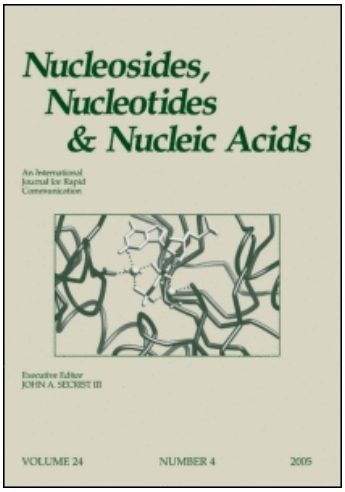

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PHARMACOKINETICS OF A NEW ANTI-HIV AGENT: 2',3'-DIDEOXY-2',3'-DIDEHYDROTHYMIDINE (d4T)

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Abstract. D4T is one of several drugs being considered for antiretroviral therapy in the treatment of AIDS. Pharmacokinetic studies showed that d4T was well absorbed, predominantly eliminated as unchanged drug and able to penetrate the blood-brain barrier.

A number of 2',3'-dideoxynucleosides have been shown to inhibit the in vitro infectivity and cytopathic effect of the human immunodeficiency virus (HIV).[1] These compounds, as their 5'-triphosphates, inhibit viral reverse transcriptase by competing with the natural substrate at the same binding site on the enzyme.[2] Dideoxynucleoside triphosphates can also be incorporated into growing DNA chains which then blocks further DNA elongation because they lack the 3'-hydroxyl group required for further polymerization.[1] The pharmacokinetic and metabolic properties of 2',3'-dideoxy-2',3'-didehydrothymidine have been determined in various animal species and compared to AZT. Concentrations of unchanged d4T in these studies were determined by using a preliminary HPLC assay with a lower limit of quantitation of approximately 0.5 µg/ml.

D4T was administered in solution orally and intravenously to fasted male CD-1 mice at a dose of 25 mg/kg. Semilog plots of the mean plasma concentration of d4T after each route of administration are shown in Figure 1. After oral administration, the compound was rapidly absorbed and reached a maximum concentration of 23 µg/ml by 5 minutes. The elimination half-life was 17 minutes, and the bioavailability was calculated to be 98%. At the same dose, AZT exhibited similar plasma concentration versus time profiles. C_{max} after oral administration of AZT occured by ten minutes. The half-life and bioavailability were

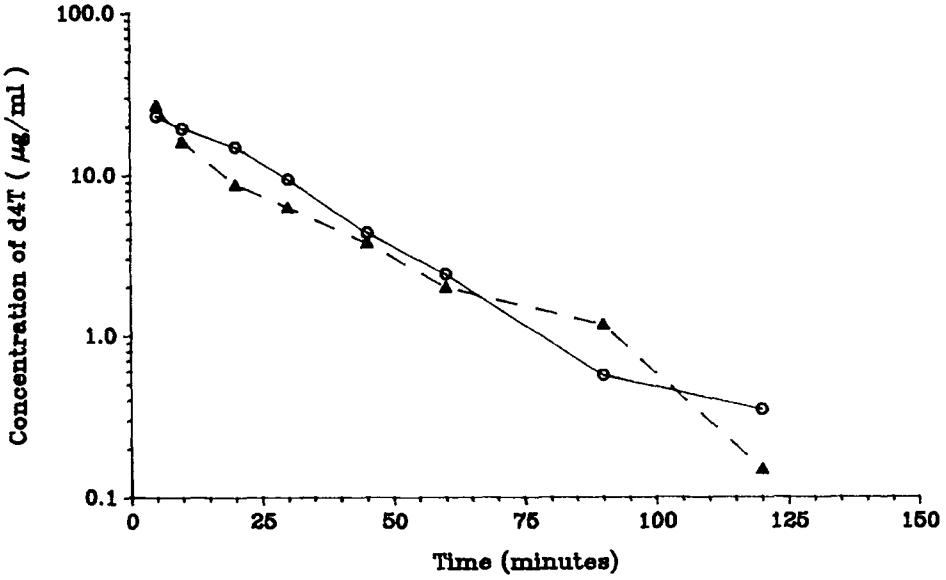

FIGURE 1. Mean plasma concentration of d4T measured after oral (O__O) and I.V. (▲--▲) administration of 25 mg/kg of d4T.

found to be 24 minutes and 100% respectively. A summary of the pharmacokinetic parameters for d4T and AZT are shown in Table 1.

