

Therapeutic monitoring as an aid in rationalising aminoglycoside dosage techniques in the neonate

L. L. SPRUYT, G. F. KIRSTEN, D. P. PARKIN, G. J. MÜLLER, A. KRIEGLER

Summary

General pharmacokinetic parameters applicable to adults are not suitable in neonatal practice owing to wide interpatient variations in respect of fluid balance, renal clearance and metabolic rates. We attempted to determine whether acceptable blood levels of gentamicin or tobramycin are obtained with dosage regimens and dosage techniques which are generally recommended.

Forty neonates receiving aminoglycosides were studied. After administration of the drug as a slow, constant intravenous infusion into the 'Y' connection of the infusion set, peak levels were found to be subtherapeutic. Trough levels were also very low. After administration of the same dose of gentamicin or tobramycin as a bolus into the butterfly connection of the infusion set, however, high therapeutic levels were obtained.

We therefore recommend that gentamicin and tobramycin be administered as an intravenous bolus injection and that blood levels be monitored constantly in order to individualise therapy.

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Therapeutic monitoring of several drugs has become standard practice in modern hospitals in which these facilities are available. The major aims of this approach are to improve the efficacy of pharmacotherapy of the specific disease and to avoid potential toxic or side-effects.¹ Furthermore, therapy can be individualised effectively by using blood level data in suitable nomograms² or using such data to calculate pharmacokinetic parameters such as drug clearance, volume of distribution, etc.³

Aminoglycosides are a valuable group of antibiotics for the treatment of serious, often life-threatening, Gram-negative infections such as septicaemia. They have, however, a narrow therapeutic range due to their potential oto- and nephrotoxicity. Blood level determinations are a valuable adjunct to avoiding toxicity while at the same time ensuring effective bactericidal concentrations. Wide variations in blood levels in regimens employing standard dosage schedules (intramuscular or slow intravenous infusion) have been observed in our laboratory for

patients treated with aminoglycosides at Tygerberg Hospital, Parowvallei, CP. This was especially true for neonates, in whom intramuscular injections are not recommended because of limited muscle mass. Slow intravenous infusion via the 'Y' connection of the infusion set was therefore the standard technique employed in our hospital (Fig. 1).

In this article peak and trough levels of gentamicin and tobramycin in neonates after administration by two different intravenous dosage techniques are compared.

