Pharmacokinetics of zidovudine after the initial single dose and during chronic-dose therapy in HIV-infected patients

KEITH GALLICANO¹, JAN SAHAI², ERIC ORMSBY¹, D. WILLIAM CAMERON², ATTILA PAKUTS¹ & IAIN MCGILVERAY¹

¹The Bureau of Drug Research, Health & Welfare Canada, and ²The Department of Medicine, Ottawa General Hospital, Ottawa, Canada

The pharmacokinetics of zidovudine in 10 symptomatic HIV-infected men were assessed after administration of the initial 200 mg oral dose at the start of therapy (day 1) and on one occasion during non steady-state conditions of chronic-dose therapy (200 mg every 4 h while awake on day 21–66; 5 doses per day). The following mean ($\pm$ s.d.) pharmacokinetic parameters were determined on day 1 and during chronic therapy, respectively: $C_{\max}$ (4.09 ± 2.54 vs $3.82 \pm 1.03 \mu\text{mol l}^{-1}$), oral clearance (40.7 ± 12.9 vs $41.1 \pm 8.4 \text{ ml min}^{-1} \text{ kg}^{-1}$) and terminal half-life (68.4 ± 29.4 vs $65.1 \pm 13.1 \text{ min}$). Mean pharmacokinetic parameters on day 1 were $< 10\%$ different ($P > 0.34$) from those determined during chronic therapy. Differences in means of 21% for clearance and 36% for $C_{\max}$ could be detected with a power of 80% at the 5% significance level. Intra-subject coefficients of variation were 17% for clearance and 32% for $C_{\max}$, respectively. This study suggests that within a group of patients whose stage of HIV infection and general health are relatively stable, first-dose pharmacokinetic parameters provide a good estimate of multiple-dose pharmacokinetic parameters.

Keywords zidovudine pharmacokinetics intra-subject variability

Introduction

Several studies have documented significant inter-subject [1,2] and within-day [3] variability in zidovudine (3'-azido-3'-deoxythymidine) pharmacokinetics. If repeated monitoring of serum concentration of zidovudine within a patient is required, such as for participation in multi-period drug trials, an estimate of the intra-subject variability of pharmacokinetic parameters is also valuable. Although there is some information [2,4] on intra-subject variability, there remains a need for further data, particularly in HIV-positive patients without concurrent opportunistic infections. For this reason, HIV-positive males whose stage of HIV infection and general health remain stable once zidovudine therapy has begun were monitored.

AIDS-related complex) with normal renal and hepatic functions participated in this repeated-measures study after ethics approval and written informed consent were obtained. Females were excluded because of the unknown effects of cyclical changes on zidovudine pharmacokinetics. At entry, patients had received no previous zidovudine therapy. Their mean age was 36 (range 25–59) years and their weight was 76 (range 60–100) kg. Patients were excluded on the basis of the following: use of any other systemic medication 1 week before or during the study; weight deviating by more than 20% from ideal; serum creatinine $>150 \mu\text{mol l}^{-1}$; results of liver function tests greater than twice normal; serum albumin values $<37 \text{ g l}^{-1}$; any evidence of opportunistic infection; or gastrointestinal dysfunction.

Methods

Patient selection

Ten homosexual, symptomatic (CD4 T lymphocytes $<500/\text{mm}^3$) HIV-infected men (three AIDS and seven

Study design and blood sampling

Each patient began zidovudine therapy with a single 200 mg dose (two 100 mg capsules of Retrovir; Burroughs Wellcome Inc., Canada) followed after 24 h by multiple dosing. Pharmacokinetic studies were conducted at the start of therapy (day 1, visit 1) and on

one occasion during chronic therapy (day 21–66, visit 2). During chronic therapy patients were receiving 200 mg zidovudine every 4 h while awake (5 doses per day) because they found it inconvenient to take zidovudine during the night. Patients were studied 8 h after their evening dose, during non steady-state conditions, to allow construction of a concentration-time curve similar to that after the initial single dose. On both study days, to minimize any effects of circadian rhythm on zidovudine disposition, patients ingested two zidovudine capsules sequentially (within 15 s) with 150 ml tap water between 08.00 h and 09.00 h after a 10 h overnight fast. They then remained in a seated position for 2 h to minimize any positional effects on zidovudine pharmacokinetics. Food was allowed 4 h after drug administration.

On each study day, serial blood samples were obtained from an indwelling venous catheter, immediately before drug administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, and 4 h after the dose. Serum was isolated by centrifugation at 2500 rev min⁻¹, 24° C and samples were stored at -80° C until analysis (within 12 weeks). All serum samples were heated at 58° C for 30 min before freezing to inactivate the HIV.

