The effects of indomethacin and naproxen on zidovudine pharmacokinetics

M. BARRY¹, J. HOWE¹, D. BACK¹, A. BRECKENRIDGE¹, R. BRETTE², R. MITCHELL², N. J. BEECHING³ & F. J. NYE³

¹Department of Pharmacology and Therapeutics, University of Liverpool, ²City Hospital, Edinburgh and ³Regional Infectious Diseases Unit, Fazakerley Hospital, Liverpool

The effects of indomethacin and naproxen on zidovudine (ZDV) pharmacokinetics were studied in six patients with the acquired immunodeficiency syndrome (AIDS), AIDS related complex (ARC) or asymptomatic HIV disease using a placebo-controlled cross-over design. Indomethacin 25 mg twice daily or naproxen 250 mg twice daily did not alter ZDV pharmacokinetics compared with placebo. The mean AUC value for the glucuronidated metabolite, GZDV, was reduced from $26.6 \pm 11.7 \mu\text{mol l}^{-1} \text{ h}$ in the presence of placebo to $20.9 \pm 8.3 \mu\text{mol l}^{-1} \text{ h}$ (95% C.I. of the difference 1.39–9.98; $P < 0.05$) following treatment with naproxen 250 mg twice daily for 3 days. The small decrease in plasma GZDV in the naproxen phase reflects an increase in clearance of ZDV to other metabolites and/or a decrease in the formation clearance to GZDV and/or an increase in the clearance of GZDV. A decrease in formation clearance to GZDV would be consistent with the results of *in vitro* studies reported previously. No significant increase in ZDV concentration in the presence of naproxen may reflect a lower sensitivity of parent drug measurements to selective inhibition of parallel pathways of metabolism. The clinical significance of these findings is unknown but toxicity may be increased if a decreased formation of GZDV is accompanied by shunting of metabolism to 3'-amino-3'-deoxy-thymidine which is alleged to be cytotoxic.

Keywords zidovudine pharmacokinetics indomethacin naproxen HIV

Introduction

Following oral administration of zidovudine (ZDV) approximately 65% of the drug is systemically available. The mean volume of distribution is 1.4 l kg^{-1} with plasma protein binding less than 25% [1]. The drug has an elimination half-life of approximately 1 h, being metabolised extensively to an ether glucuronide 3'-azido-3'-deoxy-5'- β -D-glucopyranuronosylthymidine, GZDV [2]. This metabolite is rapidly excreted in the urine. Interference with the conjugation of ZDV or its renal excretion by other drugs could lead to enhanced ZDV effect and/or increased toxicity. We have previously examined the effects of a number of drugs which themselves undergo glucuronidation on the conjugation of ZDV by human liver microsomes [3]. Significant inhibition of ZDV glucuronidation *in vitro* was demonstrated with indomethacin, naproxen, chloramphenicol, probenecid and ethinyloestradiol. Probenecid has been shown to increase the AUC and elimination half-life of ZDV in patients with AIDS or ARC [4]. In our *in vitro* study the most marked inhibition of ZDV glucuronidation

was in the presence of the non-steroidal anti-inflammatory drugs which are often used for relief of non-specific fever and musculoskeletal pain in patients with the human immunodeficiency virus (HIV), including those with ZDV induced myopathy [5]. In this study we investigate the effect of indomethacin and naproxen on ZDV pharmacokinetics in patients with different stages of HIV infection.

Methods

Patients

Six patients (five male), aged 30 to 54 years, with sexually acquired HIV infection participated in this study. Two patients had asymptomatic HIV infection (CDC Group II), one patient had progressive generalised lymphadenopathy (CDC Group III) and three patients

had AIDs, according to the revised CDC definition [6]. Of the three patients with AIDS one had previous *Pneumocystis carinii* pneumonia (CDC Group IV C₁) and two had recurrent oral candidiasis (CDC Group IV C₂); all three received cotrimoxazole 960 mg daily as prophylaxis for *Pneumocystis carinii* pneumonia. All patients had normal liver function as assessed by the Pugh classification (Pugh score <5) [7]. Values of urea and creatinine were in the normal range, indicating no evidence of renal dysfunction. The patients did not have a history of peptic ulcer disease or bleeding tendency and did not receive medications that would be expected to interfere with ZDV glucuronidation. Approval for the study was obtained from the local Ethics Committee and each patient provided written informed consent.

