Lack of Absorption of Didanosine after Rectal Administration in Human Immunodeficiency Virus-Infected Patients

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The feasibility of rectal administration of didanosine (DDI) was studied in six human immunodeficiency virus-infected patients. After oral intake of a DDI solution (100 mg/m² of body surface area) combined with an antacid (Maalox), pharmacokinetic parametric values were in accordance with previously published data; the mean ± standard deviation for terminal half-life was 59.5 ± 15.0 min, that for peak concentration was 5.2 ± 3.9 μmol/liter, and that for the area under the time-concentration curve (AUC) was 494 ± 42 min · μmol/liter. After rectal administration of a similarly prepared DDI solution (100 mg/m² of body surface area), plasma DDI levels were below the detection limit (0.1 μmol/liter) at all time points in five of the six patients, and in the remaining patient the AUC after rectal application was only 5% of that after oral administration. We conclude that oral administration of DDI cannot be easily replaced by rectal application.

Didanosine (DDI) is an important component of antiretroviral therapy for human immunodeficiency virus (HIV)-infected children (7) and adults (6). At present only an oral formulation is available. DDI is rapidly degraded by gastric juice (8, 13). To ensure sufficient oral absorption it has to be administered together with an appropriate buffer to a patient with an empty stomach. Despite these arrangements, the average bioavailability is reported to be low (<40% [13] and highly variable (2 to 89% [1]). In addition, drug intake is inconvenient and the neutralization of the gastric juice may interfere with the absorption of other drugs (14). Therefore, in order to avoid these disadvantages it is desirable to evaluate other routes of administration. In HIV-infected patients we have previously demonstrated a substantial absorption of zidovudine after rectal administration (16). In an animal model rectal application of DDI resulted in a mean bioavailability of about 15% (2). The aim of the present study was to evaluate the pharmacokinetics of DDI after rectal administration in HIV-infected patients.

Patients and methods. Six HIV-infected male outpatients under treatment with DDI (100 to 120 mg/m² of body surface [BS] twice daily) were studied after their informed consent was obtained. The mean age of the patients was 30 years (range, 7 to 46 years), mean weight was 55 kg (range, 25 to 66 kg), and mean BS was 1.56 m² (range, 0.9 to 1.8 m²). The CD4 cell count ranged from 105 to 393 cells/μl (mean, 220 cells/μl). Disease stages according to the Centers for Disease Control classification (5) were as follows: for one patient, A1; for two patients, A2; and for three patients, C3. At the time of this study all patients had a hemoglobin level of >80 g/liter, neutrophil count of >1,000/μl, no evidence or prior history of pancreatitis or neuropathy, and no apparent opportunistic infections and did not manifest diarrhea or rectal ulcers.

Pharmacokinetic investigations were done in the morning. Patients fasted overnight and DDI treatment was withheld for the last 12 h. For drug administration DDI (Videx powder for children) was dissolved in distilled water and mixed with an equal volume of magnesium hydroxide–aluminum hydroxide (Maalox) to a final concentration of 10 mg/ml. This solution was administered at a dose of 100 mg/m² of BS for both parts of the study (after oral administration and rectal application). For rectal application DDI was given via a lubricated nasogastric tube inserted about 8 to 10 cm proximal to the external anus. Then, the tube was flushed with air. There was no evidence of leakage of the DDI solution during the study period of 4 h. Blood samples were collected by a peripheral indwelling catheter before and 30, 60, 90, 120, 150, 180, and 240 min after drug administration. The investigations after rectal application were done 1 week subsequent to those after oral administration.

Drug assay. Concentrations of DDI in plasma were determined by high-performance liquid chromatography (10). In brief, 0.5 ml of plasma was extracted with methanol on a 500-μl SPE column (Bond Elut; ICT, Frankfurt, Germany). Samples were run isocratically on a 250 mm by 4.6 mm (height by outside diameter) Supersphere endcapped 5-μm RP-18 column (Merck, Darmstadt, Germany). The mobile phase consisted of a 50 mM potassium hydrogen phosphate solution, methanol, and triethanolamine (85/15/0.05 [vol/vol/vol]) adjusted to pH 4.0 with phosphoric acid. Concentrations of DDI were calculated by measuring peak height and referring to external standards and an internal standard (didehydrothymidine [D4T]). Retention times for DDI and D4T were about 5.35 and 6.40 min, respectively. The lower limit of detection (defined as threefold signal/noise ratio) was 0.1 μmol/liter. The method yielded linear results over the concentration range up to 50 μmol/liter (correlation coefficient [r²] was 0.9985, x-intercept was 0.15, and y-intercept = −0.03). Intra- and interassay coefficients of variation were 4.9 and 6.7%, respectively.

