Absorption of 2',3'-Dideoxyinosine from Lower Gastrointestinal Tract in Rats and Kinetic Evidence of Different Absorption Rates in Colon and Rectum

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This study explored the rectal route of administration for 2',3'-dideoxyinosine (ddI). Rats were given a rectal infusion of nonradiolabeled ddI (200 mg/kg in 0.7 mL saline) over 35 min along with an intravenous (iv) bolus injection of [8-^{3}H]ddI (20 μCi, equivalent to 2.1 μg), which was used to calculate the absolute rectal bioavailability of ddI. Maximal plasma concentrations of rectally administered unlabeled ddI were 5.4 ± 2.2 μg/mL and were reached at the end of the infusion. The rectal bioavailability averaged 15.6 ± 4.4% (n = 9). The second aim of this study was to examine the kinetics of ddI absorption from the colorectal region. Analyses of the absorption rate–time profiles by the Loo–Riegelman and deconvolution methods showed biphasic absorption: a rapid phase during infusion and a slow phase postinfusion. These profiles were inconsistent with a mammillary model with absorption from a single site with one apparent rate constant. The model which gave the best fit for infusion and postinfusion data consisted of two different sites (colon and rectum) with different apparent absorption rate constants. The two sites were connected by a first-order transfer of drug solution from rectum to colon. The apparent absorption rate constant in the rectum was 39-fold higher than that in the colon. In conclusion, these results show absorption of ddI from the colorectal region and suggest the rectal route as an alternative to the oral route. The data further suggest different absorption sites in the colorectal region, with a more rapid absorption in the rectum than in the colon.

KEY WORDS: 2',3'-dideoxyinosine (ddI); didanosine; anti-AIDS drug; rectal infusion; rectal bioavailability; rectal and colonic absorption.

INTRODUCTION

2',3'-Dideoxyinosine (ddI) suppresses proliferation of the human immunodeficiency virus (HIV). The antiviral efficacy requires constant drug exposure and therefore treatment is life-long (1). Ideally, the route of administration should be noninvasive and result in effective viral inhibitory concentrations over the dosing interval with minimum host toxicity. Initial studies in patients receiving ddI orally showed a low and highly variable systemic bioavailability, ranging from 6 to 50% (2). This indicates that a large percentage of the dose is lost prior to reaching the systemic circulation. The loss could be due to incomplete absorption, presystemic elimination, and/or acid degradation in the stomach. ddI is unstable in an acid environment with a degradation half-life of 14 min at pH 2.3 (3). In phase I and II trials, coadministration of ddI with antacid or buffer to adult patients resulted in an improved bioavailability of 38 ± 15% (2) or 16–54% (4). Another study involving coadministration of ddI and an antacid orally to children resulted in bioavailabilities ranging from <5 to 89% (5). Chewable tablets are the currently used formulation (6,7). While coadministration with antacid shows some improvement in the oral bioavailability, the large variations suggest that other routes need to be explored. Furthermore, for neonates and patients who cannot tolerate chewable tablets and for patients who are dependent on nursing care, the special care required to coadminister ddI solutions with milk or antacids may introduce a compliance problem. A noninvasive, simple administration route to avoid the extra handling may have clinical application. The present study evaluated the rectal route for delivering ddI. The kinetics of the drug absorption from colon and rectum were also examined.

MATERIALS AND METHODS

Chemicals. ddI (MW 238.2, Lot No. 234-b-1) and ftorafur [N^1-(2-tetrahydrofuranyl)-5-fluorouracil] were provided by the National Institutes of Health (Bethesda, MD). [8-^{3}H]ddI (sp act, 11 mCi/mg; Lot No. 5549-117) was provided by Research Triangle Institute (Research Triangle Park, NC) under contract with the National Institutes of Health. All other chemicals and solvents were obtained from Sigma Chemical Co. (St. Louis, MO) and Fisher Scientific Co. (Cincinnati, OH). The purities of unlabeled and tritiated ddI were checked by high-pressure liquid chromatography (HPLC) and were >99.8 and 97.9%. All chemicals were used as received. ddI, at a concentration of 60 mg/mL saline, showed a maximum degradation of 3% after 2 weeks of storage at 4°C.

Rectal Administration. Suppositories represent the standard vehicle for rectal delivery. Formulation of ddI in polyethylene glycol based suppositories was attempted. However, due to the limited solubility of the drug, a suppository volume of >3.5 mL was needed to deliver the desired dose. Rats could not retain suppositories of this large size. Drug delivery was therefore by our previously developed nonsurgical rectal infusion method (8). The drug solution was infused through polyethylene tubing held in the core of a plug. The plug was inserted into the rectum for a distance of 0.5 cm. The anal sphincter closed in a ridge in the plug and formed a seal around it. Infusion was by a Harvard infusion pump (Harvard Apparatus, South Natick, MA).

