently outside the desired range. The inventory of our own results over the past few years showed that about one third of the initial trough serum levels were too high, particularly in prematures neonates, and that in view of these results a more appropriate dosing schedule should be found.

The limitation of administration of aminoglycosides to neonates lies in the long elimination half-life; therefore the only way to effectively reduce trough serum levels without compromising adequate peak levels is by further increasing the dosing interval. It is difficult to define the desired therapeutic range for aminoglycosides. Peak levels of >4 to 5 mg/L are generally accepted as necessary for antibacterial efficacy with administration three times a day[18-21]; however, questions are being raised about the underlying fundament of this assumption.[3] What is known is that efficacy of aminoglycosides is related to the peak level/MIC ratio and AUC[1,21] and that in vitro ratios of 10:1 prevent emergence of aminoglycoside-resistant pathogens.[22] In the first week of life, the pathogens for which tobramycin is indicated as therapy are mainly acquired through the birth passage. By far the most common pathogen in this group of gram-negative bacteria is *E. coli*.[27] In a recent survey of the Dutch population, the MIC_{90} for *E. coli* was found to be 1 mg/L,[23] and although in theory a peak serum concentration of 10 mg/L

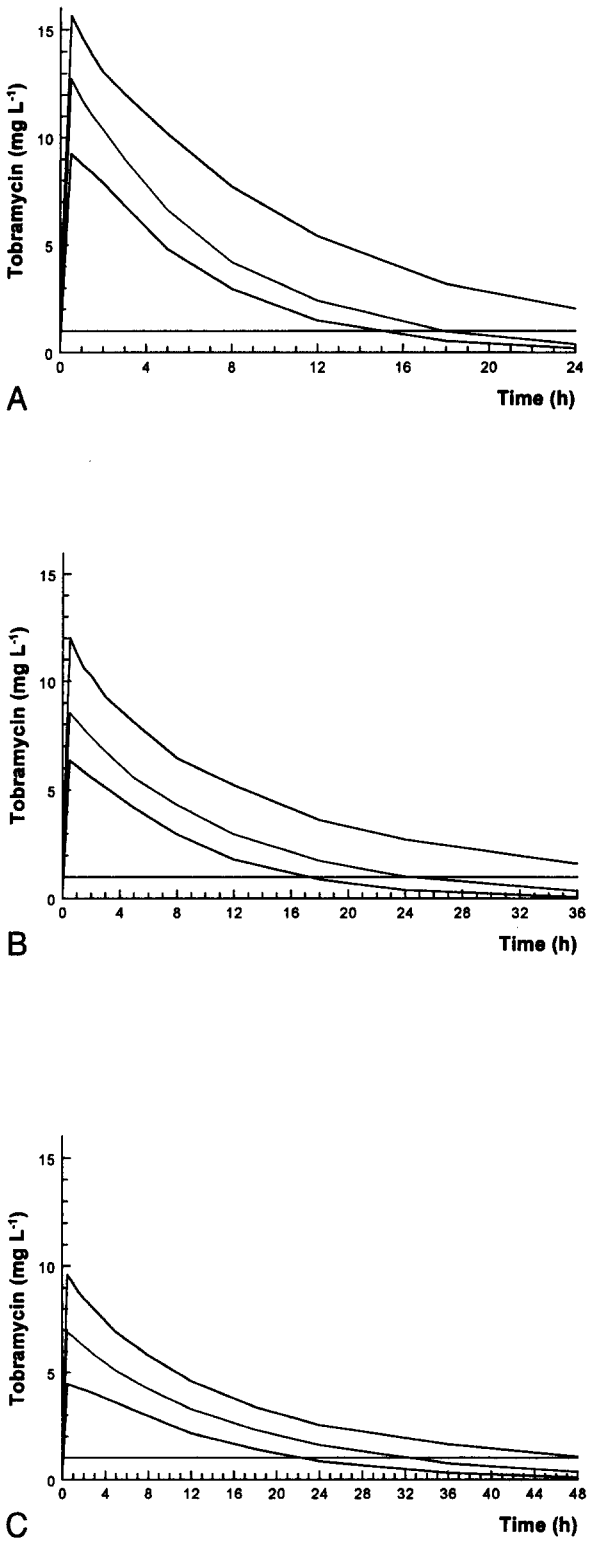

Fig. 1. Predicted tobramycin concentration curves with revised dosing recommendation. **A,** 4 mg/kg every 24 hours. **B,** 4 mg/kg every 36 hours. **C,** 4 mg/kg every 48 hours. Curves are 95th, 50th, and 5th percentiles.

