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The Kinetic Profile of Gentamicin in Premature Neonates

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Abstract

The kinetic profile of gentamicin in premature infants has been studied to enable the development of optimized dosage schedules for neonatal intensive-care units and to stress the relationship between the pharmacokinetic parameters and several demographic, developmental and clinical factors which might be associated with changes in gentamicin disposition.

Sixty-eight newborn patients of 24- to 34-weeks gestational age and 600–3100 g current weight in their first week of life, undergoing routine therapeutic drug monitoring of their gentamicin serum levels, were included in this retrospective analysis.

Gentamicin pharmacokinetic parameters were determined through non-linear regression by using a single-compartment open model. By regression analysis the current weight (g) was shown to be the strongest co-variate, and both gentamicin clearance ($L\,h^{-1}$) and volume of distribution (L) had to be normalized. Additionally, gentamicin clearance depended on gestational age with a cut-off at 30 weeks, which allowed the division of the overall population into two subsets (<30 weeks and between 30–34 weeks of gestational age).

The younger neonates (<30 weeks of gestational age) showed a lower gentamicin clearance (0·0288 vs 0·0340 $L\,h^{-1}\,kg^{-1}$), a slightly higher volume of distribution (0·464 vs 0·435 $L\,kg^{-1}$), and a longer half-life (11·17 vs 8·88 h) compared with the older subgroup (30–34 weeks of gestational age).

On the basis of the pharmacokinetic parameters obtained, we suggest loading doses of 3·7 and 3·5 mg kg^{-1} for the two subgroups of neonates (<30 weeks and 30–34 weeks of gestational age), respectively. The appropriate maintenance doses in accordance with the characteristics of the patients should be 2·8 mg kg^{-1}/24 h and 2·6 mg kg^{-1}/18 h for neonates <30 weeks and between 30–34 weeks of gestational age, respectively. Finally, when compared with previous studies, the information obtained on the pharmacokinetics and determinants of the pharmacokinetic variability of gentamicin in neonates was shown to be consistent.

Over the past few decades, the importance of applying pharmacokinetic principles to the design of drug regimens has been increasingly recognised by clinicians (Li et al 1999). This is especially true in neonatology, where patients are at risk because of the lack of knowledge about their special needs, lack of clinical data for them, insufficient drug labelling, and limited dosage forms (Zenk 1994).

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Gentamicin is an aminoglycoside antibiotic frequently used to treat Gram-negative bacillary infections and suspected sepsis in neonates. Obstetrical and neonatal disease procedures required for the management of critically ill neonates are associated with an increased risk of infections (Paap & Nahata 1990). The risk of toxicity or poor efficacy is further increased due to the recognized wide intra- and interpatient variability in the pharmacokinetic parameters of gentamicin, strongly dependent on the dynamic maturational process of the newborn (Lesko et al 1990; Semchuk et al 1995).

Gentamicin is ototoxic and nephrotoxic in the adult and, although toxicity in neonates is not well documented, it may be reasonable to expect similar or more pronounced effects in infants. Thus, gentamicin monitoring of serum concentrations as well as the individualization of dosage regimens is recommended to assure adequate levels and to avoid potentially toxic levels, preventing prolonged serum peak concentrations above $10\,mg\,L^{-1}$ and trough concentrations above $2\,mg\,L^{-1}$ (Morselli 1989). To achieve this goal, the initial dosage regimen should reflect the likely requirements of the individual as determined by measurable clinical characteristics (Thomson et al 1988). In addition, varying assessments of the most appropriate physical and age-related predictors of gentamicin concentrations in neonates confirm the need for continuing study (Murphy et al 1998).

The purpose of our work was to determine the kinetic profile of gentamicin in a group of neonates for which concentrations were monitored as part of their routine clinical care. The influence of several demographic, developmental and clinical factors on drug disposition was investigated to develop gentamicin dosage guidelines for patients in neonatal intensive-care units.