All chemicals used were of analytical grade or better and purchased from Merck. Pure DDI was a kind gift of the Bristol-Myers Squibb Company, Syracuse, N.Y.

Pharmacokinetic analysis. Maximum concentration (Cmax), time to maximum concentration (Tmax), terminal elimination half-life (t1/2b), and area under the time-concentration curve...
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was applied. In contrast, in rats Bramer et al. (2) administered

within the range of a standard dose of a therapeutic regimen,

squares regression analysis. The AUC 0–

time concentration curve, and t_{1/2b} was determined by least-
squares regression analysis. The AUC_{p-a} was calculated by

using the linear-trapezoidal rule and extrapolated to infinity

(C_{last}) with approximation of the last data point. For calcula-
tions the pharmacokinetic software package Topfit 2.0 was

used (9).

Results. After oral application, the mean ± standard devi-
ation for C_{max} was 5.2 ± 3.9 μmol/liter, the mean T_{max} was

55.0 ± 23.0 min, and that for t_{1/2b} was 59.5 ± 15.0 min. The mean

AUC was 494 ± 412 min · μmol/liter after 30, 60, and 90

min, respectively. The corresponding AUC after rectal appli-
cation in this patient was 5.3% of that after oral administra-
tion.

Discussion. In this study we attempted to compare the phar-
macokinetics of DDI after oral and rectal administration. After

oral application the pharmacokinetic parametric values in all

patients were in good agreement with previously pub-
lished data (1, 8, 11). Surprisingly, after rectal application no measurable absorption of DDI was detected in five of the

six patients. In the sixth patient only very low levels of DDI

were found in comparison to those observed after oral ad-

ministration. Overall, this indicates a nearly complete pre-
systemic elimination of DDI when it is applied rectally in

humans.

In rats, however, rather similar bioavailabilities were dem-

onstrated after oral (16% [15]) and rectal (15% [2]) adminis-

tration. In the latter investigation DDI was infused in a manner

such that the drug was deposited in the rectum and colon. The

authors were able to show a 39-fold higher absorption rate in

the rectum as compared to the colon. In our study, we applied

DDI in a way that should lead to drug deposition exclusively in

the rectum. Nevertheless, we did not detect any significant

absorption of DDI.

In the present study, a single dose of 100 mg/m² (equivalent

to approximately 2.5 to 5 mg/kg of body weight), which is

within the range of a standard dose of a therapeutic regimen,

was applied. In contrast, in rats Bramer et al. (2) administered

dose of 200 mg/kg of body weight. Even if the body surface

rule is taken into consideration, this represents a strikingly

higher dose. Assuming similar rectal bioavailabilities in hu-

mans and in rats (approximately 15%) we would have expected

an average AUC after rectal application of about half of that

observed after oral administration (approximately 30 to 40%)

in humans. However, rectal absorption may not necessarily

depend on the dose in a linear manner. In rats, a significant

presystemic loss of DDI after rectal application was observed.

This was mainly due to degradation by enzymes in the “intes-
tinal contents” and to a smaller extent to first-pass metabolism

in the intestinal epithelium or in the liver (3). This presystemic

loss may occur in humans as well. Thus, a standard “oral” dose

applied rectally may be rapidly degraded before significant

absorption occurs. In liver homogenates, metabolism of DDI

was shown to be saturable (3), and this may be true for the

degradation capacity of the intestinal contents, too. In the

study in rats the high dose of DDI may have exceeded the

saturability of the degrading enzymes. Furthermore, Bramer et

al. (2) supposedly reduced these intestinal contents by exten-
sive enemas prior to drug application. In addition, these ene-

mas might have caused mucosal damage that facilitated ab-

sorption of DDI in the rats.

Finally, DDI was rectally applied in a solution containing

Maalox, which possibly may have impaired the absorption of

the drug. DDI has a pKa of 9.12 (4, 12). The DDI-Maalox

solution is supposed to be neutral if instilled into the rectum

and neutral to slightly acidic in the stomach. Thus, it is not

likely that the pH difference between the stomach and the

rectum may lead to markedly different ionization states of

DDI. Furthermore, DDI is quite soluble at neutral pH (12)

and therefore probably does not precipitate out of the Maalox

solution in the rectal environment. Taken together, these ob-

servations suggest that it is not likely that rectal application of

DDI together with a buffered solution accounts for the lack of

absorption in humans.

We conclude that oral administration of DDI cannot be

easily replaced by rectal administration as suggested by the

results of an animal study unless high-dose application or spe-
cific stabilizers are evaluated.

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