Br. J. clin. Pharmac. (1992), **33**, 657–660

The effect of a protein meal on zidovudine pharmacokinetics in HIV-infected patients

JAN SAHAI[1], KEITH GALLICANO[2], GARY GARBER[1], IAIN McGILVERAY[2], NANCI HAWLEY-FOSS[1], NATALIE TURGEON[1] & D. WILLIAM CAMERON[1]
[1]Division of Infectious Diseases, Department of Medicine, Ottawa General Hospital and [2]Bureau of Drug Research, Health & Welfare, Canada

Eleven HIV-infected men participated in a randomized, two-treatment, two-period cross-over study to determine the effect of a 25 g protein meal on zidovudine pharmacokinetics. On two separate occasions, 1 week apart, each patient received 200 mg zidovudine in a fasting state or immediately following the protein meal. A protein meal significantly decreased C_{max} [532 (228 s.d.) *vs* 802 (452 s.d.) ng ml^{-1}, $P = 0.004$] and increased mean residence time (138 (26 s.d.) *vs* 114 (26 s.d.) min, corrected for lag times, $P = 0.001$). However, AUC, t_{max}, terminal half-life and renal clearance were not significantly altered ($P > 0.05$). The power to detect a 20% change in AUC was 98% at the 5% significance level. In contrast to fat-containing foods, protein-based meals may not alter the extent of zidovudine absorption.

Keywords zidovudine pharmacokinetics protein supplement

Introduction

Factors that affect zidovudine absorption may be important determinants of clinical response. High fat meals significantly decreased the extent of zidovudine absorption and peak plasma zidovudine concentrations, and increased the time to achieve peak concentrations (Lotterer *et al.*, 1991; Unadkat *et al.*, 1990). Thus it is recommended that patients take zidovudine on an empty stomach.

Many HIV-infected patients receive protein supplements (Althoff *et al.*, 1989). Protein-based meals can affect the pharmacokinetics of high clearance drugs (Liedholm *et al.*, 1990; Olanoff *et al.*, 1986). Since zidovudine is a highly cleared drug with a large first-pass effect (Blum *et al.*, 1988), a protein-based meal may affect its bioavailability. The purpose of this study was to determine the effect of a protein supplement on zidovudine pharmacokinetics in HIV-infected patients.

The results of this study were presented at the VIIth International AIDS Conference, Florence, Italy, 16–23 June, 1991.

Methods

Patient selection

Eleven symptomatic HIV-infected men participated in this randomized, two-period, two-treatment, cross-over study after internal review board approval and written informed consent were obtained. Each patient was receiving 200 mg zidovudine every 4 h while awake. Their mean age was 35 (7 s.d.) years and their weight was 71 (12 s.d.) kg. Patients were excluded on the basis of the following: use of any other medication 1 week before or during the study; weight deviating by more than 20% from ideal; serum creatinine > 150 μmol l^{-1}; results of liver function tests greater than twice normal; any evidence of opportunistic infection; or gastrointestinal dysfunction.

Study design and sample collection

On each study day, following an overnight fast, patients received zidovudine between 08.00 and 08.30 h. 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 a single dose. In one phase of the study, the patients received a single 200 mg dose of zidovudine (two 100 mg capsules of Retrovir; Lot 9E575, Burroughs Wellcome Inc., Canada) immediately after 25 g protein (33 g powdered ProMod protein supplement; Lot RBPM24557, Ross Laboratories, Canada) diluted in 220 ml orange juice. In the other phase of the study, patients received zidovudine following 220 ml orange juice. Zidovudine capsules were administered with 150 ml tap water. Patients remained fasting for 4 h after zidovudine

Correspondence: Dr Jan Sahai, Ottawa General Hospital, 501 Smyth Road, Ottawa, Ontario, Canada, K1H 8L6

administration. There was a 7 day washout period between the two regimens during which time patients received their usual zidovudine doses.

