Population pharmacokinetics of amikacin in patients with haematological malignancies

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The aim of this study was to analyse the pharmacokinetic behaviour of amikacin in patients with haematological malignancies using a mixed-effect model and sparse data collected during routine clinical care. The patient population comprised 207 haematology patients divided into two groups: one for computing the population model (n = 134) and the other for validation (n = 73). A one-compartment model was used and the following covariates were tested for their influence on clearance and volume of distribution: age, gender, weight, parenteral nutrition, creatinine clearance, stage of antineoplastic treatment (induction, consolidation, intensification), number of weeks postchemotherapy, clinical diagnosis, Eastern Cooperative Oncology Group score, neutropenia, hypoalbuminaemia, concomitant medication (vancomycin and/or amphotericin B), overhydration, and autologous or allogenic bone marrow transplant. The non-linear mixed-effect model (NONMEM) was used to assess the population pharmacokinetic model of amikacin in these patients. Apart from bodyweight and renal function, acute myeloblastic leukaemia and hypoalbuminaemia proved to be the most important covariates explaining the interindividual variability in amikacin pharmacokinetics in patients with haematological malignancies. The predictive performance of this population model for amikacin serum concentrations seems suitable for clinical purposes.

Introduction

Aminoglycoside antibiotics are widely used in the management of serious infections caused by Gram-negative organisms in patients with solid or haematological malignancies, and as empirical therapy for febrile episodes in neutropenic patients.\textsuperscript{1-4} Despite this widespread use, only limited data are available on aminoglycoside disposition in this kind of patient.\textsuperscript{5-14} Information on drug disposition in target populations allows clinicians to optimize the design of dosage regimens both ‘a priori’ and later in the course of therapy. Individualization of dosage requirements is especially necessary in high-risk populations, such as patients with malignancies, due to the life-threatening nature of infections in neutropenic patients and the narrow therapeutic index of aminoglycosides. Increased aminoglycoside distribution volumes and clearances have been noted in patients with malignancies.\textsuperscript{5,6,8-10,12,13} However, these kinetic alterations are not uniform in all subgroups of malignancies and cannot be attributed to any single variable such as malignancy type, degree of neutropenia, disease state, total exposure or type of chemotherapy. Furthermore, no combination of factors has been described to accurately predict which patients will require larger dosages of aminoglycosides.

Limitations in previous work in this area include analysis of various aminoglycosides simultaneously, the inclusion of mixed populations (e.g. haematology–oncology patients), population size (≤30 patients) and methodological issues (e.g. standard approach). Accordingly, the aim of the present study was to characterize amikacin pharmacokinetics in a large population representative of patients with an underlying haematological malignancy using sparse data collected during routine clinical care. Our main objectives

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were to evaluate the effects of several clinical and physiopathological factors on the disposition kinetics of this drug and to find potential predictive factors for dosage individualization.

**Patients and methods**

**Patients**

Data were collected retrospectively from 207 inpatients with an underlying haematological malignancy and who were admitted to the Haematology Department of our institution between January 1990 and December 1996. All patients received amikacin in combination with ceftazi-dime or piperacillin–tazobactam as first-line therapy for their febrile neutropenia. Serum drug concentrations were monitored by our Clinical Pharmacokinetic Service. A total of 285 febrile episodes were evaluated. Due to intra-individual physiopathological changes if the time period between each febrile episode was more than 1 month, we considered each febrile episode as an individual course of amikacin for the population analysis. Forty-five patients had two febrile episodes (90 courses), 15 patients had three episodes (45 courses), one patient had four episodes (four courses) and 146 patients received only one course of amikacin therapy.

Because the widespread applicability of amikacin population pharmacokinetic parameters was being explored, individuals were not excluded on the basis of age, concurrent disease states or drug therapy. The criteria for inclusion were the availability of amikacin dosage regimens, serum drug concentrations, and the precise timings of dose administration and blood sampling over the entire course of amikacin therapy.

