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The pharmacokinetics of amikacin in critically ill adult and paediatric patients: comparison of once- versus twice-daily dosing regimens

P. E. Marik[a], I. Havlik[b], F. S. E. Monteagudo[b] and J. Lipman[a]

[a]Intensive Care Unit, Baragwanath Hospital, and [b]Department of Clinical and Experimental Pharmacology, University of the Witwatersrand Medical School, Johannesburg, South Africa

The pharmacokinetic profile of amikacin was analysed by a two-compartment model in 100 critically-ill adult and paediatric patients with normal renal function. In addition the serum amikacin levels in 200 patients randomized to receive a once- or twice-daily dosing regimen are reported. The mean volume of distribution (Vd_1) was 0·33 l/kg in the adult patients, 0·50 l/kg in patients 6 to 12 months of age and 0·58 l/kg in patients less than 6 months old. The elimination half-life was prolonged, being 3·45, 2·86 and 5·02 h for the respective age groups (normal 2 h). The clearances (dose/AUC) were 0·051, 0·068 and 0·063 l/h/kg respectively. Within each group of patients there was a large variation in the pharmacokinetic parameters, with the Vd_1 varying by a factor of 6 and the elimination half-life by a factor of 10.

All patients receiving a once-daily dose of amikacin had therapeutic peak concentrations. In comparision, therapeutic concentrations were achieved in only 48% of adult and 44% of the paediatric patients receiving the twice-daily dosing regimen. Furthermore the amikacin trough concentrations were significantly higher in the patients who received a divided daily dose. As a consequence of the pharmacokinetic profile of amikacin in critically ill patients a once-daily dosing regimen may be more effective and less toxic than the conventional twice-daily dosing regimen.

Introduction

Aminoglycosides are a valuable group of antibiotics against most Gram-negative aerobic bacteria. Despite the associated nephro- and oto-toxicity, and the increasing incidence of resistance, these antibiotics remain drugs of choice for serious Gram-negative infections (Siegenthaler, Bonetti & Luthy, 1986; Young & Hindler, 1986).

Aminoglycosides are highly charged drugs which are minimally protein bound, insoluble in lipids and have a volume of distribution similar to that of the extra-cellular space (Mangione & Schentag, 1980; Ristuccia & Cunha, 1985). The pharmacokinetic profile of aminoglycosides is altered in the septicaemic critically ill patient (Zaske *et al.*, 1976; Zaske, Cipolle & Strate, 1980; Mann *et al.*, 1987; Townsend *et al.*, 1989). This altered pharmacokinetic profile has a profound effect on the bactericidal activity and toxicity of these drugs.

Correspondence: Dr P. E. Marik, PO Box 1270, Highlands North 2037, Johannesburg, South Africa.

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Aminoglycosides (unlike β-lactam antibiotics) cause concentration-dependent bacterial killing. Both in-vitro and in-vivo studies have demonstrated that the higher the concentration of the drug the greater the bacterial kill and the better the clinical outcome (Moore, Lietman & Smith, 1987; Bush & Levison, 1988; Dellamonica *et al.*, 1988; Shah *et al.*, 1988). In comparison to the β-lactam antibiotics, aminoglycosides have a long post-antibiotic effect (PAE), the duration of which is dependent upon the peak serum concentration (Wilson & Rolinson, 1979; Bundtzen *et al.*, 1981; Isaksson *et al.*, 1988). Aminoglycosides have a very narrow therapeutic index, with oto- and nephro-toxicity being the most important complications. It has been estimated that 10–30% of patients treated with an aminoglycoside develop drug-induced azotaemia or renal failure (Moore *et al.*, 1984*a*; Humes, 1988). The concentration of drug in the inner ear and renal tubular cell is the prime determinant of toxicity. The uptake of aminoglycosides at both these sites is a saturable zero-order kinetic process (Tulkens & Laurenti, 1984; Giuliano *et al.*, 1986; Tran Ba Huy, 1988). This would imply that a raised trough level rather than an elevated peak level is more likely to be associated with toxicity. This has been confirmed in both animal and human experiments (Reiner, Bloxham & Thompson, 1978; Brummett, 1981; Pechère & Bernard, 1984; Tulkens & Laurenti, 1984; Whelton, 1984; Tulkens *et al.*, 1988; Wood *et al.*, 1988). Taking these factors into account an 'ideal' dosing regimen would be one that produced the highest peak level with the lowest trough.

