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Population pharmacokinetic analysis of amikacin and validation on neonates using Monte Carlo method[1]

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KEY WORDS pharmacokinetics; Bayes theorem; computer simulation; reproducibility of results; Monte Carlo method; amikacin; newborn infant; drug administration schedule

ABSTRACT

AIM: To make programs for population pharmacokinetic analysis and to assess the ability of this method in pharmacokinetic parameter estimation and in the prediction of serum concentrations. **METHODS**: Data of amikacin as a model drug were collected from 42 neonates with 142 serum samples. A one-compartment open model was used to describe the kinetics of amikacin after the intravenous infusion. Following Sheiner's idea of population pharmacokinetics, we made the programs to evaluate population parameter and individual parameter. The target function minimality was obtained from Monte Carlo algorithm. The validation of the population analysis was performed using classic pharmacokinetic program 3p87 for antitheses. The predictability of the developed method was evaluated by computing precision and accuracy of serum concentration predicted using the parameter estimates. **RESULTS**: The stability of our self-made program was good. The population parameters obtained from this approach were in conformity with those from 3p87, and the interindividual variability was relatively small. For the learning sample and the validation sample, predicted and observed concentrations were all close with correlation coefficient 0.995 and 0.990, respectively. Most of predicted errors were found $< \pm 1$ mg/L, and *RMSD* and *BIAS* were 0.58 and -0.07 for the validation sample, respectively. The choice of blood sampling time was an important factor for the predictive performance. An early sampling time after the infusion was observed to be the best sampling time. **CONCLUSION**: The estimation program of population parameter and individual parameter made by us ran stably, and allowed us to use sparse data to estimate population pharmacokinetic parameters. It provided accurate estimates of these parameters and satisfactory ability of serum concentration prediction. Therefore, it can be used for the population pharmacokinetic analysis and individualization of dosage regimen.

INTRODUCTION

Dosage adjustment based on individual pharmacokinetic parameters is of considerable importance for effective and safe use of drugs with narrow therapeutic range. In routine clinical therapy, taking multiple blood samples from a patient is always difficult not only due to economic restriction but also on ethical grounds. To overcome this practical problem, numerous studies have been performed. The Bayesian feedback method allows us to estimate individual parameters using a very limited number of measurements such as one or two points, and has been reported to be more useful than other non-Bayesian methods using a small number of samples[1]. The performance of such methods depends on good estimates of the distributions of the population parameters (mean and variances)[2]. Up to now the more currently available population software package for this purpose has been the nonlinear mixed-effect model (NONMEM). Successful application of this approach has been described for several drugs, zidovudine[3], cisplatin[4], lamotrigine[5], amiodarone[6], terfenadine[7], vancomycin[8], perfloxacin[9], and so on. But, NONMEM program is very expensive to use. At present there is no suitable program for population pharmacokinetics analysis. The purpose of this study was, using the Monte Carlo algorithm, to creat an estimation program for population and individual pharmacokinetic parameters. Amikacin was used as a model drug to validate the accuracy of this method.

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MATERIALS AND METHODS

Data The data comes from the neonates hospitalized in our hospital. All patients received amikacin for severe infections at a dosage of 7.5 – 10 mg/kg by a single intravenous infusion. During the trials, 2 – 4 serum samples were collected for each patient at different intervals from the time of administration. Concentration of amikacin collected from the samples was measured by fluorescence polarization immunoassay (FPIA) method using TDX from Abbott Corp. Analyses of quality control samples showed a constant coefficient of variation of <5 % and recovery of 100.3 % ± 2.5 % for this analytical method.

The subjects were randomized into 2 groups: the first, the learning sample, constituted of about two third of the samples (30 subjects totaling 94 concentrations) and was intended for the estimation; the second, the validation sample, constituted of about one third of the samples (12 subjects totaling 48 concentrations) and was intended for the validation.

With respect to the demographic characteristics of the subjects, Tab 1 displays the distribution of genders and descriptive statistics of body weight, gestational age, and postnatal age, in both samples. The 2 groups were very similar in terms of demographic characteristics (the independent sample t test; $P>0.05$).

Tab 1. Distribution of characteristics of the neonates. L: Learning Sample, $n=30$. V: Validation Sample, $n=12$.

