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Effects of Standard Breakfast on Pharmacokinetics of Oral Zidovudine in Patients with AIDS

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The influence of a standard breakfast on the single-dose pharmacokinetics of zidovudine (AZT) after oral administration of 100 and 250 mg of AZT was studied in 27 subjects with advanced human immunodeficiency virus infection (Centers for Disease Control stage IV). Concentrations of AZT and the 5′-glucuronide metabolite (GAZT) in serum and urine were measured by a high-pressure liquid chromatographic method. Pharmacokinetic analysis was done by an open one-compartment model as well as noncompartmentally. The results were summarized as medians with 50% confidence ranges because of the high degree of interindividual variability. Peak levels in plasma were moderately reduced after administration of 100 mg AZT in the nonfasting group (1.79 μmol/liter in the fasting group [F], 1.12 μmol/liter in the group that received breakfast [B]) and were markedly reduced after administration of 250 mg AZT (6.51 μmol/liter [F], 1.79 μmol/liter [B]). The terminal half-life in plasma was prolonged almost twofold after breakfast with 100 and 250 mg of AZT (100 mg, 36.4 min [F] and 51.6 min [B]; 250 mg, 35.3 min [F] and 63.6 min [B]). Recoveries (AZT and GAZT) in urine varied with both dosages, reflecting more a problem of accounting for the metabolite GAZT in urine than a relevant difference (100 mg, 115% [F] and 76.5% [B]; 250 mg, 71% [F] and 99.4% [B]). Our data suggest that absorption of AZT in human immunodeficiency virus-infected subjects is extremely variable, with a high degree of interindividual differences. Furthermore, breakfast had a marked influence on the absorption of AZT, suggesting that the drug should be taken in a fasting state.

Absorption of drugs administered orally may vary extensively by concomitant food intake and may result in a clinical efficacy of the applied drug different from that when the drug is taken in the fasting state (1, 8, 23). The antiretroviral drug 3′-azido-3′-deoxythymidine (zidovudine or AZT) has been studied in many clinical trials. Those controlled trials showed that AZT can prolong survival and decrease the frequency of opportunistic infections in many patients with AIDS or AIDS-related complex (7, 17, 24). Recent trials indicate that in asymptomatic human immunodeficiency virus (HIV)-infected patients (with CD4 counts of less than 500/μl), daily dosages of 500 mg of AZT (100 mg five times) have been effective in delaying disease progression (22). On the other hand, most studies on the clinical efficacy of AZT were performed without prior evaluation of the influence of food intake on the bioavailability of the drug. Pharmacokinetic data for AZT administered to adults and children with HIV infection showed that after oral dosing in a fasting state, rapid absorption occurred, with peak concentrations in plasma occurring within 0.5 to 1.5 h (2, 5, 11, 14, 16, 18). The dose-independent kinetics of AZT given at up to 10 mg/kg of body weight and the bioequivalences of different formulations were described after oral dosing (3, 6). In clinical practice, many patients take AZT with a meal to reduce gastrointestinal side effects, but until now, only very limited data concerning the effect of food intake on the pharmacokinetics of oral AZT have been published. Data from two papers suggested reduced peak concentrations in serum after certain meals (high-fat, protein-enriched meals) (19, 21).

The present study was performed to evaluate the influence of a standard breakfast on the various pharmacokinetic parameters after the administration of different dosages of AZT; these results might contribute to a better understanding of the varying efficacy of AZT.

MATERIALS AND METHODS

Patients. Twenty-seven patients (3 women, 24 men) with HIV infection (stage III [n = 2] and IV A to C of the classification of the Centers for Disease Control participated in the study (mean CD4 count, 141/μl [range, 5 to 494/μl] in the group that received 100 mg of AZT; a mean CD4 count, 85/μl [range, 16 to 200/μl] in the group that received 250 mg of AZT). Of the 27 patients, 18 were pretreated with AZT (500 to 1,000 mg/day) and stopped taking AZT for a washout period of 1 week. Written informed consent was obtained from all patients. The mean age of the patients was 39 years (range, 24 to 64 years); the mean body weight was 66 kg (range, 52 to 86 kg). None of the patients had signs of diarrhea or symptoms of malabsorption. No concurrent medication other than aerosolized pentamidine was allowed on the study day. One patient took theophylline, which could not be discontinued because of bronchial asthma.

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Results of routine laboratory tests of hepatic and renal function were within the normal ranges.

