Gentamicin Dosing and Pharmacokinetics in Low Birth Weight Infants

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NAKAIE, S., YAMADA, M., ITO, T., CHIBA, Y., SASAKI, E., SAKAMOTO, M., TADA, K., YAMADA, T. and MORI, S. Gentamicin Dosing and Pharmacokinetics in Low Birth Weight Infants. Tohoku J. exp. Med., 1988, 155 (3), 213-223 — Monitoring of serum gentamicin concentrations and one-compartment pharmacokinetic analysis were performed in 41 preterm low birth weight infants (20 with birth weight of <1,500 g and 21 with birth weight of ≥1,500 g) in the first week of life. Our dosing regimens, which were 2.0 mg/kg every 24 hr for the <1,500 g group and 2.0 mg/kg every 12 hr for the ≥1,500 g group, successfully achieved the desired peak (4-8 μg/ml; 87.8%) and trough (≤3 μg/ml; 97.5%) concentrations on the 4th day of treatment. In a one-compartment pharmacokinetic analysis, a large intersubject variability of pharmacokinetic parameters were observed on the 1st day of treatment. When we compared the parameters of the 1st day with those of the 4th day, apparent decreases in Vd and TBC were observed. The mean values for TBC and T1/2 or Kd of the two birth weight groups were significantly different from each other on the 4th day of treatment, suggesting a less maturity of renal functions in the <1,500 g group. The modified method of Sawchuk and Zaske was proven impractical in predicting steady-state serum concentrations because of an underestimation probably caused by the dramatic alteration of Vd due to a diuresis soon after birth. Based on these results, we recommend the above-described dosing regimen and emphasize the importance of a close monitoring of serum gentamicin concentrations and toxicities, instead of the individualized dosing approach in low birth weight infants in the first week of life. —

gentamicin; low birth weight infants; therapeutic drug monitoring (TDM); pharmacokinetic analysis; dosing regimen

Prolonged rupture of membrane and chorioamnionitis play a causative role in developing bacterial infections associated with preterm deliveries. Preterm low birth weight infants associated with intra-uterine infections who are supposed to have gram-negative bacterial infections were often treated soon after birth by an aminoglycoside, in spite of their immature renal function (Leake et al. 1976; Arant 1978) and insufficient diuresis (Costarino and Baumgart 1986).
Gentamicin in the most commonly used aminoglycoside in low birth weight infants. The effective and safe therapeutic concentration range has been suggested to be below 2 μg/ml in trough and over 4 μg/ml but not to exceed 12 μg/ml in peak concentrations (Jackson and Arcieri 1971; Dahlgren et al. 1975). Several recent studies in preterm low birth weight infants have shown that a currently recommended gentamicin dosage for neonates in the first week of life, that is, an intravenous dose of 5 mg/kg/day divided into two doses (McCracken and Nelson 1977), would result in potentially toxic levels (Szefler et al. 1980; Mulhall et al. 1983; Husson et al. 1984; Koren et al. 1985). Although the toxic range of gentamicin in neonates has not been precisely defined, several reports suggest a new therapeutic range, such that trough concentrations should not exceed 2–3 μg/ml and peak concentrations should maintain below 8–10 μg/ml (Taylor and Finn 1981; Rajchot et al. 1984; Koren et al. 1985). Because of the narrow therapeutic range of gentamicin (McCracken and Jones 1970; Anderson et al. 1972) and of its large intersubject variability in pharmacokinetic parameters, routine therapeutic drug monitoring (Taylor and Keane 1976; Assael et al. 1977; Rameis et al. 1983) and individualized dosing regimens (Sawchuk and Zaske 1976; Sawchuk et al. 1977; Evans et al. 1978; Edgren et al. 1984; Kalenga et al. 1984) have been recommended in an attempt to provide a maximum potential benefit with a minimum risk of possible toxicity associated with gentamicin therapy.

In this prospective study, we assessed the distribution of initial peak, steady-state trough and peak concentrations of gentamicin in 41 low birth weight infants during the first week of life, and compared the pharmacokinetic parameters between the initial and the 4th day dosing. We adopted an individualized gentamicin dosing approach to the neonates using the modified method of Sawchuk and Zaske (1976) and Sawchuk et al. (1977) to assure the applicability of the method soon after birth in low birth weight infants with an immature renal function and insufficient diuresis. On the basis of these data, we suggest a guideline for gentamicin dosing according to the two subgroups defined by birth weight.

Methods

Study Population. Forty-one low birth weight infants who received gentamicin in combination with ampicillin for suspected or proven serious infections in the first week of life were prospectively studied between May, 1985, and April, 1987, in Neonatal Intensive Care Unit, Sendai Red Cross Hospital, Sendai, after informed consent was obtained from either of the parents.

