Br. J. clin. Pharmac. (1986), **21**, 325–327

Tobramycin pharmacokinetics in very low birth weight infants

M. C. NAHATA, D. A. POWELL, DIANE E. DURRELL & MARCIA A. MILLER
Colleges of Pharmacy and Medicine, The Ohio State University, and Children's Hospital, Department of Pediatrics, Columbus, Ohio, USA

Tobramycin is commonly used at a dose of 2.5 mg kg^{-1} 12 h^{-1}, but this regimen often results in trough serum concentrations exceeding 2 mg l^{-1}. Because of limited data in infants weighing less than 1,000 g at birth, we studied eight newborn infants (gestational age 24–30 weeks; postnatal age 3·4 days; birth weight 0.60–0.97 kg) at a modified dosing regimen of 2.5 mg kg^{-1} 18 h^{-1} or 3.0 mg kg^{-1} 24 h^{-1}. Tobramycin peak and trough serum concentrations ranged from 6.0–10.8 (7.8 ± 1.5) mg l^{-1} and 1.2–2.4 (1.7 ± 0.4) mg l^{-1}, respectively. Serum concentration exceeded 2 mg l^{-1} in seven of eight patients at 12 h and two of eight at 18 h; none had a trough serum concentration above 2 mg l^{-1} at 24 h. Total body clearance ranged from 0.55 to 0.82 (0.69 ± 0.10) ml min^{-1} kg^{-1}; apparent volume of distribution ranged from 0.44 to 0.71 (0.59 ± 0.10) l kg^{-1}; and elimination half-life ranged from 7.7 to 12.6 (9.9 ± 1.5) h. These data indicate that the modified dosage regimen of 2.5 mg kg^{-1} 18 h^{-1} or 3.0 mg kg^{-1} 24 h^{-1} appears to be more acceptable than the current regimen in achieving effective and safe peak and trough serum concentration of tobramycin in newborn infants weighing less than 1 kg at birth.

Keywords tobramycin pharmacokinetics newborn infants

Introduction

Tobramycin is frequently used in newborn infants with presumed or proven bacterial infection, particularly in institutions with a high incidence of gentamicin-resistant gram negative microorganisms. The serum concentrations of tobramycin are routinely monitored in these patients to individualize therapy. It is important to note that current North American dosage guidelines for tobramycin use in newborn infants do not consider gestational age or birth weight of the patient (PDR, 1983). We have recently reported that these factors should be taken into account to select optimum tobramycin doses in infants weighing 1.0 to 3.5 kg at birth (Nahata *et al.*, 1984a). Little is known, however, about the pharmacokinetics of tobramycin in newborn infants with a birth weight of less than 1 kg. This knowledge is necessary to develop specific dosage guide-lines for this population, which has the highest mortality among newborn infants (McCormick, 1985). The objective of this study was to examine the pharmacokinetics of tobramycin in very low birth weight infants weighing less than 1 kg.

This paper was presented in part at the annual meeting of the American Society for Clinical Pharmacology and Therapeutics, San Antonio, Texas, March 1985.

Methods

Eight infants (five males, three females) were enrolled in the study on the third to fifth postnatal day. Gestational ages ranged from 24 to 30 weeks and birth weights ranged from 0.60 to 0.97 kg. The patients were receiving tobramycin for presumed or proven bacterial infection.

Correspondence: Dr M. C. Nahata, College of Pharmacy, The Ohio State University, 500 West 12th Avenue, Columbus, OH 43210, USA

Written, informed consent was obtained from the legal guardians prior to enrolment into the study. Renal function was considered normal in all patients based on a serum creatinine concentration of less than 70 μmol l^{-1} and a lack of any clinical evidence. All patients had physiological jaundice (elevated serum concentration of indirect bilirubin), but none exhibited any sign of hepatic dysfunction. Blood gases were frequently monitored to maintain adequate oxygenation in all patients. Concomitant drugs included ampicillin in all patients, theophylline in one patient, phenobarbitone in two patients and secobarbitone in one patient.

Tobramycin was administered i.v. over 20 min at doses ranging from 2.5 mg kg^{-1} every 18 h to 3.0 mg kg^{-1} every 24 h with an IMED infusion pump (IMED, San Diego CA). Because the method of infusion can affect tobramycin serum concentration (Nahata *et al.*, 1984b), our previous findings were considered to assure complete delivery of tobramycin (Nahata *et al.*, 1984c). At the time of the study, the patients had received tobramycin for at least 48 h. Steady-state conditions were further confirmed by two similar trough serum concentrations of tobramycin. A research nurse and technician performed or supervised drug administration and specimen collections.

Blood samples (0.3–0.4 ml) were obtained from an umbilical arterial line not being used for tobramycin administration or by heel prick in 'microtainer' plastic tubes (Becton-Dickinson) just prior to beginning the infusion (0 h) and at 0.5, 1, 2, 4, 6, 8, 12, 18 and 24 h after starting the infusion. Blood was allowed to clot and serum was separated by centrifugation and immediately stored at −50°C.

The serum concentration of tobramycin was measured by an EMIT® method (SYVA, Palo Alto CA) within 30 days of sample collection. The method was sensitive to tobramycin at 0.9 mg l^{-1}. The maximum day-to-day and within-day coefficient of variation of the assay was less than 5%. Tobramycin concentration was not affected by storage.

Area under the serum concentration-time curve (AUC) was calculated by the trapezoidal method. Total body clearance (CL_T) was obtained by dividing tobramycin dose by AUC. Elimination rate constant (λ) was determined from the linear regression analysis of natural log terminal serum concentration-time data. Apparent volume of distribution during the elimination phase was calculated by dividing CL_T by λ. Elimination half-life was determined as $0.693\ \lambda^{-1}$.

