Didanosine Pharmacokinetics in Patients with Normal and Impaired Renal Function: Influence of Hemodialysis


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The pharmacokinetics of didanosine were investigated following oral administration of a single 375-mg dose to eight human immunodeficiency virus-seropositive patients with normal renal function and eight human immunodeficiency virus-seropositive uremic patients. In uremic patients, the plasma half-life was longer than that in control patients (respectively, 4.5 ± 2.2 and 1.6 ± 0.4 h). The ratio of total plasma clearance to absolute bioavailability was four- to fivefold lower in uremic patients than in patients with normal renal function (respectively, 491 ± 181 and 2,277 ± 738 ml/min). Because of the decrease in elimination, concentrations in plasma were higher for uremic patients than for control patients; the maximum concentrations of drug in plasma were, respectively, 3,978 ± 1,607 and 1,948 ± 994 ng/ml; the areas under the concentration-time curve were, respectively, 14,050 ± 4,262 and 3,000 ± 956 ng · h/ml. Didanosine was removed by hemodialysis with an extraction ratio of 53% ± 8%, a hemodialysis clearance value of 107 ± 21 ml/min, and a fractional drug removal during a 4-h dialysis of 20% ± 8% of the dose. Dosage adjustments are necessary in uremic patients.

MATERIALS AND METHODS

Patients. Sixteen HIV-seropositive patients were studied. Each patient gave informed written consent for the study, which was approved by the Ethics Committee of the School of Medicine, University of Rouen, Rouen, France. The 16 patients were divided into two groups as follows, according to the status of their renal function. The control group was formed of eight patients (one female) with normal renal function (creatinine CL, 115 ± 22 ml/min/1.73 m²), ranging in age from 25 to 53 years (33 ± 10) and weighing from 52 to 75 kg (63 ± 8). The uremic group included eight patients (one female) with chronic severe renal impairment (creatinine CL, <2 ml/min/1.73 m²) treated by hemodialysis, ranging in age from 28 to 48 years (37 ± 8) and weighing from 45 to 69 kg (56 ± 8). These uremic patients were studied both between and during hemodialysis sessions.

Study design. After an overnight fast, the patients were given a single oral dose of 375 mg of didanosine (sealed-foil packets containing 375 mg of didanosine, 2.94 g of sodium citrate, 2.13 g of dibasic sodium phosphate, 0.12 g of citric acid, and 14.5 g of sucrose) with 120 ml of drinking water. The packets were provided by Bristol-Myers Squibb Company, Paris, France. Food was allowed at 3 h after dosing and at other normal meal times.

Blood samples (3 ml) were collected into lithium-heparinized Vacutainer tubes. For the control group, venous blood samples were drawn through an indwelling cannula prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 16, and 24 h after the dose.

The uremic patients were first studied between dialysis sessions; didanosine was administered the day before dialysis (30 h before the session), and blood samples were collected into the arteriovenous fistula just before didanosine administration and at 0, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 16, 24, and 30 h postdosing. One week later, the uremic patients received a second dose of didanosine on the day of dialysis. Blood samples

Didanosine (2',3'-dideoxynosine) is a purine nucleoside analog with in vitro activity against human immunodeficiency virus (HIV). Didanosine possesses a higher therapeutic ratio than zidovudine (3, 17, 20). The pharmacokinetics of didanosine were studied in patients with AIDS and AIDS-related complex during Phase I studies (9, 10, 13); bioavailability is 35 to 45% for doses of up to 10 mg/kg of body weight and 20 to 25% for doses of over 15 mg/kg; bioavailability is also dependent on oral-dosage forms and on conditions of administration such as the presence of food or antacids (10). Protein binding is less than 5%, and distribution volume is 50 to 60 liters/70 kg. After intravenous administration, 40 to 70% of the dose is excreted unchanged in urine; elimination is fast, with a half-life (t1/2) of 1.0 to 1.5 h; total plasma clearance (CL) and renal clearance (CLR) are 600 to 800 and 300 to 400 ml/min, respectively. Didanosine demonstrated linear pharmacokinetic behavior over the dose ranges of 0.4 to 16.5 mg/kg intravenously and 0.8 to 10.2 mg/kg orally.