The following data were retrieved from each patient’s medical record at entry: clinical diagnosis, age, gender and ECOG performance status (grades from zero to four according to the standards of the Eastern Cooperative Oncology Group). The patient data obtained on the day of each amikacin monitoring were: total bodyweight (TBW), serum creatinine (CRs), parenteral nutritional support, stage of antineoplastic treatment (induction, consolidation, intensification or maintenance), number of weeks post-chemotherapy, concomitant medication (vancomycin and/or amphotericin B), and the presence or absence of bone marrow transplant (BMT), neutropenia (absolute neutrophil count of <100/mm³), hypoalbuminaemia (serum albumin concentration <3.5 g/dL) and a positive hydric balance. Creatinine clearance ($C_{\text{CR}}$) was calculated by the method of Cockcroft and Gault. Amikacin courses were divided into two sets: one for computing the population model ($n = 180$) and the other for validation ($n = 105$). The main criterion for assigning amikacin courses to each set was chronological: the first set contained data obtained from approximately two-thirds of the time evaluated (January 1990 to December 1994) and the second set corresponded to data obtained between January 1995 and December 1996. This kind of criterion could explain some of the differences in the incidence of covariates between both sets. Patient characteristics are summarized in Table I.

As the study involved retrospective routine collection of clinical data and required no additional blood samples other than those ordinarily requested by the clinical pharmacokinetic service, informed consent and ethical approval were not obtained.

**Serum sampling and drug analysis**

Initial amikacin dosing regimens were chosen by attending physicians. Amikacin was administered od in 154 courses, and in two or three divided doses in 131 courses. All doses were administered over 30–60 min as intermittent, iv infusions. Blood sampling was ordered as required clinically. Thus, amikacin serum concentrations after first doses and/or after steady state were obtained. The sampling times for peak amikacin concentrations varied (30–180 min post-infusion), whereas most trough serum levels were obtained within 60 min of the infusion. Figure 1 shows the number of amikacin serum concentrations in relation to blood sampling times. Amikacin serum concentrations were determined by fluorescence polarization immunoassay (TDx Abbott, North Chicago, IL, USA). The intraday coefficient of variation for the assay was <5%.

**Population analysis**

A one-compartment open population model with first-order elimination was used. The corresponding pharmacokinetic parameters—clearance ($Cl$) and volume of distribution ($V_{d}$)—were initially modelled as a function of individual attributes or covariates according to the following equation:

$$Pm = \sum_{i=1}^{n} \theta_i \text{ Covariates}^{\theta_i+1},$$

where $Pm$ represents the pharmacokinetic parameter and $\theta$ the values to be estimated.

The covariates analysed were continuous [age, weight, creatinine clearance, number of weeks postchemotherapy and performance status at entry (ECOG)] or categorical (gender, clinical diagnosis, parenteral nutrition, stage of antineoplastic treatment, concomitant medication, BMT, neutropenia, hypoalbuminaemia and overhydration).

The statistical model accounting for interindividual variability in pharmacokinetic parameters and for residual error was initially modelled with additive (homoscedastic) and proportional (heteroscedastic) error models. A maximum likelihood objective function was estimated using an extended least squares non-linear regression method and the NONMEM computer program (version IV, level 2.0) with double precision.
Model-building process

The regression model was constructed in four steps. The difference in objective functions (asymptotically $\chi^2$ distributed) was used to compare alternative models.\textsuperscript{17}

Step 1: selection of the statistical model, where random effects (interindividual and residual components) were evaluated with the structural basic model.

Step 2: construction of the intermediate model by testing the incorporation of continuous covariates in both a linear and non-linear way.

Step 3: construction of the full model by testing the incorporation of the most influential categorical covariates into the intermediate model ($P < 0.01$). These were included in the model in a multiplicative way.

Step 4: elaboration of the final pharmacostatistical model by removing covariates from the full model if $P > 0.005$.

Additionally, after the final model had been found, each covariate was in turn deleted from it and the reduced model was tested against the full model as a final check.

Other criteria used in evaluating alternative models were: inspection of weighted residual plots, minimization of interindividual variances and improvement in their precision, a reduction in the magnitude of residual variability and the Akaike Information Criterion.\textsuperscript{18}

Validation of the population model

The population model defined was used to predict ‘a priori’ serum amikacin concentrations ($n = 149$) in the validation population. The ‘a priori’ predictions of amikacin serum concentrations were obtained by incorporating our population model into the Abbottbase pharmacokinetic program (ABBOTTBASE; Pharmacokinetic Systems, IL, USA). Predicted serum concentrations were compared with measured concentrations to determine the predictive
performance of the final model by examining three components: bias, precision and percentage of success.\(^{19}\)

In addition to standard errors we determined the standardized prediction error (SPE) to quantify the predictive performance of the final model. This is defined as the difference between the measured \((C_M)\) and predicted \((C_P)\) concentrations divided by the estimate of the standard deviation (s.d.) in predicted values \((SDC_P)\).\(^{20}\) This combined standard deviation was estimated using the variance-covariance of interindividual and residual variability provided by NONMEM.\(^{21}\)

\[
SPE = \frac{C_M - C_P}{SDC_P}
\]

