# Pharmacokinetics of amikacin in febrile neutropenic pediatric patients with acute lymphoblastic leukaemia

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**The pharmacokinetics of amikacin was investigated in six oncohematologic pediatric patients who experienced neutropenia (<1,000/mm$^3$) and fever (>38°C) induced by cancer chemotherapy. The concentration of amikacin in serum was determined by fluorescence polarization immunoassay method using Abbott TDx system. Pharmacokinetic parameters were estimated with the help of computer software, PK II. Peak serum concentration of 36.30±4.03 µg/ml was observed. The values for $AUC_{0-\infty}$, $AUMC_{0-\infty}$ and MRT were concluded to be 76.20±6.30 µg.hr/ml, 190.26±31.61 µg.hr$^2$/ml and 2.15±0.62 hrs, respectively. The $t_{\frac{1}{2}\alpha}$, $t_{\frac{1}{2}elim}$, Cl and Vd were 0.04±0.02 hr, 1.76±0.55 hr, 18.85±5.11 ml/min and 0.19±0.11 l/kg, respectively. When the present values were compared with the literature-cited values in normal as well as in diseased populations, some similarities and differences were observed. Due to polemical values reported for normal population the modifications in amikacin pharmacokinetics in pediatric cancer patients has left inconclusive. Further appraisal is required to make a firm conclusion. [Turk J Cancer 2001;31(3):114-120]**

**Key words:  Amikacin, pharmacokinetics, oncohematologic,
pediatric patients, neutropenia**

Amikacin is extensively employed for the treatment of serious, complicated and recurrent infections due to its outstanding tolerance and excellent therapeutic activity (1). In combination with β-lactam antibiotics, amikacin is used in neutropenic patients with cancer at the onset of fever (2). A marked variability in pharmacokinetics of amikacin has been reported for specific patient sub-populations (3-7). This may lead either to sub-therapeutic concentration or increased chances of toxicity of the drug. Thus, therapeutic drug monitoring and amikacin dose adjustment according to serum-drug concentrations is an integral part for designing its optimum dosage regimen and is recommended in all

patients. This necessitates obtaining information on pharmacokinetics of amikacin in such target patients, which is scarce and not reported in local environment.

The aim of the study was to evaluate pharmacokinetics of amikacin in pediatric patients taking cancer chemotherapy for acute lymphoblastic leukaemia (ALL) and experiencing neutropenia with febrile episodes and to compare the present results with pharmacokinetic information drawn from the normal population. The additional aim of the study was to evaluate the pharmacokinetic equivalence of amikacin brands for switchibility but would be presented subsequently.

## Materials and Methods

Six pediatric patients with confirmed ALL aged 3 to 11 (5.7±3.76) years, weighing 11.5-21.5 (17.03±3.65) kg suffering from neutropenia ($<1,000/mm^3$) with febrile episodes, hospitalized at Shaukat Khanum Memorial Trust Cancer Hospital and Research Center, Lahore-Pakistan were recruited in this study. The legally authorized representative of each eligible patient was informed about the objectives of study and a written consent was obtained. This study was approved and performed according to the institution's local rules. Patients were excluded from the study if they had temperature <38ºC, participating in serum level measurement of ceftazidime within 2 hours of amikacin sampling collection and had renal insufficiency or required hemodialysis.

All the patients were also receiving chemotherapy regimen, along with empirical antibiotic therapy for febrile episode. In the empiric antibiotic therapy, amikacin was coadministered with ceftazidime, a β-lactam antibiotic.

Amikacin containing amikacin sulfate (Bristol-Myers Squibb Pakistan, Pvt. Limited, Karachi-Pakistan) was diluted in 5% dextrose and infused intravenously over a period of 30 minutes at a dose rate of 50-115 mg B.D.

In each case, 3 ml of blood was collected by infusion set following established good laboratory practices at 0.00, 0.08, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 and 12 hours after the start of i.v. infusion in heparinized glass tubes. The last sample at 12th hours was taken before subsequent amikacin dosing. The serum was separated by centrifugation and the samples derived from blood were refrigerated upon collection and stored frozen at 2-8°C or colder if not analyzed within 24 hours. Before analysis, each thawed sample was completely mixed.

Amikacin concentration in each 50 µl serum sample was measured with the help of TDx analyzer (Abbott laboratories, North Chicago) by utilizing fluorescence polarization immunoassay technology in hospital's pathology laboratory after calibration and validation of the instrument with amikacin reagents, calibrators and controls, respectively. The estimation of concentration in all samples was based on triplicate measurements after automatically carrying out of all initialization checks on the instrument. The values of polarization intensity were calculated, corrected for background intensities and converted to concentration units.