In recent years, renal manifestations of AIDS and of drug abuse have assumed a particularly important role. Glomerulonephritis has emerged as a major cause of the nephrotic syndrome and of end-stage renal disease in metropolitan areas with large populations of patients with AIDS and addicts that account for about 10% or more of patients from 18 to 45 years old who are on dialysis programs (4, 6, 18).

The purpose of this study was to determine the pharmacokinetics of didanosine in patients with severe renal failure who received or did not receive hemodialysis treatment after a single oral dose of 375 mg. The results were compared with those from patients with normal renal function.

(This study was presented in part at the 31st Intercience Conference on Antimicrobial Agents and Chemotherapy in Chicago, Ill., 1991 [18a].)
were collected 0, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 7.5, and 8 h after drug administration; the 4-h hemodialysis session started 3 h after drug administration. During dialysis, blood samples were obtained each hour from the arterial line entering the dialyzer. In mid-dialysis, an additional venous blood sample leaving the dialyzer was drawn simultaneously with that entering the dialyzer. At this time, the ultrafiltration rate \( (Q_u) \) was recorded.

Immediately after blood collection, plasma was separated by centrifugation and stored frozen at \(-20^\circ\text{C}\).

Hemodialysis was performed for 4 h every 2 or 3 days with a double-needle access to an arteriovenous fistula and a single-pass dialysate delivery system with a constant dialysate flow rate of 500 ml/min. The blood flow that entered the dialyzer was kept constant between 250 and 300 ml/min. Details of the experimental conditions and the equipment used in the dialysis are given in Table 1.

During dialysis, hemodialysate samples (10 ml each) were obtained each hour.

For control patients, urine samples were collected before drug administration and during 3 periods, 0 to 12, 12 to 24, and 24 to 48 h, after drug administration. Urine samples were buffered with 200 mM potassium phosphate buffer (pH 8) (1 part urine to 2 parts buffer) to improve the stability of didanosine, which hydrolyzes rapidly under even mildly acidic conditions.

Dialysate and buffered urine samples were stored frozen at \(-20^\circ\text{C}\) until analyzed.

Assay method. Concentrations of didanosine in plasma, dialysate, and urine samples were determined by a specific reverse-phase high-performance liquid chromatography assay with detection by UV absorbance after solid-phase extraction according to the method described by Knupp et al. (14). Didanosine and internal standard (2',3'-dideoxy-3'-deoxythymidine) were supplied by Bristol-Myers Squibb Company (Syracuse, N.Y.).

The detection limits for plasma were 20 and 50 ng/ml in control and uremic patients, respectively, and 75 ng/ml for dialysate and 1 µg/ml for urine samples. Interday variabilities were 9% for spiked plasma concentrations of 200 and 1,200 ng/ml, 14 and 8% for spiked dialysate concentrations of 250 and 500 ng/ml, and 6 and 9% for spiked urine concentrations of 50 and 250 µg/ml.

Before analysis, all biological samples were heated at 57°C for 3 h to inactivate the HIV; this process does not alter didanosine (14).

Pharmacokinetic analysis. The data were analyzed by noncompartmental methods.

The terminal-phase rate constant \((\lambda_2)\) was determined by linear regression of the natural logarithms of the concentrations in plasma against time for the log-linear elimination phase, typically from 1 or 1.5 h through 8 h in control patients and from 2 or 4 h through 24 h in uremic patients.

Terminal \( t_{1/2} \) was calculated by the equation \( t_{1/2} = \frac{0.693}{\lambda_2} \).

Area under the concentration-time curve (AUC) was calculated by the trapezoidal rule from time zero to time \( t \) of the last sample and extrapolated to infinity according to the formula \( \text{AUC}_{\infty} = \frac{C_i}{\lambda_2} \), where \( C_i \) is the concentration of the drug in plasma in the last sample taken at a specified time.

