Pharmacokinetics of Saquinavir, Zidovudine, and Zalcitabine in Combination Therapy

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We investigated the pharmacokinetics of zidovudine, zalcitabine, and saquinavir in AIDS Clinical Trial Group protocol 229. Patients received either saquinavir, zalcitabine, or a combination of both, together with zidovudine three times a day. Approximately 100 patients were enrolled in each treatment arm, and intensive pharmacokinetic studies were performed on about 25 patients per arm at weeks 1 and 12. We estimated the pharmacokinetic parameters of all three drugs by using parametric and nonparametric methods. The mean values of the pharmacokinetic parameters of zidovudine (clearance [CL]/bioavailability [F], 168 liters/h; volume of distribution [V]/F, 185 liters; half-life, 0.76 h) and zalcitabine (CL/F, 25 liters/h; V/F, 92.2 liters; half-life, 2.7 h) were similar to those reported previously. For saquinavir, the mean pharmacokinetic parameter estimates using parametric methods were as follows: maximum concentration of drug in serum (Cmax), 70.8 ng/ml; time to Cmax, 3.11 h; area under the curve, 809 ng · h/ml; CL/F, 989 liters/h; V/F, 1,503 liters; half-life, 1.38 h. For all three drugs, clearance decreased with age. Weight did not influence the clearance of zidovudine, but the clearance of zalcitabine and saquinavir increased with weight. There were no differences in pharmacokinetic parameters between study weeks and arms, suggesting that there is no change in kinetics with chronic administration and that there are no significant pharmacokinetic interactions among these three drugs.

Human immunodeficiency virus protease inhibitors, such as saquinavir, are a promising new class of antiretroviral drugs. AIDS Clinical Trial Group (ACTG) protocol 229 was designed to test the hypothesis that a combination of saquinavir, zidovudine, and zalcitabine would be more effective than the combination of saquinavir with a nucleoside analog or the combination of two nucleoside analogs. The primary results of this study have been presented elsewhere (3).

Individualization of drug therapy requires an understanding of the subject-specific pharmacokinetics of a drug, as well as of the relationship between drug concentrations (drug exposure) and biological effects. One of the sources of variability in the individual response to similar or identical doses of antiretroviral therapy observed in clinical studies may be inter- and intrapatient variabilities in the pharmacokinetics of prescribed drugs. While zidovudine and zalcitabine pharmacokinetics have been described previously (4, 5), the magnitude of the variability in the pharmacokinetics of saquinavir during chronic administration has not been reported earlier. In this paper, we present standard nonparametric and parametric analyses of the pharmacokinetics of zidovudine and zalcitabine, and for saquinavir we present an additional nonparametric analysis describing the pharmacokinetic data with longitudinal splines (12). The accompanying paper (11a) reports on other sources of variability in individual response and investigates the relationship between exposure to these drugs and viral and immunologic responses.

MATERIALS AND METHODS

Study design. ACTG 229 was a phase II randomized study of three treatment regimens. The sample size was approximately 100 patients per treatment arm. Patients in arm 1 received saquinavir at 600 mg three times a day (TID) (Invirase [formerly Roche 31-8959]; Hoffman-La Roche, Nutley, N.J.) plus open-label zidovudine at 200 mg TID (Retrovir; Burroughs Wellcome Company, Research Triangle Park, N.C.). Patients in arm 2 received saquinavir 600 mg TID plus zalcitabine at 0.75 mg TID (Hivid; Hoffman-La Roche) plus open-label zidovudine at 200 mg TID. Patients in arm 3 received zalcitabine at 0.75 mg TID plus open-label zidovudine at 200 mg TID. The initial treatment duration was 24 weeks, but all of the patients were offered continuation of the same blinded regimen for up to 56 weeks until a common closing date. Patients were required to have documented HIV infection, CD4+ cell counts between 50 and 301 cells/mm3 within 30 days of study entry, and at least 4 months of prior zidovudine therapy with no toxicity at 600 mg/day. For further details regarding design and patient eligibility criteria, see reference 3.