Aminoglycoside antibiotics are usually given in two or three divided daily doses. In the critically ill patient this dosing scheme may not "maximize the drug's therapeutic potential nor minimize its toxicity" (Kapusnik & Sande, 1986). There is evidence from in-vitro animal and human studies that a once-daily dosing regimen results in greater bactericidal activity and less toxicity than conventional twice- or thrice-daily dosing (Pechère & Bernard, 1984; Whelton, 1984; Stone & Zinner, 1985; Kapusnik & Sande, 1986; Tulkens *et al.*, 1988; Van der Auwera, 1988; Wood *et al.*, 1988; de Vries *et al.*, 1990). The pharmacokinetic profile of amikacin in severely ill patients has however not been well investigated.

The aim of this study was to investigate the pharmacokinetics of amikacin in critically ill adult and paediatric patients, using a two-compartment open model, and to compare the blood levels of once- vs twice-daily regimens.

Patients and methods

This study was conducted in the intensive care unit (ICU) at Baragwanath Hospital, Soweto. Patients with a documented Gram-negative aerobic infection in whom treatment with an aminoglycoside and a cephalosporin (cefotaxime or ceftazidime) was indicated were included in this study. The study was approved by the University of the Witwatersrand Ethics Committee.

The following were excluded from the study: pregnant patients, patients with a known allergy to aminoglycosides and or β-lactam antibiotics; patients with a calculated creatinine clearance of less than 50 ml/min/1·73 m^2 or a serum creatinine greater than 160 μmol/l (less than 120 μmol/l in patients under 1 year of age); patients undergoing dialysis; patients with a history of deafness or vestibular disturbances and patients with neuromuscular diseases. In addition patients whose serum creatinine rose by more than 35 μmol/l during the first 3 days of therapy were withdrawn from the study. The deterioration in renal function in these patients was attributed to the

underlying disease process rather than aminoglycoside nephrotoxicity (Moore *et al.*, 1984*a*; Humes, 1988).

Cefotaxime and ceftazidime were given in a dosage of 1 g 6-hourly (or 100 mg/kg/day in patients weighing less than 40 kg). Amikacin was given in a total daily dose of 15 mg/kg in patients over the age of 1 year and 20 mg/kg in patients less than 1 year of age. Patients were randomized by a random number generator to receive either a once- or twice-daily dose of amikacin. The patients randomized to a once-daily dose received a loading dose of amikacin of 20 mg/kg and 25 mg/kg respectively. The amikacin was given intravenously over 3 to 5 min. The dose of amikacin was thereafter adjusted, using basic pharmacokinetic principles, to achieve a peak level of between 30–40 mg/l in the once-daily group and between 20–30 mg/l in the twice-daily group, while keeping the trough level below 5 mg/l (Mangione & Schentag, 1980; Ristuccia & Cunha, 1985; Miller, 1988).

For the purposes of this study patients less than 1 year old were classified in a paediatric group. This group was sub-divided into patients older or younger than 6 months. These cut-off ages were chosen in respect of the changes in total and interstitial body water and renal function that occur within the first year of life, and which approximate the adult values by 1 year of age (Goldsmith, 1978; Winters, 1982).

A detailed pharmacokinetic study was done on the second day of treatment in 100 patients. Blood samples (0·5–2 ml) were drawn from an arterial line at 10, 20, 30, 40 min and 1, 2, 4, 8 and 12 h (and at 24 h in patients receiving a once-daily dose). All patients had a peak (1 h post dose) and trough level taken every second or third day.

The aminoglycoside samples were assayed using an enzyme-linked immuno-assay (EMIT). The coefficient of variation was less than 10% for both control and interbatch samples. The lower limit of sensitivity for the assay was 0·1 μg/ml.

