Pharmacokinetic evaluation of 3'-azido-2', 3'-dideoxyuridine-5'-O-valinate-hydrochloride as a prodrug of the anti-HIV nucleoside 3'-azido-2', 3'-dideoxyuridine

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3'-Azido-2', 3'-dideoxyuridine (AZDU, AzddU, CS-87) has been shown to have potent anti-HIV activity in vitro. However, the compound exhibits a relatively short half-life and incomplete oral bioavailability in humans. In an effort to improve the pharmacokinetic properties of AZDU, prodrug 3'-azido-2', 3'-dideoxyuridine-5'-O-valinate hydrochloride (AZDU-VAL) was synthesized by the esterification of 5'-OH function in AZDU. The objective of this study was to investigate the bio-transformation and pharmacokinetics of AZDU-VAL along with its antiviral parent compound AZDU following intravenous and oral administration to rats. Adult male Sprague-Dawley rats were administered AZDU or AZDU-VAL by intravenous injection or oral gavage. Concentrations of AZDU-VAL and AZDU were determined by HPLC. Pharmacokinetic parameters were generated by area-moment analysis. The bioavailability of AZDU after oral administration was approximately 53%. The terminal phase half-life of the nucleoside analogue ranged between 0.6 h after intravenous administration and 1 h following oral administration. In vivo the prodrug was rapidly and efficiently biotransformed to yield AZDU following intravenous and oral administration. The apparent availability of AZDU was virtually complete following oral administration of prodrug AZDU-VAL averaging 101%. The bioavailability of AZDU following intravenous administration of AZDU-VAL averaged 106%. In summary, the disposition of AZDU was dose dependent over the dose range of 25-100 mg/kg. Renal clearance and steady state volume of distribution were lower at the higher dose level. Prodrug AZDU-VAL demonstrated improved oral bioavailability as evidenced by complete absorption and efficient bioconversion to AZDU. The results suggest that AZDU-VAL may be a promising prodrug for the delivery of AZDU.

Keywords: 3'-azido-2',3'-dideoxyuridine, AZDU, AZDU-VAL, prodrug, pharmacokinetics

Introduction

3'-Azido-2',3'-dideoxyuridine (AZDU, AzddU, CS-87, uravidine) is a nucleoside analogue similar in structure to 3'-azido-3'-deoxythymidine (AZT, zidovudine). AZDU has been shown to have significant anti-HIV activity in vitro in human peripheral blood mononuclear cells (Schinazi et al., 1987). Anti-human immunodeficiency virus (HIV-1) activity of 3'-azido-2', 3'-dideoxyuridine in dilution of cell line (Chu et al., 1989) was significantly reduced human bone marrow toxicity as compared to AZT (Schinazi et al., 1987). The nucleoside analogue has been reported to inhibit HIV-1 replication in human peripheral blood mononuclear cells (PBMC) infected with HIV-1 in the 0.18 to 0.46 µM range (Chu et al., 1989). In the human T-cell lines M T-4 and ATH B, the median effective AZDU concentration for inhibition of HIV-mediated cytopathic effects was 0.4 µM. The 50% inhibition of cell growth occurred only at concentrations of 200 µM or greater (Balzarini et al., 1987), and compared to AZT, AZDU demonstrated significantly less in vitro toxicity (36-fold) to human bone marrow cells (BMC) (Schinazi et al., 1987). Metabolic studies showed that AZDU is sequentially phosphorylated to its mono-, di-, and triphosphate metabolites by cellular kinases. The 5'-triphosphate of AZDU (AZDU-TP) is known to be the active form of the
compound inhibiting HIV-1 and simian immunodeficiency virus (SIV) reverse transcriptase at concentrations of 5.9 and 4.1 μM, respectively (Eriksson et al., 1989). In rat hepatocytes, AZDU has been shown to be metabolized to 3'-azido-2',3'-dideoxyuridine (AMDU), through an azido reduction pathway similar to other 3'-azido-2', 3'-dideoxyxinosines and AZDU-glucuronide (GAZDU) (Cretton et al., 1992). Preclinical studies have demonstrated that the pharmacokinetic characteristics of AZDU and AZT were similar in mice, rats and rhesus monkeys (Doshi et al., 1989; M anouilov et al., 1995; Boudinot et al., 1990).