Pharmacokinetic study design, sampling, and analytical methods. In a subgroup of patients at three designated sites, intensive blood sampling over one dosing interval was performed at week 1 and again at week 12, yielding intensive pharmacokinetic studies of 20 to 25 patients per arm. Samples were collected immediately predose and at 1, 2, 3, 4, 6, and 8 h after dosing. A breakfast was consumed 30 min before taking the dose, since it had been shown that the presence of food increases the bioavailability (F) of saquinavir. All study medications were taken simultaneously, and patients did not receive additional study medications within the pharmacokinetic assessment sampling period.

Plasma was separated by centrifugation within half an hour of blood collection, stored at −20°C, and shipped. Samples were assayed for saquinavir by a validated radioimmunoassay developed by Roche within the Bioanalytical Group of the Department of Metabolism and Pharmacokinetics, Huntingtondon Center Ltd., Cambridgeshire, United Kingdom. Briefly, standards and samples were incubated overnight at ambient temperature with sheep saquinavir antiserum and iodinated tracer ([125I]-tyrosyl-saquinavir). Bound and free saquinavir were separated by an incubation of a second antibody covalently coupled to cellulose followed by an incubation (20 min) and a centrifugation step. Radioactivity was measured in the bound fraction using a gamma counter. The detection limit was 1 ng/ml.

The mean levels of interassay precision for standards and quality control samples were ±0.8% and ±9.4%, respectively. The mean levels of intra-assay precision and accuracy for the quality control samples were ±5.0% and ±2.4%.

Zidovudine was assayed by high-pressure liquid chromatography with UV detection. The detection limit was 25 ng/ml. The mean levels of interassay precision for standards and quality control samples were ±3.8% and ±4.4%.

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respectively. The mean levels of intra-assay precision and accuracy for the quality control samples were 7.3% and 5.7%, respectively. Zalcitabine was assayed by using solid-phase extraction coupled to atmospheric pressure ionization and mass spectrometry/mass spectrometry detection. The detection limit was 0.5 ng/ml. The mean levels of interassay precision for standards and quality control samples were 7.5% and 9.0%, respectively. The mean levels of intraassay precision and accuracy for the quality control samples were 7.0% and 9.2%, respectively.

**Pharmacokinetic Analysis.** For patients in the intensive pharmacokinetics group, we estimated \( C_{\text{mean}} \), \( T_{\text{max}} \), AUC, and clearance (CL/F) for all three drugs, for each week and arm separately, by standard nonparametric methods. \( C_{\text{mean}} \) was established as the maximum observed concentration of drug in plasma and \( T_{\text{max}} \) was the time at which \( C_{\text{max}} \) was observed. The area under the plasma concentration-time curve (AUC) was calculated by using the trapezoidal rule. CL/F was calculated as dose/AUC. Mean values were calculated as follows. For patients who had intensive pharmacokinetic sampling done at weeks 1 and 12, the mean of the parameter estimates for both weeks was used as the mean value. For patients who had intensive pharmacokinetic sampling at only 1 week, the single estimate was used as the mean value. Subsequently, the arithmetic average, standard deviation (SD), and standard error of the mean (SEM) of all of the individual means were calculated. The interpatient variability, expressed as the percent coefficient of variation (CV), was calculated by dividing the SD of each parameter estimate by its mean and multiplying the result by 100. The intrapatient-interoccasion variability was obtained by calculating the CV of the ratio of individual week 12 to week 1 parameter estimates for \( C_{\text{mean}} \), \( T_{\text{max}} \), AUC, and CL/F.