Results

Steady-state peak and trough serum concentration of tobramycin ranged from 6.0 to 10.8 (7.6 ± 1.5) mg l^{-1} and 1.2 to 2.4 (1.7 ± 0.4) mg l^{-1}, respectively. Seven of eight infants had a serum concentration above 2 mg l^{-1} at 12 h. In two patients, the serum concentration exceeded 2 mg l^{-1} at 18 h. None of the patients receiving tobramycin dose every 24 h had a trough serum concentration above 2 mg l^{-1}.

Total body clearance of tobramycin ranged from 0.55 to 0.82 ml min^{-1} kg^{-1}. A trend was observed for an increase in clearance with increase in gestational age. Apparent volume of distribution during elimination ranged from 0.44 to 0.71 l kg^{-1}. Elimination half-life of tobramycin ranged from 7.7 to 12.6 h.

Table 1 Tobramycin pharmacokinetic parameters

Patient	*Gestational age (weeks)*	*Birth weight (kg)*	*Dose (mg)*	*Dosing interval (h)*	*Total clearance ml min^{-1} kg^{-1}*	*Apparent distribution volume (l kg^{-1})*	*Elimination half-life (h)*
1	24	0.60	1.5	18	0.55	0.44	9.4
2	28	0.77	2.2	24	0.64	0.56	10.0
3	30	0.78	2.0	18	0.76	0.51	7.7
4	28	0.80	2.4	18	0.82	0.67	9.5
5	30	0.81	2.0	18	0.81	0.66	9.4
6	29	0.84	2.5	24	0.62	0.68	12.6
7	28	0.87	2.2	18	0.61	0.49	9.2
8	30	0.97	3.0	24	0.70	0.71	11.7
Mean					0.69	0.59	9.9
s.d.					0.10	0.10	1.5

Discussion

Our findings suggest that although tobramycin peak serum concentration was within therapeutic range, trough serum concentration exceeded 2 mg l^{-1} in seven of eight infants at the presently recommended dosing interval of 12 h. Although unproven for infants, studies in adults have demonstrated a relationship between nephrotoxicity and gentamicin trough serum concentration above 2 mg l^{-1} (Dahlgren *et al.*, 1975); thus, it has been recommended to maintain trough serum concentration below 2 mg l^{-1} in infants (Klein, 1981). Our observations indicate that tobramycin doses of 2.5 mg kg^{-1} every 18 h or 3.0 mg kg^{-1} every 24 h may be considered to achieve adequate peak and potentially safe trough serum concentration in very low birth weight infants.

The interpatient variation in tobramycin pharmacokinetic parameters may be up to two-fold in low birth weight infants. The average total body clearance of 0.69 ml min^{-1} kg^{-1} in this study involving infants less than 1 kg was markedly lower than our previously reported clearance of 1.0 ml min^{-1} kg^{-1} in 1.0 to 1.25 kg, 1.1 ml min^{-1} kg^{-1} in 1.26–2.0 kg, and 1.28 ml min^{-1} kg^{-1} in 2.1 to 3.5 kg birth weight infants (Nahata *et al.*, 1984a). This explains the need for a lower daily dose in infants weighing less than 1 kg compared to those above 1 kg birth weight. The trend for a direct relationship between tobramycin clearance and gestational age is consistent with a correlation between glomerular filtration and gestational age in low birth weight infants (Arant, 1978).

Because of a substantial interpatient variation in pharmacokinetics and narrow therapeutic range of tobramycin, its serum concentrations are routinely monitored to maximize efficacy and minimize potential for toxicity. At the commonly used doses of 2.5 mg kg^{-1} 12 h^{-1}, trough serum concentration exceeds 2 mg l^{-1} in most infants, which frequently requires alteration of dosage regimens. We recommend initial tobramycin doses of 2.5 mg kg^{-1} 18 h^{-1} or 3.0 mg kg^{-1} 24 h^{-1} in very low birth weight infants. These doses can be later modified based on tobramycin serum concentrations and clinical condition of these infants.

We appreciate the assistance of Doctors J. Menke, R. McClead, R. Bickers, C. Anderson and R. Gregoire for providing patients.
The study was supported by Lilly Research Laboratories.

References

Arant, B. S. (1978). Developmental patterns of renal functional maturation compared in the human neonate. *J. Pediatr.*, **92**, 705–712.

Dahlgren, J. G., Anderson, E. T. & Hewitt, W. L. (1975). Gentamicin blood levels: A guide to nephrotoxicity. *Antimicrob. Agents Chemother.*, **8**,58–62.

Klein, J. O. (1981). Antimicrobial agents for infants and children, In *Textbook of Pediatric Infectious Diseases,* eds. Feigin, R. D. & Cherry, J. D. Philadelphia: W. B. Saunders Co.

McCormick, M. C. (1985). The contribution of low birth weight to infant mortality and childhood morbidity. *New Engl. J. Med.*, **312**, 82–90.

Nahata, M. C., Powell, D. A., Durrell, D. E., Miller, M. C. & Glazer, J. P. (1984a). Effect of gestational age and birth weight on tobramycin kinetics in newborn infants. *J. Antimicrob. Chemother.*, **14**, 59–65.

Nahata, M. C., Powell, D. A., Durrell, D., Miller, M. & Glazer, J. P. (1984b). Effect of infusion methods on tobramycin serum concentration in newborn infants. *J. Pediatr.*, **104**, 136–138.

Nahata, M. C., Powell, D. A., Durrell, D., Miller, M. & Glazer, J. P. (1984c). Delivery of tobramycin by three infusion systems. *Chemotherapy*, **30**, 84–87.

Physician's Desk Reference. (1983). 37th edition. Oradell, N.J.: Medical Economics Co.

(Received 14 August 1985, accepted 24 October 1985)