Variables	Sample	$\bar{x}$	s	Minimal value	Maximal value
Body weight	L	2.9	0.9	1.25	4.30
(kg)	V	2.5	0.9	1.40	3.74
Gestational age	L	38	4	31	42
(weeks)	V	37	4	31	42
Postnatal age	L	10	7	1	25
(days)	V	11	7	1	27

		Percentage of neonates	
		Male	Female
Gender	L	56.7 %	43.3 %
	V	58.3 %	41.7 %

Method for population analysis The population analysis of amikacin was performed using the Monte Carlo method. This approach requires one to assume a pharmacokinetic (PK) model and a statistical model including a residual error model.

The mathematical model describing the kinetics of amikacin after intravenous infusion is a one-compartment open model. This model includes two kinetic parameters constituting a vector θ: the volume of distribution V_d and the elimination rate constant K_e. After administration of an infusion rate K_0 and time τ, the equations of the model describing the concentration C as a function of the time t are

$$C(t)=\frac{K_0}{K_e V_d}(1-e^{-K_e\tau})\ e^{-K_e t}$$

In the target population, the kinetic parameter θ is assumed to be random, and the concentrations of two different subjects are considered independent. For a subject i, with vector of kinetic parameters θ_i, the jth concentration y_{ij} measured at time t_{ij} was written as the sum of the concentration predicted for this subject by the PK model at the time for the corresponding dose, $f(\chi_{ij}, \vec{\theta})$, and for a residual error ϵ_{ij}

$$y_{ij}=f(\chi_{ij}, \vec{\theta})+\epsilon_{ij}$$

where j varies from 1 to n_j, and n_j is the number of concentrations from subject i. The residual error ϵ_{ij} was assumed to arise from a zero mean normal distribution. In this analysis, the variance model for the residual error ϵ_{ij} was fully specified as follows. The residual error includes three kinds of errors: measurement error due to the analytical method, error of the PK model with respect to the data, and error in sampling or in recording of the dosing history.

Pharmacokinetic parameters typically exhibit skewed population distributions with constant coefficients of variation and thus a common approach is to assume lognormal population distributions for PK parameters. We modeled interindividual error variability assuming:

$$\ln\theta_{k_i}=\ln\theta_k+\eta_{k_i}$$

where θ_{k_i} are the kinetic parameters for subject i, θ_k are population pharmacokinetic parameters, η_{k_i} are normal errors with mean zero and variance $\sigma^2_{\theta_k}$.

From the PK and residual error models, the likelihood of the concentrations of an individual can be deduced for a given vector of kinetic parameters θ. The likelihood of the vector y_i of concentration of subject i is the product of the likelihoods of each measurement. The maximum likelihood estimates of the population parameters are those values of the objective function $O(\vec{\theta},\Omega,\Sigma)$ that minimize.

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$$O(\vec{\theta},\Omega,\Sigma)=\sum_{i=1}^{N}[\ln|V_i(\vec{\theta},\Omega,\Sigma)|+(\vec{y}_i-\vec{f}(\chi_i,\vec{\theta}))'\ V_i^{-1}(\vec{\theta},\Omega,\Sigma)(\vec{y}_i-\vec{f}(\chi_i,\vec{\theta}))]$$

where the variance matrix Ω is a diagonal matrix, described as follows: $\Omega=\begin{pmatrix}\sigma^2_{\theta_1} & & 0\\ & \ddots & \\ 0 & & \sigma^2_{\theta_p}\end{pmatrix}$, it implies that the error in parameter estimates is associated with interindividual variability, Σ is the variance-covariance matrix of intraindividual random error, symbol $|V_i(\vec{\theta},\Omega,\Sigma)|$, $V_i^{-1}(\vec{\theta},\Omega,\Sigma)$, $(\vec{y}_i-\vec{f}(\chi_i,\vec{\theta}))'$ denote Jacobian matrix, inverse matrix and transposed matrix, respectively.

With a nonlinear $\vec{f}(\chi_i,\vec{\theta})$ the integrals cannot be evaluated analytically and hence some form of approximation is required, even before the maximization issue is addressed. We took a one-order Taylor series expansion. The objective function was then numerically minimized with respect to $\vec{\theta},\Omega,\Sigma$. Within our program the minimization routine was the Monte Carlo algorithm. This procedure was repeated until convergence of the minimization routine.