Serial blood samples were obtained immediately before drug administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6 and 8 h after the dose. They were centrifuged at 2500 rev min^{-1}, and sera were stored at −30° C until analysis (within 4 weeks). Patients were requested to empty their bladders completely before receiving zidovudine, and urine samples were collected at 2, 4, 6, and 8 h after dosing. The total volume of urine voided within each interval was recorded and a 10 ml aliquot of each sample stored at −30° C until analysis (within 8 weeks).

Drug assay

All serum and urine samples were heated at 56° C for 30 min to inactivate the HIV. Serum samples (0.1 ml) were analyzed in duplicate for zidovudine by radioimmunoassay (ZDV-Trac™, ^{125}I kit, Incstar Corporation) according to kit instructions (Tadepalli *et al.*, 1990) except that samples were diluted 20- or 40-fold with 25 mM phosphate buffer (pH 6.8) and all volumes were reduced by 50%. Urine samples (0.1–1.0 ml) were diluted at least 1000 times with buffer and analyzed for zidovudine as above by radioimmunoassay. The lower and upper limits of quantitation were 0.22 and 60 ng ml^{-1}, respectively, for diluted samples. Serum and urine samples from both regimens for each patient were analyzed on the same day to minimize analytical variability. In-house quality-control samples containing both zidovudine and its glucuronide metabolite were analyzed in duplicate concurrently with the patient's samples.

Predicted concentrations of zidovudine in quality-control samples underestimated the nominal values, with the average deviations ranging from −4.5 to −14%. Within and between assay coefficients of variation (CV) were < 4 and < 13%, respectively, for serum and urine samples.

Dissolution

The dissolution profile of zidovudine from six Retrovir capsules sampled from the same lot (9E575) as that used *in vivo* was determined at 37° C in 900 ml media (0.1M HCl or 0.05M phosphate buffer, pH 7.2) using baskets operating at 100 rev min^{-1}. Dissolution experiments were also conducted in the presence of 4 g ProMod powder, mixed at 100 rev min^{-1} in 0.05M phosphate buffer. The amount of zidovudine dissolved was determined by u.v. spectroscopy at 280 nm or by the h.p.l.c. procedure of Hedaya & Sawchuk (1988) for the protein experiments.

Data analysis

Serum zidovudine concentration *vs* time data were analyzed by model-independent methods. The parameters included the maximum serum drug concentration (C_{max}), time of maximum serum drug concentration (t_{max}), terminal half-life ($t_{½,z}$), area under the serum drug concentration-time curve (AUC), area under the first moment of the serum drug concentration-time curve (AUMC).

Individual AUC and C_{max} data were corrected for residual predose concentrations of zidovudine using the following equations:

$$C_{max}^{corr} = C_{max} - C(0)e^{-\lambda_z \cdot t_{max}}$$

$$AUC^{corr} = AUC - [C(0)/\lambda_z]$$

where $C(0)$ is the predose concentration at time zero and λ_z is the terminal disposition rate constant.

The oral clearance (CL_o) was calculated by dividing the dose by AUC. The mean residence time (MRT) was calculated from AUMC/AUC, and corrected for lag time by replacing t by [t–observed lag time] in the trapezoidal functions. The renal clearance (CL_R) of zidovudine was calculated from the amount excreted divided by AUC.

Statistical analysis

Differences in mean pharmacokinetic parameters of zidovudine between treatments were evaluated by analysis of variance (ANOVA) appropriate for a crossover study with unbalanced sequences. All pharmacokinetic data, except t_{max}, $t_{½,z}$ and MRT, were logarithmically transformed, and the least-squares geometric and arithmetic means were used in the ANOVA calculations. Statistical significance was defined as $P < 0.05$. Results are expressed as arithmetic means (± s.d.) in the text and least-squares means in Table 1. Since some patients had measurable predose serum concentrations of zidovudine, the ANOVA was repeated for AUC and C_{max} values corrected for residual drug concentrations.