Serum amikacin concentration–time data were analysed using a non-linear least-squares regression analysis computer program assuming a two-compartment pharmacokinetic model (NONLIN). The standard coefficients (A, B, α, β) for the two-compartment model were determined. The following pharmacokinetic variables were calculated for each patient: distribution half-life ($\alpha\ t_{\frac{1}{2}}$), elimination half-life ($\beta\ t_{\frac{1}{2}}$), volume of central compartment (V_1), volume of peripheral compartment (V_2), total volume of distribution (Vd_f), and amikacin clearance (dose/AUC).

The serum creatinine was recorded daily for all patients while undergoing treatment and for at least 3 days after the aminoglycoside had been stopped. Aminoglycoside induced nephrotoxicity was defined as an increase in the serum creatinine of greater than 35 μmol/l after the third day of treatment (Moore *et al.*, 1984*a*; Humes, 1988).

Results

Two hundred patients completed the study. Twelve patients were subsequently excluded due to a rise in serum creatinine of > 35 μmol/l during the first 3 days of treatment. A detailed pharmacokinetic assessment was performed on 40 adult patients (Group 1), 30 patients between the ages of 6 months and 1 year (Group 2) and 30 patients less than 6 months old (Group 3). Peak and trough amikacin levels were available for all 200 patients.

As can be seen from Table I the pharmacokinetic profile of amikacin varied between the three age groups of patients. The volumes of distribution and the clearances were considerably smaller in the adult as compared with the paediatric groups. Consequently

Table I. Mean pharmacokinetic parameters (range in parentheses) for amikacin in patients of different age groups (Group 1, > 1 year; Group 2, 6 months–1 year; Group 3, < 6 months)

	Group 1	Group 2	Group 3
No. of patients	40	30	30
Age	34 years (1–70)	28 weeks (24–52)	8 weeks (1–23)
Pharmacokinetic parameters			
$\alpha\ t_{\frac{1}{2}}$ (h)	0·24 (0·05–0·52)	0·31 (0·03–0·58)	0·44 (0·12–0·99)
$\beta\ t_{\frac{1}{2}}$ (h)	3·45 (1·09–6·47)	2·86 (0·63–6·28)	5·02 (1·46–11·89)
V_1/kg (l/kg)	0·14 (0·02–0·26)	0·18 (0·02–0·34)	0·21 (0·12–0·38)
V_2/kg (l/kg)	0·19 (0·09–0·36)	0·32 (0·18–0·45)	0·37 (0·23–0·60)
Vd_t/kg (l/kg)	0·33 (0·17–0·61)	0·50 (0·22–0·73)	0·58 (0·32–0·98)
Cl (dose/AUC)/kg (l/h/kg)	0·051 (0·021–0·105)	0·068 (0·018–0·129)	0·063 (0·036–0·108)
Serum-creatinine concentration (μmol/l)	95·32 (13–160)	72·48 (25–118)	62·9 (15–120)

V_1, Volume of central compartment; V_2, volume of peripheral compartment; Vd_t, total volume of distribution; Cl(AUC), clearance from area under curve.

in order to achieve adequate blood levels the average daily doses were higher in the paediatric group of patients (Table II). Furthermore, within each group of patients, there was a large inter-patient variation in the pharmacokinetic variables. This is reflected in the wide range of dosage requirements.

The creatinine clearance (ml/min) of the adult patients was correlated with the amikacin clearance (l/h) using Spearman Rank correlation. The correlation coefficient was 0·46 (N.S.).

The mean peak and trough amikacin blood levels in each group of patients is shown in Table III. All patients who received a once-daily dose had therapeutic peak levels (greater than 20 mg/l). However only 44% of paediatric and 48% of adult patients who received the twice-daily regimen had therapeutic peak blood levels. Furthermore, all the patients who received the once-daily dosing regimen had trough levels < 5 mg/l whereas only 77% of adults and 79% of paediatric patients treated with the twice-daily dosing regimen had similar levels.