Founded on the vector evaluation of population parameters, the least squares method based upon the Bayesian feedback estimates the individual parameter values which minimize the following sum of squares.

$$O\ \vec{\theta}_i=\sum_{i=1}^{N}\frac{[\,y_{ij}-f(\chi_{ij},\vec{\theta}_i)\,]^2}{\sigma^2_\varepsilon}+\sum_{k=1}^{p}\frac{(\ln\theta_{k_i}-\ln\theta_k)^2}{\sigma^2_{\theta_k}}$$

where y_{ij} is an observed drug concentration in serum, $f(\chi_{ij},\vec{\theta}_i)$ is a predicted drug concentration, σ^2_ε is the variance of measured concentration, n is the number of measurements, p is the number of parameters, θ_{k_i} is the value of parameter k for an individual, and θ_k and $\sigma^2_{\theta_k}$ are the mean and variance of population pharmacokinetic parameters, respectively.

Validation method Traditional pharmacokinetic program 3p87 (Two-Stage method) for collation was used, to evaluate the individual parameter, the means and the corresponding standard deviation, and to detect the consistency of population pharmacokinetic parameter. Statistical comparisons were performed using SPSS 8.0 for Windows.

The validation of the population analysis was performed in two stages. The first stage consisted of evaluating the adequacy of the PK model and the relevance of the residual error model on the data of the learning sample. In the second stage, the predictability of the population model was studied on the validation sample. In the learning sample, the observed concentrations y_{ij} were compared to predicted concentrations $f(\chi_{ij},\vec{\theta}_i)$ through the residuals R_{ij} with

$$R_{ij}=y_{ij}-f(\chi_{ij},\vec{\theta}_i) \qquad (1)$$

In the validation sample, the predicted and observed concentrations were compared through the same expressions as in Eq(1) but these were called prediction errors PE_{ij}. Under the assumption that the population model is correct, the standardized prediction errors obey a distribution with a zero mean and a variance equal to 1. The mean and variance of standardized prediction errors were thus computed and compared, respectively, to 0 and 1.

Bayesian forecast The individual pharmacokinetic parameters of amikacin were estimated using one serum concentration measurement at a time for each patient. For example, when 4 data points were available for a subject, the Bayesion estimation was executed 4 times using a different point, then the predictive performance was discussed in relation to the blood sampling time.

Precision and accuracy of serum concentration predicted using the parameter estimates were described as the root mean squared different (RMSD) and *BIAS*

$$RMSD=\sqrt{\frac{1}{n}\sum_{i=1}^{n}(C_{pred}-C_{obs})^2}$$

$$BIAS=\frac{1}{n}\sum_{i=1}^{n}(C_{pred}-C_{obs})^2$$

where C_{pred} represents the serum concentrations at time t_i predicted by the Bayesian analysis using one-point data measured at time t_i and C_{obs} is the observed concentrations, n is the number of measurements.

RESULTS

The Monte Carlo method in our program (MCMPK) results in variability in the parameter estimates. That is, if the same set of data are analyzed a number of times with MCMPK, different estimates will result. To show the extent of this variability the learning sample was analyzed 4 times and the results are shown in Tab 2. Where the product of K_e and K_1 is the variance of K_e, the product of V_d and K_2 is the variance of V_d, and K_3 is the residual error, respectively. We see that there is very little "between-run" Monte Carlo variability.

Comparison of the three parameter sets identified with the Monte Carlo method and two-stage method is

Tab 2. Results from 4 repeated analyses of the learning sample using MCMPK to illustrate Monte Carlo variability.

Parameters	Operational number 1	2	3	4
O_{mn}	203.7364	203.7365	203.7364	203.7364
K_e	0.1946	0.1946	0.1946	0.1946
V_d	0.5482	0.5481	0.5480	0.5480
K_1	0.3983	0.3981	0.3980	0.3982
K_2	0.2911	0.2907	0.2907	0.2906
K_3	0.9022	0.9019	0.9021	0.9027

summarized in Tab 3. The 13 neonates with two serum determinations were not included in the two-stage method. The two methods of analysis resulted in the similar estimates for K_e and V_d of amikacin ($P > 0.05$). In addition, the extrapolated values for *Cl* from population parameters and those estimated from two-stage methods were comparable. These results indicate the consistency of the findings between the Monte Carlo method and two-stage methods of analysis.

Tab 3. Comparison of the population parameter values identified with Monte Carlo method ($n = 30$) and two-stage methods ($n = 17$).

