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# Strategies for Control of Zidovudine Concentrations in Serum

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**There are several clinical scenarios in which knowledge of zidovudine disposition may be important. This study evaluated the clinical utility of pharmacokinetic parameters for zidovudine derived from sparse serum concentration data obtained in an outpatient setting. Twelve human immunodeficiency virus-infected participants had two serum zidovudine concentration determinations obtained on two different clinic visits, 2 to 38 days apart. Zidovudine concentrations were measured by radioimmunoassay. A one-compartment oral absorption model was used to describe zidovudine disposition. Three different approaches were used to estimate pharmacokinetic parameters: Bayesian estimation with one or two concentrations and least squares with one concentration. The ability of these parameters to predict concentrations measured during the second clinic visit was assessed by calculation of precision and bias and compared with predictions using standard fixed or weight-adjusted parameters. Estimated pharmacokinetic parameters for zidovudine were consistent with literature values; there was no statistically significant difference among the parameters calculated with the three estimation strategies. Absorptive phase concentrations were poorly predicted by all methods (mean percent bias, 157 to 249%; mean percent precision, 389 to 537%). Predictive ability for concentrations obtained in the elimination phase was strikingly improved: mean percent bias, −17 to 70%; mean percent precision, 40 to 95%. Bayesian and least-squares estimated parameters were statistically better than fixed-parameter values for predicting concentrations in the elimination phase. These observations provide a modeling framework to determine pharmacokinetic disposition of zidovudine in an individual, screen for the existence of a drug interaction, and conduct concentration-controlled clinical trials.**

Zidovudine is the antiretroviral agent with which we have the greatest experience and remains the "gold standard" for treatment of human immunodeficiency virus (HIV) infection. This drug has been shown to reduce morbidity and prolong survival time in symptomatic individuals with AIDS, as well as delay the progression to AIDS in persons with early AIDS-related complex and HIV-infected asymptomatic individuals (10–12, 32). Pharmacologic characteristics of zidovudine include a low therapeutic index, severe consequences associated with therapeutic failure or toxicity, and substantial interpatient pharmacokinetic variability. Individualized dosing regimens have been necessary to achieve the desired therapeutic response and/or to minimize toxicity for other drugs, such as anticancer agents with similar properties. Yet, zidovudine is administered orally in standard fixed doses of 500 to 600 mg/day to HIV-infected adults (9, 31). A state-of-the-art National Institutes of Health conference on zidovudine therapy highlighted a lack of information on whether alternative approaches to zidovudine dosing, based, for example, on body weight, would result in greater efficacy and/or fewer adverse reactions (31).

Contemporary treatment of HIV and associated opportunistic infections results in unavoidable polypharmacy. Combinations of antiretroviral agents have been studied and are used as one therapeutic option in routine patient care (27). Prophylaxis and treatment of *Pneumocystis carinii* pneumonia, cytomegalovirus retinitis, and *Mycobacterium avium* complex are but a few examples of settings where combination therapy also occurs. Several agents are known to interact with zidovudine: cimetidine, probenecid, fluconazole, trimethoprim, clarithromycin, rifabutin, and rifampin (2, 13, 16, 17, 20, 22, 25). There are likely to be other drugs that will interact with zidovudine, and it is virtually impossible for all potential interactions to be formally evaluated prior to use of the combination in humans. Individualization of zidovudine dosage regimens may minimize the clinical effect of pharmacokinetic drug-drug interactions.