Table II. Mean (range) of daily dosages of amikacin (mg/kg) required to achieve adequate blood levels

	Group 1	Group 2	Group 3
Once daily dosing	13·8 (12·2–20·3)	20·9 (18·1–24)	18·6 (15·2–22·1)
Twice daily dosing	15·5 (12·4–24·0)	21·2 (14–26·2)	20·5 (12·3–27·4)

Table III. Mean peak and trough blood concentrations (mg/l) ±S.D. for patients receiving a once- or twice-daily dosing regimen

	Group 1 ($n = 100$)	Group 2 ($n = 45$)	Group 3 ($n = 55$)
Peak (once daily)	33·75±4·77	33·92±6·52	30·10±4·61
Peak (twice daily)	19·42±3·06	18·70±4·03	17·21±4·29
Trough (once daily)	0·77±0·84	0·46±0·11	1·30±1·56
Trough (twice daily)	3·83±2·95	3·63±1·14	4·47±3·34

Three adult patients who were randomized to the twice-daily regimen developed aminoglycoside induced nephrotoxicity (increase > 35 μmol/l) while this complication did not occur in any of the patients on the once-daily dosing regimen.

Discussion

The dosage and frequency with which antibiotics should be administered has long been a source of controversy. Most antibiotics are usually administered in doses in excess of that required to effect a cure. Due to their narrow therapeutic index aminoglycoside antibiotics are an exception to this rule, and the most effective dosing regimen for this group of drugs is still not well established (Siegenthaler *et al.*, 1986).

The dogma that, in order to achieve a cure, the antimicrobial concentrations at the sites of infection should be higher than the MIC against the infecting organism throughout therapy, has been shown not to be true with respect to aminoglycosides (Shah *et al.*, 1988). Animal and human data suggest that the most effective and safe dosing regimen is the one which produces a high peak serum concentration with a very low trough concentration (Reiner *et al.*, 1978; Pechère & Bernard, 1984; Blaser *et al.*, 1985; Kapusnik & Sande, 1986; Tulkens *et al.*, 1988; Van der Auwera, 1988; Wood *et al.*, 1988; de Vries *et al.*, 1990).

Most of the pharmacokinetic data on aminoglycosides are from studies of healthy volunteers and patients who are not critically ill (Zaske *et al.*, 1976; Mangione & Schentag, 1980; Ristuccia & Cunha, 1985; Hassan & Ober, 1986; Mann *et al.*, 1987; Beckhouse *et al.*, 1988; Zaske *et al.*, 1988; Townsend *et al.*, 1989). These studies demonstrate that aminoglycosides obey a three-compartment model. The drug distributes rapidly throughout extracellular water and highly perfused organs with a distribution phase half-life of 5–15 min. With normal renal function the elimination phase half-life is about 2 h. During this time two processes are taking place simultaneously. While most of the drug is being excreted unchanged by glomerular filtration, the remainder is being removed from the serum by uptake into body tissues. The third phase of serum decline is noted after either a single dose or after the final dose in a multiple dose regimen. The half-life of this phase normally exceeds 100 h. During this third phase intracellular aminoglycoside is released into the extracellular fluid and then excreted in the urine. This terminal phase is responsible for about 2–3% of the total clearance (Mangione & Schentag, 1980; Ristuccia & Cuhna, 1985). In clinical studies this latter phase can be ignored and a two-compartment model assumed.

Limited pharmacokinetic data are available on paediatric patients (Kaplan *et al.*, 1973; Cookson *et al.*, 1980; Sirtori, Franceshini & Lovati, 1984; Carlstedt *et al.*, 1989). The half-life has been reported to be prolonged in newborns, being inversely proportional to the birth weight and approximately double that of adults. With renal maturation the half-life reaches adult levels within a few months.

The critically ill patient with sepsis offers unique challenges in drug dosing because of physiological changes that accompany severe illness. In these patients it is important to achieve therapeutic antimicrobial levels in the serum and at the site of infection rapidly. The serum levels can be used as a guide to therapy as pharmacological studies in man suggest that the concentration of aminoglycosides in the blood reflects tissue concentration (Chrisholm *et al.*, 1973; Pennington & Reynolds, 1973; Lanao *et al.*, 1983).