Protocol

The six patients were studied using a placebo controlled cross-over design. The pharmacokinetics of ZDV at steady-state during continuous dosing were determined on three occasions, separated by at least 10 days. Each study day was preceded by oral administration of indomethacin 25 mg twice daily, naproxen 250 mg twice daily or matching placebo for 3 days. On the study day patients attended following an overnight fast from 00.00 h. An indwelling intravenous cannula was inserted in the cubital fossa for blood sampling. Indomethacin, naproxen or placebo were administered with ZDV 200 mg or 250 mg at 09.00 h and blood samples were taken at 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5 and 6 h. All samples were centrifuged within 2 h. The separated plasma was then heated at 58°C for at least 30 min in a waterbath to inactivate the AIDS virus [8].

Drug analysis

ZDV and its glucuronide metabolite (GZDV) were measured in plasma using a modification of the method of Blum *et al.* [9]. Plasma samples were spiked with 5 µM of either the internal standard A22U (Wellcome, Beckenham) or β-hydroxyethyltheophylline (Sigma) and were ultrafiltered using an Amicon Centrifree Micropartition System. The ultrafiltrates were subsequently analysed by h.p.l.c. Samples were eluted on an Ultratech 5 ODS column (4.6 mm × 250 mm) using a mobile phase of 25 mM ammonium phosphate buffer, pH 7.2, with a linear gradient of 0–30% v/v acetonitrile over 35 min followed by a return to 100% buffer over 5 min and a 5 min re-equilibrium period with 100% buffer at a flow rate of 0.6 ml min⁻¹. Retention times of

authentic standards (u.v. detection at 267 nm) were 19, 23, 26 and 28 min for GZDV (Wellcome, Beckenham), β-hydroxyethyltheophylline, A22U and ZDV (Wellcome, Beckenham), respectively. Peak height ratios of ZDV and GZDV to the internal standard were used to calculate concentrations from standard curves (range 0–20 µM and 0–40 µM for ZDV and GZDV, respectively). Intra-assay coefficients of variation were 8.1%, 1.7% and 2.1% for 0.25 µM, 2.5 µM and 20 µM ZDV respectively and 8.3%, 5.9% and 3.2% for 0.5 µM, 5.0 µM, and 40 µM GZDV respectively (*n* = 10). Interassay coefficients of variation were 7.9% for 2.5 µM ZDV and 9.8% for 5 µM GZDV (*n* = 5). The assay had a limit of determination of 0.1 µM for ZDV and 0.2 µM for GZDV.

Data analysis

Values of *C*_{max} (µmol l⁻¹) and *t*_{max} (h) were determined for ZDV and GZDV directly from the data. The elimination rate constant (*λ*_z) was calculated by log linear regression of the terminal portion of the plasma drug concentration-time curve using the method of least squares. The terminal elimination half-life (*t*_{1/2,z}) was calculated from ln 2/*λ*_z. AUC values for ZDV and GZDV were calculated using the linear trapezoidal rule with extrapolation from the last data point to infinity using *C*_(last)/*λ*_z (mean percentage of area that was extrapolated was 5.4% for ZDV and 2.3% for GZDV). The oral clearance (CL_o) of ZDV was calculated from Dose/AUC. Differences in kinetic parameters due to different treatments were tested using analysis of variance (ANOVA). A *P* value of <0.05 was considered statistically significant.