Results

Mean pharmacokinetic data are shown in Table 1 and mean concentration-time data are illustrated in Figure 1. The administration of a protein supplement resulted in a significant decrease in C_{max} (532 ± 228 ng ml^{-1})

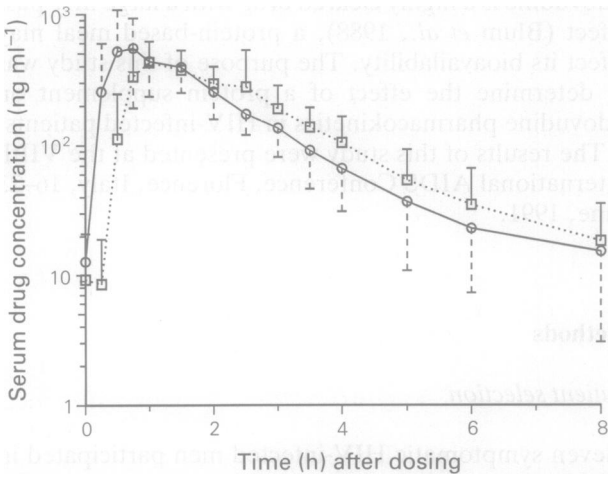

Figure 1 Mean (± s.d.) serum concentrations of zidovudine after a 200 mg dose of zidovudine administered with (□) and without (○) a protein supplement.

Table 1 Mean pharmacokinetic parameters* of zidovudine for the two regimens: 1. Zidovudine in the absence of a protein meal and 2. Zidovudine in the presence of a protein meal

Regimen	C_{max}† *(ng ml^{-1})*	t_{max} *(min)*	$t_{½,z}$ *(min)*	*MRT (min)*	*AUC*† *(μg ml^{-1} min)*	CL_O *(ml min^{-1})*	CL_O *(ml min^{-1} kg^{-1})*	CL_R *(ml min^{-1})*
1: Absence of protein	723 (717)	49	80	115	65.3 (64.0)	2997	42.9	211
2: Presence of protein	492 (487)	74	83	138	62.8 (61.5)	3088	44.2	259
Ratio 2/1‡ (× 100%)	68.1% (67.8%)	25	3.6	23	96.1% (96.0%)	103%	103%	123%
95% CI	54.6–85.0 (54.6–84.3)	−4.1–53.4	−3.3–10.6	11.6–34.5	86.5–107 (86.5–107)	92.3–115	92.3–115	97.1–155
P-value	0.004 (0.003)	0.084	0.268	0.001	0.419 (0.403)	0.551	0.549	0.077
Intra-subject CV	22.9% (22.5%)	48.0%	8.8%	9.3%	10.9% (10.8%)	11.4%	11.4%	20.9%
Inter-subject pooled CV	38.5% (38.4%)	NM	27.0%	17.3%	37.1% (36.0%)	38.1%	41.3%	32.9%

Note. C_{max}, observed peak serum drug concentration; t_{max}, observed time of peak concentration; $t_{½,z}$, apparent terminal half-life; AUC, area under the serum concentration-time curve from time zero to time of last measurable concentration; CL_O, apparent oral serum clearance; CL_R, renal clearance; CI, confidence interval; CV, coefficient of variation; NM, not measurable.
*Mean and statistical parameters are based on ANOVA using the least-squares geometric mean (LSGM) for C_{max}, AUC, CL_O and CL_R, and the least-squares arithmetic mean (LSAM) for t_{max}, MRT and $t_{½,z}$.
†Values in brackets are based on individual values corrected for residual predose concentrations of zidovudine.
‡Ratio of LSGM; t_{max}, $t_{½,z}$ and MRT values are the difference in LSAM of regimen 2 from regimen 1 (2–1).

compared with zidovudine alone (802 ± 452 ng ml^{-1}) ($P = 0.004$). Double peaking of zidovudine occurred in four fasted and six fed patients but is not explicit in Figure 1 because of data averaging.