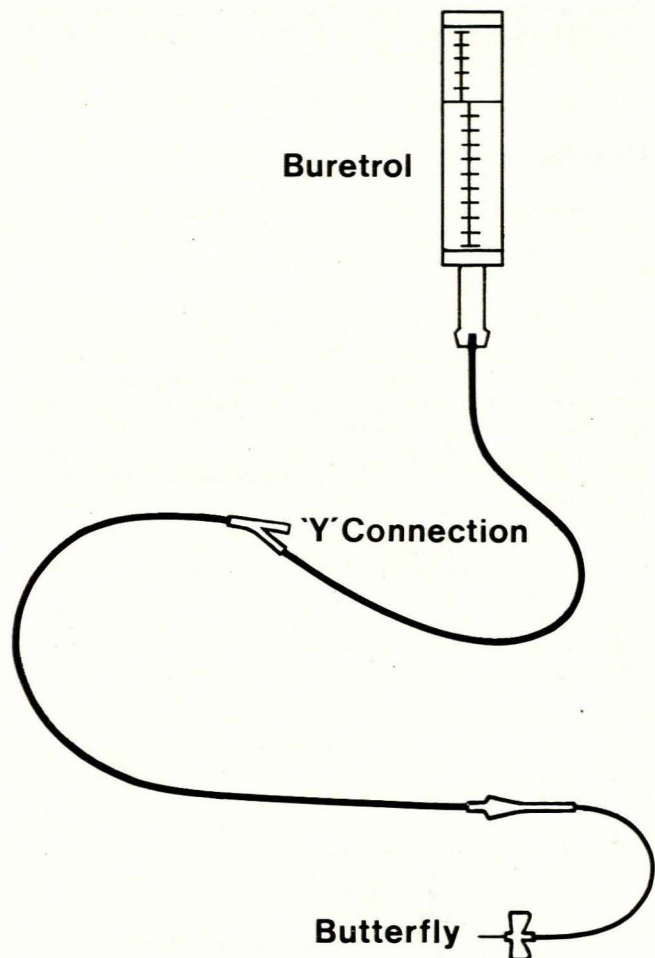


Fig. 1. Diagrammatic representation of an infusion set showing the 'Y' and 'butterfly' connections.

Departments of Pharmacology and Paediatrics, University of Stellenbosch, Parowvallei, CP

L. L. SPRUYT, B.S.C. HONS (PHARM.), M.B. CH.B.

G. F. KIRSTEN, L.K.I. (S.A.), M.MED. (PAED.), D.G.K. (S.A.)

D. P. PARKIN, B.S.C. HONS, M.B. CH.B.

G. J. MÜLLER, B.S.C., M.B. CH.B., B.S.C. HONS, M.MED.

A. KRIEGLER, TECH. DIPL.

Subjects and methods

Forty infants (in two groups of 20 each) with suspected Gram-negative septicaemia were consecutively included in the study during the time that they were hospitalised. The mean gestational age was 34 weeks and weights ranged from 1000 to 3800 g.

Gentamicin or tobramycin was administered at a dosage of 2,5 - 3,0 mg/kg as follows:

Group 1. A slow, constant intravenous infusion of the drug administered at the 'Y' connection of the infusion set, as has been the routine method of administration in the past. The desired infusion time was 30 minutes, but owing to the lack of infusion pumps this could not be accurately controlled.

Group 2. An intravenous bolus was administered at the 'butterfly' connection of the infusion set over a period of 1 minute, after which the connection was flushed with 0,5 ml sterile water, also over 1 minute.

Capillary blood samples (0,5 ml) were collected by means of a heel prick. For the determination of trough levels blood was collected immediately before administration of the next scheduled dose. Blood for peak level determinations was drawn for group 1 at 60 minutes after the start of the infusion (i.e. 30 minutes after the estimated completion of the infusion) and for group 2 at 20 minutes after bolus administration.

Blood samples were collected in 0,5 ml Eppendorf centrifuge tubes and analyses of the serum were performed by the EMIT method (Syva, Palo Alto, Calif., USA) within 12 hours after collection. Investigation by our laboratory showed no meaningful differences between arterial and venous levels of aminoglycoside after administration. Although venous blood was most often drawn, chance arterial specimens would not have influenced the results adversely. Ethical consent for the trial was obtained from the Tygerberg Hospital Ethical Committee before initiation of the project.

Results

The optimum serum concentrations for aminoglycosides vary according to the indication.⁴⁻⁷ For this group of patients trough levels of less than 2 $\mu\text{g/ml}$ and peak levels between 6 and 10 $\mu\text{g/ml}$ were desired.

From Fig. 2 it is clear that both the mean peak and the mean trough levels of gentamicin and tobramycin were generally below the optimal concentration when the drugs were administered as a slow intravenous infusion (group 1). Fig. 3 illustrates that by administering the drugs as an intravenous bolus (group 2) acceptable peak levels were obtained. Trough levels were below the 2 $\mu\text{g/ml}$ margin in 11 cases. In 9 cases in which the levels were above 2 $\mu\text{g/ml}$ they were rectified immediately by increasing the dosage interval.