Study drug. AZT (Retrovir) was administered orally in capsules of 100 mg (Ch.-B.:C7252A) or 250 mg (Ch.-B.: B7266A); AZT was obtained from Deutsche Wellcome GmbH, Burgwedel, Germany.

Drug assay. The concentrations of AZT in plasma were determined by high-pressure liquid chromatography (HPLC) as described previously (15). The concentration of the standard curve ranged between 0.1 and 10 μmol/liter. The detection limit was 0.1 μmol/liter (27 ng/ml). The interday coefficient of variation was assessed to be between 18 and 6.8% in the concentration range of 0.2 to 5 μmol/liter.

AZT and the 5'-glucuronide metabolite (GAZT) in urine were assessed simultaneously by HPLC (9). Inactivation of samples, sample preparation, and the application of 50 μl of azidoguanosine (concentration in serum, 50 μmol/liter; concentration in urine, 300 μmol/liter) as an internal standard for calculation of the results were identical to those for AZT determinations in plasma (15). The standard curve included concentrations from 0.25 to 20 μmol/liter for both parameters. The detection limit of AZT and GAZT in urine was 0.25 μmol/liter. Serum was heat inactivated at 56°C for 120 min prior to the assay (20).

The interday coefficient of variation for AZT in urine was 9.2 to 7.2% in the concentration range of 2 to 15 μmol/liter. The values for GAZT were 13.5 to 7.8% for the same concentration range.

Study design. After an overnight fast, one capsule of either 100 mg (12 subjects) or 250 mg (15 subjects) of AZT was given to the patients with 100 ml of water in the morning. Subjects were randomized into two groups which alternately stayed fasting for 2 h or received a standard breakfast before the morning dose. The breakfast was given in continental style (two slices of white bread, butter, jam, sliced Swiss cheese or ham, and black tea or coffee ad libitum), with an overall intake of 600 kcal. Subjects who had breakfast took AZT with either black tea or coffee at the end of breakfast. Fifteen subjects received 250 mg of AZT (15 fasting subjects; 14 subjects who received breakfast) and 12 subjects (12 fasting subjects; 11 subjects who received breakfast) took 100 mg of AZT.

Sampling. Blood samples (5 ml) were taken from an indwelling intravenous cannula before the first dose and at 15, 30, 45, 60, 75, 90, 105, 120, 180, 240, 300, and 360 min after oral dosing. Blood specimens were immediately centrifuged at 4°C. Urine samples were collected for a longer period (0 to 6, 6 to 12, and 12 to 24 h) after drug administration to find primarily GAZT, which may be detectable in urine for a longer period than in serum (21). The volume was noted, and 10 ml was saved for analytical procedures. All samples were stored at −80°C before being sent to the laboratory for HPLC and were analyzed within 4 weeks. No drug activity could be detected in plasma or urine before dosing.

Pharmacokinetic analyses. The pharmacokinetic parameters for the fasting and nonfasting subjects were derived by analysis of the individual data by using an open one-compartment model (12) for extravascular administration as well as noncompartmentally (8). The equation for the model is a regression function, as follows: $C(t) = p_1 \cdot [\exp(-p_2 \cdot t') - \exp(-p_3 \cdot t')]$, where $t' = t - t_{lag}$ and $C(t)$ is drug concentration at time t.

$$p_1 = \frac{f \cdot \text{dose}}{V} \cdot \frac{k_a}{k_a - k_{el}}$$

where k_{el} (also p_2) is the elimination rate constant, k_q (also p_3) is the absorption rate, f is bioavailability, and V is volume of distribution. The area under the curve (AUC) was obtained as the sum of the AUC from 0 to 6 h (AUC_{0-6}) calculated by the linear trapezoidal method and the AUC from 6 h to infinity ($AUC_{6-\infty}$) calculated as the ratio of the AZT concentration in plasma at 360 min and the elimination rate constant (k_{el}). The AUCs (as well as all other values) were calculated for each patient separately.

The mean residence time (MRT) was calculated as the time after application required for eliminating 63.2% of the substance, solving the equation:

$$\int_{t_{log}}^{MRT_{obs}} C(t) \cdot dt = 0.632 \cdot AUC_{tot}$$

where MRT_{obs} is the observed MRT, t_{lag} is lag time, and AUC_{tot} is total AUC. Recovery from urine was calculated as a percentage of the administered oral dose determined by HPLC. When calculating the percentage of the dose recovered, the recovery of GAZT was corrected for the different molecular weight of this compound (molecular weight of GAZT, 486.59) relative to that of the administered compound (molecular weight of AZT, 267.24).