To determine CNS penetration, ^{14}C-d4T was administered orally at 25 mg/kg to fasted male CD-1 mice, and brain and plasma concentrations of radioactivity were measured. As shown in Figure 2, the concentration of d4T in the brain was essentially constant from 15-60 minutes after dosing (approximately 0.5-0.8 µg equivalents/gm of brain tissue), while the brain to plasma ratio for d4T over the same time interval was found to increase from 0.03 to 0.3. In a similar study with ^{14}C-AZT, the concentration of radioactivity in the brain was similar to that found for ^{14}C-d4T at the same dose. The brain to plasma ratios were found to be similar to d4T for at least 30 minutes after dosing. These data indicate that d4T and AZT cross the blood-brain barrier and penetrate the CNS to approximately the same extent and that concentrations of either drug are much higher in plasma than in brain.

The urinary excretion and metabolite profiles were examined in the rat, dog and monkey after oral administration of 25 mg/kg of ^{14}C-d4T.

TABLE 1. Summary of pharmacokinetic parameters for d4T and AZT.

		C_{max} (μg/ml)	t_{max} (min)	$t_{\frac{1}{2}}$ (min)	AUC (μg·min/ml)	Cl_T (ml/min)	V_d (ml)
d4T	I.V.	--	--	18	694	43	19
	Oral	23	5	17	680	--	--
AZT	I.V.	--	--	21	961	31	16
	Oral	22	10	24	1008	--	--

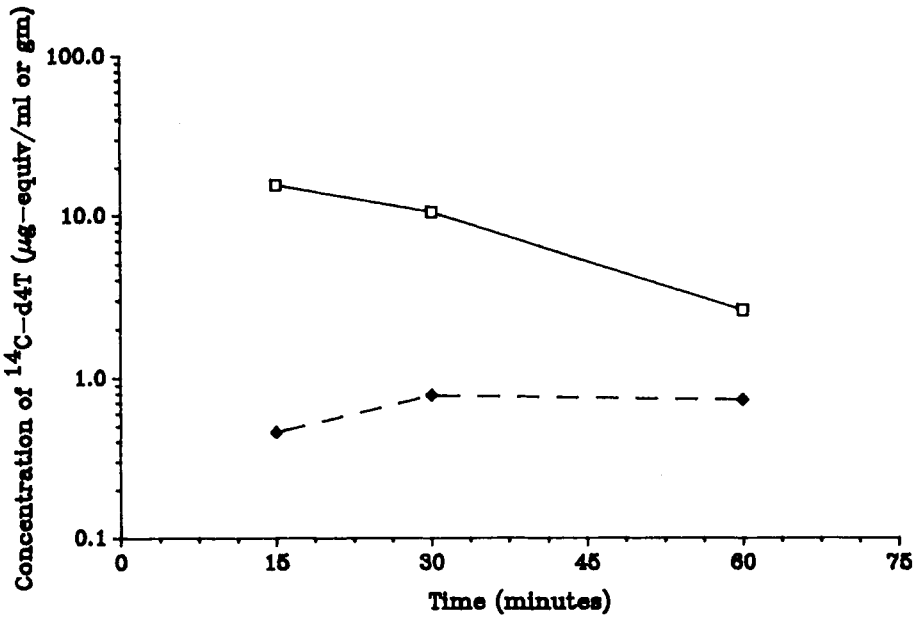

FIGURE 2. Mean concentration of ^{14}C-d4T measured in the brain (♦--♦) and in the plasma (□__□) after oral administration of 25 mg/kg of d4T.

The mean percent of radioactive dose excreted in the urine in the first 24 hours of the rat, dog and monkey was 74%, 78% and 51% respectively. Injection of urine from each of these species directly onto an HPLC column showed that almost all of the radioactivity eluted at the retention time of d4T. Further, treatment of urine with β-glucuronidase/sulfatase showed no qualitative or quantitative changes in the urinary profiles. These results show that unlike AZT, d4T is not conjugated to glucuronic acid in dog and monkey.[3]

In conclusion, these results indicate that d4T is rapidly absorbed, completely bioavailable in the mouse after oral administration, able to cross the blood-brain barrier and is excreted primarily in the urine as unchanged drug. The pharmacokinetic properties of d4T and AZT are similar in the mouse. However, unlike AZT, which has been reported to be extensively metabolized to a glucuronide conjugate in the monkey and man, no conjugate was observed for d4T in the urine of any of the species studied.

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