Results

Mean plasma concentration of ZDV and GZDV during the three study phases are shown in Figure 1 and pharmacokinetic parameters are summarised in Table 1. Administration of indomethacin and naproxen did not alter ZDV kinetics compared with placebo (Table 1). Following oral administration of ZDV, plasma concentrations of GZDV were approximately five-fold higher than those of the parent drug. Terminal plasma concentrations of GZDV declined in parallel with those of ZDV (Figure 1). Indomethacin and naproxen did not affect values of *C*_{max}, *t*_{max} or *t*_{1/2,z} for GZDV, but naproxen did decrease its AUC value significantly (26.6 ± 11.7 µmol l⁻¹ h for the placebo phase and 20.9 ± 8.3 µmol

Table 1 Pharmacokinetic parameters describing the fate of ZDV and GZDV in six HIV-positive patients following treatment with ZDV and indomethacin (25 mg twice daily), naproxen (250 mg twice daily) or placebo (twice daily) for 3 days. Parameters are expressed as mean ± s.d. with the exception of *t*_{max} which is expressed as mean (range)

	ZDV			GZDV		
	Control	Indomethacin	Naproxen	Control	Indomethacin	Naproxen
<i>C</i> _{max} (µM)	4.3 ± 1.6	4.1 ± 1.8	4.2 ± 1.2	17.3 ± 5.6	15.4 ± 6.2	13.4 ± 5.1
<i>t</i> _{max} (h)	0.75 (0.5–1.25)	0.5 (0.5–0.75)	0.75 (0.5–1.25)	1.00 (0.5–1.75)	1.00 (0.75–1.00)	0.75 (0.5–1.5)
<i>t</i> _{1/2,z} (h)	1.0 ± 0.1	1.1 ± 0.3	1.0 ± 0.4	0.9 ± 0.3	0.9 ± 0.1	0.9 ± 0.2
AUC (µmol l ⁻¹ h)	5.5 ± 0.8	4.9 ± 1.5	5.2 ± 1.2	26.6 ± 11.7	21.7 ± 10.6	20.9 ± 8.3*
CL _o (ml min ⁻¹)	2613 ± 552	3132 ± 1165	2808 ± 803			

*Significantly different from placebo, *P* < 0.05.

Figure 1 Mean plasma ZDV (▲) and GZDV (●) concentrations in six HIV patients following treatment with a) placebo one tablet twice daily, b) indomethacin 25 mg twice daily and c) naproxen 250 mg twice daily, each taken for 3 days.

$l^{-1}h$ following naproxen; 95% C.I of the difference 1.39 to 9.98; $P < 0.05$), Table 1.

Discussion

The pharmacokinetic parameters describing the fate of ZDV and GZDV during the placebo phase of this study were consistent with those obtained by others [10 11]. Consistent with ZDV therapy all patients had a raised mean corpuscular volume which appears within weeks of commencing treatment and has been used as an index of compliance [12]. Cotrimoxazole has been shown not to interfere with ZDV pharmacokinetics and therefore was unlikely to influence the results of this study [13]. The high oral clearance of ZDV is, in part, a consequence of a substantial first pass effect [14]. However, a discrepancy between a high extra-renal clearance and the hepatic extraction ratio assessed from estimates of oral bioavailability suggest that the liver is not the only site of ZDV metabolism [15]. The present *in vivo* study indicated no effect of indomethacin or naproxen on plasma concentrations of unchanged ZDV, in contrast

to the results of our *in vitro* study [3]. This may be attributed to a concentration difference as the marked inhibitory effects of the non-steroidal agents *in vitro* were produced at higher concentrations than those *in vivo*. Peak plasma concentration of indomethacin and naproxen in the present study would be expected to be less than $8 \mu M$ and $350 \mu M$, respectively [16 17]. The failure of naproxen to influence ZDV kinetics is consistent with the results of Sahai *et al.* [18] who gave naproxen 500 mg twice daily to patients treated with ZDV. However, in the present study, administration of naproxen 250 mg did cause a 20% reduction in the AUC of GZDV. This reflects an increase in the clearance of ZDV to other metabolites and/or a reduction in the formation clearance to GZDV and/or an increase in the clearance of GZDV. A decrease in the formation clearance to GZDV would be consistent with the results of *in vitro* studies reported previously. Despite the absence of a significant increase in ZDV concentrations following naproxen, toxicity may be increased if a decrease in the formation of GZDV was accompanied by shunting of metabolism to 3'-amino-3'-deoxythymidine which is alleged to be cytotoxic [19].

