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**Original Articles**

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**GENTAMICIN THERAPY IN PRETERMS: A COMPARISON OF TWO DOSAGE REGIMENS****Lalitha Krishnan and S.A. George**

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**Objective:** To compare the pharmacokinetic profile of gentamicin given as a once daily dose as against the conventional twelve hourly dose in preterm neonates. **Design:** Randomized double blind study. **Setting:** Tertiary level Neonatal Intensive Care Unit. **Subjects:** Eighteen preterms admitted during the period January 1994 to May 1994. **Methods:** The babies were randomly assigned to receive either the once daily (plan O, 4 mg/kg Q 24 h) or the conventional (plan C, 2.5 mg/kg Q 12 h) gentamicin dosage regimen. Blood was collected for the first peak level one hour after the first dose of gentamicin. Trough and peak-2 levels were collected before and one hour after the dose due at 48 hours, respectively. Assays were done using fluorescence immunoassay and the pharmacokinetic estimations were calculated using the three measured levels on a simplified one-compartment open model. Serum concentration time curves were plotted using the computerized Bayesian forecasting. Student Y and Mann-Whitney U tests were applied as required. **Main outcome measures:** Initial peak levels and steady state trough and peak levels in both groups. **Results:** Optimum therapeutic peak level after the first dose was achieved only with the once daily gentamicin regimen (mean level 5.88 vs 3.88  $\mu\text{g/ml}$   $p = 0.000$ ). Mean trough levels remained over 2  $\mu\text{g/ml}$  in the conventional regimen (2.76 vs 1.96  $\mu\text{g/ml}$   $p = 0.019$ ) group. Mean peak levels at the steady state were not significantly different in either regimen (6.65 vs 5.45  $\mu\text{g/ml}$  in conventional  $p = 0.177$ ). None of the neonates showed nephrotoxicity. **Conclusion:** Once daily dose (4 mg/kg) of gentamicin has logistic and monetary benefits in addition to the obvious pharmacokinetic advantage.

**Key words:** Dosage Gentamicin, Preterm neonates.

**G**ENTAMICIN, in combination with beta-lactam antibiotics, has been widely used in neonates with suspected or documented Gram negative bacterial infections. It exhibits a narrow range between toxic and therapeutic dosages but in developed countries measurement of serum gentamicin levels has led to its more effective usage(1). Bacterial activity of

aminoglycosides is dependent on plasma concentration of the drug and peak concentration over 5  $\mu\text{g/ml}$  in the first 24 hours is associated with improved therapeutic response in life threatening bacterial infections(2). Studies have also illustrated that because of longer elimination half lives of aminoglycosides in neonates, daily dose regimens may be less toxic and more

effective in this age group(3,4). Data on once daily gentamicin has been reported in term babies(5) but little information is available in preterms.

Although gentamicin is very liberally used in neonates in the developing countries, levels are rarely measured in babies due to limited availability of the technique and prohibitive cost. Only one report has so far appeared in literature from the Indian sub continent in this context(6). The aim of the present study was to compare the pharmacokinetic profile of gentamicin in bigger preterm neonates (32-36 wks) who were assigned to receive either once a day or twice daily regimen.

### Subjects and Methods

Eighteen neonates admitted to the Neonatal Intensive Care Unit of the Kasturba Hospital, Manipal during the period January to May 1994 formed the material for the study. The inclusion criteria were neonates requiring gentamicin therapy as per unit protocols, those who were between 32-36 weeks gestation and aged less than 96 hours at start of therapy. The serum creatinine was below 1 mg/dl before therapy. The infants had not received gentamicin previously and their mother also had not received gentamicin before delivery. Babies were randomly assigned to receive one of the two gentamicin dosage regimens: (i) Conventional (Plan C): 2.5 mg/kg every 12 hours; and (ii) Once daily (Plan O): 4.0 mg/kg every 24 hours.

All doses were given by the intravenous route. Gentamicin was followed by a beta-lactam antibiotic (ampicillin, cloxacillin, crystalline penicillin or ceftazidime) in all cases. Only one brand (Schering 10 mg/ml) was used for all babies. The required dose, was given as a one minute bolus into existing intravenous lines, followed by a flush with 0.5 ml normal saline.

Blood collection for gentamicin levels was done as follows: (i) Peak-1: Blood collected one hour after first dose; (ii) Trough: Blood collected just prior to the dose of gentamicin due at 48 hours after start of therapy; and (iii) Peak-2: Blood collected one hour after the dose given at 48 hours.