Parameter	Analysis	Estimated value ($\bar{x} \pm s$, *CV* %)
$K_e(h^{-1})$	Monte Carlo method	0.19 ± 0.08, 42.1 %
	Two-Stage method	0.15 ± 0.07, 46.7 %
$V_d(L \cdot kg^{-1})$	Monte Carlo method	0.55 ± 0.16, 29.1 %
	Two-Stage method	0.64 ± 0.22, 34.4 %
Cl ($mL \cdot h^{-1} \cdot kg^{-1}$)	Monte Carlo method	103 ± 25, 24.3 %
	Two-Stage method	100 ± 30, 30.0 %

K_e, elimination rate constant; V_d, volume of distribution; *Cl*, clearance; *CV*, coefficient of variation.

The intersubject variability of K_e and V_d estimated from the base model was 42.1 % and 29.1 %, respectively. The CV for K_e (46.7 %) and V_d (34.4 %) estimated using the two-stage analysis was consistent with that estimated by MCMPK; however, the CV by two-stage method was slightly greater. The reason for this is overestimation of variability by the two-stage analysis because residual error can not be calculated separately as it can be using Monte Carlo analysis.

For the learning sample, predicted and observed concentrations were close since the plot of the 94 predicted *vs* observed concentrations was around the line of unit slope (Fig 1A). No trend was observed in the plot of the residuals *vs* predicted concentrations (Fig 1B). The mean and variance of the residuals were 0.102 and 0.552, respectively. These results indicate the good adequacy of the model.

For the validation sample, the plot of the 48 predicted *vs* observed concentrations also showed points around the line of unit slope, and conformed with the learning sample (Fig 1C). The plot of the prediction errors *vs* predicted concentrations was satisfactory since most of predicted errors were found $< \pm 1$ mg/L (Fig 1D). The mean and variance of the prediction errors were 0.068 and 0.581, respectively, which are close to a zero mean and a variance equal to 1.

From all these results, we considered that the predictability of the population model was satisfactory.

Tab 4 represents the influence of blood sampling time on the precision and accuracy for the prediction of serum amikacin concentrations in the validation sample. "All" means that predicted concentration was calculated by the Bayesian feedback using all the concentration data for the patient. "The sampling time: 0.5, 4, 8, 12" denotes that those values were estimeted through single serum levels. The precision was the best when blood was taken shortly after the infusion ($t = 0.5$), furthermore the dependency of *RMSD* on sampling time was obvious in other periods. At the same time, *BIAS* also showed a dependency on the sampling time. The downward *BIAS* was observed when the sampling was made at $t = 4$ h whereas an upward *BIAS* was observed at later sampling time. Provided that 1 mg/L might be an acceptable threshold for *RMSD* and *BIAS*, taking into account the therapeutic range of amikacin (peak level: 20 – 25 mg/L, trough level: < 5 mg/L), the number of points that exceeded 1 mg/L was 8.3 % for "all" and 14.6 %, 22.9 %, 37.5 %, 45.8 % for the sampling time "0.5, 4, 8, 12 h", respectively.

Tab 4. Precision and accuracy of serum concentration predicted in relation to the blood sampling time.

Parameter	All	The sampling time/h 0.5	4	8	12
r	0.9904	0.9834	0.9606	0.9556	0.9368
RMSD	0.5786	0.7748	1.2060	1.2973	1.6270
BIAS	−0.0684	0.1244	−0.4343	0.4278	0.7359

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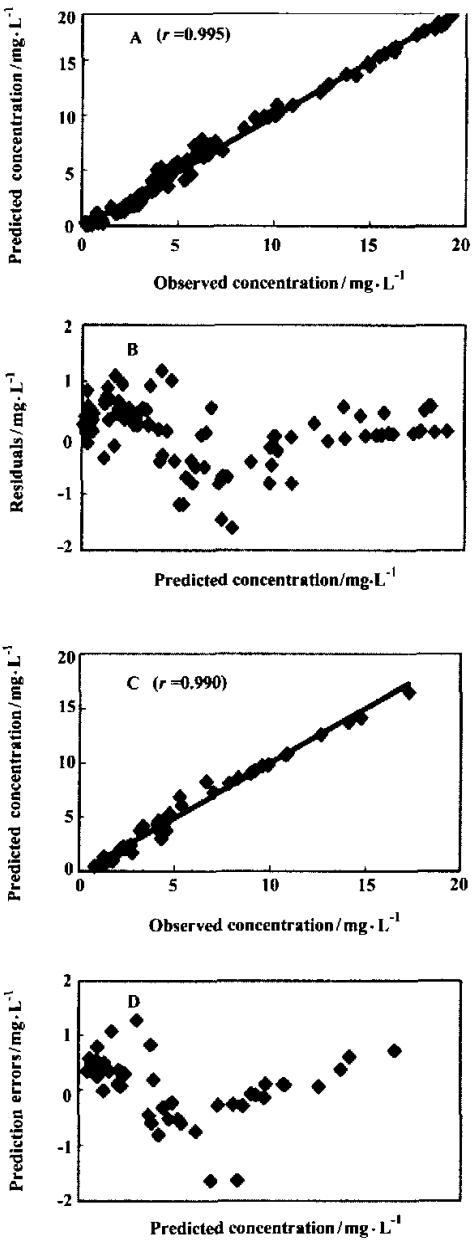