In addition, the intensive pharmacokinetic data for all three drugs were also fitted to a one-compartment model with first-order absorption by using the NONMEM software program (1). This program produces estimates of the population parameters of the one-compartment model, including log phase, absorption rate constant \( k_a \), CL/F, and volume of distribution V/F. The observations at weeks 1 and 12 were modeled together, as statistical analysis of the estimates obtained by the nonparametric methods described above showed no differences in parameters between weeks. We investigated the influences of age, weight, and length of prior zidovudine therapy on the individual CL and V of all three drugs. The interindividual variability in all parameters was assumed to follow a log-normal distribution. For zidovudine, we did not include any interindividual variational parameters in the log phase during the absorption phase. Intraindividual variability was modeled by using a constant plus proportional variance model according to the expression \( C_{\text{obs}} = C_e + \sqrt{V(C^2 + \sigma_i^2)} \cdot \epsilon_i \), in which \( C_{\text{obs}} \) is the observed concentration, \( C_e \) is the expected concentration, \( \sigma_i \) is a parameter to be estimated, and \( \epsilon_i \) is a normally distributed random variable with mean zero and unknown variance \( \sigma^2 \). The population estimates of the intensively studied group provided a prior distribution from which we produced individual empirical Bayes estimates of each patient’s parameters. We calculated the individual estimates of \( C_{\text{mean}} \), \( T_{\text{max}} \), AUC, and half-life (\( t_{1/2} \)) by using the individual empirical Bayes estimates for \( k_a \), CL/F, and V/F and calculated the mean, SD, and SEM of the different parameters from the individual Bayes estimates. Intraindividual variability, expressed as the percent CV, was subsequently calculated by dividing the standard deviation of each parameter by its mean and multiplying the result by 100.

Since the saquinavir data were not well described by any standard pharmacokinetic model, we used longitudinal splines (12) to describe the individual saquinavir concentration-versus-time profiles, from which individual \( C_{\text{mean}} \), \( T_{\text{max}} \), AUC, and CL/F values could then be estimated. A longitudinal spline is composed of a template spline, common to all subjects, and a distortion spline describing the subject’s difference from the template. The individual longitudinal spline estimates are empirical Bayes estimates, as above. Each individual spline was constrained to have identical values at the beginning and end of a (steady-state) dosing interval, to have a decreasing tail, and to have its \( T_{\text{max}} \) near the population mode of individual data-based \( T_{\text{max}} \) values. The mean, SD, SEM, and interpatient-interoccasion variabilities were computed as described above for the standard nonparametric methods.

### Statistical Analysis

Analysis of variance was used to test for differences in weight, age, and prior zidovudine therapy among treatment arms. Analysis of variance was also used to test for differences among treatment arms in the estimates of \( C_{\text{mean}} \), \( T_{\text{max}} \) AUC, and CL/F of zidovudine obtained by nonparametric methods and in the individual empirical Bayes estimates of \( k_a \), CL/F, V/F, \( C_{\text{mean}} \), \( T_{\text{max}} \) AUC, and \( t_{1/2} \) of zidovudine obtained by parametric methods. We used a paired t test to test for differences in pharmacokinetic parameters obtained by nonparametric methods for all three drugs between weeks. In doing so, we pooled individual drug kinetics across treatment arms. An unpaired t test was used to test for differences between treatment arms in the estimates of \( C_{\text{mean}} \), \( T_{\text{max}} \) AUC, and CL/F obtained by nonparametric methods and in the individual empirical Bayes estimates of \( k_a \), CL/F, V/F, \( C_{\text{mean}} \), \( T_{\text{max}} \) AUC, and \( t_{1/2} \) obtained by parametric methods for saquinavir and zalcitabine. For all estimates obtained by nonparametric methods, we used the mean values as described above for pharmacokinetic analysis to test for differences between treatment arms.

### RESULTS

There were no significant differences in weight, age, or prior zidovudine therapy among treatment arms for patients in the intensive pharmacokinetics groups. The mean ages (±SD) of patients exposed to saquinavir, zidovudine, and zalcitabine were 41.5 ± 9.74, 39.4 ± 9.66, and 38.8 ± 9.21 years, respectively. The mean weights (±SD) of patients exposed to saquinavir, zidovudine, and zalcitabine were 78.1 ± 11.6, 77.1 ± 11, and 77.2 ± 11.1 kg, respectively, and the median duration of prior zidovudine therapy (range) was 740 days (15 to 2,252 days).

