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Lack of Pharmacokinetic Interaction between Intravenous 2′,3′-Dideoxyinosine and 3′-Azido-3′-Deoxythymidine in Rats

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We investigated the pharmacokinetic interaction between 3′-azido-3′-deoxythymidine (AZT) and 2′,3′-dideoxyinosine (ddI), given to rats by intravenous injection. For both compounds, the clearances, terminal half-lives, and fractions of the dose excreted unchanged in urine were not altered by the other drug ($P > 0.05$), indicating no pharmacokinetic interaction between the two drugs.

2′,3′-Dideoxyinosine (ddI) and 3′-azido-3′-deoxythymidine (AZT) are effective agents in the treatment of patients afflicted with the human immunodeficiency virus (4, 19, 20). Both nucleoside analogs are converted intracellularly to their triphosphates, which are potent inhibitors of the reverse transcriptase needed for viral replication (6, 8). Drug combinations are now used to reduce toxicity, explore therapeutic synergy, and reduce the risk of human immunodeficiency virus resistance (6, 11, 21). For example, AZT is being used in combination with ddI (11), dideoxycytidine, or acyclovir (18, 21). In this study, we investigated the pharmacokinetics of ddI and AZT given to rats separately and in combination by the intravenous route, to gain insights into the possible pharmacokinetic interaction of these two drugs.

ddI (lot 234-B-1), AZT (lot RK03-222), and ftorafur [N^1-(2-tetrahydrofuranyl)-5-fluorouracil] were gifts from the National Cancer Institute (Bethesda, Md.). High-pressure liquid chromatographic (HPLC) analysis showed that these compounds were >98% pure. Permanent catheters were implanted into the right jugular veins of female Fischer rats (ages, 5 to 6 months; pretreatment weights, 200 ± 21 g [mean ± standard deviation; $n = 18$]) at least 16 h before the study. Between 8 and 10 a.m. the rats received a dose of ddI and/or AZT by intravenous injection. In patients, the concentrations in plasma are less than 10 to 20 μg/ml for AZT (9) and ddI (10). In this study, we used a dose of 40 mg/kg to give maximal concentrations in plasma of approximately 100 μg/ml for both drugs, because pharmacokinetic interactions such as inhibition of drug metabolism are expected to be more pronounced in the presence of higher concentrations in plasma. The intravenous dose (pH 7.0) was administered over 30 s. Serial venous blood samples (0.25 ml) were obtained over 180 min, and the plasma fractions were stored at −20°C until analysis. ddI and AZT were extracted from plasma samples as described elsewhere (15), with a slight modification that ftorafur was used as the internal standard. Both compounds were analyzed by HPLC. The mobile phase was 10 mM sodium phosphate buffer (pH 5.0) and 4% acetonitrile for ddI and 10 mM sodium phosphate buffer (pH 6.9) and 10% acetonitrile for AZT. The detection limit for both compounds in plasma was 0.1 μg/ml. The intraday variations were 5.1% for ddI and 7.4% for AZT. The interday variations were about 10% for both drugs. Urine samples were diluted 10- to 100-fold, spiked with the internal standard solution, and analyzed by HPLC without extraction.

The plasma concentration-time data for ddI were analyzed by noncompartmental and compartmental methods described previously (16). In the compartmental analysis, the data were computer fitted to a two-compartment open model for ddI and a one-compartment model for AZT, with elimination from the central compartment. Data were analyzed by using an equation for a zero-order input for the dose infusion over 30 s, as described previously (16). A weighting function of 1/concentration was used. Model selection was based on the F test and the Akaike criterion (3, 17). For computer fitting, the NLIN routine of Statistical Analysis Systems (Cary, N.C.) was used (13). Statistical analysis was performed by using the unpaired Student's t test. P values of less than 0.05 were considered statistically significant.

ddI and AZT were given intravenously alone or simultaneously to three groups of rats in a parallel study design. Figure 1 shows the superimposable plasma concentration-time profiles for ddI given alone (group 1; $n = 6$) or

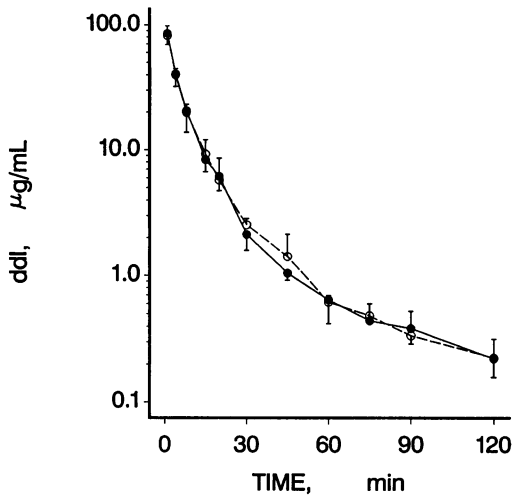

FIG. 1. Plasma concentration-time profiles for ddI in the absence or presence of AZT in rats. Group 1 animals ($n = 6$) were given ddI alone (closed circles). Group 3 animals ($n = 5$) were given ddI and AZT simultaneously (open circles). The dose of each drug was 40 mg/kg, and they were administered by intravenous injection over 30 s. Values are means ± standard deviations.