Materials and Methods

Patients

A completely retrospective study was performed on 68 premature infants in the neonatal intensive-care unit at the Coimbra University Hospital, who were receiving intravenous gentamicin for severe infective process occurrences between 1996–1999. Patients were excluded if complete medical records could not be obtained, serum concentration–time data were incomplete or inconsistent with nursery database (sampling time errors), or dose administration times were not documented. All the selected patients had a postnatal age of below one week and two available gentamicin serum concentrations (peak and trough) obtained according to routine clinical protocol. Twenty-eight neonates were excluded from the overall available study population (102 patients) due to the bimodal distribution related with their gestational age (>34 weeks), as can be observed in Figure 1, and our interest in focussing the analysis exclusively on premature neonates. Six of the remaining 74 patients were excluded because they had postnatal age values above the allowed limit for the present work (up to one-week-old).

Gentamicin dosage and sampling procedure

Gentamicin was administered through a 10-min slow intravenous infusion at standard doses (mean value of $3{\cdot}46 \pm 0{\cdot}76\,mg\,kg^{-1}$/day), either alone or combined with another antibiotic, in accordance with institutional guidelines practised in our neonatal intensive-care unit. A standard $2{\cdot}5\,mg\,kg^{-1}$ dose was administered and the interval between doses was selected on the basis of patients' weight: 24, 18 and 12-h intervals for weights <1200, 1200–2000 and <2000 g, respectively.

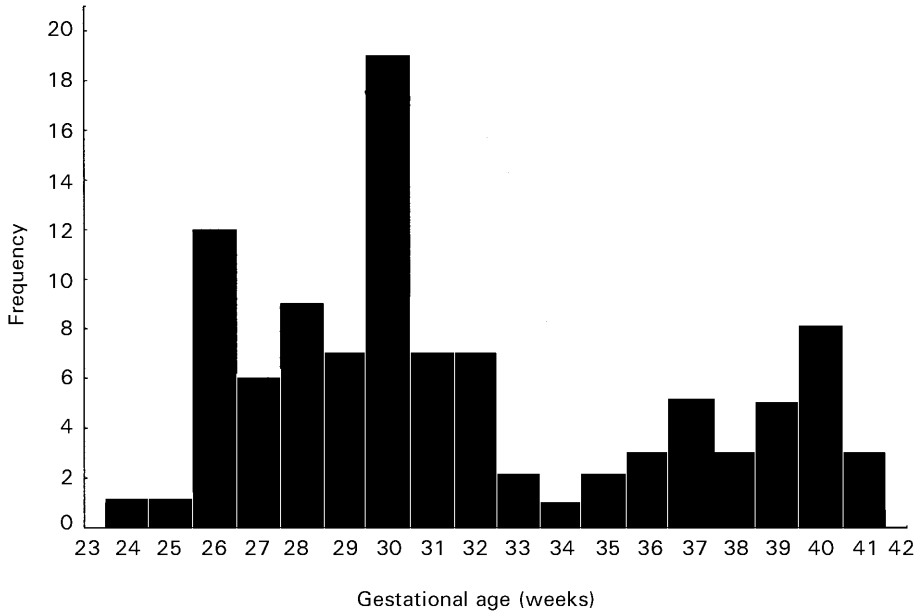

Figure 1. Frequency of distribution of gestational age for the overall study population (102 neonates).

Blood samples were collected 1 h after administration (peak level) and 30 min before the next dose (trough level). Monitoring of gentamicin serum concentrations (peak and trough levels) was always performed between 24 and 48 h after starting the therapy. Subsequent dosage regimens, based on the first set of gentamicin measurements, were optimized by the pharmacy service by applying pharmacokinetic criteria. Periodic dosage adjustments were performed according to the results obtained from drug monitoring and clinical evaluation. The assumed target concentrations for gentamicin were defined to be 0·5–2 and 6–10 mg L^{-1} for trough and peak levels, respectively. Trough levels above 2 mg L^{-1} and peak levels above 10 mg L^{-1} were considered potentially toxic (Besunder et al 1988; Faura et al 1991).

Serum samples were collected via heel capillary prick and analysed by a fluorescence polarization immunoassay technique (TDx; Abbott Diagnostics) at the Laboratory of Hormonology and Therapeutic Drug Monitoring of Coimbra University Hospital. Intra- and interday coefficients of variation were $<6\%$ in our institution.

Pharmacokinetic analysis

The kinetic analysis was carried out assuming a single-compartment open model with zero-order absorption (short infusion) and first-order elimination. The individual pharmacokinetic parameters were determined by fitting the data using a weighted least-squares non-linear regression method (PKS; Abbott Diagnostics).