The pharmacodynamic properties of zidovudine are still not well understood, but clinical data suggest a narrow, albeit not yet explicitly known, therapeutic window. In asymptomatic patients with CD4 cell counts $<500/mm^3$ enrolled in a placebo-controlled study, zidovudine therapy (1,500 or 500 mg/day) was shown to delay progression of HIV disease (32). Evidence for diminishing effect of zidovudine with the higher study dose or a higher area under the curve has been observed (26). French investigators, in a study of 36 patients with AIDS, have found a trend towards an increased likelihood of an opportunistic infection when the mean steady-state concentration of zidovudine from intermittent oral dosing was below 200 ng/ml; the occurrence of anemia was 4.3 times greater ($P < 0.05$) when the mean steady-state concentration was 800 ng/ml versus 600 ng/ml (21). Finally, relationships between the efficacy and toxicity of zidovudine and systemic exposure were shown in HIV-infected children receiving continuous infusion therapy (8). A steady-state zidovudine concentration of approximately 3 μM (802 ng/ml) produced 90% of the maximal return in CD4 lymphocytes and was also the best value for discriminating which patients would become granulocytopenic. These authors

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concluded that monitoring of zidovudine concentrations in the individual patient was necessary to obtain the desired effect while minimizing the potential for toxicity.

There are a number of clinical scenarios in which knowledge of zidovudine disposition may be important. These include lack of initial response, drug- or dose-limiting toxicity, and loss of response or a new toxicity in a previously stable patient. Antiretroviral therapy will be long-term and must be primarily outpatient based. Cost, nuisance, time constraints, and subject tolerance preclude obtaining large numbers of blood samples in the outpatient clinic. Therefore, pharmacokinetic approaches capable of accommodating a limited number of measurements are needed. The objective of this study was to evaluate the predictive performance of pharmacokinetic parameters for zidovudine derived from sparse serum drug concentration data obtained in an outpatient setting.

(This work was submitted in partial fulfillment of the requirements for the Master of Science degree at the University of Minnesota [S. E. Noormohamed].)

## MATERIALS AND METHODS

**Subjects and drug administration.** Participants were persons with laboratory-documented HIV infection, aged 18 to 60 years, currently stabilized on at least 300 mg of zidovudine per day, and with Karnofsky performance status of at least 60% and stable bone marrow, renal, and hepatic function. Exclusion or termination criteria were presence of an active opportunistic infection requiring therapy, three or more liquid stools per day, nausea or vomiting, zidovudine-associated anemia (hemoglobin level of less than 7 g/dl) or neutropenia (absolute neutrophil count less than 1,000 cells per $mm^3$), or noncompliance with prescribed medications or scheduled clinic visits. Participants in this study continued to take zidovudine and any other concomitant medications prescribed by their physician; no alterations in these drugs or dosing regimens were made as part of participation in this study.

This study was conducted in the HIV Clinic at the University of Minnesota. Two clinic visits at least 2 days apart were required for each participant. Subjects were given a medication diary to record the exact times of zidovudine administration for 2 days prior to each clinic visit. Each clinic visit was arranged to coincide approximately with a scheduled zidovudine administration time. At each clinic visit, the participant took the scheduled dose of zidovudine and two blood samples for determination of zidovudine concentration were obtained. At the first visit, one sample was obtained 15 to 20 min following the dose of zidovudine; the second sample was obtained 3.5 to 5 h postdose. The selection of these sampling times was guided by an optimal sampling strategy employing *D*-optimality criteria and a one-compartment oral absorption structural model with the pharmacokinetic parameters for zidovudine taken from previous investigations (7, 14). Subject acceptance was determined to preclude obtaining the three samples needed for a completely optimal design. Thus, strategies for two measured observations were investigated by fixing one model parameter, first the absorption rate constant and then the distribution volume. The duration of time a participant could be expected to remain in the outpatient clinic forced constraints on the length of time postdose at which a sample could be collected. The final windows selected for obtaining blood samples during the first visit ranged from 32 to 100% of optimal. During the second clinic visit, blood samples for measurement of zidovudine concentration were collected in a similar fashion except that the time frames were widened to allow greater schedule flexibility for the participant. Collection windows were 0.25 to 1.5 h for the first postdose sample and >1.5 to 5 h postdose for the second sample.

This investigation was approved by the Committee on Use of Human Subjects in Research. All subjects were informed about the study and gave their written consent before participating. They received the routine medical care (physical, clinical, and laboratory evaluations) that was the standard of practice for our HIV Clinic.