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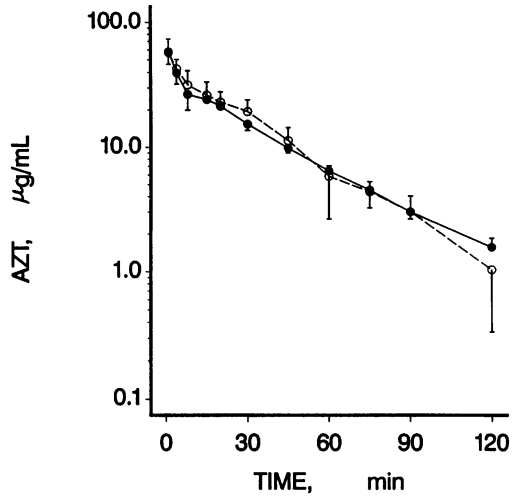

FIG. 2. Plasma concentration-time profiles of AZT in the absence or presence of ddI in rats. Group 2 animals (n = 5) were given AZT alone (closed circles). Group 3 animals (n = 6) were given ddI and AZT simultaneously (open circles). The dose of each drug was 40 mg/kg, and they were administered by intravenous injection over 30 s. Values are means ± standard deviations.

simultaneously with AZT (group 3; n = 6). Figure 2 shows the superimposable concentration-time profiles for AZT given alone (group 2; n = 5) or simultaneously with ddI (group 3; n = 6). The pharmacokinetic parameters of ddI (Table 1) and AZT (Table 2) were similar to those published previously (12, 16) and were not altered by the addition of the other drug. The volume of distribution at steady state of AZT showed a small decrease (17%) when it was coadministered with ddI. This decrease was not statistically significant.

Theoretically, pharmacokinetic interactions between AZT and ddI can occur at the sites of transport, absorption, metabolism, and renal elimination. The present study was designed to examine the interaction in metabolism and renal elimination between ddI and AZT. In patients, AZT is primarily excreted in urine as unchanged drug or as the glucuronide form (18). In rats, AZT is primarily eliminated by renal excretion as unchanged drug, and the amount of AZT-glucuronide in urine is <5% of that of AZT (12). AZT is actively secreted by rat and human kidneys, and renal excretion could be inhibited by other compounds that are eliminated by organic anion transport systems (7, 12). The mechanism of renal elimination of ddI has not been reported. We showed a decreasing renal clearance (CL) for ddI with doses increasing from 8 to 200 mg/kg, suggesting a saturable component in the renal elimination of ddI. In the present study, the mean renal CL of ddI was 25% lower in animals that received the ddI-AZT combination than it was in animals that received ddI alone. This difference did not reach statistical significance ($0.05 < P < 0.10$). The renal CL value of one animal (animal 4) appeared to be unexpectedly low. Exclusion of this animal from the analysis did not alter the statistical result. It is interesting that the renal CL of AZT similarly showed a slight trend of decreased values after ddI coadministration. A minor interaction between the renal secretion mechanisms of ddI and AZT cannot be ruled out.

The conversion of ddI and AZT to their active nucleotides represents a minor metabolic pathway. In T lymphocytes exposed to ddI or AZT, phosphorylation to active intracellular nucleotides accounts for <10% of the drug metabolism (6, 19). Hence, catabolism to inactive metabolites represents the major metabolic pathway, ddI, a purine nucleoside analog, is a substrate for purine nucleoside phosphorylases which cause the breakdown of ddI to hypoxanthine (5, 14). Hypoxanthine is further metabolized by the purine metabolism pathway to the excretion products uric acid in humans and allantoin in rats. The pyrimidine analog AZT is not expected to be a substrate or an inhibitor of the purine nucleoside phosphorylases. Our findings show that there are no metabolic interactions between AZT and ddI.