The infants were divided into two groups according to a birth weight, the <1,500 g and ≥1,500 g groups. Their clinical characteristics and dosing regimens are shown in Table 1. The <1,500 g group included 20 neonates (11 females, 9 males) weighing from 1,000 to 1,480 g, ranging in gestational age from 27 to 32 weeks and having a postnatal age between 0 and 3 days at the time of the initial dosing. The ≥1,500 g group contained 21 neonates (6 females, 15 males) weighing from 1,570 to 2,465 g. Their gestational age ranged from 30 to 38 weeks and their postnatal age ranged from 0 to 7 days. No neonate had an apparently
impaired renal function or heart failure when enrolled in the study.

**Gentamicin dosing and specimen collection.** The dosage of gentamicin was 2.0 mg/kg every 24 hr for the <1,500 g group and 2.0 mg/kg given every 12 hr for the ≥1,500 g group. Gentamicin was infused at a constant rate with a syring pump over a period of 30 min. Blood samples (50 μl of serum each) were obtained from a heek prick to determine near-peak concentration 15 min after the dosing on the 1st and 4th day of treatment, and for estimating a near-trough concentration the samples were collected within one hr before the second dosing and the dosing on the 4th day of treatment.

Urine volume, urinary contents, and serum urea nitrogen and creatinine levels were monitored daily for the detection of renal impairment throughout the treatment and for one week after the treatment was discontinued.

**Gentamicin assay.** Serum gentamicin concentrations were determined by a substrate-labelled fluorescent immunoassay (SLFIA) using an Ames TDA gentamicin kit, Diluter, and Fluorostat (Ames, Elkhart, IN, USA) (Burl et al. 1977; Place et al. 1983).

**Pharmacokinetic analysis.** A modified one-compartment open pharmacokinetic model with first-order elimination was used to calculate pharmacokinetic parameters and to simulate serum gentamicin concentrations at the steady-state (Sawchuk and Zaske 1976). The serum concentration-time data from the dosing on the 1st and 4th day of treatments were applied to a single exponential term by linear regression analysis using 15-min post-infusion near-peak and near-trough concentrations measured within one hr before the next dosing (Hamilton and Evans 1981). The elimination rate constant (Kd), elimination half life (T1/2), and the serum concentrations on the regression line at the beginning (Cmax) and the bottom (C0) of the post-infusion phase were calculated from the slope of the fitted line. The apparent volume of distribution (Vd) of gentamicin was calculated as follows.

\[
V_d = \frac{K_d}{K_d - C_0 e^{-K_d T}} \left( 1 - e^{-K_d T} \right)
\]

where \( K_d \) is the infusion rate of gentamicin dose, T is the infusion time and \( C_0 \) is the preinfusion serum concentration. Total body clearance of gentamicin (TBC) was calculated from:

\[
TBC = V_d \cdot K_d
\]

The steady-state peak concentration (\( C_{max}^s \)) and trough concentration (\( C_{max}^t \)) were simulated as follows:

\[
C_{max}^s = \frac{K_0}{K_d \cdot V_d} \left( 1 - e^{-K_d \cdot \tau} \right)
\]

\[
C_{max}^t = \frac{K_0}{K_d \cdot V_d} \left( e^{K_d \cdot \tau} - 1 \right)
\]

where \( \tau \) is the dosing interval. The required dosing interval was obtained from the desired
ratio of $C_{\text{min}}/C_{\text{max}}$ as follows:

\[ \tau = -\frac{1}{K_d} \ln \left[ \frac{C_{\text{max}}}{C_{\text{min}}} \right] + T \]

Calculations were done on a scientific calculator Casio Fx-3600p (Casio Tokyo).

**Statistical analysis.** The results are expressed as mean ± s.d. The student $t$-test was used to determine the statistical significance of difference. The predetermined level of significance was $p < 0.05$.

**RESULTS**

*Serum Gentamicin concentration.* In the $< 1,500 \text{ g}$ group the mean ($\pm$ s.d.) peak concentration at the initial dosing was 4.28 $\pm$ 1.71 $\mu$g/ml and 5.03 $\pm$ 1.23 $\mu$g/ml on the 4th day. The mean trough concentration on the 4th day was 1.52 $\pm$ 0.73 $\mu$g/ml (Fig. 1). The desired peak concentration (4–8 $\mu$g/ml) was achieved in 10 neonates (50.0\%) at the initial dosing and in 16 (80.0\%) on the 4th day. There was no significant difference between the mean peak concentrations observed on the 1st and 4th days. On the 4th day the trough concentrations in 5 (25.0\%) of the 20 neonates exceeded 2 $\mu$g/ml but were less than 3 $\mu$g/ml. In the $\geq 1,500 \text{ g}$ group the mean peak concentration at the initial dosing was 4.31 $\pm$ 1.53 $\mu$g/ml and 5.98 $\pm$ 1.05 $\mu$g/ml on the 4th day. The mean trough concentration on the 4th day was 2.29 $\pm$ 0.48 $\mu$g/ml. The desired peak concentration was achieved in 10 neonates (47.0\%) at the initial dosing and in all 21 neonates on the 4th day. A significant difference was observed between the mean peak concentrations on the 1st and 4th days ($p < 0.01$). Fourteen (66.6\%) of 21 neonates had a trough concentration of more than 2 $\mu$g/ml on the 4th day. In a neonate (4.7\%) the trough value exceeded 3 $\mu$g/ml (Fig. 1, right).