**Pharmacokinetic parameter estimation.** Zidovudine in the serum samples was measured by radioimmunoassay (RIA) with the ZDV-Trac RIA kit (INCStar Corp., Stillwater, Minn.). Blood samples obtained for analysis of serum zidovudine concentration were centrifuged, separated from the cells, and stored at −20°C until analyzed. The RIA for zidovudine is a direct equilibrium approach in which radiolabelled zidovudine competes with sample zidovudine for a limited number of zidovudine antibody-binding sites. Six zidovudine standards at nominal concentrations, ranging from 0.35 to 287.2 ng/ml (1.31 to 1,077.15 nmol/liter), are included in each assay. The coefficient of determination for the regression analysis of the standard curve must be greater than 0.99 for the assay to be considered acceptable. The intraday coefficients of variation for the assay at high (2,700 ng/ml) and low (27 ng/ml) concentrations were 6.2 and 4.6%, respectively. The interday coefficients of variation for high and low zidovudine concentrations were 5.3 and 9.7%, respectively. The sensitivity of the RIA method for zidovudine is approximately 0.267 ng/ml (1 nmol/liter); the minimum quantifiable concentration was 27 ng/ml.

Each participant's complete zidovudine dosing history (with dose expressed as milligrams per kilogram of body weight) for at least 2 days before and including the first clinic visit and the corresponding measured serum zidovudine concentrations were tabulated. A one-compartment oral absorption model with no lag phase was used to describe the disposition of zidovudine. The one-compartment model was parameterized as follows: first-order absorption rate constant ($k_a$), volume of distribution ($V/F$), and first-order elimination rate constant ($k_{el}$). Three approaches to parameter estimation were used to fit the concentration-time data. The first approach used both of the measured concentrations obtained during the first clinic visit and Bayesian estimation to determine $k_a$, $V/F$, and $k_{el}$ (Bayesian-Two). The second used only the concentration obtained 3.5 to 5 h postdose and Bayesian estimation to obtain estimates of all three parameters (Bayesian-One). The last approach (One-Parameter) constrained the model to one identifiable parameter, $k_{el}$, with estimates obtained by weighted (inverse variance of the assay) least-squares regression. All models were developed with the ADAPT II package of modeling programs (Biomedical Simulation Resource, University of Southern California, Los Angeles) implemented on a VAX 6000-520 (7).

The approach to Bayesian estimation of pharmacokinetic parameters minimized the following objective function:

$$\sum_{i=1}^{m} \frac{(C_i - \hat{C}_i)^2}{SD^2_{C_i}} + \sum_{j=1}^{n} \frac{(P_j - \hat{P}_j)^2}{SD^2_{P_j}}$$

where $C_i$ to $C_m$ represent measured concentrations; $\hat{C}_i$ to $\hat{C}_m$ are the predicted concentrations given the estimated individual pharmacokinetic parameters $\hat{P}_j$ to $\hat{P}_n$. $P_j$ to $P_n$ are the population pharmacokinetic parameters. $SD^2_{C_i}$ is the variance of the measured concentrations, and $SD^2_{P_j}$ is the variance of the population pharmacokinetic parameters. A priori (and standard deviation) values for the model parameters used in the Bayesian analysis were developed from patients without renal or hepatic insufficiency (14); these values were as follows: $k_a$, 1.5 (0.48) $h^{-1}$; $V/F$, 2.46 (0.52) liters/kg; and $k_{el}$, 0.77 (0.17) $h^{-1}$. For the One-Parameter approach, $k_a$ was fixed at 1.5 $h^{-1}$, and $V/F$ was fixed at 2.46 liters/kg.