Several co-variates were assessed to explain the pharmacokinetic behaviour of gentamicin in our population: birth weight, current weight, gestational age, postnatal age, and postconceptional age. The serum creatinine concentration was used to estimate the clearance of creatinine (mL min^{-1} kg^{-1}) according to the method developed by Schwartz et al (1976).

Statistical analysis

The available information (pharmacokinetic parameters and co-variates) was studied by linear regression analysis to assess the strength of correlation between variables. Multi-variate regression analysis (stepwise multiple regression) was used to evaluate the most important co-variates for explaining the pharmacokinetic behaviour of gentamicin in our population. Subset analysis employed the *t*-test, analysis of variance, and correlation analysis, applied when appropriate. A value of $P \leq 0{\cdot}05$ was regarded as indicative of significance. The co-variate values were expressed by their median and interquartile ranges, while mean values and corresponding standard deviations were used to characterize the obtained pharmacokinetic parameters. Statistical analysis was performed using the Statistica software package.

Results

Of the 102 patients for whom data were collected, 68 were included in the present pharmacokinetic analysis. Mean weights (birth and current), ages (gestational, postnatal and postconceptional), and clearance of creatinine for the selected study population are shown in Table 1. Despite the use of a putative appropriate gentamicin dosage schedule in our neonatal intensive-care unit, the obtained gentamicin serum trough and peak levels showed some variability ($2{\cdot}27 \pm 1{\cdot}04$ and $7{\cdot}80 \pm 1{\cdot}66$ mg L^{-1}, respectively). Potentially toxic serum levels, expressed by trough levels above 2 mg L^{-1}, as well as by peak levels above 10 mg L^{-1}, were observed in 50% and 7·4% of the patients, respectively. Additionally, subtherapeutic concentrations were observed in 7·4% of the neonates (peak levels $\leq$6 mg L^{-1}).

Table 2 shows the relationships determined between the pharmacokinetic parameters for the overall population and the studied co-variates. The strongest correlations were obtained between current weight (CW; g) and both gentamicin clearance (CL; L h^{-1}) and volume of distribution (Vd; L), indicating that current weight is the best co-variate for explaining the kinetic profile of gentamicin in our population (Figures 2 and 3). Equations expressing these relationships are:

$$\mathrm{CL\ (L\,h^{-1})} = -0{\cdot}002 + 3{\cdot}386 \times 10^{-5} \times \mathrm{CW(g)} \quad (1)$$

$$\mathrm{Vd\ (L)} = 0{\cdot}122 + 3{\cdot}362 \times 10^{-4} \times \mathrm{CW\ (g)} \quad (2)$$

Table 1. Summary of patient data.

	n	Median	Interquartile range
Case studies	68		
Male/female	30/38		
Birth weight (g)	–	1200	875–1500
Current weight (g)	–	1200	800–1350
Gestational age (weeks)	–	29·50	27·00–30·00
Postnatal age (days)	–	3·00	2·00–4·00
Postconceptional age (weeks)	–	30·00	27·50–30·57
Clearance of creatinine (mL min^{-1} kg^{-1})	–	1·31	1·01–1·54