Animal Protocols. Female Fischer rats (Charles River Breeding Laboratories, Kingston, NJ) were used. The rats were 172 ± 6 days old (range, 164–179 days) and had a body weight of 207.4 ± 11.6 g (range, 185.1–224.7 g). Rats were housed in metabolism cages 2 days before and throughout the experiment. Permanent catheters were implanted in the right jugular veins under ether anesthesia 1 day before the study. Food was withheld from midnight until 2 hr after treatment ended. Treatment was administered between 9:30 and 11 AM. There was no restraint of the rat during procedures. To remove feces from the rectum, saline enemas were given at midnight and repeated at 2–3 hr before treatment. Rats were infused with a rectal dose of unlabeled ddI, 200

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mg/kg in physiologic saline (pH 7.4), at a volume of about 0.7 mL and at a rate of 0.021 mL/min over 35 min through the rectal plug. The plug was left in the rectum for an additional 150 min to prevent leakage. At 5 min after the infusion started, an iv injection of 20 μCi of [8-^{3}H]ddI (equivalent to 2.1 μg) was administered over 0.5 min through the venous catheter. Serial blood samples of approximately 200 μL were withdrawn through the catheter for up to 12 hr. Samples were kept on ice to avoid ddI degradation by serum phosphorylases. The blood samples were centrifuged at 13,000*g* for 3 min and an 100-μL aliquot of plasma was removed for analysis. ddI does not absorb onto the catheter (8).

Movement of Solution in Colon and Rectum. To identify the appropriate volume and infusion rate of the drug solution, the distribution of a dye solution (0.2% trypan blue) in the lower intestinal tract as a function of the infusion volume was examined. A rat was anesthetized under ether and a midsection incision was made from superior to the urethral orifice to inferior to the diaphragm. Feces were removed by saline enemas. To prevent tissue dehydration during the experiment, the incision wound was covered with saline soaked gauze supported by a wire mesh. The infusion volumes, i.e., 0.73 and 1.45 mL, were infused at 0.021 and 0.056 mL/min to different rats. The movement of the dye solution within the translucent intestine over time was monitored visually.

Sample Analysis. Previous work in our laboratory showed that the concentration of ddI in blood was equivalent to that in plasma (9). Plasma samples were analyzed by a previously described method (9,10). Ftorafur was used as the internal standard (1.6 μg/400 μL). Samples were extracted using solid-phase extraction columns (SPE-C_{18}, Supelco, Bellafonte, PA). The extract was analyzed by HPLC using a reversed-phase μBondapak C_{18} column (Waters Associates, Milford, MA) and an aqueous mobile phase containing 30 m*M* sodium acetate and 4% acetonitrile, pH 4.5. The elution volumes for ddI and ftorafur were 19 and 22 mL, respectively. For analysis of [8-^{3}H]ddI, the HPLC eluent was fractionated and the radioactivity in individual fractions determined by liquid scintillation counting. The concentration of the sum of labeled and unlabeled ddI was quantitated by UV absorbance. The maximum concentration of [8-^{3}H]ddI was <4% of the unlabeled ddI. Therefore, the UV absorbance represented mainly the unlabeled ddI and no correction for the [8-^{3}H]ddI concentration was necessary. Separate plasma standard curves were constructed for the labeled and unlabeled ddI. These standard curves were linear over the concentration range of 0.1 to 50 μg/mL for unlabeled ddI (r^2 = 0.9993) and 0.04 to 40 ng/mL for labeled ddI (r^2 = 0.9974). Urine and feces samples were analyzed in order to evaluate the mass balance. The urine samples were diluted 10-fold with 100 m*M* phosphate buffer (pH 6.9) and 100 μL was used for analysis. The feces samples were soaked overnight at 4°C in 10 mL of water, then homogenized mechanically, and 100 μL of the aqueous supernatant was removed for analysis. Degradation of ddI in feces under these conditions was insignificant. The urine and feces samples were extracted and analyzed in the same manner as the plasma samples. The standard curves of unlabeled ddI in feces and urine were linear over the concentration range of 0.5 to 550 μg/mL (r^2 = 0.9995).

Data Analysis. The plasma concentration–time profile of the iv tracer dose of [8-^{3}H]ddI was used to calculate the drug clearance (CL) in order to determine the absolute bioavailability of the concomitantly administered rectal dose. The simultaneous determination of the CL during absorption of the rectal dose was to avoid significant inter- and intra-animal variability which may occur due to the nonlinear disposition of ddI (9). The plasma concentration–time data of the iv tracer dose were analyzed using compartmental and noncompartmental methods (11–13). In the compartmental analysis, a two- or three-compartment open model with a zero-order infusion over 0.5 min was used to fit the iv tracer data. The microconstants defining the model were obtained using the NONLIN84 pharmacokinetic data analysis program (14).

The rectal bioavailability (*F*) of the unlabeled ddI was calculated using the plasma data with Eq. (1) and using the urine data with Eq. (2) (12). Fe_{iv} and Fe_{rectal} are the fractions of the iv and rectal doses excreted unchanged in urine in 24 hr. The AUC_{rectal} was calculated using the log trapezoidal rule.

$$F = \frac{AUC_{rectal} \times CL_{iv}}{Dose_{rectal}} \quad (1)$$

$$F = \frac{Fe_{rectal}}{Fe_{iv}} \quad (2)$$

Kinetics of Absorption from Colon and Rectum. The absorption of ddI from the rectum and colon was analyzed by three methods. The Loo–Riegelman (15) and deconvolution (16) methods give the drug input into the systemic circulation as a function of time. We proposed two additional mammillary models to evaluate the observed biphasic absorption.