The plasma was immediately separated and stored at  $-20^{\circ}$  C. Estimation of levels was done using the TDX analyzer(7) (Abbott Laboratories, Abbott Park, III 60064, USA). The pharmacokinetic estimations were calculated using the three measured levels and the single compartment open model(8). The serum concentration time curves were plotted for each neonate separately using the computerized Bayesian forecasting.

Clinical data and investigation values were stored on DBase III programme. The computer fitted graphs were generated by the Pharmacy Department, Hospital for Sick Children, Toronto, Canada. Analysis of data was done on the Statistical Package for Social Sciences (SPSS/PC+) and EPI Info 5.0.

### Results

A total of 18 preterms were studied. The characteristics of the study population are given in *Table I*. The median age of commencement of gentamicin was 2 h vs 5 h in Plan O and Plan C, respectively and the mean serum creatinine levels in the two groups were 0.52 and 0.57 mg/dl, respectively. The mean peak and trough levels in the two groups are shown in *Table II*. There was no nephrotoxicity in either group at the end of therapy. Samples of the computer generated graph for a typical baby in each group are shown in *Figs. 1 & 2*.

### Discussion

This prospective randomized study compared the pharmacokinetics of once

daily (Plan O) regimen in preterms to the conventional (Plan C) twice daily regimen. All levels were measured in the first week of life and hence the discussion may

pertain only to the early neonatal period. More work will have to be carried out in older neonates before giving once daily gentamicin in that group. Most studies on neonatal dosage of gentamicin have focussed on achieving trough concentration

**TABLE I - Characteristics of the Study Population.**

Characteristic	Plan C	Plan O
No. of babies	9	9
Male: Female	6:3	7:2
AGA:SGA*	6:3	7:2
Inborn:Outborn	8:1	6:3
Mean birth weight(g)	1739	1940
Standard deviation	527	510
Mean gestational age(wks)	34.0	34.1
Standard deviation	1.9	1.5

\*AGA=Appropriate for gestation; SGA=Small for gestation

**TABLE II - Serum Gentamicin Levels in Two Groups.**

Gentamicin levels (Hg/ml)	Plan C	Plan O	p value (two tailed)
MeanPeak-1	3.88	5.88	0.000
SD	0.76	1.10	
Mean Trough	2.76	1.96	0.019
SD	0.70	0.60	
MeanPeak-2	5.45	6.56	0.177
SD	1.67	1.66	

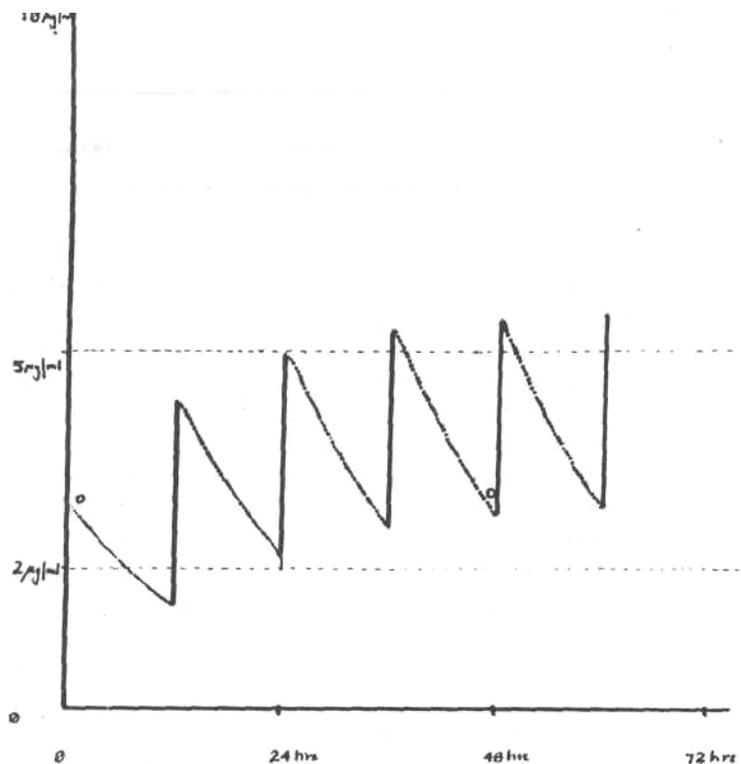


Fig. 1. Serum concentration time curve in a baby on twice daily dose of gentamicin (Plan C).