The calculations were performed by standard methods (10). If applicable, the results are normalized for a 70-kg body weight or a 1.73-m^2 body surface area. For statistical analysis, the Wilcoxon signed-rank test for paired data was used.

As discussed below, the concentrations, and hence the pharmacokinetic parameters, differed markedly (see Fig. 1). Therefore, the usual calculations of arithmetic means and standard deviations were not justified. Instead, we summarized our results as medians. In addition, the 50% confidence range is given to provide information about the degree of precision.

RESULTS

The concentrations of AZT determined by HPLC in 12 fasting patients after the administration of 100 mg of AZT are given in Fig. 1. The wide range of values that was obtained is demonstrated in Fig. 1. The respective regression curves are also included for the medians. Because of the lack of concentrations above the detection limit in serum, no median values were available for 5 and 6 h after drug intake.

In Fig. 2, the serum assays are summarized graphically on the basis of the regression curves for the medians. In order to compare both dosages, the concentrations obtained from those taking the 250-mg dose were recalculated for a nominal dose of 100 mg (per 70 kg of body weight). Figure 3 demonstrates the results of the urine assessments (sampling period from 0 to 24 h after drug administration). The excretion of AZT in urine was rather low (<10%), but the total amount of the metabolite GAZT found in urine (expressed as the percentage of the administered AZT dose) was about 10-fold higher.

The derived pharmacokinetic data, given as median values with 50% confidence intervals, are summarized in Table 1.

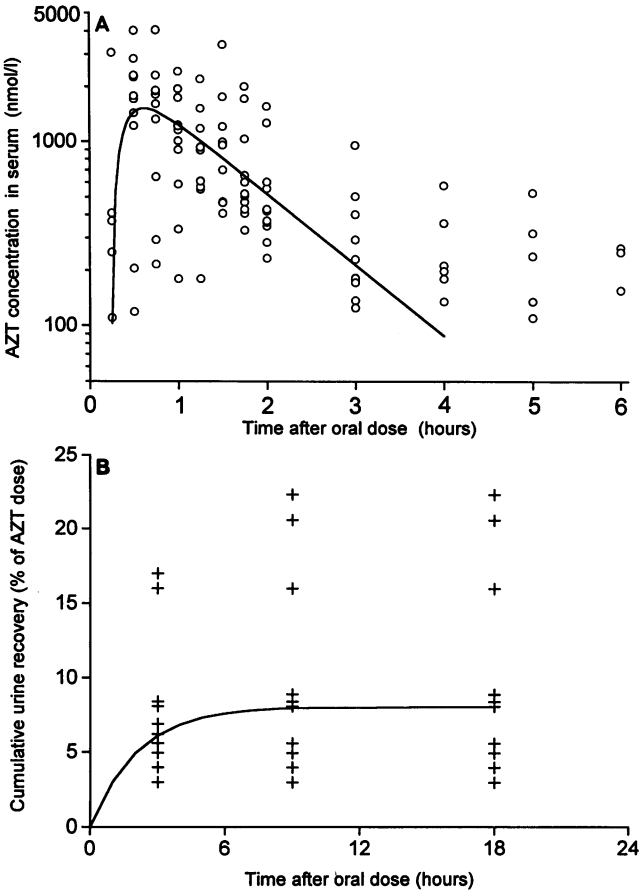

FIG. 1. Concentrations of AZT in serum of individual subjects (A) and cumulative recovery in urine (B) after administration of oral doses of 100 mg of AZT to 12 fasting patients. Also included are the respective regression curves based on the median values. Note that the median allows consideration of the concentrations below the detection limit. However, no median can be calculated if not more than 50% of the measurements are above the detection limit. In panel B, the results for the collection period from 0 to 6 h, 0 to 12 h, and 0 to 24 h after drug administration are entered at 3, 9, and 18 h, respectively. Note that in two patients, no AZT concentrations could be found above the detection limit.

Pharmacokinetics of AZT in plasma of fasting subjects. Rapid absorption occurred after a t_{lag} of 15.0 min (range, 3.5 to 60 min) after administration of 100 mg of AZT and 13.1 min (range, 1 to 28 min) after administration of 250 mg of AZT. MRT, calculated as the observed MRT, was 109 min in those who received 100 mg of AZT and 65 min in those who received 250 mg of AZT; the MRT reflects the time when two-thirds of the applied drug was eliminated from plasma.

