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Research Article

GENTAMICIN POPULATION PHARMACOKINETICS IN INDIAN PEDIATRIC PATIENTS

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ABSTRACT

Objective: The objective of this study was to characterize gentamicin population pharmacokinetics (PKs) in Indian pediatric patients.

Methods: Population PK analysis was performed with nonlinear mixed-effect model software. The data set was inspected using both first order (FO) and FO conditional estimate (FOCE) methods by the inclusion of both patient and pathological conditions.

Results: A total of 26 patients were involved in this study with 54 observations. The patient covariates, including body weight, gender, age, and creatinine clearance (CLCR), were analyzed in a stepwise fashion to identify their potential influences on gentamicin PKs. The final model gives the clearance (CL) and volume of distribution (V) by FO method as CL=θ1*(CLCR/35.14)+θ3*(WT/14.25)+θ5*(AGE/6.14)*EXP(θ1), V=θ2*(WT/14.25)+θ4*(CLCR/35.14)+θ6*(AGE/6.14)*EXP(θ2) and by FOCE method as CL=θ1*(CLCR/35.14+)θ3*(AGE/6.14)*EXP(θ1), V=θ2*(WT/14.25)+θ4*(CLCR/35.14)+θ6*(AGE/6.14)*EXP(θ2).

Conclusion: The final model estimates of CL and V were 0.0014 L/hr/kg and 0.646 L/kg, respectively, and by FOCE method were 0.0014E-06 L/hr/kg and 0.774 L/kg, respectively. These parameters will be helpful in individualizing the loading and maintenance doses in pediatric patients.

Keywords: Population pharmacokinetics, Gentamicin, Nonlinear mixed-effect model, Pediatrics.

INTRODUCTION

Gentamicin is the most frequently used aminoglycoside antibiotic in the prevention and treatment of serious Gram-negative infections. This can be attributed to their efficient bactericidal nature, a low development rate of resistance, synergistic effect with other antibiotics, postantibiotic effect, and their low cost [1]. Nevertheless, the clinical use of aminoglycosides is restricted by their potential nephrotoxicity and ototoxicity. The therapeutic range of gentamicin is marked by values between 5-10 mg/L in serum. The therapeutic efficacy of gentamicin is conformed to the peak serum concentration and the adverse effects to the trough concentrations. The clinical response rate increased to 90% with a peak to minimum inhibitory concentration ratio of 10:1 [2]. It is recommended that trough concentrations of gentamicin be kept below 1-1.5 μg/mL [3,4]. However, there is a correlation between the toxicity and length of treatment and that's why nowadays treatment modalities of gentamicin have changed from multiple dosing to once-daily administration [3].

The once-daily administration of aminoglycosides compared to 2 or 3 times a day is beneficial in reducing the renal toxicities in patients [5]. Recent studies by van Maarseveen *et al.* concluded that the time of administration of aminoglycosides has no effect on the pharmacokinetics (PKs) and/or the incidence of nephrotoxicity. Hence, it is advised that the therapy should be started immediately after severely hospitalized infectious patients and later the maintenance doses should be optimized with therapeutic drug monitoring for efficacy and toxicity balance [6]. Extended interval dosing of gentamicin in pre-term infants [7] and neonates [8] has been shown to be safe, provides gentamicin levels in desirable levels and requires fewer dosage adjustments than the conventional interval dosage schedule. A recent study concluded that gentamicin dose of 8 mg/kg is great likely to achieve peak concentrations >16 mg/L in critically ill children and will require dose intervals >24 hrs; thereby, therapeutic drug monitoring is essential [9]. Even gentamicin in pediatric febrile neutropenic patients at a dose of 7 mg/kg once daily does not provide desired levels [10]. Further study is required to guarantee that once daily gentamicin administration for pediatric oncology patients provide adequate clinical success [11]. Preterm and term newborn infants show broad inter individual variability in PK parameters of gentamicin. Considerable knowledge and use of anticipatory covariates could lead to quicker attainment of therapeutic concentrations and a reduced need for concentration monitoring [12]. Dosing table was proposed for the individualization of gentamicin extended interval dosing in neonates for better prediction of peak and trough concentrations early in the treatment [13]. However, selection of the dose was based on the PK data derived from a general patient population and is likely to be insufficient to achieve target peak drug concentration in critically ill patients owing to differences in PKs [14].