### Zidovudine and Zalcitabine

Table 1 shows the results expressed as mean values ± SEM from parametric and nonparametric analyses of the pharmacokinetics of zidovudine and zalcitabine. The mean values based on parametric or nonparametric individual estimates were comparable. In the parametric analysis of the zidovudine population, CL/F appeared to decrease nonlinearly with age and was modeled by using the equation \( CL = \theta_1 \cdot \exp[\theta_2 \cdot (age - 50)] \) for ages >50 and \( \theta_1 \) for ages ≤50, where \( \theta_1 \) and \( \theta_2 \) were population values to be estimated and 50 was the age estimated by the NONMEM program at which clearance started to decrease significantly with age. Of 73 patients exposed to zidovudine, six were older than 50.

In the zalcitabine population analyses, CL appeared to diminish with age and to increase with weight. V was not influenced by these covariates. CL was modeled by using the equation \( CL = \theta_1 \cdot \exp[\theta_2 \cdot (age - mean\ age)] + \theta_3 \cdot weight, \) where \( \theta_1 \), \( \theta_2 \), and \( \theta_3 \) were population values to be estimated. We also included a nonrandom lag phase to improve the fit.

Scatterplots of the data from the intensively studied group and the fitted curves and concentration-versus-time curves of individual representative patients are shown in Fig. 1. As is apparent in the right-hand panels, the pharmacokinetics of zidovudine and zalcitabine are reasonably well described by a one-compartment model. In a number of cases, however, the

### TABLE 1. Mean pharmacokinetic parameters of zidovudine and zalcitabine for all arms at weeks 1 and 12∗

<table>
<thead>
<tr>
<th>Drug (no. of patients) and method</th>
<th>Log phase (h)</th>
<th>( k_a ) (h⁻¹)</th>
<th>( C_{\text{max}} ) (ng/ml)</th>
<th>( T_{\text{max}} ) (h)</th>
<th>AUC (ng · h/ml)</th>
<th>CL/F (liters/h)</th>
<th>V/F (liters)</th>
<th>( t_{1/2} ) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (73) Nonparametric</td>
<td>NA*</td>
<td>435 ± 23.8</td>
<td>2.12 ± 0.09</td>
<td>1,020 ± 44.1</td>
<td>243 ± 15.0</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Parametric</td>
<td>0.52</td>
<td>347 ± 14.7</td>
<td>1.29 ± 0.06</td>
<td>1,260 ± 36.1</td>
<td>168 ± 4.43</td>
<td>185 ± 28.0</td>
<td>0.76 ± 0.11</td>
<td></td>
</tr>
<tr>
<td>Zalcitabine (53) Nonparametric</td>
<td>NA*</td>
<td>6.97 ± 0.26</td>
<td>2.69 ± 0.14</td>
<td>29.5 ± 1.07</td>
<td>27.5 ± 1.07</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Parametric</td>
<td>0.649</td>
<td>1.48 ± 0.19</td>
<td>5.51 ± 0.16</td>
<td>3.18 ± 0.15</td>
<td>25.0 ± 0.79</td>
<td>92.2 ± 1.93</td>
<td>2.70 ± 0.12</td>
<td></td>
</tr>
</tbody>
</table>

* The values are means ± SEM calculated as in Materials and Methods.

**NA**, not available.
observed concentrations showed considerable departure from the smooth model predictions, resulting in different estimates of $C_{\text{max}}$ and $T_{\text{max}}$ by parametric and nonparametric methods.