Finally, we estimated the 68% prediction interval.\(^{21}\) To obtain an estimation of the accuracy of this interval, we determined the proportion of measured concentrations within the expected 68% prediction interval and, if this rate differed significantly from 68% \((P < 0.05)\), by comparing the 95% confidence limits for the observed proportion of levels inside the prediction interval.\(^{22}\)

**Results**

**Population model**

Preliminary analysis of the basic pharmacokinetic model combining different error models pointed to the superiority of the proportional error model for estimating interindividual variability and the additive error model for estimating residual variability. Accordingly, both variability error models were used in all subsequent analyses. Patient covariates were tested individually for \(Cl\) and \(V_d\). Continuous covariates were tested on the basic model to obtain the intermediate model and the categorical covariates were tested on this latter model to obtain the full-final model. The complete results of the analysis are summarized in Table II. The model-building process for characterizing amikacin pharmacokinetics in patients with haematological malignancies is shown in Table III. The mean values obtained for amikacin clearance and volume of distribution from the simplest basic model were 5.04 L/h and 30.1 L, respectively. The corresponding figures for interindividual variability, expressed as the coefficient of variation, were 59.7 and 17.0%, respectively. The residual variability for

<table>
<thead>
<tr>
<th>Covariates</th>
<th>(CI) (L/h)</th>
<th>(V_d) (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance</td>
<td>301.47(^a)</td>
<td>0</td>
</tr>
<tr>
<td>Bodyweight</td>
<td>14.27(^b)</td>
<td>9.93(^a)</td>
</tr>
<tr>
<td>Gender</td>
<td>2.31</td>
<td>0</td>
</tr>
<tr>
<td>Acute myeloblastic leukaemia</td>
<td>8.63(^a)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic myeloid leukaemia</td>
<td>2.97</td>
<td>0</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>0</td>
<td>5.62</td>
</tr>
<tr>
<td>Bone marrow transplant</td>
<td>2.37</td>
<td>1.57</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td>0</td>
<td>3.22</td>
</tr>
<tr>
<td>Hypoalbuminaemia</td>
<td>0</td>
<td>8.65(^b)</td>
</tr>
<tr>
<td>Positive hydric balance</td>
<td>0.57</td>
<td>0</td>
</tr>
<tr>
<td>Concomitant medication vancomycin</td>
<td>0</td>
<td>3.72</td>
</tr>
<tr>
<td>Stage of antineoplastic treatment consolidation</td>
<td>6.52</td>
<td>1.73</td>
</tr>
</tbody>
</table>

Basic model: \(Cl = \theta_1; V_d = \theta_2\). Objective function value (OFV), 2249.3. Intermediate model: \(Cl = \theta_1; Cl\) creatinine; \(V_d = \theta_2\) bodyweight; OFV, 1933.3.

\(^a\) A reduction in OFV of >6.6 U was considered statistically significant, i.e. \(P < 0.01\).

\(^b\) Relative s.d. >50%. 

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**Figure 1.** Number of amikacin serum levels in relation to blood sampling times. \((C_t\) corresponds to sampling times other than those specified in the figure.)
Amikacin in haematology patients

Table III. Structural evolution related to the model-building process

<table>
<thead>
<tr>
<th>Model</th>
<th>Pharmacokinetic parameters</th>
<th>Stage</th>
<th>Objective function value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>$Cl = 5.04$</td>
<td>initial status</td>
<td>2249.32</td>
</tr>
<tr>
<td></td>
<td>$V_d = 30.1$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>$Cl = 1.15 Cl_{CR}$</td>
<td>after step 1</td>
<td>1933.36</td>
</tr>
<tr>
<td></td>
<td>$V_d = 0.42$ TBW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-final</td>
<td>$Cl = 1.11 Cl_{CR} (1 + 0.20$ AML)</td>
<td>after step 4</td>
<td>1916.44</td>
</tr>
<tr>
<td></td>
<td>$V_d = 0.37$ TBW (1 + 0.30$ H)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: $Cl_{CR}$, creatinine clearance; TBW, total bodyweight; AML, acute myeloblastic leukaemia; H, hypoalbuminaemia.