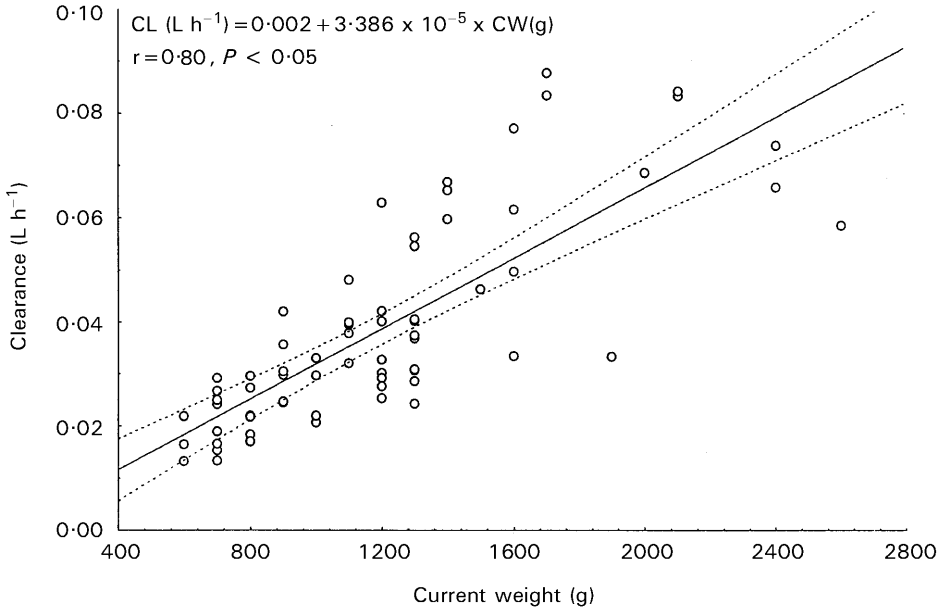

Figure 2. Relationship between current weight and gentamicin clearance.

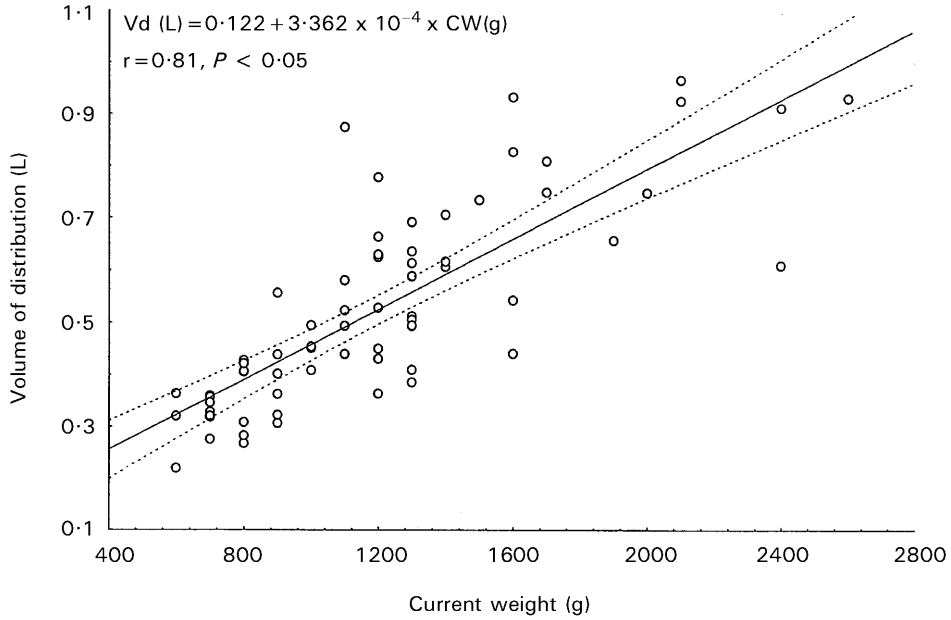

Figure 3. Relationship between current weight and gentamicin volume of distribution.

Significant correlations were also obtained between birth weight (g), gestational age (weeks) and postconceptional age (weeks) for both gentamicin CL ($L\,h^{-1}$) and Vd (L). This can be easily explained by the strong correlation between all of these variables and the current weight ($r = 0{\cdot}97$ between current and birth weights; $r = 0{\cdot}99$ between gestational and postconceptional ages; $r = 0{\cdot}74$ between current/birth weight and gestational/postconceptional age), which means that we were working with dependent variables and only the strongest should be considered (current weight in the present work). After normalization of the pharmacokinetic parameters by the current weight, the influence of gestational and postconceptional ages as continuous variables became weak (for clearance) or not statistically significant (for volume of distribution). The correlation between clearance of creatinine (mL min^{-1} kg^{-1}) and gentamicin clearance ($L\,h^{-1}$ kg^{-1}) was weak, despite being statistically significant, indicating that clearance of creatinine (mL min^{-1} kg^{-1}) was not an

Table 2. Significant correlations (r-values) between gentamicin pharmacokinetic parameters and several co-variates.

