Toxoplasma encephalitis is the most common cause of focal central nervous system lesions in human immunodeficiency virus (HIV)-infected patients (5). Primary treatment of an acute infection typically uses an initial sulfadiazine dose of 1,000 to 2,000 mg administered four times a day (QID) for 6 to 8 weeks, followed by 500 to 1,000 mg administered QID as maintenance, in combination with pyrimethamine (5). QID dosing of sulfadiazine has a large potential for nonadherence. The purpose of this study was to evaluate sulfadiazine pharmacokinetics in HIV-infected patients and to determine whether sulfadiazine administered twice daily (BID) achieves drug exposure comparable to that achieved by the standard QID regimen.

Subjects were enrolled if they had documented HIV infection, had a screening CD4 cell count of <500/mm³, were ≥18 years old, were not receiving therapy with a sulfonamide or an agent that affects sulfonamide metabolism, and had laboratory values within protocol-defined limits. Exclusion criteria included previous hypersensitivity to sulfonamides, current therapy for an opportunistic infection, active malignancy, and pregnancy. The design was a randomized, open-label crossover study in which each patient received two drug regimens: 1,000 mg of sulfadiazine QID for 4 days, followed by a morning dose on day 5, and 2,000 mg of sulfadiazine BID for 4 days, followed by a morning dose on day 5. There was a washout period between regimens of 5 days. Doses were administered in the BID regimen at 8 a.m. and 5 p.m. The QID regimen was given at 8 a.m., 12 p.m., 4 p.m., and 8 p.m.

Serial blood samples were drawn following administration of the morning dose on the fifth day after the initiation of each new regimen. Plasma samples were collected over 48 h and assayed by a validated high-performance liquid chromatography method (12).

Sulfadiazine concentration-time curves determined after administration of the last dose to 48 h were fitted to candidate pharmacokinetic models (WinNonLin; PharSight, Mountain View, Calif.). Model discrimination was done by Akaike’s information criterion and examination of actual and computer-fitted concentrations (residuals) (13). These parameters were then used to simulate full concentration-time curves for BID and QID dosing at steady state. The area under the concentration-time curve over a 24-h dosing interval at steady state (AUC) was calculated as the area under the fitted concentration-time curve. The maximum and minimum drug concentrations in serum (Cmax and Cmin, respectively) were determined directly from the concentration-time profiles. Data were log transformed for statistical analysis. Differences between AUC values were determined by two-way analysis of variance.

Eight subjects were enrolled in and completed the study. Their mean age was 43 years, and their ages ranged from 38 to 56. Seven patients were male. Four patients were African American, three were Caucasian, and one was Hispanic. The mean CD4 cell count at enrollment was 457/mm³, with a range of 222 to 835/mm³, and the median viral load was 1,368 copies/ml (range, <50 to 6,692 copies/ml). Three patients were coinfected with hepatitis B, and none was coinfected with hepatitis C. Three patients were at CDC stage A1, one was at stage A2, and two each were at stages B2 and C2. Six patients were receiving highly active antiretroviral therapy.

A one-compartment model with no lag time and 1/y² weighting provided the best fit of the sulfadiazine concentration data with a mean r² value of 0.99. Pharmacokinetic parameter estimates from the modeling of the sulfadiazine concentration data and parameters used for subsequent simulations for the two groups are given in Table 1. Simulated concentration-time profiles at steady state for both regimens are shown in Fig. 1. The simulated AUC and steady-state Cmax and Cmin were very similar between the two regimens. Elimination half-lives were also similar between groups, with a mean 11.9 h for BID dosing and 10.8 h for QID dosing. The small differences between the BID and QID dosing regimens were not statistically significant.
A trial is unlikely to be undertaken in developed countries, especially during the chronic maintenance (suppressive) phase of anti-Toxoplasma therapy. While a randomized trial comparing the relative efficacies of the two regimens is desirable, such a trial is unlikely to be undertaken in developed countries, given the costs and the difficulties in completing such a study in the era of highly active antiretroviral therapy. BID dosing of sulfadiazine was used in one recent study during maintenance therapy (9). Alternative regimens for sulfadiazine therapy with a twice- or thrice-weekly dosing regimen have been proposed to limit the incidence of adverse events and improve adherence. However, these regimens have generally not been shown to be as effective as daily administration (6, 8, 9).