Table IV. Parameter estimates for the final model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>s.e. (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_1$</td>
<td>1.110</td>
<td>3.19</td>
<td>1.04, 1.18</td>
</tr>
<tr>
<td>$\theta_2$</td>
<td>0.200</td>
<td>34.30</td>
<td>0.06, 0.33</td>
</tr>
<tr>
<td>$\theta_3$</td>
<td>0.373</td>
<td>7.13</td>
<td>0.32, 0.42</td>
</tr>
<tr>
<td>$\theta_4$</td>
<td>0.304</td>
<td>42.76</td>
<td>0.04, 0.56</td>
</tr>
<tr>
<td>$CV_{Cl}$</td>
<td>28.7%</td>
<td>18.37</td>
<td>23.00, 33.53</td>
</tr>
<tr>
<td>$CV_{V_d}$</td>
<td>26.2%</td>
<td>26.19</td>
<td>7.79, 36.21</td>
</tr>
<tr>
<td>$CV_{\sigma}$</td>
<td>34.1%</td>
<td>15.69</td>
<td>28.40, 39.03</td>
</tr>
</tbody>
</table>

Abbreviations: $CV$, coefficient of variation; s.e.; standard error; CI, confidence intervals.

this basic model was 7.13 mg/L, accounting for a variation coefficient of 41.6% at serum amikacin concentrations of 8.75 g/L, corresponding to the mean value in our patient population.

Stepwise incorporation of patient covariates and the use of the criteria defined to evaluate the goodness of fit afforded the final population model. The final population model accounting for amikacin pharmacokinetics in haematology patients was: $Cl = 1.11 Cl_{CR} (1 + 0.20$ acute myeloblastic leukaemia), $V_d = 0.37$ TBW (1 + 0.30 hypoalbuminaemia).

Table IV shows the population parameter estimates and associated percentage relative standard errors of the final model. Figure 2 depicts the plot of the predicted versus observed amikacin serum concentrations from the basic to the final model, showing the improvement in the goodness of fit.

Validation analysis

From the final population model and the patient characteristics of the validation population, we obtained the individual ‘a priori’ estimates of clearance and volume of distribution of amikacin in each patient. These values and the actual amikacin dosage regimens allowed us to predict

Figure 2. Correlation analysis between predicted ($C_{\text{pred}}$) and observed ($C_{\text{obs}}$) amikacin concentrations for the basic (a) and final (b) models. Small and large dots represent single and repeated values, respectively.
the corresponding amikacin serum concentrations, which were later compared with the measured values.

Table V shows the values of the normal and standardized prediction errors of ‘a priori’ predicted amikacin serum concentrations obtained in the validation patients. The proportion of measured concentrations within the expected 68% prediction interval was 60.4% (CI 95%: 49.6–65.9) for ‘a priori’ predictions.

**Table V. Validation analysis of the final model**

<table>
<thead>
<tr>
<th>Prediction errors (PEs)</th>
<th>Value (s.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean prediction error (MPE)</td>
<td>1.69 (5.5)</td>
</tr>
<tr>
<td>absolute prediction error (APE)</td>
<td>4.25 (3.9)</td>
</tr>
<tr>
<td>mean squared prediction error (RMSE)</td>
<td>5.82</td>
</tr>
<tr>
<td>Standardized prediction errors</td>
<td></td>
</tr>
<tr>
<td>mean prediction error (SMPE)</td>
<td>0.25 (1.18)</td>
</tr>
<tr>
<td>absolute prediction error (SAPE)</td>
<td>0.94 (0.75)</td>
</tr>
</tbody>
</table>

*a A total of 149 concentrations of amikacin were predicted and compared.

*b MPE = ΣPE/n, where PE is the difference between the predicted and the actual value; absolute prediction error, APE = 2ΣPE/n; root mean squared prediction error, RMSE = (ΣPE^2/n)^0.5.

The proportion of measured concentrations within the expected 68% prediction interval was 60.4% (CI 95%: 49.6–65.9) for ‘a priori’ predictions.

**Discussion**

Understanding the variability associated with pharmacokinetics and identifying subpopulations with special features can provide clinicians with relevant information for dosage individualization. The population approach allows the pharmacokinetic characterization of drugs in a target population, the associated interpatient and residual variability, and the covariates affecting such variability by using data collected in patients receiving such therapy.