Extensive work on gentamicin population PKs was carried out in various populations[15-17]. The paucity of PK data of many drugs in neonates, infants, and children is related to blood sampling restrictions in this population. One way to dodge this problem is to collect sparse samples from many individuals and study the data by means of a population-based approach. Because PK parameters for gentamicin are completely distinguished by large intra- and inter-individual variability, it is necessary for serum concentrations to be monitored for gentamicin to attain target concentrations. The monitoring of serum level data and interpretation within the clinical context allows the clinician to establish a reasonable individualization of the dosing schedules. Dosage accommodation based on individual PK parameters is of significant importance for effective and safe use of drugs.

Population PKs is the study of the sources and parallels variability in plasma drug concentrations between individuals illustrative of those in whom the drug will be used clinically when pertinent dosage regimens are administered [18]. Population PKs solicits to discover which definite pathophysiological factors cause alteration in the dose-concentration relationship and to what degree so that the suitable dosage can be recommended. Sheiner *et al.* have developed a computer

program, nonlinear mixed effects model (NONMEM) that used routine clinical PK data to approximate population PK parameters [19,20]. This approach appraises the influence of fixed effects (age, gender, weight, race, etc.) on PK parameters and the inter-individual variability of these parameters. In addition NONMEM estimates non-persistent variability, which may result from intra-individual variability, measurement errors and model misspecification. A relatively large number of patients are required for this method but it does not require a large number of drug concentrations per patient. But no such study was undertaken in Indian population, and there are no reports of population PKs of gentamicin in Indian pediatric patients. Hence, to produce typical population values of clearance and volume of distribution of gentamicin in Indian population we have undertaken this work.

METHODS

Patient selection

The patients admitted to the Pediatric ward of M.G.M. Hospital, India between the ages of 1-12 years of either sex were included in the study. Informed assent was obtained from the parents of the patients to participate in the study. Institutional Ethics Committee authorization was taken before initiation of the study. Demographic data was collected from the patients, which included name, sex, age, height, weight, disease status, concomitant diseases, and concomitant medications taken along with gentamicin.

This study included 26 (14 were males and 12 females) Indian pediatric patients, who were on long-term intravenous therapy with gentamicin. After reaching the drug to steady state, few blood samples (1-3) from each patient were collected at different time points (0-9 hrs). The collected samples were stored at −80°C until further analysis was carried out. Serum samples containing gentamicin were analyzed by microbiological assay.

Assay procedure

Serum samples containing unknown concentrations of antibiotic were diluted at 1:2, 1:4, and 1:5 in sterile pooled human serum. Seeded agar plates were used, each with two bores filled with the reference standard and two bores filled with the patient's undiluted or diluted serum. The plates were incubated for 4 hrs at 37°C. Zone diameters of the reference standard and patient's serum were measured and averaged. Correction of the zone diameter was completed by adding or subtracting the difference between the mean zone diameter of reference standard obtained in the assay plate and zone diameter of the correction point of 6 µg/mL in the standard curve. A calibration curve in the range of 0.5-50 µg/mL was established (R^2=0.9898) in serum matrix. The final result (µg/mL) was derived from the standard curve and multiplied by the dilution factor.

Serum creatinine test

Serum creatinine test was performed by modified Jaffe's method using monozyme creatinine kit [21].

Pharmacostatistical analysis

The population PK study was performed using Wings for NONMEM (WFN, Icon Development Solutions; Version VI) developed by Dr. Nick Holford, with FORTRAN power station compiler. Data files were created using excel and notepad. All the demographic data, the concentration of gentamicin obtained at different time intervals were used in the compilation of the data sheet.