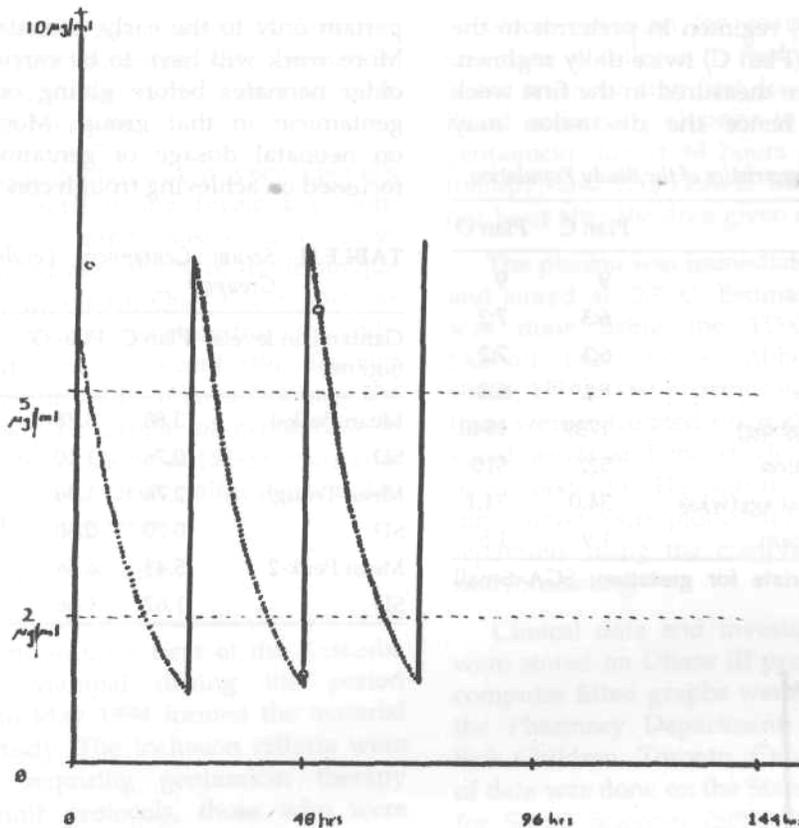


Fig. 2. Serum concentration time curve in a baby on once daily dose of gentamicin (Plan O).

of 2  $\mu\text{g/ml}$  or less(9) because levels above this are considered to cause nephrotoxicity. Also, bactericidal activity of gentamicin is dependent on plasma concentration and higher peak concentrations are associated with improved therapeutic response in life threatening bacterial infections(10). It is generally accepted that peak serum concentration of  $> 5 \mu\text{g/ml}$  are necessary for bactericidal efficiency (2). Most dosing guidelines do not address the need to achieve therapeutic peak concentration above 5  $\mu\text{g/ml}$  early in the therapeutic course. Moore(2) reported a 20% increase in mortality in Gram-negative sepsis if serum gentamicin levels do not exceed 5  $\mu\text{g/ml}$  in the first 24 hours. This has been seen by others as well(11). Gal(12) demonstrated

the achievement of adequate therapeutic levels with a loading dose of gentamicin (5  $\mu\text{g/ml}$ ) followed by the conventional dosage. Skopnik(5) evaluated the pharmacokinetics of once daily gentamicin (4 mg/kg) in term neonates and found that good peak levels were achieved and the trough levels were never toxic. These results compare with our observations (Table II).

Trough levels in the present study remained over 2  $\mu\text{g/ml}$  in the conventional regimen as has also been reported by others(5,13,14). This has been explained by pharmacokinetic data which indicate that elimination half lives are longer in neonates(4). None of the once daily dose babies had trough levels in the toxic range.

The steady state peak levels were not very different in the two groups as has also been seen by others(5).

In this study gentamicin was infused as a bolus over one minute as recommended earlier(15) and none of the initial peak levels rose over 10  $\mu\text{g}/\text{ml}$  in both groups. Continuous low dose infusions have been proved to be more nephrotoxic especially in preterm neonates(16). All the babies in this study received only intravenous gentamicin but other workers(6) have shown that pharmacokinetics of intramuscular gentamicin is comparable to the intravenous route. Since most neonates who receive gentamicin in India do so by the intramuscular route, the results of this study may be extended to them as well.

In conclusion, the results of this study indicate that once daily dosage regimen of gentamicin in preterm neonates (32-36 weeks) guarantees initial peak serum concentration above the minimal inhibitory concentration of Gram negative bacteria and trough concentration below potentially toxic levels of 2  $\mu\text{g}/\text{ml}$ . Thus switching over to once daily dose (4 mg/kg) of gentamicin will have logistic and monetary benefits in addition to the obvious pharmacokinetic advantage.

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