Pharmacokinetic Interaction Between Intravenous 2′,3′-Dideoxyinosine and Pentamidine in Rats

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Purpose. This study examined the pharmacokinetic interaction between 2′,3′-dideoxyinosine (ddI) and pentamidine.

Background. ddI and pentamidine are often coadministered to patients with acquired immunodeficiency syndrome, and are both associated with pancreatic toxicity. Information on potential interaction would be useful to assess the need for dose modification and the basis of the higher incidence of pancreatic toxicity associated with coadministration of the two drugs.

Methods. ddI (200 mg/kg) and pentamidine (10 mg/kg) were administered by continuous infusion to rats over 3 hr, either alone or concomitantly. Drug analysis was by high pressure liquid chromatography with UV or fluorescence detection, or by radioimmunoassay.

Results. Pentamidine coadministration significantly increased the apparent volume of distribution at steady state of ddI from 1.4 to 3.4 l/kg ($p = 0.004$), and increased the mean residence time from 36.3 to 50.0 min ($p = 0.015$). Pentamidine enhanced the distribution of ddI from plasma into pancreas ($p = 0.001$) and muscle ($p = 0.026$). ddI distribution into spleen and liver was also increased, with differences approaching statistical significance ($p = 0.08$ and 0.06, respectively). In contrast, ddI coadministration did not affect the total body clearance but increased the urinary excretion and the renal clearance of pentamidine by about 5-fold ($p = 0.0003$).

Conclusions. These data indicate that pentamidine increased the distribution of ddI into pancreas and muscle, whereas ddI increased the renal elimination of pentamidine.

KEY WORDS: 2′,3′-dideoxyinosine; pentamidine; pharmacokinetic interaction.

INTRODUCTION

2′,3′-dideoxyinosine (ddI) has significant antiretroviral activity, and is used to treat patients infected with the human immunodeficiency virus (HIV) (1). Similar to other dideoxynucleoside analogs, the mechanism of action of ddI is to inhibit the viral reverse transcriptase and hence viral replication (2–3). In comparison with other dideoxynucleosides, ddI has several potential advantages, including activity against 3′-azido-3′-deoxythymidine-resistant strains of HIV, a long intracellular half-life, and minimal bone marrow suppression (4). The major dose-limiting toxicities are peripheral neuropathy and acute, life-threatening pancreatitis (5–7). The cause of ddI induced pancreatitis is not understood.

Pneumocystis carinii pneumonia is a major cause of death in patients with acquired immunodeficiency syndrome (AIDS), and is treated by pentamidine, an aromatic diamidine (8). The usefulness of pentamidine is limited by its side effects including nephrotoxicity, hypotension, abnormal liver function, hypoglycemia and pancreatic toxicity (9–11). Pentamidine has been reported to cause damage to β islet cells (12).

AIDS patients often receive a combination of drugs including ddI and pentamidine. Several reports documented that up to 80% of AIDS patients receiving concurrent pentamidine and ddI therapy develop clinical pancreatitis (13–14). It is not known whether the pancreatitis seen in patients receiving both drugs is due to the cumulative toxicity of the two drugs and/or to a pharmacokinetic interaction. The present study investigated the pharmacokinetic interaction of pentamidine and ddI in rats.

MATERIALS AND METHODS

Chemicals

ddI (MW 238.2, lot no. 234-6-1), [ribose-2′,3′-^{3}H]ddI (specific activity 124 mCi/mg; lot No. 7009-93), and ftorafur (N′-(2-tetrahydrofuranyl)-5-fluorouracil) were provided by the National Institutes of Health (Bethesda, MD). Pentamidine (lot no. 29F5603), melphalan (lot no. 79F07001), and triethylamine (lot no. 50H0805) were purchased from Sigma Chemical Co. (St. Louis, MO). All high performance liquid chromatographic (HPLC) solvents and reagents were of analytical or HPLC grade and were purchased from Fisher Scientific (Fair Lawn, NJ). HPLC analysis showed that ddI, [^{3}H]-ddI, and ftorafur were > 98.9, > 96%, and > 98% pure, and that pentamidine and melphalan were > 95% pure. Rabbit IgG, rabbit anti-ddI antiserum (lot no. 053H8828), radioimmunoassay buffer, and rabbit IgG immunoprecipitation reagent were purchased from Sigma Chemical Co. The cross-reactivity of the anti-ddI antiserum for other purine analogs was minimal, 0.54% and 0.002% for dideoxyadenosine and hypoxanthine, and < 0.001% for inosine, adenosine, uric acid, and caffeine (15). Solvable tissue gel solubilizer and Atomlight scintillation cocktail were purchased from DuPont Biotechnology Systems (Boston, MA). All chemicals were used as received. Storage of solutions of ddI, ftorafur and pentamidine in saline and melphalan in methanol at −70°C for up to five months gave negligible (< 5%) degradation.