There were no significant differences between weeks or treatment arms in the individual estimates of $k_a$, $\text{CL/F}$, $V/F$, $C_{\text{max}}$, $T_{\text{max}}$, AUC, or $t_{1/2}$ of zidovudine and zalcitabine obtained by parametric or nonparametric methods (data not shown).

Table 2 shows the interpatient and intrapatient-interoccasion variabilities of the different parameters. For both drugs, but for zidovudine in particular, the interpatient and intrapatient-interoccasion variabilities were fairly large.

**Saquinavir.** Table 3 shows the results expressed as means ± SEM for parametric and nonparametric analyses of the pharmacokinetics of saquinavir. We chose to present all three methods to allow comparison to previous or future analyses of saquinavir pharmacokinetics using one of the three methods. As can be seen in Table 3, the parameter values estimated by parametric or nonparametric methods were fairly similar, except for $C_{\text{max}}$, for which the estimate was much lower by parametric methods. This is probably due to the fact that the data are not well described by the pharmacokinetic model used here. A scatterplot of the data of the intensively studied group and the fitted curve is shown in Fig. 1 together with a concentration-versus-time curve of an individual patient. CL appeared to diminish with age and to increase with weight. $V$ was not influenced by these covariates. CL was modeled by using the equation $\text{CL} = \theta_1 \cdot \exp(\theta_2 \cdot \text{(age - mean age)}) + \theta_3 \cdot \text{weight}$, where $\theta_1$, $\theta_2$, and $\theta_3$ were population values to be estimated. As demonstrated in Fig. 1C, the plasma concentration-versus-time curve for saquinavir showed considerable variability and was not well described by the one-compartment pharmacokinetic model. For this reason, we have also described the data by means of splines (see Materials and Methods).

Table 4 shows the interpatient and intrapatient-interoccasion variabilities of the different parameters of saquinavir obtained by different methods. For all of the methods used, the interpatient and intrapatient-interoccasion variabilities were very large. This is further illustrated in Fig. 2, which provides an overview of the spread of the estimates of $C_{\text{max}}$, AUC, and $\text{CL/F}$. For the estimates per week, only the estimates based on nonparametric methods are shown since observations at weeks 1 and 12 were modeled together by using parametric methods. As can be seen in Fig. 2, the spread of the estimates of $\text{CL/F}$ was less when longitudinal splines or parametric methods were used. There were no significant differences between weeks or treatment arms in the individual empirical Bayes estimates of $k_a$, $\text{CL/F}$, $V/F$, $C_{\text{max}}$, $T_{\text{max}}$, AUC, and $t_{1/2}$ obtained by parametric methods, standard nonparametric methods, or nonparametric spline methods (data not shown).

**TABLE 2. Interpatient and intrapatient-interoccasion variabilities of zidovudine and zalcitabine pharmacokinetic parameters**

<table>
<thead>
<tr>
<th>Analysis method, variability, and drug</th>
<th>$k_a$</th>
<th>$C_{\text{max}}$</th>
<th>$T_{\text{max}}$</th>
<th>AUC</th>
<th>$\text{CL/F}$</th>
<th>$V/F$</th>
<th>$t_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonparametric</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercalibration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>NA</td>
<td>47</td>
<td>36</td>
<td>37</td>
<td>53</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>NA</td>
<td>27</td>
<td>38</td>
<td>26</td>
<td>28</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Intrapatient-interoccasion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>NA</td>
<td>75</td>
<td>58</td>
<td>85</td>
<td>67</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>NA</td>
<td>27</td>
<td>51</td>
<td>20</td>
<td>24</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Parametric, intrapatient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>NA</td>
<td>36</td>
<td>43</td>
<td>27</td>
<td>23</td>
<td>130</td>
<td>120</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>92</td>
<td>22</td>
<td>41</td>
<td>26</td>
<td>23</td>
<td>15</td>
<td>32</td>
</tr>
</tbody>
</table>

* The values were determined as described in Materials and Methods.

b NA, not available.
and the parametric model estimates. However, the CL/F values obtained without splines and the mean values of the pharmacokinetic parameters for saquinavir are similar to those reported in previous studies, taking into account the 64% bioavailability of saquinavir and a mean population weight of 70 kg (5; for a review, see reference 13). The finding that the CL of zidovudine decreases in patients over 50 is consistent with the finding of a longer t1/2 in patients over 60 (7). For zalcitabine, the values of the pharmacokinetic parameters reported here are similar to those reported previously (4). There have been no previous reports on the influence of age on the pharmacokinetics of zalcitabine with which to compare our finding that CL decreases with age.