Drug assay

Serum samples (0.1 ml) were analyzed in duplicate for zidovudine by radioimmunoassay (ZDV-TracTM, ¹²⁵I kit, Incstar Corporation). The kit instructions were followed, except that samples were diluted 20- or 40-fold with 25 mM phosphate buffer (pH 6.8) and all volumes for samples and reagents were reduced by 50%. Samples from both study periods for each patient were analyzed on the same day to minimize inter-day contributions of the analysis to intra-subject variability. In-house quality-control samples containing both zidovudine and its glucuronide metabolite, prepared in serum obtained from normal volunteers and stored with the study samples, were analyzed in duplicate concurrently with the patient's samples. Zidovudine concentrations were interpolated from a plot of the percent of tracer that is maximally bound to antibody (B/B₀) vs zidovudine concentration. Final zidovudine serum concentrations were calculated by correcting for the dilution factor. Quantitation was based on a four-parameter logistic analysis (GraFit Version 1.0, Erithacus Software Ltd) of the best curve-fit through the five undiluted buffer standards. The lower limit of quantitation (LLQ) was defined as the quantity of zidovudine required to displace 10% of the tracer and the upper limit (ULQ) was defined as the quantity required to displace 90% of the tracer that is maximally bound to antibody. For all curves the LLQ was the lowest standard-curve sample (0.22 or 0.29 ng ml⁻¹) and the ULQ ranged between 100 and 200 ng ml⁻¹, depending on the curve fit and the concentrations of the standards supplied by Incstar.

Predicted concentrations of zidovudine in quality-control samples (*n* = 86) underestimated the nominal values, with the average deviations ranging from -8.8 to -15.9%. Within and between assay coefficients of variation (CV) for measurements of zidovudine were

<6 and <12%, respectively, in 43 quality-control samples analyzed in duplicate.

Data analysis

Serum zidovudine concentration vs time data were analyzed by noncompartmental methods. The highest observed concentration and the corresponding sampling time were defined as *C*_{max} and *t*_{max}, respectively. Terminal half-life (*t*_{1/2}) was calculated from the final slope (-λ_z) of the log-linear concentration-time curve by least-squares linear regression. At least four points were used to estimate -λ_z, the selection of which was based on the data set for which the mean-square residual (MSR) term from the regression was minimized. Area under the serum drug concentration-time curve (AUC) and area under the first moment of serum drug concentration-time curve (AUMC) were estimated by trapezoidal and log-trapezoidal methods from time 0 to *t* of last measureable sample (*t*_z = 4 h), and extrapolated to infinity using the calculated serum concentration at *t*_z [5]. The segment of total AUC and AUMC that was extrapolated to infinity averaged 7.7 (4.2 s.d.)% and 25.8 (11.3 s.d.)%, respectively.

To account for residual predose level of drug during the non steady-state period of chronic therapy, individual serum drug concentrations at each sampling time were corrected as follows:

$$C_{\text{corrected}} = C_{\text{observed}} - C_{\text{residual}} \text{ where } C_{\text{residual}} = C(0)e^{-\lambda_z \cdot t}$$

C(0) is the predose concentration at time zero.

The oral clearance (CL_o) was calculated by dividing the dose by AUC. The mean total residence time (MTRT) was calculated from the ratio {AUMC/AUC}.

Statistical analysis

Differences in mean pharmacokinetic parameters of zidovudine between treatments were evaluated by repeated-measures analysis of variance (ANOVA). All pharmacokinetic data, except *t*_{max}, *t*_{1/2} and λ_z were logarithmically transformed and the geometric and arithmetic means were used in the ANOVA calculations. Statistical significance was defined as *P* < 0.05. Results are expressed as arithmetic mean ± s.d. in the text and tables.

For logarithmically transformed data, the approximate intra-subject and inter-subject coefficients of variation for each pharmacokinetic parameter were calculated as CV_w ~ {MSR}^{1/2} and CV_b ~ {(MS-MSR)/2}^{1/2}, respectively, where MS is the subject mean-square. The respective equations were divided by the arithmetic mean of the two treatment means to obtain the exact CV values for *t*_{max}, *t*_{1/2} and λ_z data.