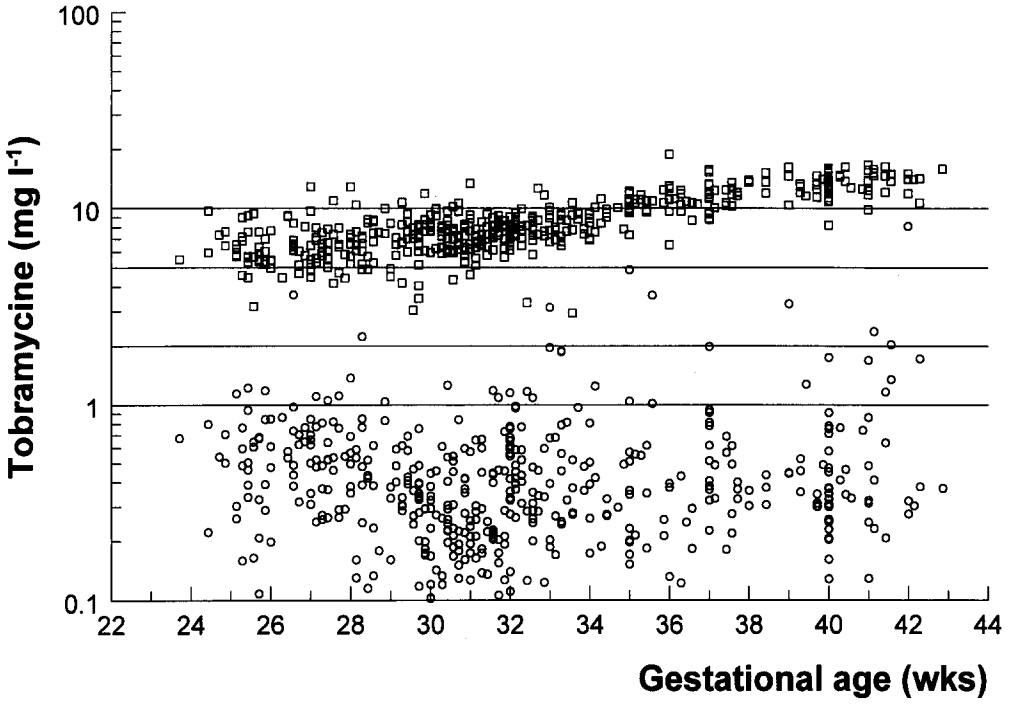

Fig. 2. Predicted tobramycin peak *(squares)* and trough *(circles)* levels with revised dosing recommendation.

Table II. Predicted tobramycin concentrations with use of revised dosing recommendation

	Gestational age groups (wk)				
Tobramycin (mg/L)	*GA < 28*	*28 ≤ GA < 32*	*32 ≤ GA < 37*	*GA ≥ 37*	*Total*
Trough ≤ 1	75 (91.5%)	161 (96.4%)	116 (90.6%)	82 (88.2%)	434 (92.3%)
1 < Trough ≤ 2	6 (7.3%)	5 (3.0%)	9 (7.0%)	7 (7.5%)	27 (5.7%)
Trough > 2	1 (1.2%)	1 (0.6%)	3 (2.3%)	4 (4.3%)	9 (1.9%)
Peak < 5	11 (13.4%)	10 (6.0%)	2 (1.6%)	0 (0.0%)	23 (4.9%)
5 ≤ Peak ≤ 10	69 (84.1%)	149 (89.2%)	92 (71.9%)	6 (6.5%)	316 (67.2%)
Peak > 10	2 (2.4%)	8 (4.8%)	34 (26.6%)	87 (93.5%)	131 (27.9%)
TOTAL	82 (17.4%)	167 (35.5%)	128 (27.2%)	93 (19.8%)	470 (100%)

GA, Gestational age.
Numbers are the number of patients; numbers in parentheses are the percentages of the total in the group.

would be optimal, a peak/MIC ratio of 5 can be considered to be effective.