The absence of differences in the pharmacokinetic parameters of zidovudine and zalcitabine between arms indicates that these drugs do not affect each other’s pharmacokinetics. This agrees with previous findings (8). No differences in pharmacokinetic parameters for saquinavir between arms were observed. However, power calculations demonstrate that there was only a 30% chance of finding as much as a 30% difference in the AUC between arms 1 and 2, indicating that only interactions that result in large effects could have been detected.

As mentioned in the introduction, understanding of the pharmacokinetics of a drug is a prerequisite for optimization and individualization of drug therapy. Although high interpatient variability in pharmacokinetics generally implies that therapeutic drug monitoring may be useful in detecting patients with undetectable or very low drug concentrations, additional high intrapatient-intracessation variability decreases the utility of such drug monitoring. In a recently published monotherapy study, exposure to a saquinavir dose of 3,600 mg/day was associated with a higher mutational rate and de-

### TABLE 3. Pharmacokinetic parameters of saquinavir for all arms at weeks 1 and 12

<table>
<thead>
<tr>
<th>Analysis method (no. of patients)</th>
<th>kₑ (h)</th>
<th>Cₘax (ng/ml)</th>
<th>Tₘax (h)</th>
<th>AUC (ng · h/ml)</th>
<th>CL/F (liters/h)</th>
<th>V/F (liters)</th>
<th>t₁/₂ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonparametric</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard (46)</td>
<td>NA</td>
<td>185 ± 24.2</td>
<td>3.98 ± 0.2</td>
<td>621 ± 68.8</td>
<td>1,740 ± 190</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Spline (45)</td>
<td>NA</td>
<td>163 ± 23.2</td>
<td>3.76 ± 0.09</td>
<td>717 ± 65.2</td>
<td>1,110 ± 74.5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Parametric (45)</td>
<td>0.137</td>
<td>70.8 ± 6.14</td>
<td>3.11 ± 0.27</td>
<td>809 ± 70.2</td>
<td>989 ± 77.0</td>
<td>1,503 ± 188</td>
<td>1.38 ± 0.24</td>
</tr>
</tbody>
</table>

CV (%) = SEM calculated as described in Materials and Methods.

### TABLE 4. Intertatient and intrapatient-intracessation variabilities of the pharmacokinetic parameters of saquinavir

<table>
<thead>
<tr>
<th>Variability and analysis method (no. of patients)</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cₘax</td>
</tr>
<tr>
<td>Intertatient</td>
<td></td>
</tr>
<tr>
<td>Parametric (45)</td>
<td>58</td>
</tr>
<tr>
<td>Nonparametric</td>
<td></td>
</tr>
<tr>
<td>Standard (46)</td>
<td>89</td>
</tr>
<tr>
<td>Spline (45)</td>
<td>95</td>
</tr>
<tr>
<td>Intracessation, nonparametric</td>
<td></td>
</tr>
<tr>
<td>Standard (41)</td>
<td>105</td>
</tr>
<tr>
<td>Spline (42)</td>
<td>67</td>
</tr>
</tbody>
</table>

CV (%) = SEM calculated as described in Materials and Methods.