The mean residence time (MRT) was calculated by the following formula (19):

\[
\text{MRT} = \frac{\int_0^\infty t\, c\, dt}{\int_0^\infty c\, dt}
\]

The total plasma CL was calculated as \( CL = \frac{F \cdot \text{dose}}{\text{AUC}} \), where \( F \) is the absolute bioavailability.

The apparent volume of distribution \((V_{\text{area}})\) was calculated by the formula \( V_{\text{area}} = \frac{CL}{\lambda_2} \).

Because \( F \) could not be measured in this study, only \( CL/F \) and \( V_{\text{area}}/F \) values are reported.

Peak concentration of drug in plasma \((C_{\text{max}})\) and time to peak concentration \((T_{\text{max}})\) were experimental values.

The fraction (\( F_p \)) of the dose of didanosine that was excreted unchanged in urine was calculated by the equation \( F_p = \frac{A_{\text{u}}}{Dose} \), where \( A_{\text{u}} \) is the total amount of unchanged didanosine excreted in 48 h.

\( CL_R \) was calculated according to the formula \( CL_R = \frac{A_{\text{u}}}{AUC} \).

The 4-h dialysis CL \((CL_{4h})\) was calculated by the following formula (7):

\[
CL_{4h} = \frac{Q_p C_A - (Q_p - Q_u) C_v}{C_A}
\]

where \( C_A \) and \( C_v \) are, respectively, the concentrations in plasma that entered and left the dialyzer; \( Q_p \) is the plasma flow that entered the dialyzer, derived from the blood flow, \( Q_u \) and the hematocrit \((Ht) [Q_u = Q_h (1 - Ht)] \); and \( Q_u \) is the ultrafiltration rate displayed on the dialyzer.

The dialyzer extraction ratio \((E)\) was \( E = CL_{4h}/Q_u \).

The amount of didanosine removed by a 4-h hemodialysis session was assessed by direct (X1) and indirect (X2) indices (15) as follows:

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**TABLE 1. Equipment and experimental conditions for hemodialysis of didanosine**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Membrane and area (dialyzer chamber)</th>
<th>Dialysate flow (ml/min)</th>
<th>Blood flow (ml/min)</th>
<th>Hematocrit</th>
<th>( Q_u ) (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Polysulfone, 1.1 m² (F 60, Fresenius)</td>
<td>500</td>
<td>250</td>
<td>0.24</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>Cellulose acetate, 1.6 m² (Ca 170, Baxter)</td>
<td>500</td>
<td>300</td>
<td>0.36</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>Cellulose acetate, 1.6 m² (Ca 170, Baxter)</td>
<td>500</td>
<td>300</td>
<td>0.27</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>Cuprophan, 1.2 m² (SN, Gambro)</td>
<td>500</td>
<td>300</td>
<td>0.22</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>Polysulfone, 1.1 m² (F 60, Fresenius)</td>
<td>500</td>
<td>250</td>
<td>0.30</td>
<td>10</td>
</tr>
<tr>
<td>6a</td>
<td>Polycrilonitrile, 1.2 m² (3000 S, Ospal)</td>
<td>500</td>
<td>300</td>
<td>0.23</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>Polysulfone, 1.1 m² (F 60, Fresenius)</td>
<td>500</td>
<td>250</td>
<td>0.29</td>
<td>40</td>
</tr>
<tr>
<td>8a</td>
<td>Polycrilonitrile, 1.2 m² (3000 S, Ospal)</td>
<td>500</td>
<td>300</td>
<td>0.36</td>
<td>17</td>
</tr>
</tbody>
</table>

*Patient underwent hemodiafiltration (hemodialysis plus hemofiltration).*
RESULTS

Mean concentrations in plasma versus time profiles of didanosine in controls and uremic patients between dialysis are shown in Fig. 1. Concentrations of didanosine in plasma were under the detection limit 10 h after drug administration for control patients and 24 h after administration for uremic patients.

The mean pharmacokinetic parameters for the two groups of patients are listed in Table 2.

The $t_{1/2}$ and MRT of didanosine were significantly longer in uremic patients than in control patients, and concentrations in plasma were significantly higher in uremic patients; AUC was $14,050 \pm 4,262 \text{ng} \cdot \text{h/ml}$ in uremic patients and $3,000 \pm 956 \text{ng} \cdot \text{h/ml}$ in patients with normal renal function.

