Clinical pharmacokinetics of zidovudine: inter and intraindividual variability and relationship to long term efficacy and toxicity

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Summary. The variability of the pharmacokinetics of zidovudine after its oral administration to 36 AIDS patients has been investigated by measuring the plasma and urine levels of zidovudine and its metabolite on Days 1 and 35 of continuous treatment. A two-phase absorption model was first defined from well-documented data in 12 subjects. The population characteristics of the kinetic parameters for both days were estimated by a nonparametric method.

On Day 1, the mean (coefficient of variation) volume of distribution of zidovudine was 94.41 (90%), its mean half-life was 0.81 h (107%) and its mean oral clearance was 117 l·h⁻¹ (57%) and on Day 35, these values were, respectively, 1121 (139%), 0.75 h (181%) and 295 l·h⁻¹ (196%). The results confirm the large interindividual and intraindividual variation in zidovudine kinetics.

The four covariates included in the population analysis (body weight, serum haemoglobin, creatinine and bilirubin) did not show clear relationship to the kinetic parameters.

Thirty-four subjects were follow-up clinically for 99 days to 367 days after initiation of zidovudine therapy. The relationship between individual kinetic parameters (determined by Bayesian estimation), mean concentration profiles and outcome was studied through survival analysis. Long-term efficacy was defined as the prevention of opportunistic infections, which occurred in 13 patients. No clinical or kinetic variables, nor the individual zidovudine concentration profiles were found to predict the occurrence of an opportunistic infection. Toxicity was defined as a 20%-decrease in serum haemoglobin, which occurred in 13 patients. A significant relationship between mean daily concentration and toxicity was found, with an hazard of occurrence of toxicity 4.3-times larger when the mean steady state concentration was 0.8 mg·l⁻¹ than 0.6. The results indicate that zidovudine dosage should be individualised.

Key words: Zidovudine, AIDS; plasma concentration-response, population pharmacokinetics, toxicity, efficacy

Various proofs of the efficacy of zidovudine (azidothymidine, AZT), including lower mortality and fewer opportunistic infections in human immunodeficiency virus (HIV)-infected patients, have been reported (Volberding et al. 1990) since the first studies in 1986 (Yarchoan et al. 1986; Fischl et al. 1987). The most commonly-reported adverse effect has been haematologic toxicity (Richman et al. 1987). A general review of the pharmacokinetic and pharmacodynamic properties of zidovudine and its therapeutic efficacy was published in 1989 (Langtry and Campoli-Richards 1989). In HIV-infected patients, its pharmacokinetics has been clearly established after oral and intravenous administration (Collins and Unadkat 1989). Briefly, after oral administration, zidovudine undergoes hepatic first-pass extraction. The major route of elimination is biotransformation in the liver, and, in humans, the major metabolite is the glucuronide derivative (GAZT). Only a small amount of an administered dose is recovered unchanged in urine and urinary excretion of GAZT represents most of the dose. The total clearance is large and it has the short average elimination half-life of about 1 h.

We have performed an analysis of the interindividual and intraindividual variability of zidovudine kinetics after its oral administration to 36 AIDS or AIDS-related complex patients using kinetic measurements on the first and the 35th days of therapy. A compartmental model was used to describe the kinetics of the two compounds. This model was devised from well-documented data using standard estimation methods. We then analysed the interindividual variability of zidovudine kinetics separately on Days 1 and 35 using the nonparametric maximum likelihood method (NPML) (Mallet 1986; Mallet et al. 1988). Four covariates, body weight, serum haemoglobin, bilirubin and creatinine were incorporated in the analyses. A specific analysis of intraindividual variability due to non constancy of the parameters was also performed.

In the published population analyses of zidovudine kinetics, considerable interindividual variability has been observed (Unadkat et al. 1988; Gitterman et al. 1990). For various drugs which exhibit large kinetic variability it is accepted that plasma concentration is better related to the
effect than the administered dose (Thomson and Whiting 1992). However, present analyses of zidovudine efficacy and toxicity have not incorporated kinetic information (Creagh-Kirk et al. 1988; Steinberg et al. 1989). In 34 patients, we have analysed the relationships between the kinetic parameters and mean concentrations on one hand, and efficacy or toxicity on the other by survival analysis (Escalona et al. 1991). Inefficacy and toxicity were both defined by discrete events, namely the occurrence of an opportunistic infection and a 20% decrease in haemoglobin level, respectively. This attempt to study both pharmacokinetics and pharmacodynamics of zidovudine is a step towards better clinical use of the drug.

### Materials and methods

#### Preliminary analysis

Twelve of the 47 patients in the protocol ANRS 01 (DiQuet et al. 1989), with well-documented kinetic data, were analysed as first step in building the pharmacokinetic model. In this protocol, patients were randomly assigned to receive daily 1.2 g of zidovudine, every 6, 8 or 12 h, or 200, 300 or 600 mg t.i.d. On the first day of treatment, only one dose was given and 11 blood samples were collected at 0.16, 0.33, 0.66, 1.5, 2, 2.5, 3, 4, 6 and 8 h after administration. The 12 patients in this preliminary analysis were selected by choosing at random 2 patients from each dose group.