Serum level-time data of amikacin in each pediatric patient was used to calculate pharmacokinetic parameters of drug by employing an iterative non-linear, least square-weighted regression analysis using PK II (a computer program for PCK calculation MS DOS, ver 2.10, Borland Inc., U.K. 1988). The

choices between 1, 2, and 3 compartment models were determined by using minimum Akaike Information Criterion (MAIC) test which uses the Akaike information criteria (8,9). Mean values and standard deviation of mean of all parameters were calculated by using a computer program SPSS.

## Results and Discussion

There was no dropout of any patient during the study. Serum concentrations of amikacin in 6 patients following intravenous infusion over a period of 30 minutes of drug and pharmacokinetic parameter based on this data has been shown in table 1 and graphically in figure 1.

Use of 6 patients is insufficient and any differences from previous studies are difficult to interpret. Such limitations usually encounter during studies in target patients. However, such studies would be of empiric value.

**Table 1**
**Mean±SD serum concentration and pharmacokinetic parameters of amikacin after i.v. infusion of the drug in 6 cancer patients**

| Parameters | Values (Mean$\pm$SD) |
|---|---|
| Concentration ($\mu$g/ml) at hours | |
| 0.08 | $36.30 \pm 4.03$ |
| 0.25 | $27.68 \pm 2.60$ |
| 0.50 | $23.15 \pm 1.89$ |
| 1.00 | $19.33 \pm 0.67$ |
| 2.00 | $12.08 \pm 3.19$ |
| 4.00 | $4.37 \pm 0.79$ |
| 8.00 | $1.70 \pm 0.38$ |
| 12.00 | $0.41 \pm 0.23$ |
| $C_{max}$ ($\mu$g/ml) | $36.30 \pm 4.03$ |
| $AUC_{0-\infty}$ ($\mu$g.h/ml) | $76.20 \pm 6.30$ |
| $AUMC_{0-\infty}$ ($\mu$g.h$^2$/ml) | $190.26 \pm 31.61$ |
| MRT (hr) | $2.15 \pm 0.62$ |
| $t_{1/2\alpha}$ (hr) | $0.04 \pm 0.02$ |
| $T_{1/2elim}$ (hr) | $1.76 \pm 0.55$ |
| Cl (ml/min) | $18.85 \pm 5.11$ |
| Vd (l/kg) | $0.19 \pm 0.11$ |

Compartmental Model

According to the MAIC values implemented in PK II, amikacin serum concentration-time data in all patients fitted to a two compartment open model. In a preceding study, the pharmacokinetic of amikacin assumed one-compartment model in neonates with bacterial infection (10). However, as reported by Maller et al (11) a bi-compartmental approach is appropriate for describing pharmacokinetics of amikacin since triexponential equation is inapplicable due to undetectability of a slow terminal elimination phase in serum drug-concentration profile. On the other hand, a uni-exponential equation leads to erratic conclusions about the elimination rate of amikacin.

The exact reasoning of this variation cannot be presented. However, this may be attributed to fluctuations in volume of distribution (Vd) and modifications in the physiological and biochemical parameters under influence of disease. Use of different computational approaches for the calculation of amikacin pharmacokinetics can be added as a source of this variation.
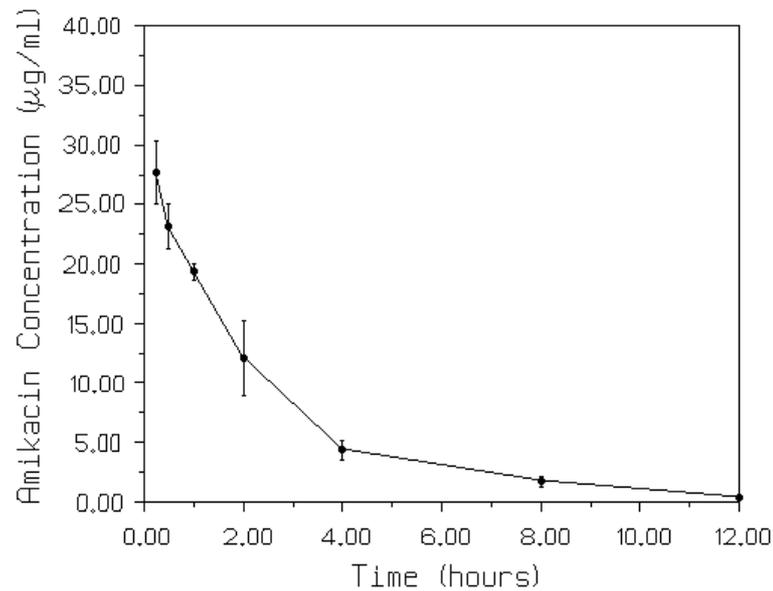


Fig 1. Mean±SD serum amikacin concentration in six cancer patients after i.v. infusion

Serum Concentration

Mean serum concentration of amikacin following short-term infusion in 6 pediatric patients in this study was measured as 36.30±4.03 µg/ml. The normal cited values of serum concentration of amikacin are 19 to 43.8 mg/l in children (12). The present value of amikacin concentration is in the same order of magnitude of 43.7±13.8 and 31.46 µg/ml observed in neutropenic and in cystic fibrosis pediatric patients, respectively (13,14). However, this value varied widely from 21 µg/ml in hematologic malignant patients (5).