In control patients, the amount of didanosine recovered in urine represented $12.4\% \pm 6.3\%$ of the administered dose and $CL_{ur}$ was $277 \pm 143 \text{mL/min}$. It should be pointed out that the variability in urinary excretion is high.

Figure 2 shows the mean concentrations of didanosine in plasma for uremic patients between and during hemodialysis; there was a slight rebound in concentrations in plasma after completion of dialysis.

On the day of dialysis, $C_{\text{max}}$ and $T_{\text{max}}$ values of didanosine were, respectively, $3,293 \pm 1,584 \text{ng/ml}$ and $1.2 \pm 0.5 \text{h}$. These values did not differ from those determined 1 week before, between dialysis sessions.

The parameters of didanosine dialysability are listed in Table 3. Hemodialysis CL was high ($107 \pm 21 \text{mL/min}$). The fractional drug removal indicates that $20\% \pm 8\%$ of the total pool of didanosine was removed during a 4-h hemodialysis session. The amounts of didanosine removed by dialysis computed from hemodialysis CL ($19.6 \pm 8.7 \text{mg}$) were in close agreement with those computed from dialysate concentrations ($21.4 \pm 11.1 \text{mg}$).

Between 3 and 7 h after drug administration, the $t_{1/2}$ (in) and $t_{1/2}$ (out) of didanosine were, respectively, $1.9 \pm 0.2 \text{h}$ and $2.6 \pm 0.5 \text{h}$ ($P < 0.01$).

The results of multiple-dose-simulated kinetics are summarized in Table 4: trough, average, and peak concentrations in plasma were calculated after 5 days of treatment with different dosage regimens.

DISCUSSION

Control patients. After a single oral dose of didanosine (375 mg), the plasma pharmacokinetic data are comparable to those obtained by other authors for HIV-seropositive patients without renal impairment (9, 10, 12, 13); however, the urinary excretion value was lower for our patients.
(12.4 ± 6.3% dose) than for the patients described in those reports (23% ± 4% for Knupp et al. [13] and 17% ± 8% for Knupp et al. [12]). We have no complete explanation for this discrepancy. Lower and variable urinary excretion values could be the consequence of the absorption variability; Hartman et al. [10] have shown that there is a wide range of variation in the bioavailability of didanosine, probably stemming from individual differences in gastric acid production and gastric emptying time.

Uremic patients. The $t_{1/2}$ of didanosine was increased in uremic patients, reaching values threefold higher than those obtained in patients with normal renal function; this is in agreement with the renal elimination of the drug, which accounts for 60% of the dose after intravenous administration (13). Assuming nonmodified bioavailability of didanosine in uremic patients, the volume of distribution was not modified by renal insufficiency and oral CL was four- to fivefold lower in uremic patients. This lower elimination rate leads to higher concentrations of didanosine in plasma for uremic patients: $C_{\text{max}}$ and AUC values are two- and fivefold higher in uremic patients than in control group patients.

A small rebound of plasma didanosine concentrations was observed in all patients at the end of hemodialysis. This phenomenon is known and usually appears for drugs with a large volume of distribution and high dialysis CL (15).

Didanosine was cleared by hemodialysis; $CL_{\text{HD}}$ (107 ± 21 ml/min) represents 40% of the $CL_{\text{R}}$ measured in patients with normal renal function. This dialysability is the consequence of the aqueous solubility, the low molecular mass (236 Da), and the small plasma protein binding (5%) of didanosine (8). However, the removal by dialysis is low: the proportion of the pool of didanosine in the body at the start of hemodialysis removed during a 4-h dialysis period was 20% ± 8% and, as shown Fig. 2, concentrations in plasma during and between dialysis are close. Consequently, a replacement dose is not necessary and the next scheduled dose should be administered after each dialysis session.