Parameter	Clearance ($L\,h^{-1}$)	Clearance ($L\,h^{-1}\,kg^{-1}$)	Volume of distribution (L)	Volume of distribution ($L\,kg^{-1}$)
Birth weight (g)	0·79*	N.A.	0·80*	N.A.
Current weight (g)	0·80*	N.A.	0·81*	N.A.
Gestational age (weeks)	0·73*	0·32*	0·70*	N.S.
Postnatal age (days)	N.S.	N.S.	N.S.	N.S.
Postconceptional age (weeks)	0·73*	0·34*	0·70*	N.S.
Clearance of creatinine ($mL\,min^{-1}\,kg^{-1}$)	N.S.	0·45*	N.A.	N.A.

*$P \leq 0{\cdot}05$. N.S., not statistically significant. N.A., not assessed.

Table 3. Gentamicin pharmacokinetic parameters obtained from two newborn patient subgroups established in accordance with their gestational age (n = 68).

	Group I, gestational age < 30 weeks (n = 34)			Group II, 30 ≤ gestational age ≤ 34 weeks (n = 34)		
	CL ($L\,h^{-1}\,kg^{-1}$)	Vd ($L\,kg^{-1}$)	$t_{1/2}$ (h)	CL ($L\,h^{-1}\,kg^{-1}$)	Vd ($L\,kg^{-1}$)	$t_{1/2}$ (h)
Mean	0·0288*	0·464	11·17*	0·0340*	0·435	8·88*
s.d.	0·0080	0·091	2·89	0·0094	0·094	2·81
C.V.	27·8%	19·6%	25·9%	27·6%	21·6%	31·6%
Range	0·0179–0·0484	0·329–0·781	6·21–18·20	0·0185–0·0524	0·257–0·653	5·05–16·7

s.d., standard deviation. C.V., coefficient of variation. *$P \leq 0{\cdot}05$.

important co-variate in explaining gentamicin clearance in this kind of population. Finally, there was no significant correlation between postnatal age (days) and gentamicin clearance and/or volume of distribution. This suggested that we were unable to find the effect of time-dependency on its kinetic profile, a reasonable observation bearing in mind the small range (six days) presented by this co-variate in the study population.

Multi-variate regression analysis was also performed to determine whether multiple characteristics were correlated with the pharmacokinetic variables. To minimize mathematical redundancy, multiple linear regressions combining related characteristics (dependent co-variates such as postnatal and postconceptional ages) were avoided. Gentamicin clearance ($L\,h^{-1}$) and volume of distribution (L) served as dependent variables and the available co-variates were used as independent variables. Characteristics that were continuous variables (gestational and postnatal ages) were applied as dichotomous variables to investigate the possible time-dependency and maturation-dependency of the kinetic profile of gentamicin. The results obtained suggested that gentamicin clearance depended on the gestational age with a value of 0·0288 $L\,h^{-1}\,kg^{-1}$ (C.V. = 27·8%) for patients < 30 weeks of gestational age and 0·0340 $L\,h^{-1}\,kg^{-1}$ (C.V. = 27·6%) for patients between 30–34 weeks of gestational age. Bearing in mind the present results, the overall population was divided into two subsets in accordance with gestational age as categorical variable; the kinetic profile of each of these subgroups can be observed in Table 3.

Discussion

The use of clinical pharmacokinetics in antimicrobial chemotherapy has been fruitful. The adverse effects associated with the use of antimicrobials with narrow therapeutic windows have been reduced and the likelihood of successful therapy has been improved (Li et al 1999). Due to the immunological incompetence of the premature newborn, and the morbidity and mortality associated with neonatal sepsis, it is obvious that early attainment and maintenance of therapeutic concentrations would be beneficial. For this reason it is important to characterize the kinetic profile of gentamicin in this kind of patient with particular attention. Thus our selection, supported by the bimodality of our population regarding its gestational age, allowed us to focus on the pharmacokinetic analysis for which greater interest exists, particularly as there is a chronic lack of information available for this age group. To support our choice, the worryingly high percentage of potentially toxic trough serum levels observed in our population (50% of the patients) must be emphasized, and highlights the importance of appropriate "a priori"

dosage schedules and monitoring gentamicin serum levels.