**Model evaluations.** The patient-specific pharmacokinetic parameters obtained with the three estimation approaches (Bayesian-Two, Bayesian-One, and One-Parameter) were evaluated for agreement. Oral clearance (CL/F) was calculated, and values for CL/F and $k_{el}$ from all three approaches were compared with analysis of variance (ANOVA). Pharmacokinetic parameters from the two Bayesian estimation strategies were also compared with Student's *t* test. A *P* level of $<0.05$ was used to reflect statistical significance in both instances. Lastly, the predictive ability of these pharmacokinetic parameters was determined. This was accomplished by evaluating the precision and bias with which the parameters predicted the concentrations actually measured during the second clinic visit (28). The dose-concentration history for 2 days prior and including the second clinic visit was constructed like that for the first visit. The pharmacokinetic parameters from each of the three estimation procedures were then used to obtain simulated values of the concentrations measured during the second clinic visit. For comparison purposes, the a priori values for $k_a$ and $k_{el}$, with a weight-adjusted $V/F$ (Weight Adjusted) and with a fixed $V/F$ (Fixed) were also used to obtain predictions of the second set of zidovudine concentrations. The predictive performance of these five approaches was evaluated by calculation of the mean percent prediction error and percent root mean squared error as measures of bias and precision, respectively, and their 95% confidence intervals. This predictive performance evaluation was conducted for the complete set of concentrations measured during the second clinic visit as well as for the concentrations stratified into absorptive (0.25 to 1.5 h postdose) and elimination (1.5 to 5 h postdose) phases.

## RESULTS

Twelve HIV-infected individuals receiving 300 to 600 mg of zidovudine per day were enrolled in this study. Selected clinical characteristics are presented in Table 1. Subjects ranged in age from 25 to 48 years and in weight from 67.1 to 94.7 kg (mean, 75.7 kg). Ten participants were asymptomatic while two had experienced previous AIDS-defining conditions: Kaposi's sarcoma (patient 1) and *P. carinii* pneumonia (patient 10). Concomitant drug therapy included aerosolized pentamidine for *P. carinii* pneumonia prophylaxis in three subjects (patients 1, 7, and 10), imipramine and clonazepam for panic attacks in patient 1, and ergotamine for migraine headaches in patient 7. $CD4^+$ lymphocyte counts were available for six participants and ranged from 73 to 533 cells per $mm^3$. Evaluations of other laboratory parameters (hematology and clinical chemistries) were within normal limits for all participants. No one experi-

TABLE 1. Patient characteristics[a]

| Subject no. | Age (yr) | Wt (kg) | HIV status | No. of $CD4^+$ cells/$mm^3$ | WBC ($10^3$/$mm^3$) | Hgb (mg/dl) | Cr (mg/dl) | T bili (mg/dl) | ZDV dose (mg/day) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 40 | 75 | AIDS | NA | 3.1 | 11.7 | 1 | 0.3 | 600 |
| 2 | 30 | 69 | Asympt | NA | 2.8 | 12.2 | 0.8 | 0.4 | 300 |
| 3 | 30 | 91 | Asympt | NA | 5.7 | 15.8 | 1 | 0.4 | 300 |
| 4 | 26 | 67.1 | Asympt | NA | 8.9 | 14.9 | 1 | 0.5 | 300 |
| 5 | 34 | 76.6 | Asympt | NA | 2.9 | 12.9 | 1 | 0.6 | 300 |
| 6 | 29 | 77.5 | Asympt | 350 | 3.9 | 10.5 | 0.6 | 1.2 | 600 |
| 7 | 48 | 70 | Asympt | NA | 3.2 | 13.4 | 0.9 | 0.5 | 500 |
| 8 | 40 | 75.9 | Asympt | 387 | 5 | 14.7 | 1 | 0.6 | 500 |
| 9 | 25 | 70 | Asympt | 186 | 5 | 12 | 1 | 0.5 | 600 |
| 10 | 32 | 94.7 | AIDS | 73 | 5 | 15 | 1 | 0.7 | 600 |
| 11 | 30 | 69 | Asympt | 533 | 5 | 14.5 | 0.8 | 0.6 | 600 |
| 12 | 25 | 73.7 | Asympt | 352 | 5 | 13.5 | 1 | 0.5 | 600 |

[a] Abbreviations: WBC, leukocyte count; Hgb, hemoglobin; Cr, serum creatinine; T bili, total serum bilirubin; ZDV, zidovudine; asympt, asymptomatic; NA, not available.

enced an HIV-associated opportunistic infection or any other medical condition that required an addition to or termination of drug therapy during participation in this study.