Zaske *et al.* (1980) demonstrated that the use of conventional gentamicin dosage in hospitalized patients resulted in either subtherapeutic peak or toxic trough concentrations in 60% of patients tested. Moore, Smith & Lietman (1984*b*) have demonstrated that at least 40% of patients treated with aminoglycosides had low peak serum concentrations when treated according to the manufacturer's dosage recommendations. Using a single-compartment model a number of authors have demonstrated a wide range in the pharmacokinetic variables in surgical patients with both normal and deranged renal function (Zaske *et al.*, 1976; Mangione & Schentag, 1980; Zaske *et al.*, 1980; Ristuccia & Cunha, 1985; Mann *et al.*, 1987; Beckhouse *et al.*, 1988; Townsend *et al.*, 1989). Hassan & Ober (1986) investigated the relationship between the predicted and actual pharmacokinetics in 20 patients in a surgical ICU. They found the actual volume of distribution (*Vd*) to be significantly greater than the predicted *Vd*, the correlation coefficient being only 0·43. Zaske *et al.* (1980) demonstrated a wide variation in the pharmacokinetic profile of gentamicin in surgical patients with normal renal function. These authors found the half-life varied from 0·4 to 13·3 h and *Vd* from 0·06 to 0·63 l/kg. The daily requirement for gentamicin varied from 0·7 to 12·4 mg/kg/day and averaged twice the manufacturer's recommended dosage.

In this study we found the kinetics of amikacin best fitted a two-compartment model. The average distribution half-life was approximately 18 min. Therefore, if a one-compartment model is assumed, and blood levels are assayed before the time required for equilibration, incorrect pharmacokinetic data would be obtained.

In the adult patients, the total volume of distribution was larger than that reported for healthy volunteers and non-critically ill patients. Localized oedema (e.g. ascites, pleural effusions and dependent oedema) or generalized oedema (e.g. adult respiratory distress syndrome, multiple organ failure syndrome) could account for the larger volumes of distribution of amikacin in the critically ill patients in this study. As a consequence of the increased volume of distribution a greater dose of aminoglycoside is required to achieve target blood levels. The dosage range was found to be narrower in the patients who received the once-daily dosing regimen (Table II).

The elimination half-life of amikacin was prolonged in this study. This was particularly evident in the patients less than 6 months of age. Furthermore, in the adult patients, there was a poor correlation between the creatinine clearance and the clearance of amikacin. This is in accordance with the results of other workers (Townsend *et al.*, 1989). Therefore in order to achieve a low trough level in the critically ill adult and paediatric patient, it is necessary to increase the conventional dosing interval.

The volume of distribution of amikacin was larger in the paediatric as compared to

the adult patients. This would be anticipated if one takes into account the increased interstitial and total body water of the new-born, which reaches the adult level by 1 year (Winters, 1982). The larger volume of distribution accounts for the requirement for a higher daily dose in patients less than 1 year of age.

The effect of the change in the pharmacokinetics of aminoglycosides in critically ill patients is demonstrated by examining the blood levels of the patients who were treated with the once-daily as compared to the twice-daily dosing regimen. The once-daily dose resulted in much higher peak concentrations, with all patients having a therapeutic peak and low trough concentration. In comparison only 48% of patients in group 1 and 44% of patients in groups 2 and 3 who received a twice-daily dose of amikacin had therapeutic blood concentrations. This is in spite of the paediatric patients receiving a daily dose 33% higher than that recommended by the manufacturers. In addition the trough concentrations were significantly higher in the patients who received a divided daily dose.

It could be argued that the patients receiving amikacin twice daily were underdosed. However in these patients the dosages were adjusted to maintain the trough concentrations below 5 mg/l in order to reduce the risk of nephrotoxicity. The overall incidence of nephrotoxity of 1·5% in this study (compared to that of 10–30% reported in the literature) may be a consequence of these low trough concentrations (Moore *et al.*, 1984*a*; Humes, 1988). In conclusion, in critically ill adult and paediatric patients the amikacin volume of distribution is significantly increased and the elimination half-life prolonged. Due to considerable inter-patient variation dosage adjustments should be made according to serum levels. In order to achieve therapeutic peak levels and prevent toxic trough levels a single daily dose may be preferable. The routine use of a single-daily dosing regimen must, however, await the results of clinical trials.

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