Animal Protocol

Five to six months old female Fisher retired breeder rats (Charles River Breeding Lab., Kingston, NJ) were used. The average pretreatment body weight was 231 ± 16 g (n = 20; mean ± S.D.) for the intravenous pharmacokinetic study group, and 214 ± 17 g (n = 6) for the tissue distribution study group. One day prior to the experiment, rats were anesthetized with ether and a permanent catheter (Silastic medical grade tubing, 0.02 inches i.d. and 0.037 inches o.d., Dow Corning Medical, Midland, MI) was inserted into the right external jugular vein for blood sampling. A second catheter (polyethylene PE 10 tubing, 0.011 inches i.d. and 0.024 inches o.d., Clay Adams, Parsippany, NJ) was inserted into a lateral tail vein or femoral vein for drug administration. The animals were housed in metabolic cages with access to food and water ad libitum overnight.

For the intravenous pharmacokinetic study, ddI and pentamidine were given, either alone or in combination, to three

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groups of rats in a parallel study design. Groups 1 and 2 (n = 5 each) received either ddI or pentamidine. Group 3 (n = 10) received ddI and pentamidine. On the day of the experiment, a 10 mg/kg dose of pentamidine and/or a 200 mg/kg dose of ddI were administered by infusion over 3 hr, using a syringe pump (Model 940, Harvard Apparatus, South Natick, MA) calibrated to deliver 0.0206 ml/min. These doses, when corrected for the surface area conversion factor of 1/7 (16), were equivalent to 1.4 mg/kg or one-third of the dose in humans for pentamidine and 33.3 mg/kg or three times the dose in humans for ddI. Serial blood samples (300 μl each) were collected over 12 hr. An equal volume of heparinized physiologic saline was infused to replace the lost fluid volume. Plasma samples were obtained after centrifugation at 13,000 × g for 1 min at 4°C. Urine samples were collected over 24 hr.

For the tissue distribution study, two groups of 3 animals each were given ddI, either alone or with pentamidine, as described above. At the end of the 3 hr infusion, rats were anesthetized and the abdomen was opened by midline incision. Arterial blood was withdrawn from the abdominal aorta between 11 to 45 min post-infusion. After killing the rat by exsanguination, organs including spleen, pancreas, muscle, liver, and kidney were excised. The order of collection was spleen, pancreas, liver, kidney, and muscle. The removal of tissues required about 7 min. Due to cessation of blood flow, drug redistribution among tissues during tissue removal was unlikely. Our previous study showed that ddI concentrations in tissues declined in parallel with plasma concentrations after 4–7 min post-administration. Hence, it was expected that the 10–50 min delay in the removal of blood and tissues would not alter the drug distribution profile. After excision, tissues were blot-dried, and weighed.

Sample Analysis

All samples were stored at −70°C until analysis. For the intravenous pharmacokinetic studies, plasma and urine samples were analyzed for ddI and pentamidine using previously described HPLC methods (17,18). The lower assay sensitivity limit was 100 ng/ml for ddI, and 8.6 ng/ml for pentamidine. The HPLC method could not separate ddI from interferences in tissues. Hence, for the tissue distribution study, plasma and tissue samples were extracted and analyzed by radioimmunoassay, as described previously (15). A pilot experiment examined if pentamidine interfered with the radioimmunoassay of ddI. Plasma samples were spiked with 0.625 to 10 ng of ddI, with or without the addition of 0.3 ng pentamidine. Because samples were diluted 1,000-fold prior to radioimmunoassay, the equivalent concentrations were 0.625 to 10 μg/ml for ddI and 300 ng/ml for pentamidine. The results showed that the addition of pentamidine did not alter the ddI analysis.

Data Analysis

The plasma concentration-time profiles of ddI and pentamidine were analyzed using noncompartmental method. The area under the plasma concentration-time curve (AUC) from time zero to time infinity, the total body clearance (CL), the volume of distribution at steady state (Vd_{ss}), and the mean residence time (MRT) were calculated according to standard procedures (19). Renal clearance (CL_r) was calculated as {CL} multiple by {fraction of dose excreted unchanged in urine over 24 hr, Fe}. Nonrenal clearance (CL_{nr}) is equal to total body clearance minus renal clearance. Statistical analysis was performed by using paired or unpaired two-tailed Student's t tests or a nonparametric test (Mann-Whitney test).