Results

Each patient's stage of HIV infection and general health (body weight, serum creatinine, liver enzyme measurements) remained stable for the duration of the study, and no significant adverse reactions were

Table 1 Mean pharmacokinetic parameters of zidovudine for the two visits: 1. Initial single dose and 2. Chronic therapy

Parameter	Treatment*		%D [†]	Repeated-measures ANOVA				
	1. Initial single dose	2. Chronic therapy		95% confidence limits	P	Intra- subject % CV	Inter- subject pooled % CV	Δ _{80%} [‡]
C _{max} (μmol l ⁻¹)	4.09 ± 2.54	3.82 ± 1.03	-0.1	-27.6, 37.9	0.997	31.8	21.8	36.1
t _{max} (min)	34.5 ± 10.1	37.5 ± 10.6	8.7	-11.0, 28.4	0.343	18.6	22.0	26.2
AUC (μmol l ⁻¹ min)	242 ± 57.7	229 ± 37.7	-3.7	-18.8, 14.2	0.628	16.9	12.6	21.1
CL ₀ (ml min ⁻¹)	3043 ± 879	3084 ± 544	3.7	-12.6, 22.9	0.645	16.8	16.7	21.1
CL ₀ (ml min ⁻¹ kg ⁻¹)	40.7 ± 12.9	41.1 ± 8.4	3.7	-12.5, 22.9	0.643	16.8	23.0	21.1
MTRT (min)	96.7 ± 25.6	98.5 ± 16.4	3.3	-12.3, 21.8	0.661	16.2	12.9	20.4
t _{1/2} (min)	68.4 ± 29.4	65.1 ± 13.1	-4.8	-32.3, 22.7	0.703	27.8	19.6	39.2
λ _z (min ⁻¹)	0.0112 ± 0.0029	0.0110 ± 0.0021	-1.4	-14.4, 11.6	0.813	12.9	0.2	18.2

Note. C_{max}, observed peak serum drug concentration; t_{max}, observed time of peak concentration; t_{1/2}, apparent terminal half-life; λ_z, terminal disposition rate constant; AUC, area under the serum concentration-time curve from time zero to 4 h; CL₀, clearance; MTRT, mean total residence time; CV, coefficient of variation.

* 200 mg dose. Treatment means are arithmetic means ± s.d. (n = 10): AUC, C_{max}, CL₀ and MTRT values calculated for chronic therapy are based on concentrations corrected for residual predose zidovudine levels.

† % change of geometric mean (C_{max}, AUC, CL₀ and MTRT) or arithmetic mean (t_{max}, t_{1/2} and λ_z) of treatment 2 relative to that of treatment 1. A negative value refers to a decrease.

‡ % decrease of the geometric or arithmetic means (see †) that can be detected with a power (1-β) of 80% at the 5% level of significance (α = 0.05/2).

Figure 1 Mean (± s.e. mean) serum concentrations of zidovudine after administration of a 200 mg oral dose of zidovudine, following the initial single dose (○—○) and during non steady-state chronic-dose therapy (Δ ··· Δ, dosage every 4 h while awake).

reported by any patient. No patients were anaemic (< 10 g dl⁻¹ haemoglobin) or neutropenic (< 1.0 × 10⁹ l⁻¹ neutrophils) and all patients showed an increase in mean corpuscular volume (range 6% to 12%) during the chronic-dose study period. Every patient had measurable zidovudine concentrations at all sampling times (15 min to 4 h). Mean serum drug concentrations are shown in Figure 1.

Seven of 10 patients showed measurable predose concentrations of zidovudine, ranging from 0.022 to 0.067 μmol l⁻¹ (6.0 to 18.0 ng ml⁻¹), after being off zidovudine for 8 h during chronic therapy. The ANOVA, however, indicated < 1% change in mean pharmacokinetic parameters and associated statistical parameters after correction for residual zidovudine concentrations. Table 1 therefore shows only data based on mean corrected pharmacokinetic parameters of zidovudine and their associated ANOVA parameters.

The pharmacokinetic parameters determined during chronic therapy, 3–9 weeks after beginning treatment, were not significantly different (*P* > 0.34 for all values) from those determined at initiation of drug therapy. Table 1 shows less than 10% differences between treatment means, with 95% confidence limits within ± 40%. Except for C_{max}, t_{max} and t_{1/2} values, small differences (< 22%) can be detected with a power of 80% at the 5% significance level, and are a reflection of CV_w values < 20%. C_{max} was considered highly variable within a subject (CV_w > 25%). Statistical parameters for clearance were little affected when CL₀ values were adjusted for body weight.