Considerable interindividual variability was seen in the maximum concentrations of AZT in plasma (C_{max}) of 1.8 μmol/liter (range, 0.6 to 4.6 μmol/liter) after a time to maximum concentration of AZT in serum (T_{max}) of 45 min with a dose of 100 mg of AZT and a C_{max} of 6.5 μmol/liter (range, 1.7 to 14.1 μmol/liter) after a T_{max} of 20 min with a dose of 250 mg of AZT. The AUC was 2.6 μmol · h/liter for 100 mg of AZT and 7.2 μmol · h/liter for 250 mg of AZT. No difference in total clearance could be detected after administration of 100 mg of AZT (2,483 ml/min/1.73 m^2) or 250 mg of AZT (2,143 ml/min/1.73 m^2). All values are medians.

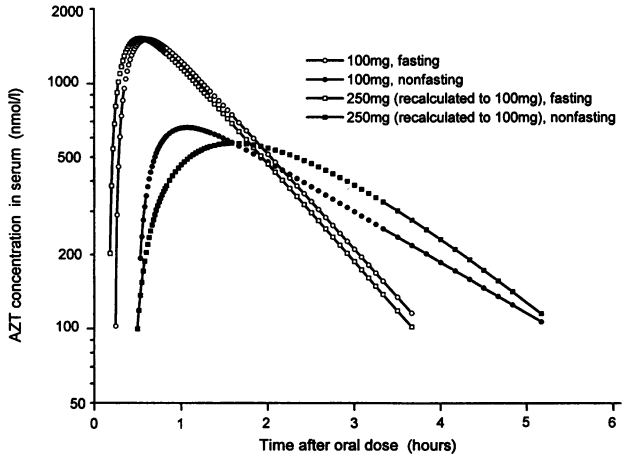

FIG. 2. Results of measurements of AZT in serum given as regression curves for the medians. In the nonfasting patients, the rate of absorption was lower and the half-life of excretion increased, resulting in a lower peak value. Remember that the individual variations were high (see Fig. 1).

Pharmacokinetics of AZT in the plasma of subjects after breakfast. After a standard breakfast, absorption was prolonged to t_{lag} of 29.7 min for those receiving 100 mg of AZT, with a wide range of 13 to 103 min, and a t_{lag} of 25.6 min for those receiving 250 mg of AZT, with a range of 11 to 44 min. Similarly, the observed MRTs were moderately to markedly extended in those receiving the 100- and 250-mg doses (131 and 187 min, respectively). The T_{max} was considerably prolonged after a standard breakfast (58 min after the 100-mg dose; 92 min after the 250-mg dose), and the C_{max} was reduced for both groups (1.1 μmol/liter after the 100-mg dose; 1.8 μmol/liter after the 250-mg dose). The interindividual variability of the peak concentrations in plasma was similar to that seen in the fasting groups. Data for total AUC (1.7 μmol · h/liter for 100-mg dose; 6.1 μmol · h/liter for the 250-mg dose) and total clearance (3,336 ml/min/1.73 m^2 for the 100-mg dose; 2,394 ml/min/1.73 m^2 for the 250-mg dose) did not appear to be affected by a standard breakfast for those receiving either dose. All values are medians.

HPLC determination of AZT in urine. The cumulative recovery of the parent compound and its metabolite after 24 h was 115% (8% AZT, 107% GAZT) after administration of 100 mg of AZT and 71% (5.6% AZT, 65.4% GAZT) after administration of 250 mg of AZT in the fasting groups. The largest amount (AZT plus GAZT) was recovered within the first 6-h sampling period (94.4 for the 100-mg group, 65.8% for the 250-mg group). After the standard breakfast, the cumulative recovery in urine after 24 h was more or less the same, with some variation between the groups given the different dosages. After administration of 100 mg of AZT, 76.5% of the applied dose was collected (6.3% AZT, 70.2% GAZT), and after administration of 250 mg of AZT 99.4% of the applied dose was collected (6.5% AZT, 92.9% GAZT). The variation in recoveries in urine between the fasting and nonfasting groups after administration of 250 mg of AZT reflected more the problem of accounting for the metabolite GAZT in urine than a statistically relevant difference. All values are medians.

