Variability in the pharmacokinetics of epirubicin: a population analysis

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Summary. Population pharmacokinetic analysis of the anticancer agent epirubicin was carried out using the program NONMEM. Data were available from 36 patients aged 20–73 years, of whom 23 were women. All subjects exhibited normal liver and renal function. Epirubicin was given as a short-term i.v. infusion over the dose range of 25–100 mg/m², and an average of 11 plasma samples/subject were taken for a period of up to 72 h after each dose. A two-compartment model was fitted to the data, characterised by the parameters clearance, volume of the central compartment, alpha and beta. Clearance was tested as a linear function of various demographic and/or biochemical features. A significant proportion of the variability in clearance could be attributed to sex, and also to age in women. For example, a 25-year-old man would display an average clearance of 95 l/h, whereas a 70-year-old woman would exhibit an average clearance of 64 l/h. Such differences in clearance might be important in the selection of epirubicin dose regimens.

Introduction

In common with other anticancer drugs [6, 10, 15], epirubicin shows a large degree of pharmacokinetic variability that may have extremely serious consequences in cancer chemotherapy. For example, Eksborg [4] reported an almost 10-fold intersubject variability in plasma epirubicin area under the curve (AUC) values when these had been normalised for dose.

Epirubicin is a stereoisomer of doxorubicin and exerts its antitumour activity via a similar mechanism. Previous work has revealed an identifiable relationship between dose and response, and clinical studies have shown epirubicin to be as effective as doxorubicin but to exhibit less toxicity at comparable doses [3]. The reduced cardiotoxicity observed for epirubicin has been attributed to differences in its metabolic degradation [14]. A study of the treatment of nasopharyngeal carcinoma found that responders exhibited lower epirubicin clearance values than did non-responders, emphasising the clinical importance of pharmacokinetic variability. However, further analysis failed to show any relationship between clearance and any other identifiable factor in the 28 patients studied [8].

The aim of the present study was to explore further and characterise the pharmacokinetic variability of epirubicin. The population pharmacokinetic data-analysis program NONMEM [1] was used. This program enables the quantification of the relationships between pharmacokinetic parameters and several pathophysiological features exhibited by a group of patients receiving this drug.

Patients and methods

Patients

Data on plasma drug concentrations were available from 36 patients, including 23 women and 13 men. All subjects had received epirubicin in a short infusion as part of a combined chemotherapy course, with the epirubicin being given at 1–2 h prior to initiation of the remaining therapy. Nine of the women had breast cancer and received 50 mg/m². Of the patients who suffered from Hodgkin’s lymphoma, five received 35 mg/m² and five were given 25 mg/m². Among the 17 subjects who exhibited a sarcoma, 16 received 100 mg/m² and the remaining patient was given 50 mg/m². All infusions were given over 3–20 min, the median duration of administration being 5 min. For measurements of epirubicin concentration, blood samples were drawn at the end of the infusion and for a further 48 h. Five patients were also sampled at 72 h. A total of 10–12 samples were obtained from each patient, giving a total of 419 concentration-time data points for the population analysis.

Demographic and biochemical data included those on sex, age, weight and serum levels of creatinine and bilirubin. The distribution of weight and age for men and women is shown in Fig. 1. The age ranged from 20 to 73 years and the weight, from 49 to 90 kg. The ranges for serum creatinine and bilirubin were 40–119 and 2–19 μmol/l, respectively; all patients showed values within the normal ranges.
Population pharmacokinetic analysis

Average values for pharmacokinetic model parameters. The concentration-time data obtained from all subjects were analysed using the NONMEM program [1], which enables the pharmacokinetic parameters of a model to be estimated and the relationships between those parameters and the pathophysiological features of a group of patients to be quantified in a single step. This contrasts with traditional pharmacokinetic analysis, which is conducted in two stages: (1) the different individuals' pharmacokinetic parameters are characterised and (2) relationships between those parameters and the pathophysiological data are sought, usually via simple or multiple linear regression.

Previous pharmacokinetic analysis of these and other epirubicin data have almost always used a three-compartment model [3, 14, 18]. However, visual inspection of the pooled concentration-time data for all subjects indicated that a two-compartment model might be alternatively applied. Using NONMEM, both models were tested. As the three-compartment model could not be justified statistically, the two-compartment model was used as the basis for investigating the influence of various demographic factors on the pharmacokinetics of epirubicin. For this reason, the parameters of this model were clearance ($Cl$), the volume of the central compartment ($Vc$) and the rate constants associated with the distribution and elimination phases, termed alpha and beta, respectively.

We tested the influence of the available demographic and biochemical factors by relating them to the pharmacokinetic parameters using linear models of the type

$$P_k = \theta_1 \cdot F_{a1} + \theta_2 \cdot F_{a2} + \ldots + \theta_n \cdot F_{an}, \quad (1)$$

where $P_k$ is the expected value for the pharmacokinetic parameter (e.g. $Cl$ or $Vc$) in any patient; $F_{a1}, F_{a2}, \ldots$ are identifiable patient factors (e.g. age, weight); and $\theta_1, \theta_2, \ldots$ are a series of regression coefficients.