There was no significant difference in the mean peak concentrations between the $< 1,500 \text{ g}$ and $\geq 1,500 \text{ g}$ groups at the initial dosing. However, both the mean

![Fig. 1. Individual serum gentamicin concentrations in the $< 1,500 \text{ g}$ birth weight group (left panel; $n = 20$) and the $\geq 1,500 \text{ g}$ birth weight group (right panel; $n = 21$).](image-url)
peak and trough concentrations on the 4th day were significantly higher in the ≥1,500 g group than in the <1,500 g group (p < 0.05 and p < 0.01, respectively).

No clinical or laboratory findings suggestive of renal impairment were observed due to gentamicin administration in the neonates studied.

Pharmacokinetic parameters. The mean pharmacokinetic parameters analyzed using the one-compartment model are summarized in Table 2. All parameters obtained at the initial dosing showed a greater intersubject variability, as can be expected from the greater ±S.D. values, than on the 4th day in both birth weight groups. In the <1,500 g group a larger intersubject variability in the pharmacokinetic parameters was observed on the 4th day, comparing with the ≥1,500 g group.

In comparison of parameters between the 1st and 4th days, significant decreases in Vd and TBC were found in the ≥1,500 g group (p < 0.01, respectively), but not in the <1,500 g group. A comparison of parameters between both birth weight groups revealed a trend toward the observation that the changes in the pharmacokinetic parameters were greater in the ≥1,500 g group than in the <1,500 g group. The mean values for Kd, T1/2, and TBC, but not Vd, observed on the 4th day in the <1,500 g group were significantly (p < 0.01, respectively) different from those in the ≥1,500 g group, although they did not differ at the initial dosing.

Simulation of steady-state serum gentamicin concentrations. Individual predicted and measured values of peak and trough serum gentamicin concentrations were compared (Fig. 2). With respect to peak concentrations, the respective mean predicted and measured values were 4.41 ± 1.77 µg/ml and 4.96 ± 1.22 µg/ml for the <1,500 g group, and 4.46 ± 1.69 µg/ml and 5.95 ± 1.14 µg/ml for the ≥1,500 g group (p < 0.01). The mean predicted values were, on the average, 18.5% less than the measured values. The respective mean predicted and measured
trough concentrations were 1.18±0.98 µg/ml and 1.44±0.66 µg/ml for the <1,500 g group and 1.71±0.66 µg/ml and 2.39±0.43 µg/ml for the ≥1,500 g group (p < 0.01). The average underestimation of the steady-state trough concentration was 24.2%.

A distribution histogram of the differences between the predicted and measured steady-state peak (C∞max − C peak) and trough (C∞min − C trough) concentrations is shown in Fig. 3. A tendency of underestimation was more striking in the ≥1,500 g group than in the <1,500 g group. When an error of ±1 µg/ml was allowed in predicting trough concentrations, the method was successful in 29 (78.3%) of the neonates studied. However, in the prediction of peak concentrations the difference within ±1 µg/ml was reliable in only 8 (21.6%) of the 37 neonates. When a more widened criteria for the peak predictability (±2 µg/ml) was allowed, the successful predictability barely increased to 20 (54.3%).
DISCUSSION

This study was designed to find an effective and safe dosing regimen of gentamicin through the serum concentration monitoring and pharmacokinetic analysis for the aminoglycoside in low birth weight infants who have an immature renal function (Leake et al. 1976; Arant 1978) and a dramatic alteration in body fluid distribution due to a physiological diuresis and an insensible water loss soon after birth (Costarino and Baumgart 1986).

Concerning the dosing regimen of gentamicin for low birth weight infants in the first week of life, a modified dosing regimen, 2.5 mg/kg every 18–24 hr, for infants of gestational age less than 35 weeks was recently recommended to avoid an elevated trough concentration (Assael et al. 1977; Finn and Pemberton 1980; Hindmarsh et al. 1983; Zarowitz et al. 1983; Edgren et al. 1984; Koren et al. 1985) instead of the standard dosing regimen for neonates, 2.5 mg/kg every 12 hr (McCracken and Nelson 1977). However, in terms of practical convenience, the dosing interval of every 12 or 24 hr was suggested to be easier to comply with than that of every 18 hr (Hindmarsh et al. 1983). Based on this concept, our dosing...
A regimen was set up as follows; a dose of 2.0 mg/kg every 24 hr for the neonates of the <1,500 g group and a dose of 2.0 mg/kg every 12 hr for the neonates of the ≥1,500 g group.