**Pharmacokinetic parameters.** A total of 49 blood samples were available for determination of zidovudine concentration. Serum drug concentrations ranged from 29 to 2,364 ng/ml in 47 samples; the concentration was <27 ng/ml in the remaining two samples. Twenty-four measured concentrations (two per participant) obtained during the first clinic visit were used for calculation of pharmacokinetic parameters. The parameters estimated with the three methods (Bayesian-Two, Bayesian-One, and One-Parameter) are presented in Table 2. Residual analysis did not demonstrate a consistent pattern of bias with any of the three methods. There was no significant difference (Student's $t$ test, $P > 0.05$) between the pharmacokinetic parameters estimated by the Bayesian-Two and -One methods. Values for zidovudine CL/F and $k_{el}$ were not significantly different (ANOVA, $P > 0.05$) among any of the three methods.

**Model evaluations.** Twenty-three measured zidovudine concentrations obtained during the second clinic visit were used to evaluate the predictive performance of the various model parameters. These measured concentrations were obtained an average of 15 days (range, 2 to 38 days) after the first clinic visit. Table 3 provides precision and bias data for the predictive performance assessment of the various model parameters. There was no difference among the five methods in terms of their predictive bias and precision for all points or for just those in the absorptive phase. However, both Bayesian methods and the One-Parameter approach were less biased than the Weight-Adjusted and Fixed methods for points in the elimination phase and for just those >3.5 h postdose. These three strategies were also less biased than the Fixed approach for points 1.5 to 3.5 h postdose. Furthermore, the Bayesian estimated parameters and those from the One-Parameter method were more precise than the Fixed values for all observations in the elimination phase and for the subset >3.5 h after the dose of zidovudine. There was no evidence that prediction error was related to the duration of time between clinic visits. Figure 1 presents deviations from the observed concentrations when the parameters from each model were used to simulate concentrations obtained during just the absorptive (0.25 to 1.5 h postdose) phase, while the values in Fig. 2 are only for the elimination phase (>1.5 h postdose).

TABLE 2. Pharmacokinetic parameters

| Subject no. | Value with pharmacokinetic model | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Two-Concentration Bayesian | | | | One-Concentration Bayesian | | | | One-Parameter Model | |
| | $V/F$ (liters/kg) | $k_{el}$ ($h^{-1}$) | $k_a$ ($h^{-1}$) | CL/F (liters/kg/h) | V/F (liters/kg) | $k_{el}$ ($h^{-1}$) | $k_a$ ($h^{-1}$) | CL/F (liters/kg/h) | $k_{el}$ ($h^{-1}$) | CL/F (liters/kg/h) |
| 1 | 1.77 | 0.59 | 1.32 | 1.05 | 1.77 | 0.62 | 1.70 | 1.09 | 0.22 | 0.54 |
| 2 | 2.65 | 0.87 | 1.39 | 2.31 | 2.65 | 1.08 | 1.69 | 2.86 | 1.15 | 2.83 |
| 3 | 2.34 | 0.84 | 1.66 | 1.97 | 2.57 | 0.85 | 1.45 | 2.18 | 0.85 | 2.09 |
| 4 | 2.88 | 1.00 | 1.45 | 2.88 | 2.65 | 0.98 | 1.61 | 2.6 | 1.04 | 2.55 |
| 5 | 2.77 | 0.91 | 1.38 | 2.52 | 2.6 | 0.90 | 1.51 | 2.34 | 0.92 | 2.26 |
| 6 | 2.69 | 0.81 | 1.27 | 2.18 | 2.55 | 0.80 | 1.40 | 2.05 | 0.80 | 1.97 |
| 7 | 5.55 | 1.63 | 0.78 | 9.05 | 5.29 | 1.38 | 0.62 | 9.35 | 6.7 | 16.49 |
| 8 | 4.48 | 1.26 | 0.98 | 5.65 | 2.81 | 1.14 | 1.85 | 3.22 | 1.35 | 3.32 |
| 9 | 2.55 | 1.11 | 2.15 | 2.83 | 3.15 | 1.09 | 1.67 | 3.43 | 1.40 | 3.45 |
| 10 | 1.08 | 1.07 | 4.15 | 1.15 | 2.72 | 0.95 | 1.60 | 2.58 | 1.04 | 2.55 |
| 11 | 3.31 | 1.27 | 1.67 | 4.2 | 2.86 | 1.25 | 1.98 | 3.58 | 1.54 | 3.78 |
| 12 | 2.63 | 0.86 | 1.45 | 2.26 | 2.6 | 0.85 | 1.47 | 2.22 | 0.86 | 2.12 |
| Mean | 2.89 | 1.02 | 1.64 | 3.17 | 2.85 | 0.99 | 1.55 | 3.12 | 1.49 | 3.66 |
| SD | 1.16 | 0.27 | 0.86 | 2.23 | 0.83 | 0.21 | 0.34 | 2.08 | 1.68 | 4.12 |
| % CV[a] | 40 | 27 | 53 | 70 | 29 | 21 | 22 | 66 | 113 | 113 |