PK model

The base model of the study was prepared using two-compartment linear model using the subroutine ADVAN3 in PREDPP module. PK parameters such as clearance (CL), volume of distribution (V), and elimination constant was calculated by CL/V, and half-life (t ½) was calculated as 0.693/K. Initial parameter estimates were obtained from the previous studies conducted.

Statistical model

The constant coefficient of variation error model reported the inter-individual variability best. A preliminary investigation was conducted using NONMEM to calculate the parameters of the base model (without addition or deletion of covariates). The influence of all covariates (age, weight, sex, creatinine clearance [CLCR]) seen. Each covariate was added to the base PK model and the distribution of plotted weighted residuals and objective function value noted. A forward stepwise model, where each covariate added individually resulted in drop in objective function value, were added cumulatively to the model. This process was continued until no further diminution in the objective function value resulted. Finally, a backward elimination step was executed by placing the coefficient of each covariate to zero and considering the change in the objective function value. The constant coefficient of variation error model delineated the inter-individual variability best. A decrease in objective function of 3.8 or greater after introduction of a single covariate into the model was regarded statistically significant ($p<0.05$) using the χ^2 distributions if the 95% confidence intervals for the estimate did not incorporate the null value. A backward elimination step was then performed to remove covariates from the full model to develop the final model. An increase in the objective function value 3.8 or greater ($p<0.05$) on withdrawal of a covariate from the full model demonstrated that the variable was significant and that covariate was retained in the final model. The data set was studied using conventional first order (FO) method which is default (Method 0) and FO conditional estimation (FOCE) method (Method 1).

RESULTS

A total of 26 patients were involved in the study with 54 observations. All the necessary information of the patients were collected in the patient data sheet (Table 1). There was a wide distribution of demographic features of patients under study. A constant coefficient of variation error model delineated the inter-individual variability best. The strength of the association between various covariates such as body weight, CLCR, age, and sex, etc., was shown by forward addition and backward elimination during covariate screening.

FO method

In the initial screening phase covariates such as total body weight, CLCR, age, and sex reduced the objective function. In the forward stepwise model building process, the cumulative inclusion of weight, sex, age, CLCR reduced the objective function by 31.3 ($p<0.01$). Finally in the backward elimination phase, only weight surpassed the objective function by 27.9 ($p<0.01$) when it was omitted individually from the model. The above investigation resulted in statistically significant associations between weight and V. The addition of other covariates also influenced the minimum objective function, but not statistically significant. However, the inclusion of weight, CLCR and age as a covariate in clearance and volume of distribution resulted in a drop in the objective function along with improvement in parameter estimates. This model also resulted in a decrease in residual variability. Scatters were improved and PRED versus DV and WRES plot patterns suggested that the model was complete. The parameter estimates obtained using the final model were given in Table 2 and the diagnostic plots were shown in Figs. 1 and 2.

The final structural model:

$$CL=\theta1*(CLCR/35.14)+\theta3*(WT/14.25)+\theta5*(AGE/6.14)*EXP(\theta1)$$

$$V=\theta2*(WT/14.25)+\theta4*(CLCR/35.14) + \theta6*(AGE/6.14)*EXP(\theta2)$$

Table 1: Patient characteristics (N=26)

Parameter	Range	Mean±SD
Age (years)	0.58-11	6.13±2.71
Body weight (Kg)	5.5-22	14.25±4.37
Dose (mg)	10-60	37.5±13.05
Serum level (µg/ml)	0.22-35	12.24±10.7
Sampling time (hrs)	0.16-8.5	2.98±2.46

Range and mean (±SD) values for patients under study. SD: Standard deviation

FOCE method

In the preliminary screening phase covariates such as weight, CLCR, age reduced the objective function value. In the forward stepwise model building process, cumulative inclusion of weight, age, CLCR reduced the objective function by 28.68 ($p<0.01$). The addition of other covariates could not influence the minimum objective function value significantly. However, the inclusion of CLCR and age as covariates in CL and weight, CLCR and age as covariates in V caused drop in the objective function value along with improvement in parameters. This gave reasonably good output with appropriate estimates of clearance and volume of distribution. Scatter plots were improved, and PRED vs. DV and WRES plots pattern suggested that the model was complete. The parameter estimates obtained using the final model were given in Table 3 and the diagnostic plots were shown in Figs. 3 and 4.

