Pharmacokinetics and Disposition of 3-Deazauridine in Humans

John A. Benvenuto, Stephen W. Hall, David Farquhar, David J. Stewart, Robert S. Benjamin, and TI Li Loo

Department of Developmental Therapeutics, The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, Houston, Texas

ABSTRACT

3-Deazauridine (3-DAU) pharmacology was studied in 20 patients who received the drug by rapid or continuous infusion. In 8 studies, the plasma clearance of 3-DAU after rapid administration was biphasic, with an average terminal t1/2 of 4.4 hr and an extrapolated volume of distribution of 0.57 liter/kg. After 5-day continuous infusion of 3-DAU, the plasma clearance was also biphasic, with an average terminal t1/2 of 21.3 hr and an extrapolated volume of distribution of 18.8 liter/kg. 2,4-Dihydroxypyridine, the aglycone of 3-DAU, was observed in plasma but not in urine of patients receiving the drug by rapid infusion. The urinary excretion of 3-DAU was low, only 7.8% 24 hr after rapid infusion and 7.2% up to 4 days after continuous infusion. Tissue distribution of 3-DAU was determined from autopsy samples of 2 patients. Not only were high levels of 3-DAU detected in the tissues studied, but 3-DAU triphosphate, the active metabolite of 3-DAU, was present in brain, lung, and liver.

INTRODUCTION

3-DAU, a uridine analog, is currently undergoing Phase 1 clinical trials as an antitumor agent. It is marginally active against L1210 leukemia in the mouse, but highly active against L1210 resistant to 1-β-D-arabinofuranosylcytosine (1, 4), producing many long-term survivors in mice bearing the latter tumor.

Although an inhibitor of nucleic acid synthesis, 3-DAU is not incorporated into DNA or RNA (5). However, intracellularly 3-DAU is readily converted to its triphosphate, which is a potent, competitive inhibitor of cytidine triphosphate synthetase (3).

Clinical pharmacokinetic studies using [3H]3-DAU showed that the drug has a terminal plasma t1/2 of 8.0 hr when administered by i.v. infusion at doses of 10 to 1200 mg/sq m (2). The urinary excretion of radioactivity was about 90% in 48 hr, and at least 90% of the radioactivity was metabolized with 10 M KOH. The KCIO4 was removed by centrifugation, the supernatants were combined and neutralized with 10 M KOH. The KCIO4 was removed by centrifugation and the samples analyzed by HPLC.

HPLC Analysis. A Waters Associates Model ALC 202/401 liquid chromatograph equipped with a Model 6000 solvent delivery system, a U6K septumless injection valve, and a Schoeffel SF-770 variable wavelength UV detector was used. Peak areas were determined by a Model 5000 solvent delivery system, a U6K septumless injection valve, and a Schoeffel SF-770 variable wavelength UV detector was used. Peak areas were determined by a Columbia Scientific Model CSI 38 integrator; standard curves, prepared by plotting peak areas against drug concentration, were linear for biological fluids at the concentrations under investigation. 3-DAU concentrations in plasma, urine, and tissue extracts were determined by using a Waters Associates µBondapak/C8 reverse phase column with a 0.1 m acetate buffer, pH 4, as eluent at a flow rate of 2 ml/min. Nucleotides in the tissue extracts were determined on a Whatman Partisil-10 Strong Anion Exchange column (2). 3-DAU concentrations in plasma, urine, and tissue extracts were determined by using a Waters Associates µBondapak/C8 reverse phase column with a 0.1 m acetate buffer, pH 4, as eluent at a flow rate of 2 ml/min. Nucleotides in the tissue extracts were determined on a Whatman Partisil-10 Strong Anion Exchange column by using a 40-min linear gradient from 0.005 M (NH4)H2PO4, pH 2.8, to 0.75 M (NH4)H2PO4, pH 3.8, at 2 ml/min. 3-DAU concentrations in plasma, urine, and tissue extracts were determined by using a Waters Associates µBondapak/C8 reverse phase column with a 0.1 m acetate buffer, pH 4, as eluent at a flow rate of 2 ml/min. Nucleotides in the tissue extracts were determined on a Whatman Partisil-10 Strong Anion Exchange column by using a 40-min linear gradient from 0.005 M (NH4)H2PO4, pH 2.8, to 0.75 M (NH4)H2PO4, pH 3.8, at 2 ml/min.

Pharmacokinetic Calculations. Pharmacokinetic parameters were determined by the following equations:

\[ C_p = A e^{-at} + B e^{-bt} \]

Terminal plasma half-life,
RESULTS

Chart 1 shows a chromatogram of patient plasma after administration of 3-DAU. The drug was well separated from endogenous constituents in both plasma and urine. In addition, in plasma of patients receiving rapid infusions of high doses of 3-DAU, 2,4-DHP, the aglycone of 3-DAU, was observed. Nucleotide analyses of autopsy samples were achieved by anion exchange; DTP, the active metabolite of 3-DAU, eluted after ATP (Chart 2) and was easily identified.

In contrast to previous studies, the urinary excretion of 3-DAU was low, amounting to 7.8% of the administered dose 24 hr after rapid infusion in 7 patients and only 7.2% up to 4 days after 5-day continuous infusion (Table 1). No metabolites of 3-DAU were observed in the urine of any patient treated with 3-DAU.

