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Short Communication

Pharmacokinetics of zidovudine and didanosine during combination therapy ☆

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Abstract

While the combination of zidovudine and didanosine is used in HIV-infected patients with more advanced disease, the possibility of a pharmacokinetic interaction between these two drugs remains controversial. Zidovudine doses of 50, 100, and 200 mg, combined with 67, 167, and 250 mg of didanosine were evaluated in 11 asymptomatic HIV-infected patients after receiving 24 weeks of combination therapy in AIDS Clinical Trials Group protocol 143. The pharmacokinetic parameters of zidovudine and didanosine were similar to those obtained with each drug given as monotherapy in other previously published studies. The renal clearance and urinary recovery of glucuronidated zidovudine was reduced when zidovudine was given in combination with didanosine, possibly due to competition for renal tubular secretion. These data suggest that no clinically important pharmacokinetic interaction occurs when zidovudine and didanosine are given together.

Keywords: Zidovudine; Didanosine; Combination therapy; Human immunodeficiency virus (HIV); Clinical trial

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Zidovudine and didanosine have demonstrated in vitro synergy at various concentrations when examined in several different cell lines (Dornsife et al., 1991; Johnson et al., 1991; Cox et al., 1992). All studies have shown synergy against zidovudine-sensitive strains of HIV, while results against zidovudine-resistant strains have been variable (Dornsife et al., 1991; Johnson et al., 1991; Cox et al., 1992). At the time ACTG 143 was initiated, there was a lack of pharmacokinetic data on low doses of zidovudine and didanosine in combination. The primary goal of this study was to examine the plasma concentration profiles of zidovudine (ZDV), glucuronidated zidovudine (GZDV) and didanosine (DDI) which result during combination therapy.

ACTG Protocol 143 was an open-label phase I/II trial of ZDV and DDI at various doses versus DDI alone in the treatment of patients with asymptomatic HIV disease. Patients were randomized to receive: ZDV 50 mg every 8 h with a DDI 67 mg sachet every 12 h (arm A), ZDV 100 mg every 8 h with a DDI 167 mg sachet every 12 h (arm B), ZDV 200 mg every 8 h with a DDI 250 mg sachet every 12 h (arm C), or a DDI 250 mg sachet every 12 h as monotherapy (arm D). Patients with a history of AIDS-defining opportunistic infections, advanced AIDS-related complex, or malignancies were not included in the study, nor were patients who were receiving alternative antiviral agents or drugs previously reported to increase or decrease ZDV or DDI concentrations. Two patients had hemophilia B requiring approximately 1500 and 4000 units of factor IX weekly.

Eleven patients were enrolled in a pharmacokinetic study after completing 24 weeks of therapy: arm A ($n = 3$), arm B ($n = 4$), and arm C ($n = 4$). No patients from arm D had pharmacokinetic studies done. Nine males and two females were evaluated. The mean (standard deviation) age, body weight, aspartate transaminase (AST), and baseline absolute $CD4^+$ lymphocyte counts were 33 (6) years, 75 (10) kg, 44 (27) U/l, and 424 (86) cells/mm^3. DDI was evaluated in 7 patients due to inadequate plasma collection. Patients were encouraged at each prior clinic visit to remain compliant with the dosing regimen up until the pharmacokinetic study day. Blood and urine samples were collected over 8 h. All samples were stored at -20°C and incubated in a 56°C water bath for 3 h to inactivate HIV.

Concentrations of ZDV and GZDV were determined by radioimmunoassay (ZDV-TracTM, INCStar, Stillwater, MN) (standard concentrations: 0.3–256 ng/ml). Inter- and intra-day coefficients of variation for this assay in plasma are $\leqslant 5\%$ for quality control samples of 4.8 and 48 ng/ml. Indirect measurement of GZDV was made by treating plasma and urine aliquots with 1 U/ml of ß-glucuronidase (Sigma Chemical Co., St. Louis, MO) at 37°C for 30 min prior to assay. DDI concentrations were measured by radioimmunoassay using commercially available reagents (Sigma Chemical Co.) and a standard curve ranging from 2.0 to 100 ng/ml. Quality control samples at 8 and 30 ng/ml yielded interday coefficients of variation of 17 and 9%, respectively. DDI urinary concentrations are not reported because unbuffered urine samples led to the breakdown of DDI. Pharmacokinetic parameters were generated with a standard non-compartmental analysis.