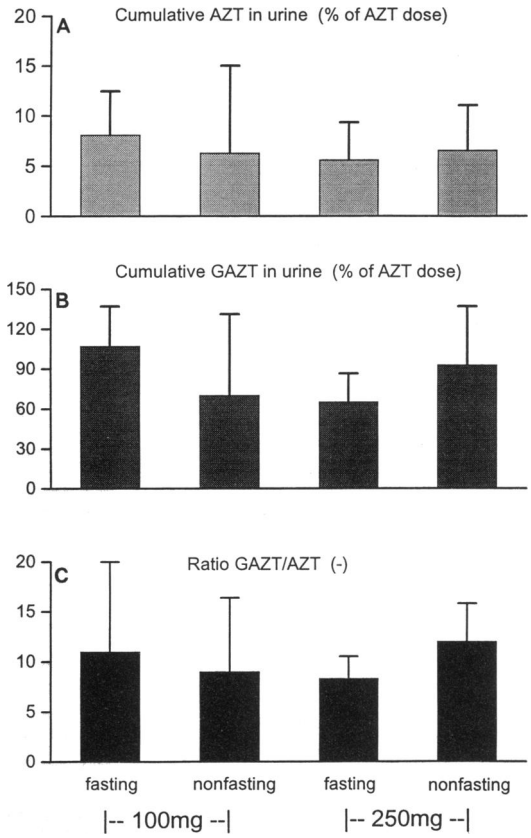

FIG. 3. Summary of the urine assay. (A) Recovery of AZT in urine from 0 to 24 h after drug administration for the four groups (median and 50% confidence range). (B) Cumulative metabolite concentration from 0 to 24 h after drug administration (given as percentage of the AZT dose). (C) Ratio of the concentrations of GATZ and AZT. Considering the high degree of individual variation, no parameter depended on either condition (fasting or nonfasting) or dose (100 or 250 mg). Calculation of the amount of GAZT in urine expressed as the percentage of the administered AZT dose was done on the basis of milligrams (urine $AZT_{equivalent}$ [mg] = mmol/liter × molecular weight of AZT × liter of urine).

DISCUSSION

AZT is widely used for delaying the progression of HIV infection (5, 7, 18, 22, 24), but only limited data on the influence of food intake on the oral pharmacokinetics of AZT have been published. Gastrointestinal side effects resulting from AZT administration occur frequently, and many patients take AZT with a meal to reduce these side effects. Two studies looked at the influence of special diets, such as a high-fat (19) or a protein-enriched (21) meal, on the pharmacokinetics of AZT, but those studies provided different statements regarding the influence of food on the absorption of AZT. However, both groups of investigators pointed out that peak concentrations in serum were reduced after food intake. In the present study, the influence of a standard breakfast on the pharmacokinetics of AZT administered orally to HIV-infected patients was studied. Comparing data for the 100- and 250-mg doses of AZT used under fasting conditions in the present study with those presented by other investigators showed good agreement with respect to mean C_{max}, T_{max}, elimination half-life, and cumulative elimination from urine (3, 12, 25). Unadkat et al. (21) found that the absorption of AZT is rapid in the absence of food, but a high-fat meal delayed absorption significantly in eight men after various oral dosing regimens of either 100 or 250 mg of AZT (T_{max} was delayed from 0.68 to 1.95 h after administration of 100 mg of AZT [$P < 0.05$]). In contrast, Sahai et al. (19) found absorption after administration of 200 mg of AZT and a protein-enriched meal in 10 men not to be significantly different in fasting and nonfasting subjects, even if their data showed a reduced C_{max} (788 ng/ml in fasting subjects and 543 ng/ml in subjects after a meal) and a prolonged T_{max} (from 52 to 75 min) as well.

The data from the present study confirmed the results of Unadkat et al. (21) in their patients (two on 250 mg of AZT and six on 100 mg of AZT). With regard to the high degree of interindividual variance of AZT absorption, however, data in small groups of patients need to be looked at very cautiously. In the present study, which had a larger number of subjects than the study of Unadkat et al. (21), absorption was delayed, and there was some variation between the two dosages. In those who received 250 mg of AZT, drug absorption was changed markedly more after food intake than it was in those who received 100 mg of AZT. The difference was probably not due to the higher dosage but to the larger number of patients studied. This assumption would be confirmed by the comparable AUC data for both groups. Looking at the individual C_{max}, t_{lag}, and T_{max} data, a marked interindividual variability could be demonstrated in all groups. These differences in absorption might lead to different efficacies of AZT in the treatment of HIV-infected patients. However, this may be difficult to prove, because even low dosages, such as 300 mg of AZT daily, showed some effect on virologic markers (4). The data presented here suggest a prominent (100-mg dose group) or even