The postinfusion plasma 3-DAU concentrations in one patient after rapid infusion of 4.8 g/sq m and in another patient after a 5-day continuous infusion of 1.5 g/sq m are shown in Chart 3. The plasma clearance of 3-DAU was biphasic after both rapid and continuous infusion; however, differences in pharmacokinetics were evident (Table 1). The terminal $t_{1/2}$, extrapolated volume of distribution, and plasma clearance are all much greater after continuous infusion. The variations in the pharmacokinetic parameters may reflect variations in renal and hepatic function. In fact, the terminal $t_{1/2}$ of 3-DAU in a patient with poor liver and kidney function who received 6 g/sq m of the drug by rapid infusion was 58 hr, and plasma clearance was only 0.38 liter/hr.

The time required to achieve constant levels of 3-DAU during continuous infusion is shown in Chart 4. This graph represents the average plasma 3-DAU levels in 3 patients receiving 1.5 g/sq m/day for 5 days. The constant level of 0.056 $\mu$mol/ml was reached in about 15 hr.

In one patient who was studied after each of 2 courses given by continuous infusion there were no differences between the postinfusion pharmacokinetics. In a second patient studied after 2 continuous infusion courses, however, there were significant differences in the plasma drug kinetics. Not only was the $t_{1/2}$ greatly decreased, but the concentration × time product and extrapolated volume of distribution were much lower after the second course. This patient had improved liver function prior to the second course. There were no differences in the initial plasma concentrations in a third patient after 3 doses of 3-DAU were given by rapid infusion.

The plasma levels of 2,4-DHP in 1 patient after rapid infusion of 5 g/sq m are shown in Chart 5. The average plasma $t_{1/2}$ of this metabolite was 33 hr in 4 patients.

The tissue distribution of 3-DAU and its active metabolite

\[
t_{1/2} = \frac{\ln 2}{\beta}
\]

Area under plasma concentration curve,

\[
C \times t_e = \frac{A}{\alpha} + \frac{B}{\beta}
\]

Extrapolated volume of distribution,

\[
V_{de} = \frac{Dose}{B}
\]

Total plasma clearance,

\[
Cl_T = \frac{Dose}{C \times t_e}
\]
Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rapid infusion (8)</th>
<th>Continuous infusion (8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (g/ sq m)</td>
<td>1.5-5.3</td>
<td>21.3</td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>4.4</td>
<td>8.0-44.8</td>
</tr>
<tr>
<td>Vde (liters/ kg)</td>
<td>0.57</td>
<td>18.8</td>
</tr>
<tr>
<td>Clf (liters/hr)</td>
<td>3.7</td>
<td>56.5</td>
</tr>
<tr>
<td>Excretion (%)</td>
<td>7.8</td>
<td>5.8-38.1</td>
</tr>
</tbody>
</table>

Means and ranges of postinfusion pharmacokinetic parameters after rapid and continuous infusions of 3-DAU. Urinary excretion is expressed as mean percentage of cumulative excretion in 6 patients 24 hr after rapid infusion and mean cumulative excretion in 5 patients 220 hr after the start of continuous infusion.

DTP were studied in 2 patients. Chart 6 shows the distribution of 3-DAU in tissues of a patient who had received 1 g/sq m/day of 3-DAU by continuous infusion; the samples were obtained at autopsy 60 hr postinfusion. Although the highest levels of drug concentration were found in kidney, there were significant concentrations of 3-DAU in brain. DTP was also present in the PCA extracts of brain tissue. The terminal plasma $t_{1/2}$ of 3-DAU in this patient was 18 hr, and the 3-DAU plasma concentration 10 hr before death was 3.8 μg/ml. The second patient had received 6 g/sq m of 3-DAU by rapid infusion and died 24 hr postinfusion. This patient had poor liver (bilirubin, 9.3) and kidney (creatinine clearance, 3) function; the plasma $t_{1/2}$ of 3-DAU was 58 hr. The tissue distribution of 3-DAU in this patient is shown in Chart 7. High-drug concentrations were detected in lung and liver tumors, however, DTP was detected only in normal lung and liver.

CSF concentrations of 3-DAU were determined in 2 patients on Day 4 of a 5-day continuous infusion of 1.5 g/sq m/day. In 1 patient, the CSF 3-DAU was 22% of the plasma concentration, while in the other it was 59% of the plasma level.
concentrations indicate that the drug is not accumulated and is rapidly cleared. These data and the low urinary excretion of unchanged drug in all patients suggest that hepatic clearance is the most important elimination pathway for 3-DAU.

Although 2,4-DHP, the aglycone of 3-DAU, was found in the plasma of patients receiving high doses of the drug by rapid infusion, it was not present in the urine. Presumably, 2,4-DHP was further metabolized to compounds that were not detectable by UV absorption.

Animal screening data suggest the use of 3-DAU for the treatment of leukemias; however, the presence of the drug and its active metabolite in brain and other tissues indicates the need for further trials of 3-DAU in the treatment of solid tumors.

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**REFERENCES**


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