Lag times ranging from 15 to 30 min were apparent in five fasted and 10 fed patients. Figure 1 shows an average observed lag time of 15 min for the absorption of zidovudine in the presence of protein. MRT, corrected for lag time, was significantly increased by 24 min when zidovudine was administered with food (138 ± 26 *vs* 114 ± 26 min) ($P = 0.001$). Protein food did not significantly alter $t_{½,z}$ or t_{max} of zidovudine, but the trend was towards an increase in t_{max} with food ($P = 0.084$).

The extent of absorption was not significantly altered when zidovudine was coadministered with the protein meal (AUC = 69.5 ± 31.9 with food *vs* 71.0 ± 30.8 μg ml^{-1} min alone) ($P = 0.550$). For the zidovudine-alone and zidovudine-protein regimens, CL_o ($P = 0.551$) values were also not significantly different, even after normalising for weight. Values of CL_R, calculated from data from nine patients, tended to increase with protein ($P = 0.077$). CL_R was not calculated for two patients because they could not void urine immediately before ZDV administration.

Seven of 11 patients had measurable predose serum concentrations of zidovudine, ranging from 5.2 to 92 ng ml^{-1}, during one or both study periods. However, the ANOVA indicated no significant change in pharmacokinetic parameters corrected for residual zidovudine concentrations. The power to detect a 20% difference in AUC for uncorrected data was 98% at the significance level of 5%.

The dissolution of zidovudine in either HCl or phosphate buffer was rapid and complete with > 90% of drug dissolved during the first 10 min. No change in dissolution profile was observed in the presence of 4 g protein in phosphate buffer.

Discussion

In the fasting state zidovudine was rapidly absorbed and cleared. The pharmacokinetic parameters derived from this study are in agreement with those published by Blum *et al.* (1988) and Singlas *et al.* (1989). The decrease in C_{max} and increases in t_{max} and MRT observed with a protein meal are probably attributable to delayed gastric emptying. The overall extent of absorption, however, was not affected by a protein meal. The bioavailability of verapamil, another high-clearance drug with a large first-pass effect, is also not affected by a high protein diet (Woodcock *et al.*, 1986).

Fatty foods have a greater propensity for inhibiting gastric emptying than protein foods (Winstanley & Orme, 1989). This may explain why the delay in onset of absorption (lag time) and change in the overall extent of absorption were not as great in this study compared to those in which fatty meals were given. The appearance of double peaking, at least in the fasted patients, may be a result of variable or interrupted gastric emptying rates of zidovudine (Clements *et al.*, 1978; Oberle & Amidon, 1987). Double peaking has been observed in fasted patients receiving cimetidine (Winstanley & Orme, 1989) and paracetamol (Clements *et al.*, 1978).

Food may also affect drug absorption by a binding mechanism or by altering the rate of drug dissolution (Winstanley & Orme, 1989). Dissolution of zidovudine at pH 1.0 and 7.2 is fast because of its high water solubility and is, therefore, not likely to limit the rate of

absorption. The *in vitro* data suggest that protein does not decrease the rate or extent of zidovudine dissolution. That MRT is significantly longer when protein is administered, even after correcting for lag time, probably reflects a slower transit time of the drug into the general systemic circulation once dissolution has occurred (Veng-Pedersen *et al.*, 1989).

The intake of dietary protein is known to influence renal function (Park *et al.*, 1989). However, the CL_R values of zidovudine were not significantly altered.

Our findings suggest that liquid protein-based meals do not affect zidovudine absorption to an extent that is likely to be of clinical significance. This is reassuring with respect to the treatment of patients receiving supplements to ameliorate malnutrition and those unable to ingest solid food owing to opportunistic infections involving the gastrointestinal tract.