[a] CV, coefficient of variation.

TABLE 3. Predictive performance

| Measurement and data | Mean value for model (95% confidence interval) | | | | |
|---|---|---|---|---|---|
| | Bayesian-Two | Bayesian-One | One Parameter | Weight Adjusted | Fixed |
| Bias (% mean error) | | | | | |
| All points | 66 (−50, 182) | 78 (−57, 212) | 86 (−60, 232) | 116 (−8, 241) | 156 (4, 308) |
| Absorptive phase | 157 (−94, 409) | 188 (−102, 478) | 207 (−107, 520) | 189 (−85, 464) | 249 (−86, 585) |
| Elimination phase | −17 (−41, 7)[a] | −23 (−46, −0.2)[a] | −25 (−49, −0.5)[a] | 50 (16, 83) | 70 (27, 113) |
| 1.5 to 3.5 h | −10 (−66, 44)[b] | −16 (−66, 34)[b] | −15 (−67, 37)[b] | 40 (−19, 99) | 71 (−14, 156) |
| >3.5 h | −23 (−38, −9)[a] | −31 (−55, −7)[a] | −34 (−59, −10)[a] | 60 (4, 115) | 69 (8, 130) |
| Precision (% root mean squared error) | | | | | |
| All points | 271 (−169, 419) | 314 (−197, 486) | 340 (−218, 528) | 304 (−239, 492) | 378 (−300, 613) |
| Absorptive phase | 389 (−265, 612) | 452 (−309, 710) | 490 (−341, 773) | 433 (−379, 721) | 537 (−477, 897) |
| Elimination phase | 40 (19, 53)[b] | 42 (24, 54)[b] | 44 (26, 57)[b] | 71 (40, 92) | 95 (28, 131) |
| 1.5 to 3.5 h | 49 (−13, 71) | 47 (−11, 67) | 48 (−18, 70) | 65 (−29, 97) | 102 (−87, 170) |
| >3.5 h | 26 (12, 35)[b] | 37 (−17, 55)[b] | 40 (6, 57)[b] | 76 (−29, 112) | 87 (−29, 126) |

[a] Significantly different (ANOVA, $P < 0.05$) from Weight Adjusted and Fixed.
[b] Significantly different (ANOVA, $P < 0.05$) from Fixed.

## DISCUSSION

In what we believe to be the first study designed to assess the clinical utility of patient-specific pharmacokinetic data for zidovudine, we found that meaningful parameters could be determined from as few as one measured observation obtained in the outpatient setting. How well these values characterize the "true" disposition of zidovudine in the participants of this study is unknown. That information would require administration of both intravenous and oral drug and extensive collection of blood and urine. Other investigators have found that two measured zidovudine concentrations were able to acceptably predict pharmacokinetic parameters such as area under the curve and, in a retrospective evaluation, were able to provide parameter estimates consistent with those of a set of six measured concentrations (4, 6). The demonstration in this study that pharmacokinetic parameters estimated from the sparse data could predict subsequent measured concentrations provides evidence that the estimated parameters were representative of actual zidovudine disposition.