The final structural model was:

$CL=\theta1*(CLCR/35.14+)\theta3*(AGE/6.14)*EXP(\theta1)$

$V=\theta2*(WT/14.25)+\theta4*(CLCR/35.14)+\theta6*(AGE/6.14)*EXP(\theta2)$

DISCUSSION

Population PK of gentamicin in pediatric patients using NONMEM was undertaken first time in India. This study population was representative of the pediatric patient population. Hence, the population parameters obtained in this study can be used in optimizing the dosage of gentamicin for individual patients in India. This will not only decrease the incidence of adverse drug effects but also help in cost-effective long-term drug therapy. A major feature of population approach is that sparse kinetic data from a large number of patients can be successfully analyzed in conjunction with factors (covariates), which may influence drug disposition. Investigation on the influence of various fixed effects parameters on gentamicin clearance and volume of distribution in Indian population was performed and it resulted in possible final regression models related to population values of CL and V.

The PKs of gentamicin investigated extensively in various populations and contrasting data published regarding the most relevant PK model. One compartment model [15,22,23] has been usually employed in clinical setting, although many studies reported that the PKs of gentamicin was better distinguished by a 2 compartment

Table 2: Parameter estimates of final model, FO method

Parameter	Meaning	Estimation
θ1	Coefficient (CL)	1.45E-03
θ2	Coefficient (V)	6.46E-01
θ3	Power for weight (CL)	1.53E-08
θ4	Power for CLCR (V)	5.36E-01
θ5	Power for age (CL)	9.01E-04
θ6	Power for age (V)	1.95E-01
ω1	Inter-patient variability (CL)	1.42E+04
ω 2	Inter-patient variability (V)	4.94E-08
ε2	Residual error	4.83E-01

FO: First order, CLCR: Creatinine clearance

Table 3: Parameter estimates of final model, FOCE method

Parameter	Meaning	Estimation
θ1	Coefficient (CL)	1.48E-09
θ2	Coefficient (V)	7.74E-01
θ3	Power for age (CL)	1.28E-08
θ4	Power for CLCR (V)	5.08E-01
θ6	Power for age (V)	2.17E-01
ω1	Inter-patient variability (CL)	1.17E+00
ω2	Inter-patient variability (V)	8.45E-02
ε2	Residual error	5.94E-01

FOCE: First order conditional estimate, CLCR: Creatinine clearance

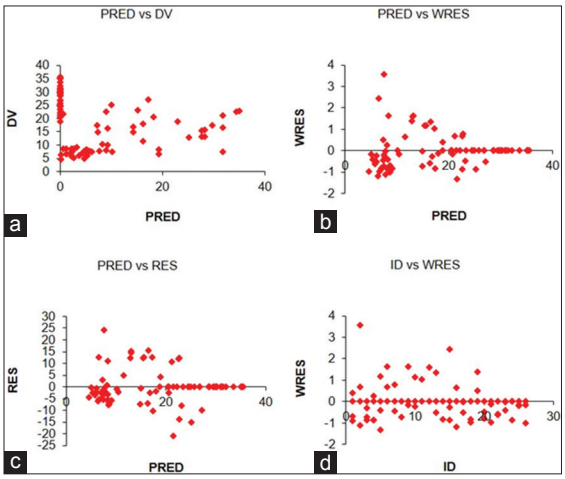

Fig. 1: (a) Scatter plot of predicted versus observed plasma gentamicin concentrations (first order [FO] method). (b) Scatter plot of predicted plasma gentamicin concentrations versus WRES (FO method). (c) Scatter plot of predicted plasma gentamicin concentrations versus residuals (FO method). (d) Scatter plot of WRES versus ID (FO method)