The Loo–Riegelman method describes the absorption rate-time profile for a two-compartment model (15). Equation (3) is a modification of the Loo–Riegelman equation to accomodate a three-compartment model. The amount absorbed (represented as a concentration term, Cp_{in}) at a specified time, t_n, is the sum of the amounts in the three compartments (Cp_1, Cp_2, and Cp_3), and the amount that has been absorbed and was subsequently excreted. The latter is the product of the elimination rate constant (k_{10}) and AUC_{rectal}.

$$(Cp_{in})_{tn} = (Cp_1)_{tn} + (Cp_2)_{tn} + (Cp_3)_{tn} + k_{10} \times AUC_{rectal} \quad (3)$$

where

$$(Cp_2)_{tn} = (Cp_2)_{tn-1}\, e^{-k_{21}\Delta t} + \left(\frac{k_{12}}{k_{21}}\right)(Cp_1)_{tn-1}\,(1 - e^{-k_{21}\Delta t}) + \left(\frac{k_{12}}{k_{21}}\right)\Delta Cp_1 - \left(\frac{k_{12}}{(k_{21})^2}\right)\left(\frac{\Delta Cp_1}{\Delta t}\right)(1 - e^{-k_{21}\Delta t})$$

and

$$(Cp_3)_{tn} = (Cp_3)_{tn-1}\, e^{-k_{31}\Delta t} + \left(\frac{k_{13}}{k_{31}}\right)(Cp_1)_{tn-1}\,(1 - e^{-k_{31}\Delta t}) + \left(\frac{k_{13}}{k_{31}}\right)\Delta Cp_1 - \left(\frac{k_{13}}{(k_{31})^2}\right)\left(\frac{\Delta Cp_1}{\Delta t}\right)(1 - e^{-k_{31}\Delta t})$$

Equation (4) is the general equation used in the deconvolution method (17,18). This method uses a staircase input function. The concentration of drug in plasma at time t_n, $Y(t_n)$, is expressed as a summation, over all time intervals before t_n, of the product of an arbitrary constant input rate I_i, and the integral of $G(t_n - x)$ between the limits $x = t_{i-1}$ and t_i. The response function $[G(t)]$ was approximated by the triexponential equation used to fit the iv [8-^{3}H]ddI data to a three-compartment model [Eq. (5)], using an iv infusion input as described by Veng-Pederson (19). R_{iv} is the infusion rate for the iv tracer dose and is equivalent to dose/t^*, where t^* is the time at the end of the infusion. $Y(t_n)$ is known and $G(t_n - x)$ is approximated. Transformation according to the staircase input principle yields the absorption rate, I_n, described in Eq. (6). The cumulative amount absorbed at t_n is described by Eq. (7).

are represented by Ag, A_1, A_2, and A_3, respectively. k_{12}, k_{21}, k_{13}, k_{31}, and k_{10} are the first-order rate constants for the intercompartmental transfer and the elimination processes. Ag_{1t^*} and A_{1t^*} are the amounts in the colorectal region and central compartments at the end of the infusion, respectively.

Model 2 is a three-compartment mammillary model where the colorectal region is depicted as two absorption sites. This model was based on the results of ARA–time plots and dye movement experiments. The ARA–time plot was biphasic with a rapid absorption rate during infusion and a slower absorption rate postinfusion. The dye movement experiments showed the presence of dye in rectum and colon during infusion and a rapid depletion of dye in the rectum after infusion, while dye in the colon remained visible for >2 hr. In model 2, the movement of drug solution from rectum

$$Y(t_n) = \sum_{i=1}^{n} I_i \int_{t_{i-1}}^{t_i} G(t_n - x)dx \tag{4}$$

$$\int_{t_{i-1}}^{t_i} G(t_n - x)\,dx = \frac{R_{iv}k_{21}k_{31}}{V_1\alpha\beta\gamma}(t_i - t_{i-1}) - \frac{A}{\alpha^2 t^*}(e^{\alpha t_i} - e^{\alpha t_{i-1}})\,e^{-\alpha t_n} - \frac{B}{\beta^2 t^*}(e^{\beta t_i} - e^{\beta t_{i-1}})\,e^{-\beta t_n} - \frac{C}{\gamma^2 t^*}(e^{\gamma t_i} - e^{\gamma t_{i-1}})\,e^{-\gamma t_n} \tag{5}$$

$$I_n = \frac{Y(t_n) - \left(\sum_{i=1}^{n-1} I_i \frac{R_{iv}k_{21}k_{31}}{V_1\alpha\beta\gamma}\right)(t_{i-1} - t_i) + \left(\sum_{i=1}^{n-1} I_i a_i\right)e^{-\alpha t_n} + \left(\sum_{i=1}^{n-1} I_i b_i\right)e^{-\beta t_n} + \left(\sum_{i=1}^{n-1} I_i c_i\right)e^{-\gamma t_n}}{\frac{R_{iv}k_{21}k_{31}}{V_1\alpha\beta\gamma}(t_{i-1} - t_i) - a_n e^{-\alpha t_n} - b_n e^{-\beta t_n} - c_n e^{-\gamma t_n}} \tag{6}$$

$$\text{Cumulative amount absorbed at } t_n = \sum_{i=1}^{n} I_i (t_i - t_{i-1}) \tag{7}$$

