Pharmacokinetics of Zidovudine after Rectal Administration in Human Immunodeficiency Virus-Infected Patients

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We evaluated the pharmacokinetics of rectally administered zidovudine (ZDV) in 10 human immunodeficiency virus-infected adults. After rectal administration of an aqueous ZDV solution (250 mg of ZDV), mean peak ZDV levels were 1.3 ± 0.7 μmol/liter (mean ± standard deviation) versus 5.0 ± 2.2 μmol/liter ($P < 0.0001$) after oral intake of a 250-mg ZDV capsule. The half-life at β phase was 87.8 ± 39.6 min for rectally administered ZDV versus 55.8 ± 20.1 min ($P = 0.035$) for orally administered ZDV. The mean area under the concentration-time curve from 0 min to infinity was 232 ± 181 μmol/liter·min after rectal administration versus 362 ± 110 μmol/liter·min after oral intake. Although the two routes were not bioequivalent, ZDV was absorbed considerably after rectal administration, with a pharmacokinetic profile resembling that of a sustained-release device.

Zidovudine (ZDV) is still a main compound of antiretroviral therapy for human immunodeficiency virus infection (8, 21). Except for in certain circumstances (6, 17), ZDV is administered orally. The drug is quickly absorbed from the gastrointestinal tract with high peak values, is rapidly eliminated, and shows considerable first-pass loss (1, 3, 14, 18). Prior attempts (9, 11, 15, 17, 19) to improve the availability of ZDV seem hardly applicable for long-term treatment.

ZDV was well absorbed from the large intestine in rats when administered rectally (13). Therefore, the aim of this study was to evaluate the pharmacokinetics of ZDV after rectal administration in humans.

Patients. Ten human immunodeficiency virus-infected male patients treated routinely with oral ZDV (two daily doses of 250 mg each) were studied after giving informed consent. The mean age of the patients was 36 years (range, 18 to 66 years), the mean weight was 66 kg (range, 59 to 78 kg), and the mean number of CD4 cells was 285/μl (range, 114 to 453 cells/μl).

Disease stages according to the Centers for Disease Control and Prevention classification system (4) were as follows: one patient was at A1, three patients were at A2, four patients were at B2, and two patients were at C3. At the time of this study all patients had hemoglobin levels of >80 g/liter, neutrophil levels of >1,000/μl, and no apparent opportunistic infections, and none were suffering from diarrhea or rectal ulcers.

Prior to pharmacokinetic investigations, patients fasted for at least 4 h and ZDV treatment was withheld for the last 12 h. For the oral part of the study patients were given a 250-mg capsule of ZDV. For rectal administration, done 1 week subsequent to the oral investigation, an intravenous solution of ZDV (20 mg/ml [Retrovir]) was diluted 1:1 with glucose solution (5%, wt/vol). Twenty-five milliliters of this ZDV dilution was administered rectally (13). Therefore, the aim of this study was to evaluate the pharmacokinetics of ZDV after rectal administration in humans.

Drug assay. Concenetrations of ZDV and its glucuronidated metabolite (GZDV) in plasma were determined by high-performance liquid chromatography (10, 14, 18). In brief, 0.5 ml of plasma was extracted on 500-mg Si-C18 columns and samples were run isocratically on a 250- by 4.6-mm supercritical 5-μm RP-18 column (Merck, Darmstadt, Germany).

Concentrations of ZDV were calculated by peak height, referring to external standards and an internal standard (BW A22U; 10 μmol/liter). Retention times for GZDV, BW A22U, and ZDV were 5.5, 7.7, and 8.5 min, respectively. The overall intra-assay and interassay coefficients of variation for spiked plasma samples were 5.6 and 7.4% for ZDV (1 μmol/liter) and 5.9 and 8.7% for GZDV (10 μmol/liter), respectively. Detection limits of the method for plasma samples were 0.1 μmol/liter for ZDV and 0.2 μmol/liter for GZDV. Measurements were linear up to 100 μmol/liter for both compounds.

All chemicals used were of analytical grade or better and were purchased from Merck. GZDV was obtained from Sigma-Aldrich, Deisenhofen, Germany. Pure ZDV and the internal standard BW A22U were a kind gift of G. Land (Wellcome Research Laboratories, Beckenham, United Kingdom).

Pharmacokinetic analysis. Maximum concentration ($C_{max}$), time to maximum concentration ($T_{max}$), terminal elimination half-life ($t_{1/2b}$), and area under the concentration-time curve (AUC) were calculated by a noncompartmental model. In detail, $C_{max}$ and $T_{max}$ were determined by visual inspection of the concentration-time curve and $t_{1/2b}$ by least-squares regression analysis of all terminal points beyond the second point after $T_{max}$. The AUC from 0 to 300 min (AUC$0–300$) and AUC$0–$∞ were calculated by the linear trapezoidal rule. Extrapolation to infinity was performed with approximation of the last data point. The pharmacokinetic software package Topfit 2.0 (12) was used for calculations.

Statistical calculations were performed with the Mann-Whitney test. Bioequivalence was assessed by using two one-sided t tests (Schuirmann’s procedure [5]) with an α value of 0.05 (90% confidence intervals). The treatment methods were considered bioequivalent if the average bioavailability of the drug after the test (rectal) administration was within ±20% of that after the reference (oral) administration.