TABLE 1. Pharmacokinetics of AZT administered orally in fasting and nonfasting subjects[a]

Dose and fasting state	t_{lag} (min)	T_{max} (min)	C_{max} (μmol/liter)	$t_{1/2}$ (min)	MRT min	AUC (μmol · h/liter)	CL/f
100 mg							
Fasting	15.0 (14.1–28.3)	45.8 (28.8–73.0)	1.79 (0.97–2.73)	36.4 (29.1–75.8)	109 (64–151)	2.58 (1.68–2.84)	2,483 (2,066–3,186)
Nonfasting	29.7 (28–58.6)	58.6 (43.6–104.4)	1.12 (0.78–1.61)	51.6 (34.6–69.5)	132 (94–173)	1.72 (1.34–2.58)	3,336 (1,883–4,209)
200 mg							
Fasting	13.1 (3.4–14.7)	20.0 (7.1–28.0)	6.51 (4.82–8.0)	35.3 (30.4–44.1)	65 (53–95)	7.29 (5.54–8.16)	2,143 (1,698–2,816)
Nonfasting	25.6 (13.8–29.6)	92.6 (60.7–116.8)	1.79 (1.53–2.17)	63.6 (59.1–92.7)	187 (131–239)	6.29 (5.35–8.19)	2,394 (1,754–2,806)

[a] Values are medians (50% confidence intervals). t_{lag}, time of drug absorption from the gut; C_{max}, maximum concentration of the drug in plasma; T_{max}, time to maximum concentration of the drug in plasma; $t_{1/2}$, terminal half-life; MRT, mean residence time, calculated as the time after application required for eliminating 63.2% of the given dose; AUC, total area under the curve, adjusted to 70 kg of body weight; CL/f, total clearance related to bioavailability (f) corrected to 1.73 m^2 of body surface.

significant (250-mg dose group) influence of a standard breakfast on the absorption of AZT in HIV-infected patients given two different dosages of AZT because of a prolonged t_{lag} and a reduced C_{max}.

However, in comparison with the high degree of interindividual variability, this effect was relatively small and did not result in a different AUC, amount of drug recovered in urine, or clearance of the drug from plasma, but only in a different shape of the curve of the concentration in plasma.

Delayed absorption has been described for many drugs after food intake and has been explained to be the result of inhibition of gastric emptying, chemical composition, and chemical binding of drugs to nonabsorbable components of the meal [1, 8, 23]. Unadkat et al. (21) favored the idea that a high-fat meal in particular led to a significant effect on the absorption of AZT because of the doubling of the gastric emptying time resulting from the fat content of the meal. The pharmacokinetic data after a standard (continental) breakfast support the hypothesis that overall absorption is retarded after food intake, independent of the composition of the meal. In the present study, a high degree of interindividual variability in the absorption of AZT, especially after food intake, was observed. In addition to the local mechanism in the gut, possible explanations for this variability may be the age of patients or undetected dysfunction of the liver, kidney, or both (5).

The first in vitro studies of AZT described a concentration in plasma of at least 1 μmol/liter as being adequate for inhibitory activity on HIV reverse transcriptase and HIV antigen expression in vitro (17, 25). In the present study, individual peak levels of AZT in plasma were above this target concentration in all subjects studied, but decreased to median levels of 0.85 μmol/liter after 2 h (250-mg dose in fasting subjects) and 0.6 μmol/liter after 4 h (250-mg dose in subjects who received breakfast). Even much earlier, concentrations in plasma after administration of 100 mg of AZT fell below the margin of 1 μmol/liter (0.8 μmol/liter after 75 min in the fasting and the nonfasting groups).

Since dosages of 100 mg of AZT given five times daily have been found to be effective for delaying progression from asymptomatic HIV infection to AIDS (22), it remains unclear which AZT levels in plasma are needed to be effective in HIV-infected patients.

The results presented here demonstrate a high interindividual variability in the absorption of AZT, particularly after food intake, with a marked influence of food intake on some pharmcokinetic parameters (e.g., C_{max}, T_{max}, and MRT). Whether higher levels of AZT in plasma will enhance virostatic activity, and therefore, whether higher levels are related to better clinical outcomes in HIV-infected patients, remains questionable with respect to the results of different clinical trials with AZT at various dosages. In the discussion on the efficacy of AZT, it needs to be considered that peak levels of the drug in serum are even more variable after food intake.

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