While the selective anti-HIV-1 activity of AZDU makes it a potential drug for AIDS therapy, preclinical and phase I clinical studies have shown that AZDU has a relatively short half-life and incomplete bioavailability. To improve its pharmacokinetic properties, a prodrug, 3'-azido-2',3'-dideoxyuridine-5'-O-valinate hydrochloride (AZDU-VAL) was synthesized. Figure 1 shows the chemical structures of AZDU and potential prodrug AZDU-VAL. This prodrug was designed based on the fact that 5'-L-valyl ester of acyclovir (L-Val-ACV) enhanced the uptake of ACV 10 times more than the parent drug and its D-isomer D-Val-ACV (Han et al., 1998a). In vitro studies using transfected Chinese hamster ovary (CHO) cells overexpressing the hPEPT1 transporter, L-Val-ACV showed strong affinity for the hPEPT1 transporter with an IC50 of 1.1 μM (inhibition of gly-sar uptake) in comparison with IC50 values of 15 µM for cephradine and 4.5 µM for enalapril (Han et al., 1998b). Furthermore, in vivo L-Val-ACV was well absorbed and rapidly converted to ACV in humans (Shao et al., 1994). More recently, Friedrichsen et al. (2002) demonstrated that L-Val-ACV was a substrate for the oligopeptide transporter in Caco-2 cells, thus explaining its higher than expected oral bioavailability. The purpose of this study was to characterize the preclinical pharmacokinetics of AZDU and prodrug AZDU-VAL following intravenous and oral administration to rats.

Materials and methods

Chemicals

3'-Azido-2',3'-dideoxyuridine (AZDU) was synthesized as previously described (Chu et al., 1989). Internal standard, 2',3'-dideoxy-2'-deoxythymidine (D4T), was obtained from Sigma Chemical Co. (St Louis, Mo., USA). The chemical purity of AZDU, AZDU-VAL and D4T, confirmed by spectral and high performance liquid chromatography (HPLC) analysis, was greater than 98%. AZDU was dissolved in 0.1N sodium hydroxide in physiological saline for intravenous administration. For oral administration of AZDU and intravenous and oral administration of AZDU-VAL, compounds were dissolved in phosphate-buffered saline, pH 7.4. A cetonitrile (HPLC grade) and all other chemicals (reagent grade) were obtained from JT Baker (Phillipsburg, NJ, USA).

Synthesis of 3'-azido-2',3'-dideoxyuridine-5'-O-valinate hydrochloride

Melting points were determined on a M el-tamp II and are uncorrected. ‘H NMR and 13C NMR spectra were recorded on a Bruker 400 A M X spectrometer for 400 MHz with Me4Si as internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br s (broad singlet). Optical rotations were performed on a Jasco DIP-370 Digital Polarimeter. TLC were performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using either silica gel 60 (220–440 mesh) for flash chromatography or silica gel G (TLC grade >440 mesh) for vacuum flash column chromatography. UV spectra were obtained on a Beckman DU-850 Spectrophotometer. Elemental analysis was performed by Atlantic Microlab Inc., Norcross, Ga, USA. DMAP (86.5 mg, 0.7 mmol), N-t-Boc valine (1.5 mg, 7 mmol) and DCC (2 g, 9.7 mmol) were added to a solution of AZDU (1.25 g, 4.95 mmol) in DMF (25 ml). After completion (ca. 48 h), the reaction mixture was filtered and the filtrate was concentrated to dryness in vacuo. The residue was dissolved in CH2Cl2, washed with water (≥50 ml), sat. NaHCO3 solution (250 ml) and dried over MgSO4, then purified by silica gel chromatography using 0–2% MeOH/CH2Cl2 to give 5'-O-N-t-Boc valiny-3'-azido-2',3'-dideoxyuridine (I) as a white solid (2 g, 89%): [α]25 D 34.2° (c 0.6, MeOH); UV (MeOH) λmax 260 nm (log ε 3.8); 1H NMR (CDCl3, δ 1H) 8.4 (s, 1H), 7.50 (d, J=7.9 Hz, 1H), 6.11 (t, J=6.0 Hz, 1H), 5.84 (d, J=7.8 Hz, 1H), 4.97 (d, J=8.8 Hz, 1H), 4.22–4.11 (m, 4H), 2.52 (m, 1H), 2.34 (m, 1H), 1.44 (s, 9H), 0.99 (d, J=6.8 Hz, 1H); 13C NMR (CDCl3, δ 13C) 172.2, 162.5, 155.6, 149.7, 139.5, 130.7, 129.4, 111.5, 93.9, 88.4, 84.1, 75.0, 49.6, 42.4, 21.4, 13.3, 12.8, 11.5, 9.9, 9.5, 7.7, 3.5; MS m/z 629 (M+1).
In vitro stability studies