Analysis by the Loo–Riegelman and deconvolution methods is limited to calculating the drug input into the plasma compartment as a function of time. The amount remained to be absorbed (ARA) versus time plots showed biphasic decline over time. We hypothesized that the biphasic profile was due to drug transfer from the rectum to colon as well as different absorption sites in the colorectal region. To account for the time-dependent movement of drug solution from rectum to colon, two mammillary models of absorption and disposition were evaluated (depicted in Figs. 3 and 4). Model 1 is a three-compartment mammillary model depicting the colorectal region as a single site with one absorption rate. The drug is infused into the colorectal region at a constant rate, R_o, which is equivalent to F*Dose/t^*. k_a is a first-order rate constant for drug transfer from colorectal region to blood (central compartment, A_1). The amounts of drug in the colorectal region, blood, and tissue compartments 2 and 3 into colon is described by a combination of zero- and first-order processes with rate constants R_a and k_T, respectively. R_a was equal to zero after infusion ended. k_{rectum} and k_{colon} are first-order rate constants describing the drug transfer from rectum and colon into blood, respectively. Ag_{2t^*} is the amount in the colon at the end of the infusion.

Equations (8) and (9) are the Laplace transformed equations describing the plasma concentration derived from the rectal infusion as a function of time for models 1 and 2, respectively.[3]

For model 1, during infusion

[3] NONLIN84 subroutines for the three-compartment Loo–Riegelman and the deconvolution methods, as well as the derivations and subroutines for the mammillary models are available from the authors upon request.

$$L[A_1] = \frac{(k_{rectum}R_0(s + k_{21})(s + k_{31}))}{(s(s + \alpha)(s + \beta)(s + \gamma)(s + \delta))} \quad (8a)$$

For model 1, post infusion

$$L[A_1] = \frac{((k_{colon}Ag_{t^*} + A_{1t^*}(s + k_{colon})(s + k_{21})(s + k_{31}))}{((s + \alpha)(s + \beta)(s + \gamma)(s + \delta))} \quad (8b)$$

For model 2, during infusion

$$L[A_1] = \frac{((k_{rectum}(R_0 - R_a)(s + k_{colon}) + k_{colon}R_a(s + k_{rectum} + k_T) + k_{colon}k_T(R_0 - R_a))(s + k_{21})(s + k_{31})}{(s(s + \alpha)(s + \beta)(s + \gamma)(s + \delta)(s + \epsilon))} \quad (9a)$$

For model 2, postinfusion

$$L[A_1] = \frac{((k_{rectum}Ag_{1t^*}(s + k_{colon}) + k_{colon}k_TAg_{1t^*} + k_{colon}Ag_{2t^*}(s + k_{rectum}k_T) + A_{1t^*}(s + k_{rectum} + k_T)(s + k_{colon}))(s + k_{21})}{(s + \alpha)(s + \beta)(s + \gamma)(s + \delta)(s + \epsilon)} \quad (9b)$$

The rate constant between the rectum, the colon, and the central compartment of models 1 and 2 were fitted using NONLIN84. The microconstants defining the disposition of an iv dose were determined during the same experiment after administration of an iv tracer dose and were fitted separately.

Statistical Analysis. Statistical analysis was done using the unpaired Student's *t* test and analysis of variance at a 5% level of significance (20). The goodness of the fitting using different models was compared using the Akaike information criterion (21) and Imbimbo criterion (22).

RESULTS

Solution Movement and Fluid Absorption in Rectum and Colon. In a pilot study, a ddI solution infused rectally over 30 min at a rate of 0.056 mL/min resulted in a peak plasma concentration at 10 min rather than at the end of infusion as would be expected for an infusion regimen. The concentration at 30 min was 46% of the peak level. At a slower infusion rate of 0.021 mL/min, a peak concentration was observed at the end of the 35-min infusion. These different concentration–time profiles suggested that the early peak concentration at the higher infusion rate and volume could be due to distribution of the drug solution to sites with slower absorption after 10 min. The distribution and movement of a dye solution as a function of infusion rate, volume, and time were examined. Anatomically, a fold is located between the transverse and the descending colon at approximately 80 mm. This fold restricts the retrograde flow. At the higher infusion rate and larger volume, the dye reached a distance of 56 mm from the anus and passed the fold at 14 min and extended past the transverse colon to the cecum (180 mm) at 25 min. At the slower infusion rate and smaller volume, the dye emerged from the pelvic area in 15 min and did not reach the colonic fold at the end of the 35-min infusion; the distances traveled at 15, 25, and 33 min were <35, 54, and 74 mm from the anus. After infusion ended, the dye solution disappeared over time, starting from the anal orifice. At 25 min postinfusion, the dye solution was not visible in the first 35 mm, which consisted of the rectum and part of the colon, and completely disappeared from the colon at 180 min (Fig. 1). The intestine was slit open for visual inspection.