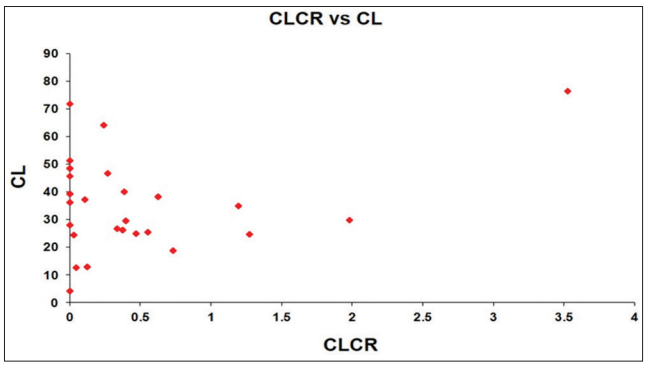

Fig. 2: Scatter plot of creatinine clearance versus clearance

model [17,24-29] and also by a 3 compartment model [12]. In our study also, 2 compartment model better delineated the PKs of gentamicin in the population studied. This statement was further substantiated by netilmycin, a gentamicin related aminoglycoside, that 2 compartment model better predicted the PKs compared to other models [30].

In our study, the main physiological variables that may influence gentamicin disposition in infants and children have been investigated. All the covariates, body weight, age and CLCR except sex have shown influence on clearance and volume of distribution of this population. Gentamicin CL and V are different in neonates, infants and adults, indicating wide interindividual variability. Gentamicin is a polar compound with low protein binding and infers that V directly related to the extracellular body fluid. As the age increases, compartmentalization of body water changes continuously, resulting in higher volume of distribution in newborns and infants compared to older children. The mean values obtained in this study were 0.646 l/kg (FO) and 0.774 l/kg (FOCE) are high compared to previous studies in infants, children and adults given IV gentamicin have found estimates of volume of distribution to be ≈ 0.2-0.5 l/kg [25,27,31-34]. The increased volume of distribution in this population because of the age groups we studied falls in the range of infants and children. Moreover, in critically ill and septic patients there is an increased V. The principle covariates that affected the volume of distribution of gentamicin are current body weight and conformed sepsis [35]. Hence, in this situation, larger doses need to be given to achieve therapeutic concentrations in critically sick neonates [26] and in critically sick adults [36-41]. Studies by

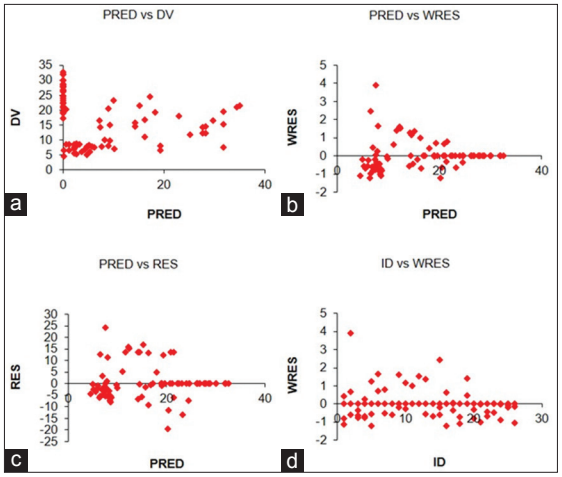

Fig. 3: (a) Scatter plot of predicted versus observed plasma gentamicin concentrations (first order conditional estimate [FOCE] method). (b) Scatter plot of predicted plasma gentamicin concentrations versus WRES (FOCE method). (c) Scatter plot of predicted plasma gentamicin concentrations versus residuals (FOCE method). (d) Scatter plot of ID versus WRES (FOCE method)

Susanna E. Medellin-Garibay that for infants, total body weight and CLCR displayed an influence on volume of distribution and clearance of the drug [29]. Volume of distribution of the central and peripheral compartments was also associated to body weight [30].