The in vitro stability of AZDU-VAL was assessed in buffer solutions at pH values of 2.6, 5 and 7.4. AZDU-VAL was dissolved in the buffers at a concentration 100 mg/ml. Buffer solutions were incubated at 37°C for at least 1 week before the study. Animal studies were approved by the University of Georgia Animal Care and Use Committee and conducted in accordance with guidelines established by the Animal Welfare Act and the National Institutes of Health Guide for the Care and Use of Laboratory Animals (National Research Council, 1996). Externally jugular vein cannulas were implanted under ketamine/xylazine (50:3:3.4 mg/kg) anesthesia the day before the experiment. Rats were fasted overnight; however, water was allowed ad libitum. The animals were randomly divided into groups of four each. A randomized oral/intravenous crossover study design with two dosing periods and a 4-day washout period between doses was used. To assess the oral bioavailability of AZDU, two doses of the nucleoside analogue were administered by intravenous bolus injection and oral gavage. One group of rats received a dose 25 mg/kg of AZDU while another was administered 100 mg/kg. To evaluate the prodrug, animals received a 100 mg/kg dose of AZDU-VAL orally by gavage and a 75 mg/kg dose intravenously by 5 min infusion. Compounds were administered intravenously via a jugular vein cannula or orally by gastric gavage. Following dosing, the animals were housed in metabolism cages. Blood samples (0.3 ml) were collected prior to and at 0.083, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8 h after drug administration from the cannulas into tubes that contained 1.8 ml 2 M ice-cold acetonitrile.

Analytical methodology

Concentrations of AZDU-VAL and AZDU were determined by reverse phase high performance liquid chromatography (HPLC). Plasma samples with 50 µl internal standard (D4T, 20 mg/ml) were added to tubes containing 1.8 ml 2 M ice-cold acetonitrile. Tubes were vigorously mixed for 30 seconds and centrifuged at 4500 g for 30 min. The supernatant was transferred to a clean tube and dried by nitrogen stream. The residual film was reconstituted with 75 µl HPLC water and 50 µl was injected onto the HPLC. Separation was achieved using a Hypersil ODS column (150x4.6 mm, 5 µm particle size, Alltech Associates, Deerfield, Ill., USA) and a mobile phase consisting of 5% acetonitrile in 40 µM sodium phosphate monobasic, pH 5.0 (v/v) at a flow rate of 2 ml/min. The compounds were quantitated at an UV wavelength of 261 nm. The retention times for AZDU-VAL, AZDU and internal standard were 46, 17.5 and 9.6 min, respectively.

Standard curves ranging from 0.5 to 25 µg/ml for AZDU-VAL and 0.1 to 50 µg/ml for AZDU were pre-
pared in blank rat plasma. AZDU-VAL and AZDU concentrations in the samples were calculated from the slope of calibration plots of the peak area ratio of drug/internal standard versus standard drug concentrations. A weighing factor of 1/concentration was used for standard curve regression analysis. Standard curves were linear in the range of 0.5 to 25 µg/ml for AZDU-VAL and 0.1 to 50 µg/ml for AZDU with the limits of quantitation 0.5 and 0.1 mg/ml, respectively. The intra- and inter-day coefficients of variation over the range of the standard concentrations were less than 10%. Extraction recoveries of AZDU-VAL, AZDU and internal standard D4T were greater than 85%.

Pharmacokinetic analysis
Pharmacokinetic parameters were determined by area-moment analysis. The maximum plasma concentrations (Cmax) and the time to achieve maximum concentrations (tmax) were determined from observed data. The area under the plasma concentration versus time curve (AUC) and the first moment (AUMC) were calculated by Lagrange polynomial interpolation from time zero to the last measured sample time, with extrapolation to time infinity by using the terminal slope (λz) (Rocci & Jusko, 1983; Yeh & Kwan, 1978). Total clearance (CL) was calculated from Dose/AUC. Mean residence time (MRT) was calculated from CL×MRT. The terminal phase half-life (t½) was calculated from 0.693/λz. The oral bioavailability (F) of AZDU was calculated from (AZDUpo/AZDUiv)×100%. Statistical analysis was performed using a one-way analysis of variance comparing the pharmacokinetic parameters. A probability level of less than 0.05 was considered statistically significant.