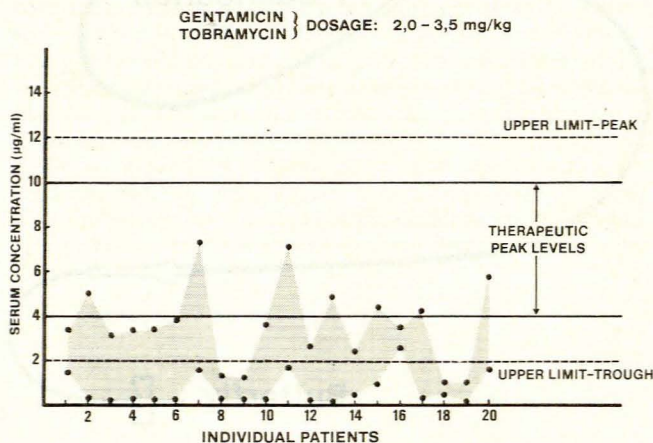


Fig. 2. Peak and trough levels of gentamicin and tobramycin after administration as a slow, constant intravenous injection.

Discussion

Individualisation of dosage regimens by clinical pharmacokinetic calculations which take into account an existing blood level achieved by a given dose as well as the dosage interval is a practical and successful approach for several drugs.^{7,8}

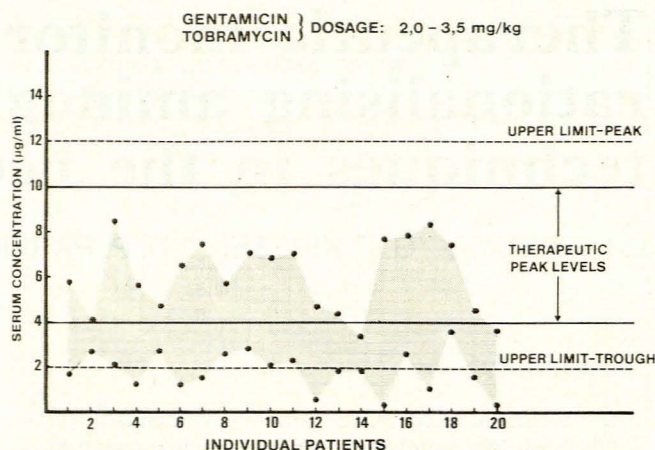


Fig. 3. Peak and trough levels of gentamicin and tobramycin after administration as a bolus injection.

In neonates, who have a relatively small mass, the degree of hydration may change drastically between doses. It is well appreciated that changes in the extracellular fluid compartment during hydration or dehydration also change the volume of distribution of aminoglycoside antibiotics. In neonates the volume of distribution of aminoglycosides has been reported as varying from 0,2 to 0,6 l/kg⁷ and from 0,4 to 0,9 l/kg.⁸ These values are higher than the 0,2 - 0,3 l/kg reported for children and adults.

In severely ill patients with Gram-negative septicaemia there may be acute variations in fluid and electrolyte status, leading to changes in extracellular fluid volume and the volume of distribution as it affects the aminoglycosides. In such patients a 6 - 12-fold range has been observed in the volume of distribution for tobramycin and gentamicin.⁹ This variation in distribution volume can profoundly affect the serum concentration/time profile. During dehydration the volume of distribution approaches the lower limit for these drugs and is accompanied by an increase in their serum concentrations. Conversely, an increased volume of distribution causes an increase in the elimination half-life, since aminoglycosides are excreted mainly in the unchanged form through the kidneys.⁸ It is therefore reasonable to argue that the pharmacokinetic instability of neonates complicates the use of pharmacokinetic parameters in the calculation of ideal doses for these and indeed for other drugs. A far more practical approach seems to be frequent monitoring of the serum antibiotic levels and adjustment of the dose and the dosage interval accordingly. Recommendations in the literature on how long after administration of a bolus injection to determine peak plasma concentrations range from 5 minutes to as much as 1 hour.¹⁰⁻¹³ In this study samples were drawn 20 minutes after administration, which in accordance with our experience was found to give a good indication of effective therapeutic levels.

It is clear from this study that when attempts were made to administer aminoglycosides by slow infusion, mean peak levels were below the therapeutic range (Fig. 2). Owing to the restricted fluid volume that a neonate may receive over a 24-hour period, infusion rates must of necessity be slow. When an antibiotic is added to the system in this way, its excretion rate may exceed the rate of infusion to such an extent that a therapeutically effective peak level is not achieved. Intravenous bolus injection, on the other hand, ensures therapeutically effective peak levels (Fig. 3).