**DISCUSSION**

As presented in Results, both interpatient and intrapatient-intracessation variabilities in the kinetics and exposure of saquinavir, zidovudine, and zalcitabine are large. It has previously been shown that the F of this formulation of saquinavir is about 18 times higher in the presence of food, but even with food the extent of absorption is only 4% with a CV of 60% (14). The low F is thought to be due largely to first-pass metabolism by cytochrome P-450 CYP3A4. It is well known that drugs with extensive first-pass metabolism can result in large changes and substantial variability in the concentrations in plasma. The F of zidovudine is about 64% in the absence of food. The incomplete absorption of zidovudine is the result of first-pass hepatic glucuronidation (2). The administration of a standard breakfast has been shown to prolong Tₘax and decrease Cₘax without any change in the total AUC or CL of zidovudine (9, 11). Recent studies in patients have also demonstrated considerable between-patient variability in zidovudine F, with low F being associated with the presence of mild diarrhea and/or low CD₄⁺ counts (6). These factors may explain the high interpatient and intrapatient-intracessation variabilities of zidovudine observed in this study.

The values obtained for the pharmacokinetic parameters of saquinavir by using splines are generally intermediate between the standard nonparametric methods obtained without splines and the parametric model estimates. However, the CL/F values obtained by using splines are about two-thirds of that obtained without splines and is comparable to the value estimated by NONMEM using the one-compartment pharmacokinetic model. Although the mean AUC increases by only 17% using splines, the mean CL/F calculated as dose/AUC decreases by 33%. This appears to be a result of the distribution of the AUC. The fact that the parametric model and the nonparametric spline method generate values that are not too dissimilar is reassuring evidence that these estimates are probably close to the true population values.

For the other two drugs, the CL/F values obtained by nonparametric methods are comparable to those obtained by using a parametric model. Moreover, the mean values of the pharmacokinetic parameters of zidovudine are similar to those reported in previous studies, taking into account the 64% bioavailability of zidovudine and a mean population weight of 70 kg (5; for a review, see reference 13). The finding that the CL of zidovudine decreases in patients over 50 is consistent with the finding of a longer t₁/₂ in patients over 60 (7). For zalcitabine, the values of the pharmacokinetic parameters reported here are similar to those reported previously (4). There have been no previous reports on the influence of age on the pharmacokinetics of zalcitabine with which to compare our finding that CL decreases with age.

The absence of differences in the pharmacokinetic parameters of zidovudine and zalcitabine between arms indicates that these drugs do not affect each other’s pharmacokinetics. This agrees with previous findings (8). No differences in pharmacokinetic parameters for saquinavir between arms were observed. However, power calculations demonstrate that there was only a 30% chance of finding as much as a 30% difference in the AUC between arms 1 and 2, indicating that only interactions that result in large effects could have been detected.

As mentioned in the introduction, understanding of the pharmacokinetics of a drug is a prerequisite for optimization and individualization of drug therapy. Although high interpatient variability in pharmacokinetics generally implies that therapeutic drug monitoring may be useful in detecting patients with undetectable or very low drug concentrations, additional high intrapatient-intracessation variability decreases the utility of such drug monitoring. In a recently published monotherapy study, exposure to a saquinavir dose of 3,600 mg/day was associated with a higher mutational rate and de-
saquinavir with a larger drug monitoring may be justifiable if a new formulation of in the study described in the following paper (11a), therapeutic count and a maximum decrease in the level of RNA in plasma

\[ C_{\text{max}}, AUC, \text{and } \text{CL/F for saquinavir estimated by parametric and } \]

\[ \text{nonparametric methods. Box plots of estimates of } \]

\[ \text{C}_{\text{max}}, \text{AUC, and CL/F for saquinavir. Abbreviations: NON-PARA, estimates obtained by using standard } \]

\[ \text{nonparametric methods, SPLINES, estimates obtained by using longitudinal } \]

\[ \text{splines, PARA, estimates obtained by using parametric methods. The interior } \]

\[ \text{line in each box is located at the median of the data. The dotted line represents the } \]

\[ 10^\text{th and 90^\text{th percentiles, and the dots represent outliers.} } \]

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