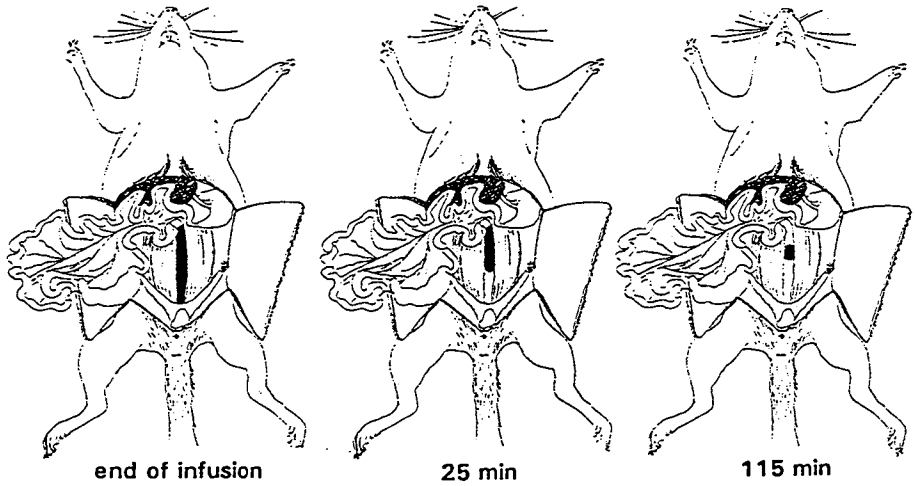

Fig. 1. Dye movement postinfusion. A 0.73-mL dye solution of 0.2% trypan blue was infused for 30 min. The dye length and distance from the anus were determined postinfusion up to 180 min. Dye solution in colorectal region at end of infusion and 25 and 120 min postinfusion.

No dye solution was left in the colon, indicating that the dye and fluid were absorbed.

Based on these data, we selected the slower infusion rate of 0.021 mL/min and a volume of 0.73 mL. This was sufficient to deliver a 200 mg/kg dose to a 220-g rat at a concentration of 60 mg/mL at pH 8.4. Based on the time required for complete absorption of 0.73 mL of dye solution, the rectal plug was left in the rectum for a total of 180 min to prevent leakage.

Plasma Concentration–Time Profiles. Figure 2A shows the plasma concentration–time profile of the iv data of [8-^{3}H]ddI in a rat. The extrapolated portion of the AUC_{iv} accounted for 2.5% of the total AUC. Computer-fitting using a two- or three-compartment model resulted in correlation coefficients of 0.85 and 0.996, respectively, between the observed and the model-predicted values. Analysis by Akaike information criterion (21) and Imbimbo criterion (22) showed that the data of all nine rats studied were best described by a three-compartment model. The parameters obtained from noncompartmental analysis (data not shown) were similar to those obtained using a three-compartment body model (Table I). The coefficients of variation of the estimates were about 30%.

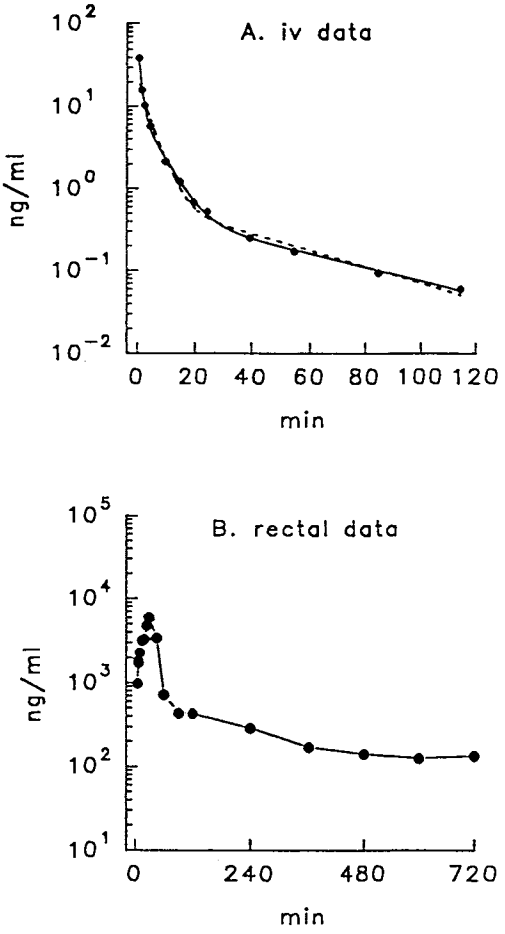

Fig. 2. Plasma concentration–time profiles. A rat was given a rectal infusion of unlabeled ddI (200 mg/kg) over 33 min and, 5 min after the start of the infusion, an iv bolus injection of 20 μCi of [8-^{3}]ddI (equivalent to 2.1 μg) over 0.5 min. The concentration of [8-^{3}H]ddI was analyzed by HPLC fractionation and scintillation counting. The first time point was taken at 1 min after the iv dose or 6 min after the initiation of the rectal infusion. (A) iv [8-^{3}]ddI data. The dashed line denotes the computer fit using a two-compartment model (r^2 = 0.8500) and the solid line denotes the fit to a three-compartment model (r^2 = 0.9960) with elimination from the central compartment. (B) Rectal unlabeled ddI data.

The nonradiolabeled ddI was infused rectally over 35 min. Figure 2B shows a representative plasma concentration–time profile. The maximum ddI plasma concentration was reached at 35 min and was 5.4 ± 2.2 μg/mL (mean ± SD; range, 2.7 to 9.3). After termination of the infusion, the concentration rapidly declined within 90 min to about 7% of the peak level and then declined at a much slower rate. The terminal half-life was 305 ± 146 min (range, 161 to 639 min). This half-life was about ninefold longer than the terminal half-life of the iv tracer dose, indicating a "flip-flop" pharmacokinetic model where absorption from the colorectal region was slower than elimination so that absorption was the rate-limiting step of the disposition.