The dialyzability of didanosine is independent of mem-

![FIG. 2. Mean concentrations of didanosine (DDI) in plasma for uremic patients during (in) and between (out) dialysis.](image)

<table>
<thead>
<tr>
<th>TABLE 3. Parameters of didanosine dialysability</th>
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<tbody>
<tr>
<td>Patient no.</td>
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<tr>
<td>1</td>
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<td>3</td>
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<td>4</td>
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<td>5</td>
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<td>6</td>
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<tr>
<td>7</td>
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<tr>
<td>8</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>SD</td>
</tr>
</tbody>
</table>

$A_{\text{D}}$, afferent concentration.
$C_{A}$, efferent concentration.
$CL_{\text{HD}}$, hemodialysis CL.
$E$, dialyzer extraction ratio.
$f_{\text{HD}}$, fraction of drug removal.
Direct index is based on dialysate concentrations; indirect index is based on $CL_{\text{HD}}$.
$C_{E}$ could not be calculated [$f_{\text{HD}}(m) > f_{\text{HD}}(a)$].
No dialysate samples.
brane characteristics such as nature, area, or permeability. Hemodialfiltration (used for patients 6 and 8 from the uremic group), in which conventional hemodialysis and hemofiltration are performed simultaneously, does not enhance didanosine removal, despite the highly permeable polyacticrilonitrile membrane and the high Q_{df}.

**Therapeutic implication.** The 50% inhibitory concentration for in vitro HIV inhibition is approximately 1,000 to 2,000 ng/ml or 5 to 10 μM (3, 17). Because of the short plasma t_{1/2}, didanosine levels remained in this range for only 2 to 3 h in control patients and for 4 to 6 h in uremic patients after oral administration of 375 mg. Initially, it was believed that continuous intravenous infusion would be necessary to maintain effective levels of didanosine in plasma (9). However, subsequent studies revealed that dideoxycytidine triphosphate, the putative metabolite active against HIV reverse transcriptase, has an intracellular t_{1/2} of 12 to 24 h (1, 11) and that didanosine could be used once or twice daily (2).

So, on the basis of plasma pharmacokinetic data, this single-dose study shows that the dosage regimen of didanosine should be modified in patients with severe renal failure; in patients with normal renal function, the usual dose of didanosine is 375 mg every 12 h (3). Assuming linear kinetics after multiple administrations, the average steady-state concentration in plasma (C_{SS}), given by the formula C_{SS} = AUC/τ, will be about 250 ng/ml; the predicted C_{max} and minimal concentrations in plasma (C_{min}) will be 1,721 and 4 ng/ml, respectively. As the plasma drug concentrations are increased in uremic patients, the same dosage regimen will lead to the following increases in the steady-state plasma drug concentrations: C_{SS} = 1,171 ng/ml; C_{max} = 4,013 ng/ml; and C_{min} = 302 ng/ml.

According to Detti (5), to maintain the same average steady state in uremic patients as in control patients, the dosage regimen should be decreased by a theoretical factor of 4.7 (ratio of AUC in uremic and control patients). Such a reduction could be obtained with a maintenance dose of 160 mg administered every 24 h. This theoretical dose can be administered easily with the several didanosine dosages marketed either in sachet (45, 67, 100, 167, 250, and 375 mg) or in tablet (10, 25, 50, 100, and 150 mg) form. As shown in Table 4, a dosage regimen of 150 or 167 mg once a day in uremic patients will lead to concentrations in plasma very close to those observed in control patients with a dosage regimen of 375 mg every 12 h.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dosage regimen (mg/h)</th>
<th>C_{max} (ng/ml)</th>
<th>C_{SS} (ng/ml)</th>
<th>C_{min} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>375/12</td>
<td>1,721</td>
<td>250</td>
<td>4</td>
</tr>
<tr>
<td>Uremic</td>
<td>375/12</td>
<td>4,013</td>
<td>1,171</td>
<td>302</td>
</tr>
<tr>
<td></td>
<td>167/24</td>
<td>1,688</td>
<td>261</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>150/24</td>
<td>1,517</td>
<td>234</td>
<td>20</td>
</tr>
</tbody>
</table>

Because of drug removal by dialysis, didanosine should be administered at the end of a hemodialysis session.

**ACKNOWLEDGMENTS**

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**REFERENCES**