RESULTS

Pharmacokinetics of ddI

Figure 1 shows the mean plasma concentration-time profiles for ddI, administered either alone or simultaneously with pentamidine. From 1 to 3 hr, the concentrations of ddI in individual animals increased by 10 to 50%, and the average concentrations increased by 29%. Table I summarizes the pharmacokinetic parameters of ddI. Pentamidine coadministration significantly increased the Vd_{ss} and MRT of ddI. Pentamidine also lowered the maximal ddI concentration by 15%, increased the ddI clearance by 25%, and increased the CL_{nr} of ddI by 30%. However, these differences were not statistically significant with the p value slightly short of the 5% level of significance.

Pharmacokinetics of Pentamidine

Figure 2 shows the mean plasma-concentration time profiles for pentamidine, administered either alone or simultaneously with ddI. From 1 to 3 hr, the concentrations of pentamidine in individual animals increased by < 15%, and the average concentrations increased by 5%. Table II summarizes the pharmacokinetic parameters of pentamidine. ddI did not alter the pharmacokinetics of pentamidine, with the exception of urinary excretion. ddI significantly enhanced the 24 hr urinary excretion and accordingly increased the CL_r of pentamidine by 5 fold.

Altered Tissue Distribution of ddI by Pentamidine

Table III summarizes the distribution of ddI in various tissues, with or without pentamidine coadministration. Because

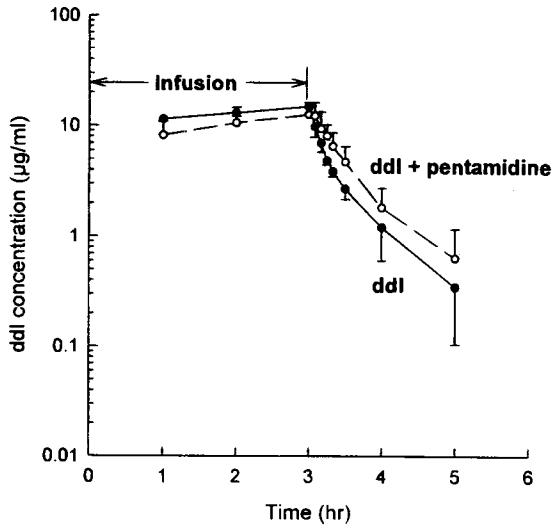

Fig. 1. Plasma concentration-time profiles for ddI in absence or presence of pentamidine. Rats were given a 3 hr intravenously infusion of (200 mg/kg) ddI alone (closed circles, n = 5) or with (10 mg/kg) pentamidine (open circles, n = 10). Mean ± one S.D. Drug concentrations were not detectable in samples collected from 6 to 12 hr (< 100 ng/ml).

Table I. Pharmacokinetics of ddI in the Absence or Presence of Pentamidine. Rats Were Given ddI (200 mg/kg), Either Alone or with Pentamidine (10 mg/kg), by Intravenous Infusion over 3 hr

Animals	Cp_{max} (μg/ml)	AUC (μg.min/ml)	CL (ml/min/kg)	Fe (%)	CL_r (ml/min/kg)	CL_{nr} (ml/min/kg)	Vd_{ss} (l/kg)	MRT (min)
Group 1 (ddI alone)								
Mean ± S.D.	14.3 ± 1.4	2586 ± 256	77.9 ± 7.2	22 ± 8	17.2 ± 6.6	60.8 ± 7.8	1.4 ± 0.7	36.3 ± 8.92
range (n = 5)	13.2 − 16.6	2379–3004	66.6–84.1	10–31	7.6–26.1	49.0–69.4	0.7–2.5	30.3–52.1
Group 3 (ddI + pentamindine)								
Mean ± S.D.	12.2 ± 3.4	2202 ± 612	97.6 ± 27.9	20 ± 7	18.9 ± 6.5	78.7 ± 20.6	3.4 ± 1.6	50.0 ± 8.88
range (n = 10)	7.7–17.6	1379–3172	63.1–145.0	9–35	8.0–30.5	43.9–129.1	1.3–5.9	35.7–66.5
p[a]	0.11	0.11	0.06	0.68	0.64	0.07	0.004	0.015

[a] Unpaired two-tailed t-test. The Mann-Whitney test gave similar results (not shown).