Fig 1. Predicted concentrations as a function of observed concentrations of amikacin in the learning sample (A) and in the validation sample (C). Residuals of the learning sample (B) and prediction errors of the validation sample (D) as the function of predicted concentrations of amikacin.

DISCUSION

The results from this study demonstrated that the estimated and extrapolated population pharmacokinetic parameters of amikacin obtained in neonates were in agreement with those calculated by two-stage analysis, suggesting that the Monte Carlo method provided accurate estimates for these parameters. The Monte Carlo method is not only equal to the two-stage method in identifying pharmacokinetic parameters but is more efficient in utilizing clinical data, is mathematically superior, and is able to include sparse data sets that the two-stage method can not use.

A review of the predicted and observed concentration profiles (Fig 1) shows the superimposability of these data. It appears, however, that the predicted concentrations of amikacin in the lower measurement were slightly overestimated. In fact, as concentrations of amikacin fall, their detectability is also reduced. Nevertheless, for concentration of amikacin less than 0.18 mg/L, the model estimated these "undectable" levels to predict the population concentrations of amikacin at the specified times. Therefore, the predicted amikacin concentrations were not overestimated.

A central purpose of the pharmacokinetic analysis is the prediction of individual concentration. The more the data, the more accurate the results can be, but the time of sampling can affect the result. A sampling time-dependency of the precision of estimated concentrations was also observed as shown in Tab 4. The results indicate that the choice of blood sampling time was an important factor for the predictive performance of the one-point Bayesian method. The best sampling time for estimating parameters would be optimal for the prediction of individual concentrations. Because the serum-drug concentration decreases with time and consequently the assay error becomes larger at a lower concentration, an early time (such as 0.5 h) of sampling after cessation of the infusion would be the best, and it would agree with Garraffo *et al*[10]. These findings imply that measuring trough levels is not always the best sampling strategy in the individualization of dosage regimen as well as the design of clinical trials[11]. The best time of sampling for different models deserves further study. Also, the choice of appropriate population parameters is one of important factors for estimation of individual parameters since the Bayesian feedback relies on previous estimates of population parameters. We should determine these population values for different groups of patients, which is similar to individual cases, in order to improve the predicted accuracy.

In addition, the Monte Carlo method is now widely

used for biomedicine research, such as molecule biology[12,13], environmental contamination[14], nuclear medicine[15], biomimetic recognition[16]. We have applied the Monte Carlo method to population pharmacokinetics in order to obtain a more accurate estimation for population and individual pharmacokinetic parameters. The method is able to obviate the problem of selecting the proper starting conditions from which to initiate the fitting procedure. It requires very low calculating original data and runs on an even keel.

In conclusion, our study provided accurate estimates of the above mentioned parameters and satisfactory ability of serum concentration prediction. Simultaneously, it allowed us to use sparse data to estimate population pharmacokinetic parameters. It made it possible to obtain the different or even particular population pharmacokinetic parameters according to patient characteristics. After the population parameter is obtained, this program will spend only several seconds by using Bayesian feedback to get the individual parameter in combination with a few serum concentration measurements from the concerned individual. Therefore, it can be used for the population pharmacokinetic analysis and pharmacokinetics-assisted individualization of dosage regimen using routine monitoring data.