Inhibition of AZT transport into blood cells by ddI appears to be unlikely, because AZT enters these cells by diffusion and does not utilize the nucleoside transport system (2). However, AZT could conceivably inhibit the transport of ddI, because AZT has been shown to inhibit the nucleoside transport system which is partly responsible for the uptake

TABLE 1. Pharmacokinetic parameters of ddI in the absence or presence of AZT[a]

Group and rat no.	CL (ml/min/kg)	V_{ss} (ml/kg)	Half-life (min)	AUC (μg · min/ml)	Fe (%)	Renal CL (ml/min/kg)
ddI alone (group 1)						
1	57.0	707	22.1	702	27.8	15.0
2	66.7	1,044	45.5	600	30.9	20.6
3	72.2	904	24.6	554	42.8	30.9
4	76.3	1,797	55.8	525	10.9	8.3
5	62.4	785	30.6	641	31.5	19.7
6	61.4	689	21.7	651	25.6	15.7
Mean ± SD	66.0 ± 7.2	988 ± 418	33.4 ± 14.1	612 ± 66	28.3 ± 10.4	18.5 ± 7.5
ddI and AZT (group 3)						
13	76.1	798	16.7	526	18.4	14.0
14	62.2	1,040	39.2	643	24.8	15.4
15	61.9	847	26.9	646	18.5	11.5
16	62.2	915	29.2	644	24.4	15.2
17	64.9	824	30.5	644	21.7	13.5
18	—	—	—	—	16.4	—
Mean ± SD	64.9 ± 6.3	885 ± 97	28.5 ± 8.1	620 ± 53	20.7 ± 3.5	13.9 ± 1.65

[a] Rats were given ddI alone or ddI and AZT. The dose of each drug was 40 mg/kg, and the drugs were injected intravenously over 30 s. The differences between the pharmacokinetic parameters are not different between the groups ($P > 0.05$). CL, clearance; V_{ss}, volume of distribution at steady state; AUC, area under the concentration-time curve; Fe, fraction of dose excreted over 24 h in urine as unchanged drug. —, incomplete plasma sampling.

TABLE 2. Pharmacokinetic parameters of AZT in the absence or presence of ddI[a]

Group and rat no.	CL (ml/min/kg)	V_{ss} (ml/kg)	Half-life (min)	AUC (μg · min/ml)	Fe (%)	Renal CL (ml/min/kg)
AZT alone (group 2)						
7	32.9	1,101	23.4	1,214	50.6	16.7
8	26.3	1,048	28.4	1,519	47.6	12.5
9	29.4	1,081	25.7	1,362	61.9	18.2
10	27.9	1,019	24.8	1,432	56.0	15.6
11	—[b]	—[b]	—[b]	—[b]	55.1	—[b]
12	24.2	1,081	27.9	1,652	68.2	16.5
Mean ± SD	28.2 ± 3.3	1,066 ± 32	26.2 ± 2.0	1,436 ± 164	56.6 ± 7.5	15.9 ± 2.1
ddI + AZT (group 3)						
13	35.0	1,208	23.9	1,144	49.6	17.4
14	34.8	899	17.5	1,150	49.1	17.1
15	24.8	807	23.1	1,613	41.2	10.2
16	21.4	846	25.6	1,872	56.2	12.0
17	23.1	771	23.2	1,733	54.2	12.5
18	28.7	727	14.5	1,394	—[c]	—[c]
Mean ± SD	28.0 ± 5.9	876 ± 173	21.3 ± 4.3	1,484 ± 305	50.1 ± 5.8	13.8 ± 3.2

[a] Rats were given AZT alone or ddI and AZT. The dose of each drug was 40 mg/kg, and the drugs were injected intravenously over 30 s. The differences between the pharmacokinetic parameters are not different between the groups ($P > 0.05$). CL, clearance; V_{ss}, volume of distribution at steady state; AUC, area under the concentration-time curve; Fe, fraction of dose excreted over 24 h in urine as unchanged drug.

[b] —, Incomplete plasma sampling.

[c] —, Incomplete collection.

of the ddI analog 2′,3′-dideoxyadenosine into blood cells (1). It is not known whether AZT inhibits the transport of ddI into blood cells.

Note that, in patients, these drugs are given orally. In the present study, we investigated the intravenous pharmacokinetics, which yields information on the major pharmacokinetic parameters, including plasma and renal clearance. These values cannot be obtained after oral administration. Interaction during absorption may alter the oral bioavailability when both drugs are given simultaneously. AZT and ddI are rapidly absorbed after oral administration, with maximal concentrations in patients obtained within 1 h (9, 10). The possibility of interaction during absorption could therefore be avoided by separate administration of the two compounds. Further studies are needed to investigate the potential interaction of these agents during absorption.

In summary, our data indicate that, in rats, AZT does not affect the elimination of ddI, and vice versa. Extrapolation of the rat data to humans needs to take into account the differences in the elimination of AZT from the two species.

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