Note: Cp_{max}, maximal concentration at end of infusion; AUC, area under the concentration-time curve; CL, total body clearance; Fe, fraction of dose excreted over 24 hr in urine as unchanged drug; CL_r, renal clearance; CL_{nr}, nonrenal clearance; Vd_{ss}, volume of distribution at steady state; MRT, mean residence time.

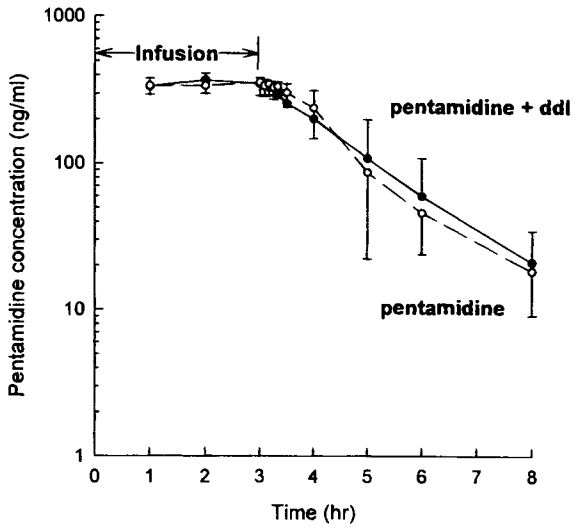

Fig. 2. Plasma concentration-time profiles for pentamidine in absence or presence of ddI. Rats were given a 3 hr intravenously infusion of (10 mg/kg) pentamidine alone (closed circles, n = 5) or with (200 mg/kg) ddI (open circles, n = 10). Mean ± one S.D. Drug concentrations were not detectable in samples collected from 10 to 12 hr (< 8.6 ng/ml).

blood and tissue samples were removed from individual animals at different times after the infusion ended, comparison of tissue distribution was done using the ratios of drug concentrations in tissue and plasma (C_{tissue}:C_{plasma}), instead of using the actual concentrations. In the absence of pentamidine, the C_{tissue}:C_{plasma} ratios, which were determined at a single time point in the present study, are consistent with the average ratios found in our previous study using multiple time points between 1 to 179 min post-administration (15). Co-administration of pentamidine significantly increased the C_{tissue}:C_{plasma} ratios in pancreas and muscle. The increases in the ratios in spleen and liver were near statistical significance, whereas the difference in kidney was not significant. Interestingly, coadministration of pentamidine increased the inter-animal variability in the ddI distribution from plasma to all five tissues, as indicated by the larger standard deviations of C_{tissue}:C_{plasma} ratios compared to those for the group receiving only ddI.

DISCUSSION

The combined use of ddI and pentamidine results in several pharmacokinetic interactions. These interactions occurred at pentamidine concentrations of between 20 to 350 ng/ml and ddI concentrations of between 0.3 to 14 μg/ml. These concentrations are clinically relevant, since the peak concentration of

Table II. Pharmacokinetics of Pentamidine in the Absence or Presence of ddI. Rats Were Given Pentamidine (10 mg/kg), Either Alone or with ddI (200 mg/kg), by Intravenous Infusion over 3 hr

Animals	Cp_{max} (ng/ml)	AUC (μg.min/ml)	CL (ml/min/kg)	Fe (%)	CL_r (ml/min/kg)	CL_{nr} (ml/min/kg)	Vd_{ss} (l/kg)	MRT (hr)
Group 2 (pentamidine alone)								
Mean ± S.D.	349 ± 35	92 ± 11	113 ± 8	1.4 ± 0.8	1.7 ± 1.2	111.5 ± 16.8	9.4 ± 1.6	1.45 ± 0.47
range (n = 5)	317–389	75–106	91–133	0.7–2.7	0.7–3.6	90.3–129.4	7.8–11.7	0.99–2.16
Group 3 (ddI + pentamidine)								
Mean ± S.D.	357 ± 68	89 ± 19	116 ± 22	8.0 ± 3.5	9.2 ± 4.1	107.0 ± 21.0	8.8 ± 1.6	1.31 ± 0.33
range (n = 10)	280–497	72–122	82–139	3.6–13.3	4.0–17.3	75.3–129.5	6.0–10.7	0.73–1.80
p[a]	0.82	0.73	0.79	0.0002	0.0003	0.66	0.48	0.49

[a] Unpaired two-tailed t-test. The Mann-Whitney test gave similar results (not shown).