Models that related age, weight, sex, and serum levels of creatinine and bilirubin to clearance were tested, as were those that related weight and sex to volume (Table 1). These models were embedded in the two-compartment pharmacokinetic model used (Fig. 2). NONMEM then estimated the $\theta$ values (Eq. 1) and/or other kinetic parameters (if these were not specified as functions of demographic factors) simultaneously.

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### Epirubicin analysis

Blood samples were drawn into ethylenediaminetetraacetic acid (EDTA)-coated Vacutainer tubes, immediately centrifuged and stored frozen until required for analysis. Epirubicin was extracted by a solid-phase extraction technique and quantified by HPLC using fluorescence assay technology. The assay was 2 ng/ml.

### Population pharmacokinetic analysis

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### Variance parameters

The distribution of the pharmacokinetic parameters in the population may be characterised by either a normal or a log normal distribution. If the distribution of any pharmacokinetic parameter $P_k$ is normal, the value for the jth individual may be described by

$$P_{kj} = \bar{P}_k + \eta_j, \quad (2)$$

where $P_{kj}$ is the value of the parameter (e.g. $Cl$ or $Vc$) for the jth individual, $\bar{P}_k$ is the mean value of the parameter for the population and $\eta_j$ represents normally distributed errors exhibiting a mean value of zero and a variance of $\sigma^2_{\eta}$. If the $P_k$ parameters are distributed log normally, the value for the jth individual is then given by

$$\ln(P_{kj}) = \ln(\bar{P}_k) + \eta_j, \quad (3)$$

Similarly, the residual (intrasubject) error in concentration may be described by either a normal or a log normal distribution. In the former case,

$$C = \frac{R_o}{[\alpha - \beta]} \left[ 1 - \frac{1}{\alpha - \beta} e^{\alpha t} - 1 \right] e^{\beta t} + \frac{R_o}{[\alpha - \beta]} \left[ 1 - \frac{1}{\alpha - \beta} e^{\alpha t} - 1 \right] e^{\beta t}$$

where $Ro$ is the infusion rate, $Cl$ is clearance, $Vc$ is the volume of the central compartment, $\alpha$ and $\beta$ are hybrid rate constants, $t$ is the length of the infusion, $t_1$ is the time elapsed since the end of the infusion, $F_{a1}, F_{a2}, \ldots$ are identifiable patient factors (e.g. age, age, weight, etc) and $\theta_1, \theta_2, \ldots$ are a series of regression coefficients.

### Table 1. List of models tested and log likelihood differences

<table>
<thead>
<tr>
<th>Model number</th>
<th>List of models tested and log likelihood differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance models:</td>
<td></td>
</tr>
<tr>
<td>1. $Cl = \theta_1$</td>
<td></td>
</tr>
<tr>
<td>2. $Cl = \theta_1 + Wt \cdot \theta_4$</td>
<td></td>
</tr>
<tr>
<td>3. $Cl = \theta_1 + Sex \cdot \theta_4$</td>
<td></td>
</tr>
<tr>
<td>4. $Cl = \theta_1 + Age \cdot \theta_4$</td>
<td></td>
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<tr>
<td>5. $Cl = \theta_1 + Bili \cdot \theta_4$</td>
<td></td>
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<tr>
<td>6. $Cl = \theta_1 + Creat \cdot \theta_4$</td>
<td></td>
</tr>
<tr>
<td>7. $Cl = (\theta_1 + \theta_3 \cdot \theta_4) \cdot ([\theta_3 + \theta_4 \cdot \theta_3])$</td>
<td></td>
</tr>
<tr>
<td>8. $Cl = \theta_1 \cdot \theta_3 \cdot (\theta_3 + \theta_4 \cdot \theta_3)$</td>
<td></td>
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<tr>
<td>9. $Cl = \theta_1 + Dose \cdot \theta_4$</td>
<td></td>
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<tr>
<td>10. $Cl = \theta_1 + SA \cdot \theta_4$</td>
<td></td>
</tr>
<tr>
<td>11. $Cl = \theta_1 + Dose/m^2 \cdot \theta_4$</td>
<td></td>
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<tr>
<td>Volume models:</td>
<td></td>
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<tr>
<td>12. $Vc = \theta_2$</td>
<td></td>
</tr>
<tr>
<td>13. $Vc = \theta_2 \cdot Wt$</td>
<td></td>
</tr>
<tr>
<td>14. $Vc = \theta_2 \cdot Sex$</td>
<td></td>
</tr>
<tr>
<td>15. $Vc = \theta_2 \cdot Sex + \theta_3 \cdot Wt$</td>
<td></td>
</tr>
</tbody>
</table>

Bili, Bilirubin; cf., as compared with model number ...; Creat, creatinine; LLD, log likelihood difference; NA, not appropriate; NS, not significant; SA, surface area (m²); Wt, weight