These differences may be attributed to diseased condition and various patient factors (PFs). Reports suggest that the PFs, like renal function, fever, hematocrit value, lean body weight and age are related to amikacin elimination and thereby influence serum concentration (15).

Area Under Serum Concentration-Time Curve and Mean Residence Time (MRT)

The area under the curve ($AUC_{0-\infty}$) of amikacin in present study was observed to be 76.20±6.30 µg.hr/ml. Drug $AUMC_{0-\infty}$ was observed to be 190.26±31.61 µg.hr$^2$/ml. Amikacin dose, as indicated by value of mean residence time (MRT), persisted in body for a period of 2.15±0.62 hours. The values of MRT in normal and diseased conditions have not been cited in children; however, in normal adults it is 2.76 hours (16).

Half Life

The distribution half life ($t_{1/2\alpha}$) of amikacin was concluded to be 0.04±0.02 hrs. The value of these parameters has not been cited in any of the preceding study.

The present value for $t_{1/2elim}$ (1.76±0.55 hrs) is in agreement with the reported usual range of 0.68-2.10 hrs in children and 1.45 hrs in febrile neutropenic pediatric patients (12,14,17,18). However, this value is less than 3.0 and 3.8±2.4 hrs in patients with hematologic malignancies (5,6). The $t_{1/2elim}$ in pediatric population is reported to be briefer than those in diseased adult population on accounts of a larger Vd and a faster clearance in infants and children (19,20).

Body Clearance

Wide variations were observed particularly for body clearance (Cl) when its values (18.85±5.11 ml/min) were compared with the cited values in normal as well as in diseased populations. The normal reported value for this parameter is 155 ml/min/1.73 m$^2$±17.4 in children (12). The amikacin is primarily eliminated by glomerular filtration and thus modifications in renal function should directly affect the drug's clearance. A large amount of variance in clearance of drug has also been explained by modifications in creatinine clearance (21). The Cl is also reported to be increased in cancer patients (5).

Volume of Distribution

The current value of volume of distribution (Vd) of amikacin was observed to be 0.19±0.11 l/kg. The normal values for this parameter have been mentioned as 0.27±0.04 l/kg in children (12). From other reports, the value of Vd has been varied from 0.38 and 0.41 l/kg in cancer patients (3,5,6).

Aminoglycoside antibiotics distribute to a volume similar to the extracellular fluid compartment (22,23). The Vd of amikacin is reported to be markedly elevated in hematologic malignancies compared with normal (3-5). This has been attributed to substantial changes in extracellular fluid compartment in patients with severe sepsis as a result of changes in state of hydration (23,24). Davis and coworkers (6) attributed this increased Vd due to lower serum albumin concentrations by an unknown mechanism. But, according to them, it may be due to low venous oncotic pressure that results in increased extracellular fluid. Since aminoglycosides are distributed readily to that space, the Vd would be increased in sepsis-induced hypoalbumineamia.

The Vd of amikacin is reported to have a substantial effect on its peak serum concentration and consequently, the dosage requirements of amikacin (24,25). In patients with contracted volume, lower dosages while for that with

expanded volumes, larger dosages of amikacin are needed to achieve desired peak levels (21). Increase in Vd and Cl causes a sub-therapeutic serum amikacin concentration if dosage adjustment of the drug is not made (6). In our study, both parameters are seemed to be descended as compared to normal reported values, however, more data and studies are needed to confirm these results.

## Conclusion

The results of present study validate the importance of obtaining information on amikacin pharmacokinetics in target patients because except few observed parameters, all were, both different and more variable than those observed in normal and diseased populations. Polemic values of pharmacokinetic parameters cited for normal and diseased conditions made a firm inference difficult. The varied parameters seemed to be of sufficient magnitude to be clinically significant. Since accurate dosage adjustment of a drug is needed to avoid possibilities of its ineffectiveness, resulting in unnecessary costs and occasionally predisposing patients to a higher risk of toxicity, further studies with more number of patients are needed in target patients in order to ensure conclusive results (22). This will help in defining more precisely optimal peak concentrations of amikacin that provide the greatest effectiveness with least toxicity.

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