Note: cp_{max}, maximal concentration at the end of infusion; AUC, area under the concentration-time curve; CL, total body clearance; Fe, fraction of dose excreted over 24 hr in urine as unchanged drug; CL_r, renal clearance; CL_{nr}, nonrenal clearance; Vd_{ss}, volume of distribution at steady state; MRT, mean residence time.

Table III. Altered Tissue Distribution of ddI by Pentamidine Coadministration. Rats Were Given ddI (200 mg/kg), Either Alone or with Pentamidine (10 mg/kg), by Intravenous Infusion over 3 hr. The Time to Remove Blood Samples and Tissues from Different Animals Varied from 11 to 45 min After the Infusion Ended, Whereas the Time for Tissue Collection from Individual Animals Was Completed in <7 min

Animals	C_{plasma} (μg/ml)	C_{tissue}:C_{plasma} for ddI				
		Pancreas	Muscle	Spleen	Liver	Kidney
ddI alone						
Mean ± S.D.	10.2 ± 3.2	0.83 ± 0.22	0.70 ± 0.14	0.22 ± 0.09	0.77 ± 0.21	12.0 ± 1.35
range	7.70–13.8	0.58–0.91	0.54–0.83	0.13–0.30	0.53–0.91	11.7–14.1
ddI + pentamidine						
Mean ± S.D.	1.86 ± 1.97[b]	2.06 ± 0.15	4.40 ± 1.85	0.63 ± 0.29	2.81 ± 1.38	29.3 ± 24.3
range	0.45–4.11	0.95–2.23	2.59–6.29	0.24–0.85	1.34–4.04	9.25–56.3
p[a]	NA	0.001	0.026	0.082	0.064	0.3

[a] Unpaired two-tailed t test.

[b] Samples were collected at later times than the group receiving only ddI.

Note: C_{tissue}:C_{plasma}, ratio of ddI concentration in tissue and plasma. n = 3 in each group. NA, not applicable because samples from the two groups were collected at different times after the infusion ended.

pentamidine in humans receiving a 4 mg/kg parenteral dose is 500 ng/ml (27) and that of ddI for a 10 mg/kg oral dose is 5 μg/ml (28). Quantitatively, the most significant changes are the increase of Vd_{ss} and MRT of ddI and the increased CL_r of pentamidine. Minor changes in other pharmacokinetic parameters, including the total clearance and CL_{nr} of ddI, were also observed.

The Vd_{ss} of ddI was more than doubled with pentamidine coadministration, suggesting an increased accumulation of ddI in tissues. This is confirmed by the increased C_{tissue}:C_{plasma} ratios of ddI in multiple tissues. These data suggest that the pancreatic toxicity occurring in patients receiving both drugs may be related to an increased accumulation of ddI in pancreas. The mechanisms and consequences of changes in ddI distribution due to pentamidine coadministration deserves further study. It is noted that ddI-induced pancreatitis has not been shown in the rat, hence this animal species is not a good model to evaluate the pharmacodynamics of pancreatic toxicity.

Renal excretion of pentamidine is a minor route of its elimination; the fraction of dose excreted unchanged accounts for < 2% of an intravenous dose (Table II). Hence, the 5-fold enhancement of CL_r of pentamidine by ddI did not result in a different total clearance of pentamidine. Our finding that the CL_r of pentamidine in rats is smaller than the literature values of the glomerular filtration rate of 6 ml/min/kg (20) is in agreement with published results in rats, dogs, and humans (21–23). The low value of CL_r and the ddI-induced increase in CL_r suggests reabsorption of pentamidine in the renal tubules that could be inhibited by ddI. It has been proposed that the nephrotoxicity of pentamidine is due to its accumulation in kidney, similar to the mechanism of nephrotoxicity of aminoglycoside antibiotics (24), which are transported into the proximal tubular cells via an active process (25). Further studies are needed to determine if an inhibition of pentamidine reabsorption and accumulation in the kidney reduces its renal toxicity. The interaction of the neutral or anionic ddI molecules with the transport of the cationic pentamidine would not be expected a priori. However, it has been proposed that another dideoxynucleoside, 3′-azido-3′-deoxythymidine, is transported by both organic anionic and cationic transport systems (26).

In summary, data of the present study indicate that pentamidine significantly altered the distribution of ddI into pancreas and muscle, whereas ddI reduced the renal excretion of pentamidine. Further studies are needed to examine the time course and the pharmacologic basis of the pentamidine-induced changes in the ddI distribution in target tissues including the lymphoid and brain tissues where the therapeutic effect is desired and the tissues where drug toxicity is expected (e.g. pancreas).

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