The utility of current weight in the empirical dosing of gentamicin has long been appreciated, and our results lend further support confirming this co-variate as the most important for clearance and volume of distribution normalization. Nevertheless, it was also confirmed that gestational age below 34 weeks influenced the kinetic profile of gentamicin in premature neonates to a considerable extent, which is a well-known phenomenon for the elimination process of kidney-dependent drugs (e.g. aminoglycosides) (Stewart & Hampton 1987; Besunder et al 1988). The aminoglycosides are eliminated from the body by glomerular filtration and Hindmarsh et al (1983) and Landers et al (1984) found a relationship between gentamicin elimination rate and maturational markers (gestational and postconceptional ages). This indicated the importance of exploring those findings to explain some of the recognized intra- and inter-individual variability in the kinetic profile of gentamicin in premature neonates. In fact, significant differences in pharmacokinetic values were found among neonates divided into two subsets according to their gestational age, with a cut-off at 30 weeks (Table 3).

In this study, the values obtained for the clearance of gentamicin in both subgroups (<30 and between 30–34 weeks of gestational age) were in accordance with the expected increased elimination capacity associated with the normal maturational process. However, it is important to stress that the mean absolute values for both subsets ($0{\cdot}0288\,L\,h^{-1}\,kg^{-1}$ for neonates <30 weeks of gestational age and $0{\cdot}0340\,L\,h^{-1}\,kg^{-1}$ for neonates between 30–34 weeks of gestational age) are statistically different and very close to those found by Delgado et al (1997) and Thomson et al (1988) in patients with similar physiopathological characteristics. Thomson et al (1988) and Fattinger et al (1991) reported that creatinine clearance did not prove to be the most important marker of the glomerular filtration rate in this kind of population, which can be explained by the unclear relationship between creatinine concentration and renal function in neonates. This is partly due to the early influence of maternal creatinine concentration and partly because of day-to-day variability and assay difficulties (Feldman & Guignard 1982).

Due to its physicochemical properties (highly polar molecule), gentamicin distribution is strongly affected by the volume of total body water. Moreover, in neonates the extracellular fluid space varies inversely with gestational age (Besunder et al 1988). The influence of this time-dependent physiological evolution can be appreciated in our results where the mean value for the volume of distribution decreased from $0{\cdot}464$ to $0{\cdot}435\,L\,kg^{-1}$ for neonates <30 and between 30–34 weeks of gestational age, respectively. Although no statistical difference was found between the values for volume of distribution in the subgroups of patients, the observed decrease in the value of this parameter with the increase in gestational age would be expected to occur and is in accordance with work by Semchuk et al (1993) and Delgado et al (1997).

The global pharmacokinetic behaviour of gentamicin in our population study can be appreciated by using the elimination half-life approach, given that it depends on both clearance and volume of distribution. As was expected, this pharmacokinetic parameter varied inversely with gestational age, with mean values of $11{\cdot}17$ h and $8{\cdot}88$ h for younger (<30 weeks) and older (30–34 weeks) neonates, respectively. In view of these results it must be emphasized that this significant difference ($P \leq 0{\cdot}05$) on elimination half-life between both subsets of patients has important consequences on the selection of the dosing interval for gentamicin administration. In fact, using the results of the present pharmacokinetic analysis, it is possible to propose "a priori" dosage regimens designed to achieve peak concentrations of approximately $8\,mg\,L^{-1}$ and trough concentrations below $2\,mg\,L^{-1}$ as described by Weber et al (1993). The initial dose (loading dose), calculated as a function of volume of distribution (Vd), should be $3{\cdot}7$ and $3{\cdot}5\,mg\,kg^{-1}$ for neonates <30 weeks and between 30–34 weeks of gestational age, respectively. The maintenance dose, calculated as the ratio of initial dose and accumulation factor, should be $2{\cdot}8\,mg\,kg^{-1}/24\,h$ and $2{\cdot}6\,mg\,kg^{-1}/18\,h$ for younger (<30 weeks) and older (30–34 weeks) neonates, respectively.

Finally, it should be stressed that these results may have important clinical implications for the use of gentamicin in neonates, especially for those with very low birth weight. Besides the "a priori" dosing schedules commented on before, the introduction of the obtained pharmacokinetic parameters in appropriate software (e.g. PKS/Abbott Diagnostics) will permit individual pharmacokinetic parameter determination through Bayesian estimation, which will probably increase the predictive accuracy of dosage readjustments. In fact, as emphasized by Fernández de Gatta et al (1996), the use of Bayesian forecasting in neonates removes the problem of limited sampling, minimizes the need for aggressive monitoring, and improves the cost-benefits of therapeutic drug monitoring.

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