Several patient subpopulations in which the pharmacokinetic behaviour of aminoglycosides is altered, including patients with an underlying haematological malignancy, have been identified. However, most studies assessing the influence of haematology subpopulations in aminoglycoside pharmacokinetics have been done with gentamicin or tobramycin.5–7,12,13,23 The few previous reports on the disposition of amikacin in haematological malignancies are flawed owing to reduced population size, inclusion of solid tumours or the use of conventional methods for population analysis.8–11 To our knowledge, no previous study on amikacin population pharmacokinetics in patients with haematological malignancies has been carried out using mixed-effect models.24 Nevertheless, this methodology has been applied to characterize the population pharmacokinetics of amikacin in other specific subpopulations.25,26

Population pharmacokinetics provides a quantitative view of the effect of several physiopathological and/or clinical covariates on the pharmacokinetic profiles of drugs. The patient covariates analysed in this study were selected taking into account previous studies and the main objective of the work. Accordingly, the most usual variables in clinical practice accounting for the type, severity, treatment, evolution or control of underlying disease were used. Moreover, these were already available in advance of dosing, allowing easy utilization of the model obtained.

The mean values obtained for amikacin clearance and volume of distribution in this study, using NONMEM, are consistent with reported values for patients with haematological malignancies in other studies using standard (two stage) approaches.9–11 Also, the mean values accounting for the effect of renal function and bodyweight on amikacin clearance and volume of distribution, respectively, were within the range quoted for this drug. Our results show that the presence of acute myeloblastic leukaemia increased amikacin clearance by 20.0%, whereas the volume of distribution increased it by 30.4% in patients with hypoalbuminaemia. Despite this, other haematological diagnoses, the severity of the disease, the time postchemotherapy, the stage of antineoplastic treatment, and the existence of neutropenia or bone marrow transplantation, among other clinical parameters studied, had no significant correlation or effect on amikacin disposition.

Two previous studies that specifically assessed the influence of malignancy type on aminoglycoside pharmacokinetics also reported increased clearance values in
patients with acute leukaemia. In these studies, a higher initial calculated creatinine clearance or a high percentage of blast cells in bone marrow at the time of presentation were associated with the observed increase in amikacin clearance. Although we have no knowledge of the underlying mechanism responsible for enhanced amikacin clearance in patients with acute leukaemia, exclusion of the other clinical variables analysed in our population model indirectly points to a physiopathological factor implicit in the diagnosis of acute myeloblastic leukaemia or to enhanced renal function in these patients. In agreement with the latter hypothesis, a recent study in children with leukaemia has shown that the glomerular filtration rate is normal and highly variable in these patients but is not apparent from the usual clinical indices of renal function.

It has been reported previously that the volume of distribution of aminoglycosides is elevated in the presence of hypoalbuminaemia. This may be due to low venous oncotic pressure, which results in increased extravascular fluid, i.e. the physiological space that accounts for the distribution of this class of drugs. An expansion of extracellular fluid has also been reported in patients undergoing bone marrow transplantation.

The population estimates of residual variability (34.1%) suggest the presence of intraindividual variability. This kind of variability may be due to other factors not evaluated in our study or to the non-intraindividual evaluation of the covariates analysed.

The procedure used in this study for validation of the population model was primarily related to the ultimate goal of the population study. The bias and precision achieved using our population model for predicting ‘a priori’ amikacin serum concentrations support the view of improved predictive performance when specific pharmacokinetic parameters are used for particular subpopulations.

The validation results offer some assurance to our population model, at least for clinical predictive purposes. In addition, the model can readily be included in clinical pharmacokinetic software, thus improving the design of initial amikacin dosage in haematology populations and providing feedback adjustments of dosage regimens to achieve desired serum concentrations. The initial amikacin doses suggested by our population model (implemented in the Abbottbase Pharmacokinetic System) are shown in Figure 3 and point to a nearly two-fold increase over conventional doses in haematology patients with simultaneous acute myeloblastic leukaemia and hypoalbuminaemia. It should be recalled that some results of population analyses may be semiquantitative at best, particularly for covariates with a significant degree of imprecision in their estimates. However, the pragmatic approach used in this study to validate the results suggests that the clinical diagnosis and the nutritional status of patients with haematological malignancies should be considered when finding a rational amikacin dosing schedule in this patient subpopulation.

A possible limitation in the present study is that the validation was made through the predictivity of serum levels without any clinical endpoint, i.e. the impact of adequate prediction on the outcome of the febrile episode or on the renal or cochleovestibular tolerance of amikacin. Thus, the clinical usefulness of this approach still remains to be demonstrated.

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References


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