ZDV clearance was similar among the patients (Table 1). One hemophilia patient (008D) had lower plasma concentrations, but compliance was confirmed in this patient. GZDV plasma concentrations exceeded ZDV by 6-fold, although the hemophilia

Table 1
Pharmacokinetic parameters for zidovudine and didanosine during combination therapy

Patient	ZDV					DDI				
	Dose (mg)	t_{max} (h)	C_{max} (ng/ml)	$t_{1/2}$ (h)	Cl/F (l/h)	Dose (mg)	t_{max} (h)	C_{max} (ng/ml)	$t_{1/2}$ (h)	Cl/F (l/h)
515B	200	1.5	401.1	1.74	157.7	250	1	408.4	1.38	280
622D	200	1.5	448.6	2.28	132.4	250	0.5	629.5	1.77	202
503G	200	1.5	569.2	2.56	138.3	250	1	254.1	1.46	213
004A	200	0.5	909	1.68	173.8		NS	NS	NS	NS
AVG	–	1.25	582 [a]	2.07	150.5	–	0.83	430.7	1.54	232
CV	–	0.40	0.39	0.21	0.13	–	0.35	0.44	0.13	0.18
516K	100	1	333.8	2.13	140.3	167	0.5	244.3	1.68	333
458E	100	0.5	494.8	2.28	139.9	167	0.5	699.7	1.38	226
610I	100	0.5	277	1.94	138.3	167	0.5	631.7	1.46	172
003C	100	1	284	1.43	153.6	–	NS	NS	NS	NS
AVG	–	0.75	347.4	1.945	143	–	0.5	525	1.51	244
CV	–	0.38	0.292	0.19	0.05	–	0	0.468	0.10	0.34
733K	50	1	225.8	2.7	101.7	67	0.5	211.9	1.07	277
013B	50	1	301.4	1.71	110.2	–	NS	NS	NS	NS
008D	50	1	91	0.78	462.1	–	NS	NS	NS	NS
AVG	–	1	206.1	1.73	225	–	NC	NC	NC	NC
CV	–	0	0.517	0.55	0.916	–	NC	NC	NC	NC
Overall mean	–	1	NC	1.93	168	–	0.64	–	1.46	243
CV	–	0.39	NC	0.28	0.59	–	0.38	–	0.16	0.23

NC, not calculated; NS, insufficient sample.

patients (004A and 008D) had higher ratios (11 and 29, respectively). A high degree of variability was seen in GZDV parameters. The GZDV AUC normalized to a 100-mg dose of ZDV was consistent among the various patients. For both ZDV and GZDV, there appeared to be an inverse relationship between dosage and renal clearance. (Table 2). The ratio of GZDV to ZDV in urine ranged from 2 to 3, which was approximately 50% lower than the plasma GZDV/ZDV ratio. Baseline DDI concentrations ranged from undetectable (i.e., $\leqslant 2$ ng/ml) to 45.6 ng/ml, whereas plasma concentrations 8 h after dosing were below assay sensitivity in all 7 patients. Calculated Cl/F values were similar among the patients (Table 1).

The range of C_{max} values that we observed suggests that achieving and maintaining plasma concentrations of ZDV and DDI, which have been noted to be synergistic in vitro, in patients may be complicated by intersubject variability in the pharmacokinetics. In vitro evaluations of this combination in various cell lines have demonstrated synergistic activity against HIV at similar concentrations, although these studies utilized static drug exposure. The ZDV : DDI molar ratio achieved in vivo was approximately 1 at 1–3 h. The ratio declined to < 1 at 0.5 h and was ≈ 3 at 6–8 h, reflecting the more rapid absorption and elimination of DDI relative to ZDV, respectively. While most in

Table 2
Individual urinary recoveries and calculated renal clearances of zidovudine and glucuronidated zidovudine stratified by dosage group