In conclusion we recommend that gentamicin or tobramycin be administered to neonates as an intravenous bolus slowly over a period of 1 minute as described above, and that blood levels be monitored routinely so that the dose and dosage

intervals can be rationally adjusted to achieve optimal therapeutic levels and avoid toxicity.

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Use of mitoxantrone-based combination chemotherapy regimens as first-line treatment for advanced breast cancer

W. R. BEZWODA, C. S. HESDORFFER, R. D. DANSEY

Summary

Three first-line combination chemotherapy regimens which included mitoxantrone were studied for the treatment of advanced breast cancer. The first combination, consisting of methotrexate, mitoxantrone (Novantrone) and 5-fluoro-uracil (MNF), gave a response rate of 17/48 (35%). Cyclophosphamide + mitoxantrone (CN) gave a response rate of 20/31 (64%) while cyclophosphamide + mitoxantrone + vincristine (CNV) gave a response rate of 28/39 (72%). The response durations for the three regimens were 6 months for MNF, 7.5 months for CN and 11.5 months for CNV. The regimens were well tolerated with an approximately equal frequency of side-effects. Cardiotoxicity was infrequent, occurring in only 2 patients out of 118 studied.

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Mitoxantrone (dihydroxyanthracenedione dihydrochloride — Novantrone); a new anthraquinone compound,¹ has demonstrated marked antitumour activity in a number of systems, including breast cancer.² Studied experimentally the efficacy of the drug as a single agent in human breast cancer has been

demonstrated in a number of phase II studies with response rates similar to those achieved with other active drugs.^{3,4} Potential advantages of this new agent include a claim that there is less cardiotoxicity⁵ and suggestive evidence that nausea and alopecia may be less frequently encountered than with other cytotoxic drugs.^{6,7} Responses to single-agent treatment are, however, rarely complete and the duration of response to single agents tends to be short. Combination chemotherapy has been shown to increase both response rate and response duration.⁸

There is, however, relatively little information available regarding the use of mitoxantrone in combination chemotherapy of breast cancer; therefore the safety and efficacy of mitoxantrone in patients with advanced breast cancer was examined.

Patients and methods

Three studies using mitoxantrone in combination chemotherapy schedules were carried out at the Breast Clinic of Johannesburg Hospital between February 1984 and December 1985. All patients included in the studies were suffering from advanced, recurrent or metastatic breast cancer, documented according to standard accepted criteria.⁹ All had at least one area of measurable disease and performance status of better than or equal to Karnofsky 50 - 60. None had had previous chemotherapy for metastatic disease. The three chemotherapy schedules were each given on day 1 of a 21-day intermittent treatment schedule and consisted of: (i) 48 patients — methotrexate (40 mg/m²) + mitoxantrone (10 mg/m²) + 5-fluoro-uracil (600 mg/m²) (MNF); (ii) 31 patients — cyclophosphamide (600 mg/m²) + mitoxantrone (12 mg/m²) (CN); and (iii) 39 patients — cyclophosphamide (600 mg/m²) + mitoxantrone (12 mg/m²) + vincristine (1.4 mg/m²) (CNV). Mitoxantrone and cyclophosphamide were given by intravenous infusion over 30 minutes while the other drugs were each administered by bolus intravenous injection.

Pretreatment investigations included full physical examination, chest radiograph, bone and liver scans, abdominal ultrasonography

Haematology/Oncology Unit, Department of Medicine, University of the Witwatersrand and Johannesburg Hospital, Johannesburg

W. R. BEZWODA, M.B. B.CH., F.C.P. (S.A.)

C. S. HESDORFFER, M.B. B.CH., F.C.P. (S.A.)

R. D. DANSEY, M.B. B.CH., F.C.P. (S.A.)