Results
The octanol/water partition coefficients were 0.01 for AZDU-VAL and 0.43 for AZDU, suggesting that AZDU-VAL is much more hydrophilic than parent drug AZDU. The in vitro chemical stability of AZDU-VAL was assessed in buffer solutions at pH 2.6, 5, and 7.4. AZDU-VAL did not demonstrate any significant degradation over the 204 h incubation period (t½=477 days) at pH 2.6. At pH 5 and pH 7.4, AZDU-VAL degraded slowly with half-life values of 30 days and 25 days, respectively.

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Mean plasma AZDU concentration versus time profiles following intravenous and oral administration of 25 and 100 mg/kg to rats are illustrated in Figure 2. Plasma concentrations of AZDU declined rapidly in an apparent biexponential fashion at both doses. The AUC increased disproportionally with dose (Table 1). The dose-normalized AUC after 100 mg/kg (1.6±0.07 µg.h.ml⁻¹·mg⁻¹·kg⁻¹) was approximately twice as high as after the lower dose of 25 mg/kg (0.8±0.05 µg.h.ml⁻¹·mg⁻¹·kg⁻¹). This difference was statistically significant. A significant twofold decrease in CL of AZDU as the dose increased from 1.4 L.h⁻¹·kg⁻¹ at 25 mg/kg to 0.7 L.h⁻¹·kg⁻¹ at 100 mg/kg was observed. Following a dose of 25 mg/kg, approximately 69% of the nucleoside was excreted unchanged in urine, whereas 44% was excreted unchanged following administration of 100 mg/kg AZDU. Renal clearance of AZDU decreased from 0.9 L.h⁻¹·kg⁻¹ following administration of 25 mg/kg AZDU to 0.4 L.h⁻¹·kg⁻¹ at a dose of 100 mg/kg. There was no significant difference in

| Table 1. Mean (SD) pharmacokinetic parameters of AZDU following intravenous (iv) and oral (po) administration of 25 mg/kg and 100 mg/kg AZDU to rats |
| --- | --- | --- | --- |
| Dose (mg/kg) | iv | 25 | 100 |
| Cmax (µg/ml) | – | 9.2±1.9 | 41±5.5 |
| Tmax (h) | – | 0.38±0.13 | 0.63±0.22 |
| AUC (µg.h/ml) | 175±10.7 | 123±0.54 | 70±1.3 |
| CL (L.h⁻¹·kg⁻¹) | 1.4±0.2 | 0.5±0.27 | 0.43±0.12 |
| CLR (L.h⁻¹·kg⁻¹) | 0.48±0.15 | 0.27±0.05 | – |
| Vss (L/kg) | 0.76±0.16 | 0.34±0.11 | – |
| MRT (h) | – | 60±0.3 | 46±0.5 |
| F (%) | – | 1.0±0.4 | 1.1±0.4 |

Dissimilar letter superscripts indicate statistically significant difference (P<0.05); iv, intravenous; po, oral.
Pharmacokinetics of AZDU-VAL

The CLss of AZDU between the lower and higher doses. The steady-state volume of distribution of AZDU also decreased significantly as the administered dose increased (Table 1). Due to comparable changes in clearance and volume of distribution, however, there were no statistically significant differences found between values of the terminal disposition half-life.

The Cmax values were 9.2 ±1.9 µg/ml following 25 mg/kg dosing and 41 ±19 µg/ml following oral administration of 100 mg/kg AZDU. The tmax values were 0.38 ±0.13 h and 0.63 ±0.22 h following oral administration of 25 and 100 mg/kg AZDU, respectively. As dose increased, dose-normalized AUC values showed a marked increase similar to that observed after intravenous administration. Following oral administration of 25 mg/kg and 100 mg/kg AZDU, the AUC values increased from 12 to 70 µg.h/ml. The oral bioavailability estimates of AZDU from the AUC values obtained after the crossover studies at doses of 25 and 100 mg/kg were 60% and 48%, respectively. These values were not statistically significantly different, and the average of AZDU oral bioavailability was 53%.