In this study, gender or sex did not exert any influence on the PKs of gentamicin, which was an accordance with other studies [42]. Another study carried out on the population PKs of gentamicin in patients with cancer by Rosario *et al*. that gender when included as a single covariate was associated with a remarkable influence on clearance but, in the final clinical factor model, the effect of gender was not significant. One probable explanation is that any gender difference is already taken into account via the difference in body surface area. Another study carried out on population PKs of gentamicin in South African Newborns by Botha *et al*. values of CL, half-life were 0.042 l/hr/kg and 8 hrs while V was 0.472 l/kg for all patients. The final model describing both CL and V included birth weight. In addition to weight, serum creatinine, gestational age, and gender influenced the gentamicin clearance. In our study also clearance influenced weight, age, and CLCR except gender.

Gentamicin is excreted mostly by glomerular filtration, and the maturation of renal system differs in neonates, infants, children, and adults thereby influencing the disposition of gentamicin [43,44]. A significant association has been demonstrated between gentamicin CL and CLCR [45]. For this reason, it was reasonable that CLCR acts as an important covariate in the gentamicin clearance equation. For the population in the current study, mean gentamicin CL obtained was 0.014 l/hr/kg by FO method and 0.014E-06 l/hr/kg by FOCE method. These values are very less compared to literature values [12,17,28]. In this population, CL was influenced by age, body weight, and CLCR. Another study of population analysis of netilmycin by Fattinger *et al*. agreed that clearance depended on body weight, both gestational and post-natal age [30]. This was in accordance with the study carried out by Mathews *et al*. In their study, the addition of weight, age, and sex and serum creatinine as covariates reduced the random component between subject variability in clearance (CL) from 94% to 36% of population parameter variability. Population PKs of gentamicin orchestrated in premature and term neonates concluded that clearance was influenced by body weight, both gestational and post-natal age [12,28]. The average population estimates of clearance were 4.21 l/hr and volume of distribution was 24.61 lt (0.38 l/kg). Gentamicin clearance was decreased in patients suffering with hypoxic ischemic encephalopathy [46]. In addition, critical illness often results in a variable degree of organ dysfunction, which may include decreased

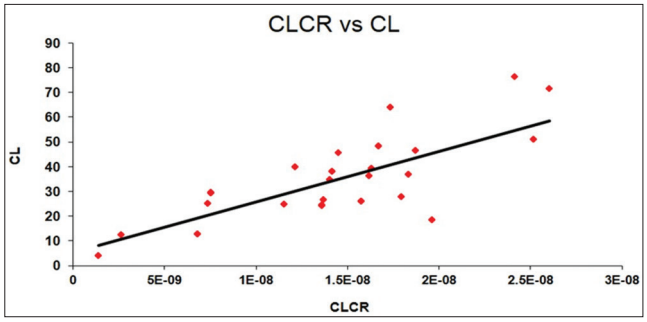

Fig. 4: Scatter plot of creatinine clearance versus clearance

renal function and consequently a reduced clearance as gentamicin primarily eliminated by kidneys.

In our study age as a covariate has an effect on both clearance and volume of distribution along with other covariates in reducing the minimum objective function which was significant statistically. The FO method gave comparable clearance results to other populations than FOCE method. The range of serum concentrations obtained in different patients was 0.22-34.96 (12.24) µg/mL. These values are somewhat higher than the values of the previous literature. This may be due to the low average values of the CLCR (35.14 mL/minutes), differences in the protein binding and differences in the metabolic enzymes of our population with that of other population.

CONCLUSION

Using NONMEM software, population PK parameter estimation was performed using both FO and FOCE methods. Final PK models were developed and influence of various covariates on CL and V studied. The estimates of CL and V generated in the final model were 0.0014 l/hr/kg and 0.646 l/kg, respectively, using FO. The estimates of CL and V generated in the final model were 0.0014E-06 l/hr/kg and 0.774 l/kg, respectively, using FOCE. The developed models may form the basis for expanding improved treatment guidelines of gentamicin in this population.

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