References

- Collins JM, Unadkat JD. Clinical pharmacokinetics of zidovudine. *Clin Pharmacokin* 1989; **17**: 1-9.
- Good SS, Koble CS, Crouch R, Johnson RL, Rideout JL, De Miranda P. Isolation and characterization of an ether glucuronide of zidovudine, a major metabolite in monkeys and humans. *Drug Metab Disp* 1990; **18**: 321-326.
- Sim SM, Back DJ, Breckenridge AM. The effect of various drugs on the glucuronidation of zidovudine (azidothymidine; AZT) by human liver microsomes. *Br J clin Pharmacol* 1991; **32**: 17-21.
- Kornhauser DM, Petty BG, Hendrix CW, *et al.* Probenecid and zidovudine metabolism. *Lancet* 1989; **ii**: 473-475.
- Dalakas MC, Illa I, Pezeshkpour GH, Laukaitis JP, Cohen B, Griffin JL. Mitochondrial myopathy caused by long term zidovudine therapy. *New Engl J Med* 1990; **322**: 1098-1105.
- Centres for Disease Control. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *M.M.W.R.* 1987; **36** (Suppl. 1): 1-15s.
- Pugh PN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649.
- McDougal JD, Martin LS, Cort SP, Mozen M, Heldebrandt CN, Evatt BL. Thermal inactivation of the Acquired Immunodeficiency Virus. *J clin Invest* 1985; **76**: 875-877.
- Blum MR, Lao SHT, Good SS, De Miranda P. Pharmacokinetics and bioavailability of zidovudine in humans. *Am J Med* 1988; **85** (Suppl. 2A): 189-194.
- De Miranda P, Good SS, Yarchoan R *et al.* Alteration of zidovudine pharmacokinetics by probenecid in patients with AIDS or AIDS related complex. *Clin Pharmacol Ther* 1989; **46**: 494-500.

- 11 Singlas E, Pioger JC, Taburet AM, Colin JN, Fillastre JP. Zidovudine disposition in patients with severe renal impairment: Influence of haemodialysis. *Clin Pharmac Ther* 1989; **46**: 190–197.
- 12 Richman DD, Fischl MA, Grieco MH *et al.* The toxicity of azidothymidine (AZT) in the treatment of patients with AIDs and AIDS related complex. *New Engl J Med* 1987; **317**: 192–197.
- 13 Pazin GJ, Ptachcinski RJ, Schillinger B, McMahon DK, Armstrong JA, Ho M. Interactive pharmacokinetics of zidovudine and prophylactic or therapeutic dosages of trimethoprim-sulphamethoxazole. *VI International Conference on AIDS*, San Francisco. 1990; Abstract p. 193.
- 14 Klecker RW, Collins JM, Yarchoan R. *et al.* Plasma and cerebrospinal fluid pharmacokinetics of 3'-azido-3'-deoxythymidine: A novel pyrimidine analog with potential application for the treatment of patients with AIDS and related diseases. *Clin Pharmac Ther* 1987; **41**: 407–412.
- 15 Howe JL, Back DJ, Colbert J. Extrahepatic metabolism of zidovudine. *Br J clin Pharmac* 1992; **33**: 190–192.
- 16 Pullar T, Myall O, Haigh JRM, Lowe JR, Doxon JS, Bird HA. The effect of allopurinol on the steady state pharmacokinetics of indomethacin. *Br J clin Pharmac* 1988; **25**: 755–757.
- 17 Van Den Ouweland FA, Franssen MJAM, Van de Putte LBA, Tan Y, Van Ginneken CAM, Gribnau FWJ. Naproxen pharmacokinetics in patients with rheumatoid arthritis during active polyarticular inflammation. *Br J clin Pharmac* 1987; **23**: 189–193.
- 18 Sahai J, Gallicano K, Garber G. *et al.* Evaluation of the *in vivo* effect of naproxen on zidovudine pharmacokinetics in patients infected with human immunodeficiency virus. *Clin Pharmac Ther* 1992; **52**: 464–470.
- 19 Cretton EM, Schinazi RF, McClure HM, Anderson DC, Sommadossi JF. Pharmacokinetics of 3'-azido-3'-deoxythymidine and its catabolites and interactions with probenecid in Rhesus Monkeys. *Antimicrob Agents Chemother* 1991; **35**: 801–807.

(Received 19 October 1992,
accepted 1 April 1993)