This study was supported by a new investigator's grant from the Ottawa General Hospital. The authors thank Mr Attila Pakuts for expert technical assistance and Burroughs Wellcome Inc. (Canada) for supplying Retrovir capsules for dissolution studies.

References

Althoff, P. H., Schifferdecker, E. & Forster, H. (1989). Imbalance of the amino acids in patients with AIDS – special treatment with adapted amino acid solution. [Abstract # Th. B.O.42] *Fifth International Conference on AIDS*. Montreal, Canada.

Blum, M. R., Liao, S. H. T., Good, S. S. & deMiranda, P. (1988). Pharmacokinetics and bioavailability of zidovudine in humans. *Am. J. Med.*, **85** (supp. 2A), 189–194.

Clements, J. A., Heading, R. C., Nimmo, W. S. & Prescott, L. F. (1978). Kinetics of acetaminophen absorption and gastric emptying in man. *Clin. Pharmac. Ther.*, **24**, 420–431.

Hedaya, M. A. & Sawchuk, R. J. (1988). A sensitive liquid-chromatographic method for determination of 3′-azido-3′-deoxythymidine (AZT) in plasma and urine. *Clin. Chem.*, **34**, 1565–1568.

Liedholm, H., Wåhlin-Bolle, E. & Melander, A. (1990). Mechanisms and variations in the food effect on propranolol bioavailability. *Eur. J. clin. Pharmac.*, **38**, 469–475.

Lotterer, E., Ruhnke, M., Trautman, M., Beyer, R. & Bauer, F. E. (1991). Decreased and variable systemic availability of zidovudine in patients with AIDS if administered with a meal. *Eur. J. clin. Pharmac.*, **40**, 305–308.

Oberle, R. L. & Amidon, G. L. (1987). The influence of variable gastric emptying and intestinal transit rates on the plasma level curve of cimetidine; an explanation for the double peak phenomenon. *J. Pharmacokin. Biopharm.*, **15**, 529–544.

Olanoff, L. S., Walle, T., Cowart, T. D., Walle, K., Oexmann, M. J. & Conradi, E. C. (1986). Food effects on propranolol systemic and oral clearance: Support for a blood flow hypothesis. *Clin. Pharmac. Ther.*, **40**, 408–414.

Park, G. D., Spector, R. & Kitt, T. M. (1989). Effect of dietary protein on renal tubular clearance of drugs in humans. *Clin. Pharmacokin.*, **17**, 441–451.

Singlas, E., Pioger, J. C., Taburet, A. M., Colaneri, S. & Fillastre, J. P. (1989). Comparative pharmacokinetics of zidovudine (AZT) and its metabolite (G.AZT) in healthy subjects and HIV seropositive patients. *Eur. J. clin. Pharmac.*, **36**, 639–640.

Tadepalli, S. M., Puckett, L., Jeal, S., Kanics, L. & Quinn, R. P. (1990). Differential assay of zidovudine and its glucuronide metabolite in serum and urine with a radio-immunoassay kit. *Clin. Chem.*, **36**, 879–900.

Unadkat, J. D., Collier, A. C., Crosby, S. S., Cummings, D., Opheim, K. E. & Corey, L. (1990). Pharmacokinetics of oral zidovudine (azidothymidine) in patients with AIDs when administered with and without a high-fat meal. *AIDS*, **4**, 229–232.

Veng-Pedersen, P. (1989). Mean time parameters in pharmacokinetics. Definition, computation and clinical implications (part II). *Clin. Pharmacokin.*, **17**, 424–440.

Winstanley, P. A. & Orme, M. (1989). The effects of food on drug bioavailability. *Br. J. clin. Pharmac.*, **28**, 621–628.

Woodcock, B. G., Kraemer, N. & Rietbrock, N. (1986). Effect of a high protein meal on the bioavailability of verapamil. *Br. J. clin. Pharmac.*, **21**, 337–338.

(Received 23 September 1991, accepted 20 January 1992)