Discussion

In this study the observed pharmacokinetic parameters (t_{max} ~ 0.5 h, C_{max} ~ 4 μmol l⁻¹) and the calculated pharmacokinetic parameters (AUC, CL₀, MTRT, t_{1/2} and λ_z) of zidovudine are comparable with those cited in the literature for a 200 mg single [6] or multiple [7] oral dose of the drug. The low intraindividual variability in AUC (CV_w = 17%) and the higher intraindividual variability in C_{max} (CV_w = 32%) are consistent with CV_w values observed in our other studies on zidovudine pharmacokinetics [8, 9]. A low intraindividual variability in AUC is important because it allows multiperiod, cross-over drug trials of zidovudine to be conducted with a high power of detecting small differences in oral clearance of the drug.

Given the potential problems in pharmacokinetic investigations in patients with HIV infection [10], low intraindividual and interindividual variabilities in zidovudine pharmacokinetics are not necessarily expected. Mentré & Mallet [4] propose that zidovudine pharmacokinetic parameters are not stationary within a subject during therapy. Their analysis also incorporated four biological covariates (body weight, serum haemo-

globin, bilirubin and creatinine) but no clear relationship between pharmacokinetic parameters and the covariates was found. In our study, however, the small changes and generally low CV_w values for pharmacokinetic parameters during the initial 9-week period of zidovudine administration suggest that, within a group of patients whose stage of HIV infection and general

health are relatively stable, first-dose pharmacokinetic parameters provide a good estimate of multiple-dose pharmacokinetic parameters. A similar suggestion has been made by Collier *et al* [11], who observed in 41 subjects less variability within a subject than between subjects in $C_{\max}$ and AUC over the initial 12-week period of zidovudine therapy.

References

- 1 Collins JM, Unadkat JD. Clinical pharmacokinetics of zidovudine. *Clin Pharmacokinet* 1989; **17**: 1–9.
- 2 Gitterman SR, Drusano GL, Egorin MJ, Standiford HC, and the Veterans Administration Cooperative Studies Group. Population pharmacokinetics of zidovudine. *Clin Pharmac Ther* 1990; **48**: 161–167.
- 3 Sothorn RB, Rhame F, Suarez C, Fletcher C, Sackett-Lundeen L, Haus E, Hrushesky WJM. Oral temperature rhythmometry and substantial within-day variation in zidovudine levels following steady-state dosing in human immunodeficiency virus (HIV) infection. In *Chronobiology: its role in clinical medicine, general biology, and agriculture, Part A*, eds Hayes DK, Pauly JE, Reiter RJ. New York, Wiley-Liss Inc., 1990; 67–76.
- 4 Mentré F, Mallet A. Relationship between intra- or inter-individual variability and biological covariates: application to zidovudine pharmacokinetics. In *Advanced methods of pharmacokinetic and pharmacodynamic systems analysis*, ed D'Argenio DZ. New York, Plenum Press, 1991; 119–128.
- 5 Purves RD. Optimum numerical integration methods for estimation of area-under-the-curve (AUC) and area-under-the-moment-curve (AUMC). *J Pharmacokin Biopharm* 1992; **20**: 211–226.
- 6 Singlas E, Pioger JC, Taburet AM, Colaneri S, Fillastre JP. Comparative pharmacokinetics of zidovudine (AZT) and its metabolite (G.AZT) in healthy subjects and HIV seropositive patients. *Eur J clin Pharmac* 1989; **36**: 639–640.
- 7 Laskin OL, De Miranda P, Blum MR. Azidothymidine steady-state pharmacokinetics in patients with AIDS and AIDS-related complex. *J infect Dis* 1989; **159**: 745–747.
- 8 Sahai J, Gallicano K, Garber G, McGilveray I, Hawley-Foss N, Turgeon N, Cameron DW. The effect of a protein meal on zidovudine pharmacokinetics in HIV-infected patients. *Br J clin Pharmac* 1992; **33**: 657–660.
- 9 Sahai J, Gallicano K, Garber G, Pakuts A, Hawley-Foss N, Huang L, McGilveray I, Cameron DW. Evaluation of the *in vivo* effect of naproxen on zidovudine pharmacokinetics in HIV-infected patients. *Clin Pharmac Ther* 1992; **52**: 464–470.
- 10 Unadkat JD, Agosti JM. Problems in pharmacokinetic investigations in patients with HIV infection. *Clin Pharmacokinet* 1990; **19**: 172–176.
- 11 Collier AC, Tartaglione T, Corey L. A reduced dose of zidovudine in patients with AIDS [Letter]. *New Engl J Med* 1991; **324**: 996.

(Received 16 December 1992,
accepted 15 April 1993)