The effect of serum concentrations on toxicity is even harder to quantify. High aminoglycoside peak levels do not increase nephrotoxicity because of drug-specific saturable uptake.[28-30] In several large meta-analytical studies, toxicity seems to be related to high predose levels, indicating that trough levels are not low long enough to prevent renal accumulation.[1,2,5,19] Commonly accepted trough level goals are <2 mg/L, but for once-a-day administration, most authors keep 1 mg/L as a safe limit.[4,17] Another point in the discussion is that renal toxicity is mostly reversible, whereas ototoxicity is usually irreversible. Most authors suggest that ototoxicity is related to

Table III. Measured tobramycin concentrations with use of revised dosing recommendation

Tobramycin (mg/L)	*Gestational age groups (wk)*			*Total*
	GA < 32	*32 ≤ GA < 37*	*GA ≥ 37*	
Trough ≤ 1	6 (85.7%)	5 (62.5%)		
1 < Trough ≤ 2	—	2 (25.0%)	2 (25.0%)	4 (17.4%)
Trough > 2	1 (14.3%)	1 (12.5%)	1 (12.5%)	3 (13.0%)
Peak < 5	1 (14.3%)	—	—	1 (4.3%)
5 ≤ Peak ≤ 10	6 (85.7%)	7 (87.5%)	6 (75.0%)	19 (82.6%)
Peak > 10	—	1 (12.5%)	2 (25.0%)	3 (13.0%)
TOTAL	7 (30.4%)	8 (34.8%)	8 (34.8%)	23 (100%)

GA, Gestational age.
Numbers are the number of patients; numbers in parentheses are the percentages of the total in the group.

total dose and duration of therapy rather than to serum aminoglycoside levels, but the relation to aminoglycoside serum levels remains unclear. This form of toxicity usually occurs in patients who have received either long or repeated courses of aminoglycosides.[3] Reports about ototoxicity in neonates are contradictory. Some authors report no relation,[31-33] whereas others did find a higher incidence.[34-36] Until conclusive evidence is given, it seems prudent to keep the duration of tobramycin therapy as short as possible.

On the grounds of a peak/MIC ratio above 10 and the MIC_{90} of *E. coli* in our population, a peak tobramycin serum concentration as high as 10 mg/L is desirable from the efficacy point of view. A trough level below 1 mg/L will have to suffice until better data about toxicity are available.

Using population pharmacokinetics, we established a better dosing scheme to meet these criteria. This resulted in the following gestational age–related regimen:

- Gestational age ≤32 weeks: 4 mg/kg/48 hours
- Gestational age >32 weeks but <37 weeks: 4 mg/kg/36 hours
- Gestational age >37 weeks: 4 mg/kg/24 hours

With this regimen most predicted peak levels were in the required range in neonates with a gestational age above 32 weeks, with acceptable predicted trough values for almost all (Table II). In the gestational age group below 28 weeks, predicted peak serum levels were arguably too low in 12 of 82 patients, but 11 of these were between 4 to 5 mg/L. The prospective evaluation showed that serum peak levels were in the desired therapeutic range in all but one patient (Table III). Measured trough levels were mildly elevated in four patients and clearly too high in three, so there is a definite need for measuring trough serum levels before the second dose. This dosing regimen also makes redundant the need for a loading dose of aminoglycosides in premature neonates, as suggested by some researchers,[11,17,37] because high enough peak levels are achieved at the first dose. In addition, the practical advantage of this proposed schedule is a fixed starting dose per kilogram of body weight, irrespective of gestational age.

A possible problem in the group that received tobramycin once every 48 hours is that tobramycin levels might be subtherapeutic for too long. Twenty-four-hour serum levels in this group (Fig. 1) show that levels in most neonates were around 2 mg/L (which is still higher than the MIC of relevant microorganisms) but dropped below 1 mg/L after approximately 32 hours. In the prospective group of 23 patients, serum trough levels did not fall too low. Furthermore, there is also the post-antibiotic effect, or post-antibiotic leukocyte enhancement effect, or sub-MIC effect, which will prevent regrowth of bacteria at sub-MIC levels of tobramycin for another period of at least hours,[38-40] so we consider this to be a safe dosing interval.

In conclusion, the information that we presented shows that acceptable therapeutic tobramycin peak and trough concentrations can be reached with a simple dosing schedule for three separate gestational age groups in the first week of life. Trough levels according to our scheme are not toxic and probably not long enough below 1 μg/ml to permit bacterial regrowth.

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