Group/ patient	Dose	ZDV		GZDV			Total recovery	
		Amount (% dose)	Cl_{renal} (l/h)	Amount (% dose) [a]	Cl_{renal} (l/h)	GZDV/ZDV	(mg)	(% dose)
515B	200	8.70	14.3	12.3	6.63	2.35	42.0	21
622D	200	8.35	11.4	15.9	6.50	3.15	48.5	24
503G	200	7.80	11.7	10.7	6.47	2.28	37.0	19
004A	200	4.41	7.67	7.59	1.92	2.86	24.0	12
AVG	–	7.32	11.3	11.6	5.38	2.66	37.8	19
CV	–	0.27	0.24	0.30	0.43	0.16	0.27	0.27
516K	100	10.1	14.6	21.9	8.17	3.60	31.9	32
458E	100	11.5	16.8	21.1	10.0	3.06	32.6	33
610I	100	12.0	17.4	26.3	10.1	3.64	38.3	38
003C	100	9.11	14.2	15.4	5.04	2.80	24.5	25
AVG	–	10.6	15.8	21.2	8.35	3.28	31.8	32
CV	–	0.12	0.10	0.21	0.29	0.13	0.18	0.18
733K	50	15.4	18.5	31.9	12.5	3.45	23.7	47
013B	50	14.1	17.5	23.7	10.4	2.78	18.9	38
008D	50	9.64	44.5	19.2	9.01	3.30	14.4	29
AVG	–	13.0	26.8	24.9	10.6	3.18	19	38
CV	–	0.23	0.57	0.26	0.1701	0.11	0.24	0.24
Mean	–		17.1		7.89	3.02		29
CV	–		0.56		0.38	0.15		0.35

[a] (GZDV/1.66)/dose.

vitro studies of ZDV/DDI combination have examined ZDV : DDI ratios < 1, the development of dose-related toxicities of DDI preclude the use of higher doses in patients.

Our pharmacokinetics results for combined ZDV and DDI after oral administration agree with previous analyses of either ZDV or DDI given alone, with the exception of an apparent 50% reduction in C_{max} relative to previous reports (Blum et al., 1988; Singlas et al., 1989; Lambert et al., 1990; Undakat et al., 1990; Hartman et al., 1991; Morse et al., 1992; Shelton et al., 1994). Prior studies of combined DDI and ZDV found no interaction in adults (Collier et al., 1993) or in children (Mueller et al., 1994). In contrast, a recent report found a prolonged ZDV half-life and increased GZDV AUC during combination therapy (Barry et al., 1993). Our sampling strategy may have contributed to the lower C_{max}, since other studies have demonstrated rapid absorption of both ZDV and DDI, with C_{max} occurring between 0.5 and 1 h after dosing.

In comparison to previous studies of ZDV monotherapy, the renal clearance of GZDV, but not ZDV, was approximately 50% lower in our study of combination therapy (deMiranda et al., 1989). Similarly, the observation that the GZDV : ZDV ratio in urine was approximately 50% of that seen in plasma is in contrast to other studies of

ZDV administered as monotherapy which indicate a ratio of ≈ 6 in both plasma and urine (deMiranda et al., 1989). Since the excretion of both GZDV and DDI are thought to depend upon renal tubular secretion, concurrent DDI may inhibit this elimination pathway for GZDV. Unfortunately, the lack of a ZDV monotherapy arm in our study precludes our elucidating a definite mechanism for the observed renal elimination patterns. In a recent report, the GZDV AUC was increased by concurrent DDI, but no data describing renal GZDV clearance is provided (Barry et al., 1993).

While our urinary recovery for ZDV of approximately 7–12% of ZDV dose is in good agreement with other studies, our GZDV recovery of 11–25% was lower than previously reported. Furthermore, the renal pharmacokinetics of ZDV and GZDV appeared to exhibit a dose-related pattern: urinary recovery and renal clearances of both ZDV and GZDV demonstrated a trend indicating a reduction with increasing doses. There is limited knowledge of renal mechanisms of ZDV and GZDV elimination and the pharmacokinetics of lower doses of ZDV in general. Since this phenomenon has not been previously reported with ZDV, it is unknown whether it is attributable to the presence of DDI or whether it would been seen with ZDV alone. Although metabolism to GZDV is minimal in the rat model, dose-dependent renal clearance of ZDV has been reported in this model (Patel et al., 1989). Human liver microsome studies have found no influence of DDI on ZDV glucuronidation (Back et al., 1991).

These data suggest that no clinically important pharmacokinetic interaction occurs following concurrent ZDV and DDI administration. This is supported by the beneficial antiretroviral outcomes which have been noted among many of the patients enrolled in ACTG 143 (Ragni et al., 1992) and in other reports of combined ZDV and DDI (Collier et al., 1993; Yarchoan et al., 1994). In addition, the renal clearance and urinary recovery of GZDV appeared to be reduced when ZDV is given in combination with DDI, a finding which may have relevance for other pharmacokinetic studies investigating the renal excretion of ZDV or DDI.

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