The pharmacokinetics of sulfadiazine appear to lend themselves to a BID regimen. Sulfadiazine has an elimination half-life of 8 to 17 h (mean 10 h) in healthy volunteers, suggesting that a less frequent dosing regimen would not compromise efficacy (2). The in vitro IC$_{50}$ of sulfadiazine with pyrimethamine for Toxoplasma gondii is 0.5 ± 0.25 μg/ml (11). The mean trough concentrations in this study of HIV-infected patients were 56.8 and 66.7 μg/ml for the BID and QID regimens, respectively. These concentrations are well in excess of the IC$_{50}$, even considering the approximately 80% protein binding of sulfadiazine. Although this study only examined drug concentrations in plasma, it is reasonable to assume that drug concentrations in tissue would equilibrate with those in plasma at steady state.

A goal of this trial was to simulate the actual conditions for treatment of toxoplasmosis. Thus, we studied the pharmacokinetics of sulfadiazine in HIV-infected subjects since patients can have concentrations of some drugs in plasma that differ markedly from those of healthy volunteers (7, 10). We also studied a QID schedule of 8 a.m., 12 p.m., 4 p.m., and 8 p.m. and a BID schedule of 8 a.m. and 5 p.m. This mimics actual dosing times for patients since, in reality, they would be very unlikely to take a QID drug every 6 h. We therefore feel that the concentrations achieved in this trial are very similar to those that might be observed in patients undergoing treatment for toxoplasmosis.

The side effect of sulfadiazine include a hypersensitivity reaction of fever, rash, and pruritis that may occur in up to 30% of HIV-infected subjects (3). It can also cause gastrointestinal complaints, nephrotoxicity, and bone marrow suppression (1, 4). All patients tolerated both the BID and QID regimens well in this study; however, they only received 5 days of therapy on each regimen. On the basis of these data, it might be advantageous to begin with a BID sulfadiazine regimen and monitor the patient’s tolerance. If adverse events were dose limiting, then a QID regimen could be tried to reduce the peak concentration, and possibly the incidence of adverse events.

This study demonstrates that BID dosing of sulfadiazine produces drug concentrations in plasma that are similar to those achieved by QID dosing in HIV-infected patients. BID dosing of sulfadiazine may be a reasonable alternative to a QID regimen and may improve adherence to therapy.Clinicians may consider BID dosing in selected patients with close monitoring of efficacy and toxicity.

We thank the patients for their willingness to volunteer for this study and the physicians and nurses of the NIAID-CCMD intramural AIDS program for their dedication to patient care.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>AUC$_{ss}$ (μg · h/ml)</th>
<th>$C_{max}$ at steady state (μg/ml)</th>
<th>$C_{min}$ at steady state (μg/ml)</th>
<th>$K_{in}$ (h$^{-1}$)</th>
<th>$K_{out}$ (h$^{-1}$)</th>
<th>V/F$^d$ (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BID</td>
<td>1,247 ± 433</td>
<td>84.9 ± 23.5</td>
<td>56.8 ± 28.5</td>
<td>2.17 ± 3.11</td>
<td>0.058 ± 0.011</td>
<td>41.3 ± 9.4</td>
</tr>
<tr>
<td>QID</td>
<td>1,134 ± 477</td>
<td>76.2 ± 26.3</td>
<td>66.7 ± 22.9</td>
<td>2.08 ± 3.40</td>
<td>0.062 ± 0.016</td>
<td>39.2 ± 15.3</td>
</tr>
</tbody>
</table>

* Data are represented as means ± standard deviations. No significant differences were found between the BID and QID dosing regimens for any of the parameters by using Student’s paired t test.
* $K_{in}$, rate constant into central compartment.
* $K_{out}$, rate constant out of central compartment.
* V/F, volume of distribution.

FIG. 1. Twenty-four-hour mean fitted concentration-time profiles of BID and QID sulfadiazine dosing regimens.
REFERENCES