Table I summarizes the rectal bioavailability of ddI. The absolute bioavailability of a 200 mg/kg dose of ddI calculated using the plasma data with Eq. (1) was about 15%. About 26% (range, 10.4 to 40.3%) of the AUC_{rectal} from time 0 to infinity was accounted for by 35 min, 45% (range, 21.6 to 60.1%) by 90 min, and 83% (range, 62.7 to 92.9%) by 720 min, which was the last sampling time.

Excretion of ddI in Urine and Feces. The fraction of the rectal unlabeled ddI dose recovered in the 24-hr urine and feces averaged 2.3 and 3.4%, respectively. The total radioactive dose excreted in 24-hr urine was 18.2 ± 5.35%, of which about 80% was unchanged [8-^{3}H]ddI. A calculation of the bioavailability in individual rats using the urinary excretion data with Eq. (2) showed an average bioavailability of 15.6 ± 8.2% (range, 7.9 to 29.5%).

After the iv [8-^{3}H]ddI dose, the total radioactivity recovered in 24-hr feces was 0.6% of the dose. In seven of nine rats, the recovery of the nonradiolabeled rectal dose in feces was 2- to 80-fold higher than the recovery of the tritiated iv dose. In the remaining two rats, the fractions of the iv and rectal doses in feces were about the same. The fraction of the rectal dose excreted in feces was 3.41 ± 5.26% (range, 0.36–15.9%; median, 1.05%).

Drug Absorption from Colon and Rectum. The ARA–time plots obtained using the Loo–Riegelman and the deconvolution methods indicate two distinct absorption phases, a rapid phase during infusion and a slow phase postinfusion (Table II).

Figures 3 and 4 depict mammillary models 1 and 2 and the experimental data. Model 1 assumed identical first-order absorption rate constants from colon and rectum. A comparison of the computer generated profile using model 1 with the experimental data showed that the peak plasma concentration at the end of infusion was overestimated by 106.8% and postinfusion data were underestimated. Model 2 assumed that the emptying process from rectum into colon was a combination of a zero- and first-order process during infusion and a first-order process postinfusion. A comparison of the computer generated profile using model 2 with the experimental data showed a >99% correlation between the model-predicted and the observed data during and postinfusion. The computer-fitted value for k_T was 0.068 ± 0.022

Table I. Pharmacokinetic Parameters for ddI After Coadministration of iv and Rectal Doses[a]

Rat no.	Intravenous administration ([8-^{3}H]ddI) $t_{1/2}^{\alpha}$ (min)	$t_{1/2}^{\beta}$ (min)	$t_{1/2}^{\gamma}$ (min)	k_{12} (L/min)	k_{21} (L/min)	k_{13} (L/min)	k_{31} (L/min)	k_{10} (L/min)	$V_{d_{ss}}$ (mL/kg)	CL_{iv} (mL/min-kg)	Rectal administration (unlabeled ddI) AUC_{rectal} (μg-min/mL)	$t_{1/2}$ (min)	F (%)
1[b]	0.9	6.3	44.7	0.122	0.138	0.061	0.017	0.526	850	83.0	270.7	289	12.5
2	1.3	4.2	42.3	0.080	0.217	0.066	0.020	0.346	1225	90.0	260.3	162	11.7
3	1.2	5.2	47.5	0.118	0.190	0.046	0.017	0.368	997	83.8	411.3	187	17.2
4	0.5	3.6	35.4	0.465	0.364	0.086	0.023	0.592	587	57.6	582.4	208	16.8
5	0.7	4.3	38.7	0.273	0.271	0.075	0.021	0.494	819	75.5	289.7	221	10.5
6	0.5	3.2	45.6	0.420	0.338	0.121	0.018	0.868	620	58.6	398.3	376	11.6
7	0.5	3.5	48.1	0.448	0.377	0.071	0.016	0.610	747	69.3	498.3	318	17.3
8	1.1	11.9	34.7	0.289	0.136	0.055	0.006	0.213	1132	62.3	692.0	639	21.5
9	0.5	5.1	34.7	0.624	0.340	0.106	0.026	0.414	1116	66.9	399.6	343	13.4
Mean	0.8	5.3	41.3	0.315	0.263	0.076	0.018	0.492	899	71.5	422.5	305	14.7
SD	0.3	2.7	5.5	0.187	0.096	0.024	0.006	0.189	230	11.7	146.7	146	3.6

[a] Rats were given a rectal infusion of unlabeled ddI (182 to 200 mg/kg) and, 5 min later, an iv infusion of [8-^{3}H]ddI (2.1 μg) over 0.5 min. Data were analyzed by compartmental analysis using a three-compartment open model and the NONLIN84 program. AUC_{rectal} is the area under the plasma concentration–time curve from time 0 to infinity, calculated by the log-trapezoidal rule. $V_{d_{ss}}$ is the volume of distribution at steady state. $t_{1/2}^{\alpha}$, $t_{1/2}^{\beta}$, and $t_{1/2}^{\gamma}$ are the half-lives corresponding to α, β, and γ phases, respectively. k_{12}, k_{21}, k_{13}, k_{31}, and k_{10} are the microconstants for the intercompartmental transfer and the elimination processes. CL_{iv} is the total-body clearance of [8-^{3}H]ddI, and $t_{1/2}$ is the terminal half-life of the unlabeled plasma concentration-time profile. Bioavailability was calculated using the plasma data with Eq. (1).