The percent mean error, as a measure of bias, and percent root mean squared error, as an index of precision, provide an understanding of the predictive ability of the five methods. Overall, the Bayesian-Two approach was the least biased and most precise. It was statistically superior to the Weight-Adjusted and Fixed methods for concentrations in the elimination phase. Both the Weight-Adjusted and the Fixed approaches had some predictive ability. There was general improvement in precision and bias between these two methods with the use of *V*/*F*, and therefore CL/F, as a weight-adjusted parameter, although this was not statistically significant. There are conflicting data in the literature as to whether weight is an important variable in *V*/*F* and CL/F of zidovudine (3, 15, 21, 24, 30). All of these investigations administered oral zidovudine, and therefore *F* was not independently identified. Interpatient variability in *F* may confound examination of relationships between patient characteristics and pharmacokinetic parameters for zidovudine. Data from the current investigation do lend some support to the argument that patient weight explains a portion of the variability seen in zidovudine concentrations among adults.

A striking difference in the predictive performance was observed between the absorptive and elimination phases of zidovudine disposition (Table 3). For example, the mean precision of the Bayesian-Two model was 271% (536 ng/ml) for concentrations obtained 0.25 to 1.5 h postdose but was 40% (47 mg/ml) for those concentrations obtained 1.5 to 5 h postdose. These data indicate that the absorptive process of zidovudine was poorly characterized in comparison with elimination. Other investigations have described differences in the absorption rate constant for zidovudine between healthy volunteers and HIV-infected persons and have noted difficulties in actually identifying the absorption rate constant (14, 15). The stratification of predictions into either absorptive or elimination phase also illustrated some difference in the precision

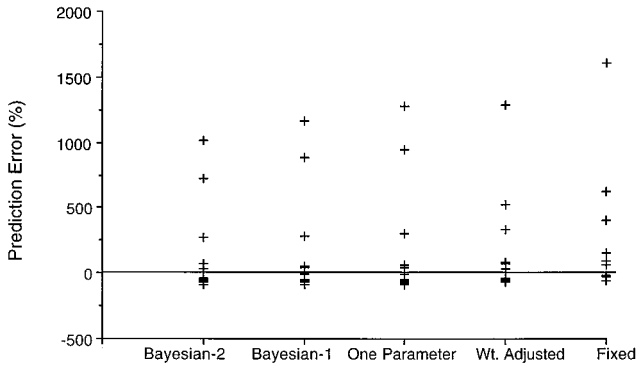


FIG. 1. Percent prediction error for concentrations measured during the absorptive phase (0.25 to 1.5 h postdose) at the time of the second clinic visit.

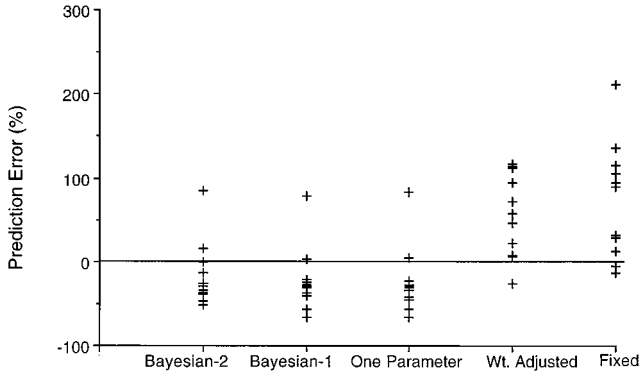


FIG. 2. Percent prediction error for concentrations measured during the elimination phase (1.5 to 5 h postdose) at the time of the second clinic visit.