Mean dose-normalized plasma concentrations of AZDU-VAL and AZDU derived from AZDU-VAL as a function of time following intravenous and oral administration of 75 mg/kg and 100 mg/kg of the prodrug, respectively, are illustrated in Figure 3. Concentrations of AZDU-VAL in plasma after intravenous and oral administration declined rapidly such that the prodrug became undetectable shortly after dosing. AZDU-VAL plasma concentrations were detectable up to 5 min after intravenous administration and for 45 min after oral administration. Due to the rapid elimination of AZDU-VAL after both intravenous and oral administration, it was not possible to calculate pharmacokinetic parameters accurately for the prodrug. Maximum dose-normalized concentrations of AZDU (Cmax) ranging from 0.53 to 0.67 µg.ml-1.mg-1.kg-1 were achieved 5 min after intravenous administration. AZDU plasma concentrations declined in an apparent biexponential manner with terminal phase half-life of 8.8 ±4.4 h. Intravenous administration of AZDU-VAL produced a dose-normalized AUC value for AZDU (0.55 ±0.51 µg.h.ml-1.mg-1.kg-1) similar to that seen when AZDU itself was administered (0.52 ±0.08 µg.h.ml-1.mg-1.kg-1). Following oral administration of 100 mg/kg AZDU-VAL, AZDU rapidly achieved a maximum concentration (Cmax) of 0.24 ±0.07 µg.ml-1.mg-1.kg-1 at tmax 0.35 ±0.14 h (Table 2). The area under the AZDU plasma concentration versus time curve following oral administration was 0.42 ±0.18 µg.h.ml-1.mg-1.kg-1. Thus, the apparent bioavailability (FAZDU) of AZDU following oral administration averaged 101%. FAZDU was nearly double that obtained by directly administering AZDU in rats (53%). The bioavailability of AZDU following intravenous administration of AZDU-VAL averaged 106%.

Discussion

3′-Azido-2′,3′-dideoxyuridine (AZDU) is a nucleoside analogue demonstrating potent anti-HIV activity in cell culture (Schinazi et al., 1987) Anti-human immunodeficiency virus (HIV-1) activity of 3′-azido-2′, 3′-dideoxyuridine in different cell lines (Chu et al., 1989). However, studies in...
animal models such as mice and rhesus monkeys, as well as studies in humans, showed that AZDU has a relatively short half-life as well as incomplete oral bioavailability (Doshi et al., 1989; Manouilov et al., 1995; Boudinot et al., 1990; Chu, unpublished results). As a continuation of the development of prodrug strategies to improve the pharmacokinetic profile of AZDU, 3′-azido-2′,3′-dideoxyuridine-5′-O-valinate hydrochloride (AZDU-VAL) was recently synthesized as a novel prodrug of AZDU by esterifying the 5′-OH function of the parent compound. Previous studies have reported that prodrugs of AZDU through esterification of the 5′-OH function of pyrimidine nucleoside analogues with various aliphatic acids showed improved pharmacokinetic distribution such as enhanced brain and lymphatic delivery and extended half-lives compared to that of parent drug AZDU (Doshi et al., 1993). The purpose of this study was to characterize the preclinical pharmacokinetics of AZDU-VAL following intravenous and oral administration to rats.

As a prelude to examining the pharmacokinetics of AZDU-VAL, the disposition of AZDU following intravenous and oral administration at two doses in the rat animal model was first characterized. The pharmacokinetics of AZDU were found to be dose dependent. Previous studies in rats demonstrated a dose-dependent disposition of AZDU following intravenous administration at doses of 10, 50, 100 and 250 mg/kg. The AUC increased proportionally with doses up to 100 mg/kg; however, the dose-normalized AUC after 250 mg/kg was 1.5-fold greater than that after the lower doses, indicating a linear kinetics over the dose range of 10-100 mg/kg (Boudinot et al., 1991). The reason that nonlinear pharmacokinetics were observed at dose 100 mg/kg in this study is likely due to the difference in the manner in which the animals were dosed. In the previous study, AZDU was administered over a 15-min infusion, whereas in this study the compound was administered as a bolus dose. As a result, a high initial drug concentration following administration of 100 mg/kg AZDU in the present study was comparable to that found in the previous study at 250 mg/kg. Consistent with previous studies (Boudinot et al., 1991), saturation of the active renal tubular secretion, as evidenced by a reduced renal clearance at the higher dose, was the primary cause of the observed dose dependent pharmacokinetics. There was no significant difference in the CL₁₈ of AZDU between the lower and higher doses, indicating that metabolism or other non-renal routes of elimination were not saturated.