[b] The dose for this rat was 182 mg/kg. All other rats received 200 mg/kg.

per min (Table II). The half-life of drug solution transfer from rectum to colon was calculated to be about 12 min. This value is consistent with the observed rapid drainage of drug solution from rectum to colon. The R_a value was 5.7 ± 3.6 μg/min, which was insignificant compared to the infusion rate of 1260 μg/min into the rectum.

The goodness of fit obtained by the two mammillary models was compared using Akaike information and Imbimbo criteria. The mean values obtained for the Akaike information and Imbimbo criteria were smaller for model 2 (187.4 and 0.035, respectively) than for model 1 (224.5 and 0.047, respectively), indicating model 2 as the better model. Table II summarizes the absorption rate constants determined by the different methods. The calculated absorption half-lives during and postinfusion were 13 and 478 min by the Loo–Riegelman method and 11 and 546 by the deconvolution method. Analysis by model 2 indicated a 39-fold higher absorption rate constant from the rectum than from the colon, with corresponding absorption half-lives of 10 and 408 min.

DISCUSSION

The first goal of this study was to explore the rectal delivery route as an alternative to the oral route. The data show that the rectal bioavailability of a 200 mg/kg dose of ddI, calculated using either plasma or urine data, was about 15%. In comparison, the oral bioavailability of an unbuffered solution of ddI (40 mg/kg) in rats was about 16% as shown in

Table II. Absorption Rate Constants[a]

Rat no.	Loo–Riegelman k_{di} (min^{-1})	k_{pi} (min^{-1})	Deconvolution k_{di} (min^{-1})	k_{pi} (min^{-1})	Mammillary model 2 k_{rectum} (min^{-1})	k_{colon} (min^{-1})	k_T (min^{-1})	R_a (ng-min^{-1})
1	0.070	0.00124	0.088	0.00150	0.079	0.00230	0.100	7466
2	0.035	0.00183	0.038	0.00139	0.054	0.00180	0.087	2630
3	0.047	0.00106	0.086	0.00170	0.100	0.00312	0.028	8204
4	0.043	0.00145	0.046	0.00050	0.055	0.00026	0.061	8294
5	0.078	0.00133	0.074	0.00171	0.085	0.00211	0.078	141.1
6	0.059	0.00196	0.049	0.00081	0.045	0.00072	0.083	8559
7	0.072	0.00219	0.095	0.00096	0.100	0.00218	0.067	7988
8	0.024	0.00049	0.029	0.00090	0.025	0.00100	0.050	72.14
9	0.041	0.00170	0.047	0.00196	0.062	0.00263	0.056	7838
Mean	0.052	0.00145	0.061	0.00127	0.067	0.00179	0.068	5688
SD	0.019	0.00052	0.024	0.00050	0.026	0.00094	0.022	3642

[a] Data were analyzed by the Loo–Riegelman and deconvolution methods, and using an open mammillary model. k_{di} is the absorption rate constant during infusion and k_{pi} is the absorption rate constant postinfusion. k_{rectum} and k_{colon} are first-order rate constants describing the drug absorption from rectum and colon into blood, respectively.

previous studies by us and other investigators (23,24). Hence, the rectal route is comparable to the oral route with respect to the absolute bioavailability and the interanimal variability. The rectal route may be an attractive alternative to the oral route, for example, for neonates who may not be able to take chewable tablets or patients who cannot tolerate oral dosing due to emesis or gastric irritation. Gastric irritation and emesis are side effects in dogs of oral 2',3'-dideoxyinosine, a prodrug of ddI (25). Another noteworthy finding was the low recovery of the rectal dose in feces. The total of the bioavailable dose and the recovered dose was less than 20%, indicating that most drug underwent presystemic degradation. The low bioavailability of an oral dose is generally attributed to the instability of ddI in the acidic environment of the stomach (3). However, the pH of the lower GI is neutral to slightly basic. Hence, the low rectal bioavailability was due to other presystemic elimination processes, as discussed below.

The second goal was to examine the absorption kinetics from rectum and colon. Evaluation of several kinetic models showed that the experimental data were best described by a model where the drug solution was transferred from rectum to colon, primarily by a first-order process. Rectum and colon were distinct absorption sites with different apparent absorption rate constants. k_{rectum} was 39-fold higher than k_{colon}. The higher absorption in the rectum could be due to several factors. One reason may be the partial avoidance of hepatic first-pass elimination of the drug absorbed from rectum but not from colon, as reported for other compounds