REFERENCES

1 Sheiner LB, Beal SL. Bayesian individualization of pharmacokinetics: simple implementation and comparison with non-Bayesian methods. J Pharm Sci 1982; 71: 1344 - 8.
2 Thomson AH, Whiting B. Bayesian parameter estimation and population pharmacokinetics. Clin Pharmacokinet 1992; 22: 447 - 67.
3 Mark M, Edmund C, James C. Pharmacokinetics of zidovudine in infants: a population analysis across studies. Clin Pharmacol Ther 1999; 66: 16 - 24.
4 Naomi N, Hiroyasu O, Yuji W, Daijiro T, Kazuhiko S, Tetsuro O, *et al*. Population pharmacokinetics and pharmacodynamics of cisplatin in patients with cancer: analysis with the NONMEM program. J Clin Pharmacol 1998; 38: 1025 - 34.
5 Hussein Z, Posner J. Population pharmacokinetics of lamotrigine monotherapy in patients with epilepsy: retrospective analysis of routine monitoring data. Br J Clin Pharmacol 1997; 43: 457 - 65.
6 Kiumars V, Steven T, Joan KB, Soong TC, James JZ. Population pharmacokinetics of intravenous amiodarone and comparison with two-stage pharmacokinetic analysis. J Clin Pharmacol 1997; 37: 610 - 7.
7 Richard LL, Denis L, Jacques G. Population pharmacokinetics of terfenadine. Pharm Res 1996; 13: 832 - 7.
8 Seay RE, Brundage RC, Jensen PD. Population pharmacokinetics of vancomycin in neonates. Clin Pharmacol Ther 1994; 56: 169 - 75
9 Bruno R, Iliadis MC, Lacarelle B, Cosson V, Mandema JW, Roux YL, *et al*. Evaluation of Bayesian estimation in comparison to NONMEM for population pharmacokinetic data analysis: application to pefloxacin in intensive care unit patients. J Pharmacokinet Biopharm 1992; 20: 653 - 69.
10 Garraffo R, Iliadis A, Cano JP, Dellamonica P, Lapalus P. Application of Bayesian estimation for the prediction of an appropriate dosage regimen of amikacin. J Pharm Sci 1989; 78: 753 - 7.
11 Chen G. Assessment of Bayesian method for predicting the pharmacokinetic parameters of the theophylline after oral administration to steady state. Chin J Clin Pharmacol 1991; 7: 20 - 4.
12 Mirny LA, Shakhnovich EI. Protein structure prediction by threading. Why it works and why it does not. J Mol Biol 1998; 283: 507 - 26.
13 Liwo A, Oldziej S, Kazmierkiewicz R, Groth M, Czaplewski C. Design of a knowledge-based force field for off-lattice simulations of protein structure. Acta Biochim Pol 1997; 44: 527 - 47.
14 Loranger S, Zayed J. Environmental contamination and human exposure to airborne total and respirable manganese in Montreal. J Air Waste Manag Assoc 1997; 47: 983 - 9.
15 Zanzonico PB. Internal radionuclide radiation dosimetry: a review of basic concepts and recent developments. J Nucl Med 2000; 41: 297 - 308.
16 Golumbfskie AJ, Pande VS, Chakraborty AK. Simulation of biomimetic recognition between polymers and surfaces. Proc Natl Acad Sci USA 1999; 96: 11707 - 12.

Monte Carlo 法用于新生儿阿米卡星的群体药动学分析和认证[1]

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关键词 药物动力学; 贝叶斯定理; 计算机模拟; 结果可重复性; 蒙特卡罗法; 阿米卡星; 新生婴儿; 给药方案

目的: 用 Monte Carlo 算法编制群体药动学分析程序并认证该方法估计药动学参数和预测血药浓度的能力. **方法**: 用阿米卡星作为模型药物, 对来自 42 名新生儿共 142 对血药浓度时间数据进行分析; 根据 Sheiner 等提出的群体药动学思想, 我们编制了估计群体参数和个体参数的程序, 目标函数最小值以 Monte Carlo 算法求得, 方法的认证采用经典药动学

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程序 3p87 作为对照，预测能力通过计算预测血药浓度的均方根误差(*RMSD*)和偏性(*BIAS*)来考察. **结果**：我们自编的程序运行稳定；本法提取的群体参数与 3p87 得到的一致，学习样本与认证样本的预测浓度与实测浓度显著相关(相关系数分别为 0.995 和 0.990)，预测误差大多数小于 1 mg/L，认证样本 RMSD 和 BIAS 分别为 0.58 和 −0.07 mg/L. **结论**：本法估计参数准确，预测血药浓度能力令人满意.

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