#### Population protocol

Thirty-six HIV infected patients, who met Criteria IV of the 1985-CDC classification, and who were taking part in a multicentre, double blind, placebo-controlled trial were analysed (Mentré et al. 1989). They initially received 500 mg zidovudine every 6 h for 28 days, and then 250 mg every 6 h. They received various concomitant therapies. Dose reduction or discontinuation of therapy were allowed in case of various events including haematologic toxicity. All subjects but two received the full dosage of 2.0 g for 28 days, followed by 1.0 g at least until Day 35. For 2 subjects, because of toxicity, the dose was reduced to 1.0 g after 8 and 18 days, respectively, which was then maintained at least until Day 35. Four plasma samples (before administration of the second dose and 0.5, 1 and 3 h after ii) were taken on the first and 35th day of therapy. Urine samples were also collected over 24 h on Days 1 and 35. Kinetic measurements on Day 35 were available only from 31 subjects.

The initial duration of the protocol was planned to be 24 weeks and biochemical and haematological parameters were supposed to be estimated every 1 to 2 weeks. For only 34 subjects (31 m and 3 f) was the exact dosage of zidovudine during therapy recorded. The initial values of clinical parameters and the follow-up findings in these 34 subjects are summarised in Table 1.

After a mean follow-up of 139 days, a total of 23 opportunistic infections was observed in 17 patients. One of the two patients with no dosage record was followed for 168 days, and another patient experienced an opportunistic infection after 108 days of treatment.

### Analytical methods

The plasma concentrations and urinary excretion of zidovudine and GAZT were assayed by HPLC. The measurement error was assumed to be gaussian and independent with a zero mean. The variance $\sigma^2(c)$ on one measurement was considered to be given by:

$$\sigma^2(c) = A^2 + (Bc)^2$$

In this conventional variance model, the standard deviation of the error is approximately proportional to the value to be measured, with a coefficient $B$ and has a lower limit $A$, when low values are measured. For the two types of observations and compounds, the constant term $A$ and the coefficient of proportionality $B$ were chosen according both to the precision of the HPLC method in the range of measurements (Good et al. 1988) and the error in the collection of the samples. The value of $B$ was chosen as 20% for the plasma concentrations of both compounds, and as 30% for urinary levels which were less precisely collected. The values of $A$ chosen were 0.007 mg/l (7 gg) for plasma concentrations (respectively urinary amounts) of zidovudine and 0.030 mg/l (30 gg) for GAZT.

### Pharmacokinetic model

The pharmacokinetic model of zidovudine and GAZT was defined with the data from the 12 subjects of the preliminary analysis, using standard compartmental models for distribution and elimination (Gibaldi and Perrier 1982). As the absorption model was more specifically studied, no urinary measurements were analysed and only combinations of certain pharmacokinetic parameters were estimated. The vector of the identifiable parameters was estimated from each individual’s measurements by a standard estimation method (Bard 1974). More specifically, the computer program PHACIN (Villa et al. 1988) was used to provide an estimate of the parameters through minimisation of the weighted least-squares criterion defined according to the measurement error model. The Akaike Information Criterion (AIC) was used to assess the best model (Akaife 1974). Using weighted least-squares with uncorrelated gaussian errors, the criterion is defined as the sum of the weighted least-squares criterion (a measure of the goodness of fit) and of a 'penalty' function, which is twice the number of parameters in the model (Landaw and Distefano 1984). The model with the smallest AIC, whatever the attained value, is the most adequate according to the principle of parsimony.

In the population protocol both plasma and urinary measurements were analysed so that all the parameters of the model defined during the preliminary analysis were identified.

### Population models

The pharmacokinetic parameters and biological covariates were assumed to be randomly distributed across the population and their population characteristics were estimated by the NPML method. More specifically, given the pharmacokinetic and measurement error models, this method provides a discrete estimate of the joint distribution of the parameters and of the covariates by maximising the likelihood of the entire set of measurements and covariates (Mallet 1986). This estimation was performed without specifying either a parametric distribution of the parameters or a regression model (termed 'second stage model') between the parameters and

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**Table 1. Initial clinical parameters and total duration of follow-up of the 34 subjects included in the population analysis of the kinetics of zidovudine and who had been followed after initiation of zidovudine therapy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (days)</td>
<td>266.2</td>
<td>94.6</td>
<td>99</td>
<td>367</td>
</tr>
<tr>
<td>Age (y)</td>
<td>37.1</td>
<td>9.4</td>
<td>21</td>
<td>71</td>
</tr>
<tr>
<td>Karnofsky score</td>
<td>94.7</td>
<td>9.9</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.8</td>
<td>7.8</td>
<td>154</td>
<td>189</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>63.8</td>
<td>8.9</td>
<td>44</td>
<td>82</td>
</tr>
<tr>
<td>Haemoglobin (g d-1)</td>
<td>12.7</td>
<td>1.6</td>
<td>9.9</td>
<td>15.3</td>
</tr>
<tr>
<td>Creatinine (mmol 1^-1)</td>
<td>83.3</td>
<td>11.6</td>
<td>65</td>
<td>106</td>
</tr>
<tr>
<td>Bilirubin (mmol 1^-1)</td>
<td>6.5</td>
<td>2.3</td>
<td>2.9</td>
<td>13</td>
</tr>
</tbody>
</table>

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