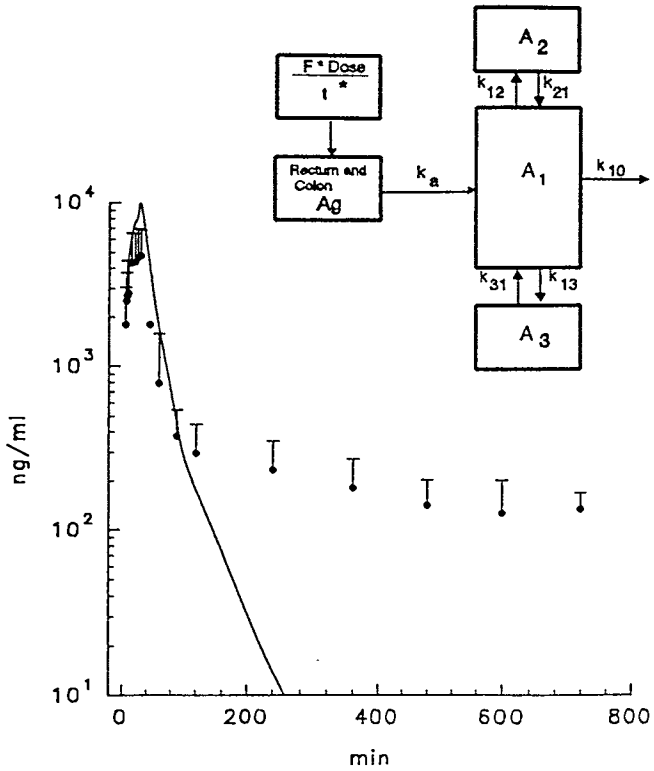

Fig. 3. Model 1. A three-compartment mammillary model (inset) with one absorption site and one absorption rate constant was fit to each data set. Circles, data means. Bars, standard deviation (n = 9). Solid line represents the average model-predicted fit.

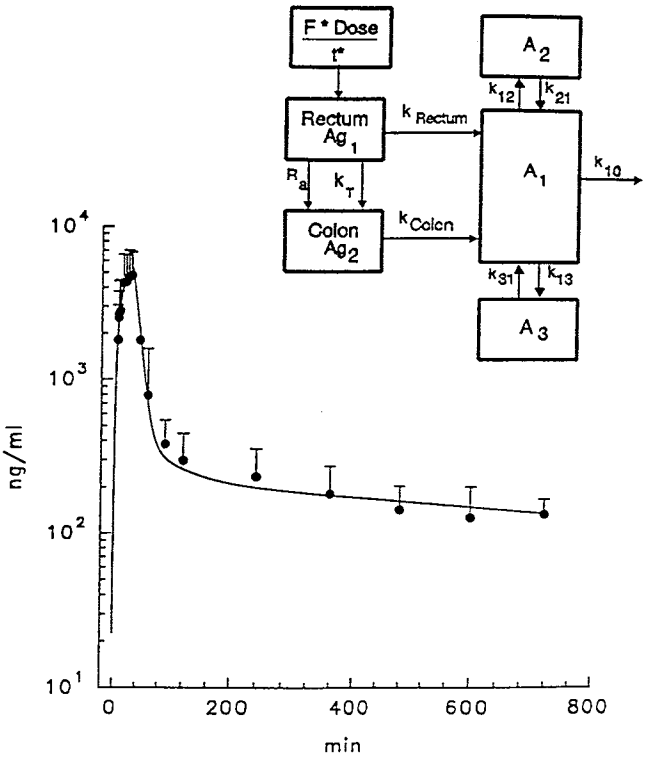

Fig. 4. Model 2. A three-compartment mammillary model (inset) with different absorption sites and absorption rate constants during and after infusion was fit to each data set. Circles, data means. Bars, standard deviation (n = 9). Solid line represents the average model-predicted fit.

with high hepatic clearance (26–29). Avoidance of first-pass metabolism allows more drug to enter the systemic circulation and hence increases the absorption rate. In a separate study,[4] we examined the first-pass elimination of ddI by the liver, duodenum, jejunum, and ileum and the degradation of ddI by intestinal microbes. This study showed that less than 20% of the infused dose was removed in the first-pass through the liver. The relatively low hepatic extraction suggests that partial avoidance of first-pass hepatic elimination would not account for the 39-fold higher rectal absorption compared to colonic absorption. Alternatively, extensive drug degradation in the colon would result in a decreased rate of absorption into the systemic circulation. This is supported by the following finding. A rapid enzymatic degradation of ddI by intestinal contents was observed. Assuming a linear relationship between the rate and the enzyme concentration and using the first-order rate constant in a 14% (w/v) enzyme solution, we calculated that the entire dose would be degraded by undiluted intestinal contents in about 1.5 hr.[4] Finally, a slower transmembrane absorption from the colon than from the rectum would agree with the proposed kinetic model. The present study showed that the absorption of a dye solution from the colon was substantially slower than from the rectum. We postulate that ddI similarly undergoes

[4] S. L. Bramer, J. L.-S. Au, and M. G. Wientjes. Gastrointestinal and hepatic first pass elimination of 2',3'-dideoxyinosine. *J. Pharmacol. Exp. Ther.*, in press (1993).

a slower absorption from the colon than from the rectum. Site-dependent absorption was also observed in a separate study where we found that ddI absorption was more rapid and complete after duodenal than after ileal infusion, while the intrinsic clearances of the duodenal and ileal tissues are similar and insignificant.[4] It appears that the ddI absorption rate in the ileum and colon was slower than in the duodenum and rectum, respectively. A slower absorption rate results in a longer residence time of ddI in the presence of intestinal microbes and, hence, a greater presystemic degradation and a lower apparent drug bioavailability.

In conclusion, ddI was absorbed from colon and rectum. Our data suggest several possibilities to optimize the rectal administration route. For example, dosing formulations which localize drug absorption to the rectal area, coadministration of absorption enhancers, or coadministration of inhibitors of microbial metabolism may increase the rectal bioavailability substantially. Maintenance of an effective viral inhibitory concentration is necessary for the therapeutic activity of ddI and other reverse transcriptase inhibitors which act by inhibiting viral replication. A formulation giving a constant release may permit a more constant absorption and yield plateau drug concentrations. The higher apparent absorption rate constant from rectum than from colon indicates the rectum and colon as two distinct absorption sites.

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