Following oral administration of 25 mg/kg and 100 mg/kg AUC values increased more than proportionally. The non-linearity of the increase in AUC is likely due to non-linear clearance as observed with the intravenous dosing. Generally an increase in AUC following oral dosing

![Figure 3. Mean dose-normalized plasma concentrations of AZDU-VAL and AZDU following administration](image-url)
which is greater than dose proportional is more likely to be attributable to a decrease in elimination than to an increase in absorption (Lin, 1994). The half-life (t_{1/2}) was approxi-
matel 1 h for both doses. The oral bioavailability esti-
mates of AZDU at doses of 25 and 100 mg/kg averaged 53%. This is somewhat lower than the 76% oral bioavail-
ability reported in mice (Manouilov et al., 1995). In rhesus monkeys, the oral bioavailability of AZDU was dose depend-
ent, with F values ranging from greater than 90% fol-
lowing administration of 33 mg/kg to less than 50% fol-
lowing 200 mg/kg (Boudinot et al., 1990).

AZDU-VAL is a salt form of parent nucleoside (Figure 1), therefore it is markedely more water soluble. The pro-
drug was highly stable at physiological pH values. To assess the pharmacokinetics and biotransformation of AZDU-
VAL to AZDU, the prodrug was administered intra-
venously and orally to rats. O wing to the linear dispo-
sition of AZDU, a somewhat lower dose of the prodrug
was given intravenously than was administered orally. Concentrations of AZDU-VAL in plasma after intra-
venous and oral administration declined so rapidly that the
prodrug became undetectable shortly after dosing. AZDU-
VAL plasma concentrations were detectable for 5 min after intravenous administration and for 45 min after oral admin-
istration. These in vivo results suggested AZDU-VAL was subject to rapid enzymatic metabolism. Since AZDU-VAL is an ester of AZDU through esterification of the 5'-OH function, it is likely to be hydrolyzed by the carboxylesterase exis-
ting in the rat blood and liver. It has been reported that
esters with lower carbon chain length from C2 to C5 were
existing in the rat blood and liver. It has been reported that
function, it is likely to be hydrolysed by the carboxylesterase

Table 2. Mean±SD pharmacokinetic parameters of
AZDU derived from the prodrug AZDU-VAL (AZDUpro)*

<table>
<thead>
<tr>
<th>Parameter</th>
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<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>75</td>
<td>100</td>
<td>100</td>
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<tr>
<td>t_{1/2} (h)</td>
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<td>0.35±0.14</td>
<td>0.08±0.00</td>
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<tr>
<td>C_{max} (µg/ml)</td>
<td>0.69±0.07</td>
<td>24±6</td>
<td>-</td>
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<tr>
<td>AUC (µg.h/ml)</td>
<td>41±8</td>
<td>42±8</td>
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</tr>
<tr>
<td>t_{max} (h)</td>
<td>7.7±2.8</td>
<td>8.8±4.4</td>
<td>1.5±0.79</td>
</tr>
<tr>
<td>F (%)</td>
<td>106</td>
<td>101</td>
<td>100</td>
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*In comparison to those obtained when AZDU was administered
intravenously.

In summary, following intravenous bolus injection, the
disposition of AZDU in rats was dose dependent over the
range of 25–100 µg/kg. Bioavailability of AZDU following
oral administration averaged 53% and was dose indepen-
dent. The prodrug AZDU-VAL was rapidly and efficiently bi-
converted to parent nucleoside drug AZDU after intra-
venous and oral administration to rats. AZDU plasma con-
centrations were above the EC50 value (0.046–0.12 mg/ml)
for up to at least 8 h and 10 h, following intravenous and oral
administration of AZDU-VAL of 75 and 100 mg/kg, respec-
tively. The significant increases in oral bioavailability make
AZDU-VAL a promising prodrug of AZDU.

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References