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Results. Rectal administration of the ZDV solution was well tolerated in all patients, and no signs of bowel irritation or stimulation of defecation were seen. The pharmacokinetic data for ZDV and GZDV are summarized in Table 1. After rectal administration, the mean $C_{\text{max}}$ was significantly lower than after oral intake (approximately 30% of that after oral intake; $P < 0.0001$). The mean AUC$_{0–300}$ was 53% of that after oral intake. Due to the significantly ($P = 0.035$) prolonged $t_{1/2}$, the mean rectal AUC$_{0–\infty}$ reached 70% of the oral AUC$_{0–\infty}$. Using the ±20% rule for bioequivalence, rectal administration was not bioequivalent to oral administration. The $T_{\text{max}}$ was significantly higher ($P = 0.035$) and there was a trend of greater $T_{\text{max}}$ for rectal administration. Thus, there were distinct differences between the pharmacokinetic profile of ZDV after rectal administration and that after oral intake (Fig. 1). Interestingly, after 150 to 180 min, the mean levels of ZDV in plasma after rectal administration exceeded those found after oral administration, but the differences did not reach significance.

In addition, we measured the levels in plasma of GZDV, the main metabolite of ZDV, which is formed by hepatic glucuronidation. For both routes of administration, the mean $C_{\text{max}}$ and mean AUC of GZDV were three to four times higher than the respective values for ZDV (Table 1). To estimate the extent of the metabolism of ZDV we calculated the mean ratios of ZDV to GZDV for the AUC for both routes of administration. This ratio was 0.29 after oral administration and 0.27 after rectal administration (the difference was not significant).

Discussion. This study compared the pharmacokinetic profiles of ZDV and GZDV in plasma after rectal administration with those found after oral intake. The pharmacokinetic parameters found for ZDV and GZDV after oral administration were in good agreement with previously published data (14, 18, 20).

We were able to demonstrate that ZDV is absorbed via the rectal route in humans. Rectal administration of the aqueous ZDV solution changed the pharmacokinetic profile markedly, with a significantly lower peak concentration and a significantly increased elimination time compared to oral intake. Although the mean rectal $C_{\text{max}}$ was only one-third of the mean oral $C_{\text{max}}$, the rectal AUC$_{0–\infty}$ was more than two-thirds of the mean oral AUC$_{0–\infty}$. This is because absorption and elimination were prolonged after rectal administration, compared with the oral route. However, the two routes of administration were not bioequivalent.

In rats, the pharmacokinetic parameters after administration

<table>
<thead>
<tr>
<th>Drug and method of administration</th>
<th>$C_{\text{max}}$ (nmol/l)</th>
<th>$T_{\text{max}}$ (min)</th>
<th>AUC$_{0–\infty}$ (nmol/l min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral ZDV</td>
<td>5.0 ± 2.2</td>
<td>19.0–59</td>
<td>30.0–95.0</td>
</tr>
<tr>
<td>Rectal ZDV</td>
<td>1.3 ± 0.3</td>
<td>0.0–1.0</td>
<td>30.0–120.0</td>
</tr>
<tr>
<td>Oral GZDV</td>
<td>13.7 ± 3.7</td>
<td>8.6–22.2</td>
<td>60.5 ± 17.4</td>
</tr>
<tr>
<td>Rectal GZDV</td>
<td>4.0 ± 1.8</td>
<td>0.0–2.9</td>
<td>9.10 ± 1.7</td>
</tr>
<tr>
<td>Rectal and oral drug administrations were not bioequivalent for this parameter according to the ±20% rule.</td>
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$C_{\text{max}}$ and $T_{\text{max}}$ were not significantly different between oral and rectal drug administrations. $P < 0.0001$. * $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$.****

FIG. 1. Concentration-time curve of ZDV after oral and rectal administration. Mean values for the 10 patients studied are shown. Error bars represent 1 standard deviation.
of an aqueous ZDV solution were similar for the oral and rectal routes, whereas after rectal administration of a hydroxypropyl cellulose suppository, markedly prolonged resorption and elimination kinetics were observed (13). In that study, however, the volume in relation to body weight of the aqueous ZDV solution used was about 10 times higher than in our investigation. It must be assumed that that higher volume would be distributed to a larger resorption area in the lower intestine, which would thus explain the absorption rate following rectal administration being closer to that of the oral route. Interestingly, the amount of drug absorbed via the rectal route in rats was two-thirds of that after oral administration and was thus very similar to our results in humans.

Pizzo et al. (17) suggested that steady-state concentrations of ZDV, achieved by continuous intravenous infusion, may be superior to intermittent oral intake with respect to neurologic improvement. Comparative studies with humans have not yet been performed. In at least two animal studies it was demonstrated that mice infected with the retroviruses Cas-Br-M murine leukemia virus (2) and LP-BM5 murine leukemia virus (7) were best treated by continuous infusions of ZDV, but it is questionable if this is true in humans because of differences between the ZDV phosphorylation patterns in human and murine cells (2). This issue must be evaluated in further studies. The pharmacokinetic profile seen in our study after rectal administration more closely resembled the characteristics of continuous intravenous drug infusion than those of intermittent oral administration. The rectal route may therefore be the easiest way to investigate the hypothesis of Pizzo et al. without the risk of the serious side effects observed after continuous intravenous infusion (17).

Gastrointestinal complications are well-known and important side effects in patients treated with ZDV (16). Rectal administration may thus be an attractive alternative for these patients. However, the safety and patient tolerance of rectal administration must be evaluated in further studies.

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REFERENCES