At the initial dosing, 21 (51.2%) of 41 neonates failed to obtain a peak concentration of 4 μg/ml, which is considered as the minimum inhibitory concentration for the most gram-negative bacilli responsible for neonatal infections (Rajchot et al. 1984). To increase the efficacy of gentamicin, though it remains unwarranted, a loading dose of 2.5–3.0 mg/kg/dose was recommended by Milner et al. (1972) and Landers et al. (1984).

The neonates of the ≥1,500 g group who received a dose of 2.0 mg/kg every 12 hr had significantly higher peak and trough concentrations at a steady-state than those of the <1,500 g group who received a same dose every 24 hr had. This suggests that the dosing interval of 12 hr might be a little short for the ≥1,500 g group and that an accumulation might occur if the 12 hr dosing interval would be employed.

Gentamicin is excreted unchanged by the kidneys and, therefore, maturation of renal function is a major determinant of gentamicin clearance (Mulhall et al. 1983). Neonates soon after birth are physiologically in an oliguric phase, then pass through a drastic diuretic phase, and their urinations become stable thereafter (Costarino and Baumgart 1986). The resultant alteration in the distribution of body fluids causes a decrease of extracellular fluid (Costarino and Baumgart 1986), having a substantial effect on the total body clearance of gentamicin as shown in the equation of \( TBC = K_d \cdot V_d \).

Evans et al. (1978, 1980) revealed that a tissue accumulation (the “deep” compartment) of gentamicin caused an apparent prolongation of \( T_{1/2} \) (thereby a decrease in \( K_d \)) by means of two-compartment analysis in children and adolescents who had no alteration in body fluid compositions, so that steady-state serum concentrations simulated according to a one-compartment pharmacokinetic model were underestimated.

In our study, although the \( K_d \) and \( T_{1/2} \) values of both birth weight groups were fairly similar on the 1st and 4th days of treatment, the values of \( V_d \) and \( TBC \) on the 4th day tended to be less than those at the initial dosing. The difference was statistically significant in the ≥1,500 g group, but not in the <1,500 g group.

The fact that neither significant prolongation of \( T_{1/2} \) nor significant decrease in \( K_d \) in both birth weight groups (especially in the ≥1,500 g group) were found serves a negative explanation for a tissue accumulation as suggested by Evans et al. (1978, 1980), although a possibility of a tissue accumulation can not be completely ruled out without use of the two-compartment pharmacokinetic analysis.

Consequently, the large \( V_d \) at birth and following drastic change of \( V_d \) may mainly explain the reason why half of the neonates administered gentamicin failed to reach the peak concentration of 4 μg/ml in both birth weight groups at
the initial dosing and why the simulation of steady-state peak and trough concentrations using the pharmacokinetic parameters at the initial dosing were underestimated. If the kinetic parameters obtained later than one week of life when an enormous amount of insensible water loss ceases, a physiological diuretic phase is over, and distribution of body fluid is stabilized, were used, the prediction of steady-state serum concentrations in low birth weight infants would be improved or become more accurate as observed in children and adults. It seems impossible to predict the steady-state serum gentamicin concentrations in low birth weight infants, based on the parameters obtained during the oliguric phase because of the subsequent alteration in their apparent volume of distribution, although successful predictions of steady-state gentamicin concentrations have been reported (Edgren et al. 1984; Kalenga et al. 1984).

When the desired steady-state peak and trough concentrations are defined to be 8.0 μg/ml and 3.0 μg/ml, respectively, the desired peak and trough concentrations were successfully achieved without any clinical and laboratory findings of renal impairment in both birth weight groups in this study. Simultaneously, the dosing intervals can be estimated from the equation (5) and each mean value of \( K_d \) on the 4th day of treatment, to be 18.0 hr for the <1,500 g group and 11.2 hr for the ≥1,500 g group. Thus, the clinically practical dosing intervals are recommended to be 24 hr for the <1,500 g group and 12 hr for the ≥1,500 g group.

In conclusion, we currently recommended a dosing regimen for gentamicin as described above and at the same time we wish to emphasize the importance of a close monitoring of serum gentamicin concentrations by taking account of the unpredictability of a steady-state serum concentration derived from the initial dosing pharmacokinetic parameters due probably to a large intersubject variability in low birth weight infants in the first week of life.

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References