and bias of the predictions between the estimation procedures. For concentrations in the elimination phase, predictions with Bayesian-Two estimated parameters had the least bias (mean, −17%, or −17 ng/ml) and were the most precise (mean, 40%, or 47 ng/ml). The predictive ability of this method, however, was not statistically better than that of the Bayesian-One and One-Parameter approaches. The data concerning predictive ability have certain implications for the pharmacodynamically linked pharmacokinetic parameter of zidovudine. If control of peak concentrations is important, then strategies that offer a clear improvement over those described here are necessary. However, if trough concentration or a clearance-derived parameter such as steady-state concentration or area under the curve is associated with effect, then one of the Bayesian methods or the One-Parameter approach is superior to fixed or even weight-adjusted values and appears suitable for clinical use.

There are several potential sources for the loss of predictive performance in the study design and pharmacokinetic approaches we developed. These include patient compliance and dosage history reporting, model misspecification, and HIV disease factors. We have had excellent experience with medication compliance by patients in our studies, including investigations of concomitant, complex regimens (33). Even so, it is certainly conceivable that both compliance and reporting were not accurate. We did not determine absolute bioavailability, assumed no lag phase, and assumed that a one-compartment model provided an appropriate characterization of pharmacokinetic behavior. However, variability exists in the bioavailability of zidovudine. Following oral administration of doses ranging from 2 mg/kg of body weight every 8 h to 10 mg/kg every 4 h, overall bioavailability averaged 65% but ranged from 60% ± 13% to 72% ± 1% (1). We have found that the addition of a lag phase improved the pharmacokinetic description of certain patients' concentration data (14). While a one-compartment model has usually been employed to describe zidovudine concentrations following oral administration, biexponential decay is observed after completion of an intravenous infusion (1). Following oral administration, distribution may not always be masked by absorption, and we have observed biexponential decay after oral administration of zidovudine in patients. The negative bias seen in the elimination phase predictions by the Bayesian and One-Parameter methods may indicate the existence of biexponential elimination. It is possible to use sparse sampling strategies to characterize the pharmacokinetic disposition of drugs obeying multicompartmental behavior, and an investigation of these models may be warranted for oral zidovudine. Lastly, infection with HIV produces a spectrum of manifestations affecting several organ systems. Malabsorption, achlorhydria, mucosal atrophy, and decreased enzyme activity have been described in patients with AIDS and no gastrointestinal symptoms (18, 19, 29). Renal disease and hepatic pathology are also associated with HIV infection and AIDS (5, 23). Whether some loss of predictive performance is a result of unrecognized effects of HIV on the gastrointestinal tract, kidney, or liver is unknown.

Almost 8 years after the introduction of zidovudine for treatment of HIV infection, our knowledge of the optimal manner in which to use this and the other available nucleoside antiretroviral agents remains quite primitive. Therapy with nucleoside antiretroviral agents does offer benefit to many HIV-infected persons, but ultimately their disease progresses. The contribution of inadequate viral suppression to disease progression is unknown, as are the consequences of pharmacokinetic and pharmacodynamic variability in the drugs used to treat HIV infection. It does seem unlikely that the "treat everyone the same" approach will ensure the highest probability of therapeutic success for all persons. Therefore, as our knowledge of relationships between the concentration of zidovudine and its pharmacologic effects increases and the unavoidable use of polypharmacy for management of the HIV-infected person expands, there will likely be an increased need for determining the pharmacokinetic disposition of zidovudine (as well as other agents) in an individual patient and adjusting the dosage according to this information. Our study demonstrates that meaningful pharmacokinetic parameters can be extracted from a sparse sampling strategy applied in an outpatient setting. Of the methods evaluated, the use of a Bayesian-estimation procedure and two measured concentrations resulted in parameters that had the greatest precision and least bias. These observations provide a modeling framework for maintenance of target concentrations in an individual patient, for screening for the existence of drug interactions, and for the conduct of concentration-controlled clinical trials. We have now initiated an evaluation of a concentration-controlled zidovudine regimen.

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