Indinavir Population Pharmacokinetics in Plasma and Cerebrospinal Fluid

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Plasma and cerebrospinal fluid (CSF) indinavir concentrations were measured by high-performance liquid chromatography. The median concentration in plasma exceeded that in CSF 10-fold. The modeled CSF curve was flat at 155 nM, and the estimated ratio of the areas under the CSF and plasma concentration-time curves was 6%. We conclude that CSF indinavir concentrations are lower than levels in plasma but exceed the clinical 95% inhibitory concentration range.

Combining nucleoside analogue reverse transcriptase inhibitors with protease inhibitors (PIs) can dramatically reduce viral replication, preserve immune function, and prolong survival. Combination regimens may also reduce human immunodeficiency virus (HIV) replication in the cerebrospinal fluid (CSF) (1, 6, 9, 13; M. Gisslen, L. Hagberg, B. Svennerholm, and G. Norkrans, Letter, AIDS 11:1194, 1997). However, the independent contribution of PIs to such reductions is unclear since PIs are highly protein bound and, therefore, may not reach therapeutic concentrations in the central nervous system (CNS) (1, 5). In fact, the failure of PIs to consistently control HIV replication in the CNS is supported by clinical studies (7; E. H. Gisolf, S. Juriaans, M. E. van der Ende, P. Portegies, R. Hoetelmans, and S. A. Danner, Sixth Conf. Retroviruses Opportunistic Infect., poster 403, 1999).

Among the currently available PIs, indinavir (IDV) binds the least to plasma proteins (~60%), which suggests that it may penetrate into the CNS well enough to be efficacious (8). Prior studies have demonstrated that IDV levels in CSF are similar to trough levels in serum (L. Stahle, C. Martin, J. O. Svensson, and A. Sonnerborg, Letter, Lancet 350:1823, 1997), very little over the dosing interval (Stahle et al., letter), and are similar to or exceed a 95% inhibitory concentration (IC50) range for clinical isolates (25 to 100 nM) (K. Brinkman, F. Kroon, P. W. Hugen, and D. M. Burger, Letter, AIDS 12:537, 1998; A. C. Collier, C. Marra, R. W. Coombs, L. Zhong, J. Stone, and B.-Y. Nguyen, IDSA 35th Annu. Meet., abstr., Clin. Infect. Dis. 25:S359, 1997). These studies estimated the CNS penetration of IDV by calculating the ratios of the concentrations in CSF and plasma. This method produces an estimate of drug exposure that is limited by its sensitivity to the interval between dosing and sample collection.

Since the ratio of the areas under the CSF and plasma concentration curves (AUCCSF/AUCplasma) accounts for variability over the entire dosing interval, it is a more accurate estimate of CSF penetration over time than the ratio of the concentrations in CSF and plasma (3, 8, 12). Martin and colleagues used pharmacokinetic modeling to support a role for active transport of IDV out of the CSF (9). In this study, we used population pharmacokinetic (PPK) methods to estimate the IDV AUCCSF/AUCplasma ratio.

Twenty-two matched CSF and plasma samples from 22 adults were selected from the specimen bank of the HIV Neurobehavioral Research Center. All patients were at steady state on IDV-containing antiretroviral regimens and were free of opportunistic conditions. All 22 subjects took 800 mg of IDV orally every 8 h with either stavudine-lamivudine (3TC) (13 of 22), zidovudine-3TC (7 of 22), stavudine-dideoxycytosine (1 of 22) or 3TC alone (1 of 22).

Blood and CSF samples were obtained within 2 h of each other. IDV levels were measured by high-performance liquid chromatography (HPLC) at Merck Research Laboratories (West Point, Pa.). The CSF assay was validated over the range of 2.8 to 2,800 nM and had a precision of <10% of the coefficient of variation. The plasma assay was validated over the range of 7 to 2,800 nM and also had a precision of <10% of the coefficient of variation. HIV RNA levels were measured by reverse transcription-PCR (AmpliC li; Roche Diagnostic Systems, Branchburg, N.J.) with a lower limit of quantitation of 50 copies/ml. Blood CD4 counts, CSF white blood cell counts, and protein levels in plasma and CSF were also determined.

PPK parameters were estimated with NONMEM software (2) using a two-compartment physiologic model (Advanz Trans1). Monte Carlo simulations were performed to estimate model-predicted quartile concentrations. Descriptive and analytical statistics were performed using JMP software (SAS Institute, Cary, N.C.).

All patients were male. Subjects had broad ranges of CD4 counts (49 to 847 cells/mm3; median, 243) and HIV RNA levels in CSF (1.7 to 3.8 log10 copies/ml; median, 1.7) and plasma (1.7 to 5.0 log10 copies/ml; median, 2.6). Levels of HIV RNA in plasma were approximately 1 log10 higher than in CSF, consistent with experience in larger studies (4, 10). The median CSF white blood cell count was 1 cell/mm3 (range, 1 to 5) and the median protein concentrations were 7,500 mg/dl in plasma (range, 6,100 to 9,000) and 38 mg/dl in CSF (range, 26 to 120).

Median IDV concentrations were 1,491 nM (range, 40 to 11,670) in plasma and 145 nM (range, 43 to 480) in CSF. Because of falling concentrations in plasma, the CSF/plasma IDV ratio increased across the dosing interval (median, 0.16; range, 0.004 to 2.28). PPK modeling (Fig. 1) estimated the maximum plasma IDV concentration to be 3,500 nM. The CSF curve was flat at approximately 155 nM, likely due to slow influx to and efflux from the CSF compartment. This concen-
FIG. 1. Plasma and CSF IDV concentrations by postdose time. Levels in plasma (circles) peaked within 2 h after dosing and then gradually declined over the remaining dosing interval. Levels in CSF (squares) remained flat, suggesting IDV influx and efflux were balanced. One patient who probably misreported his dosing time was excluded from the model. Modeled median IDV concentrations are represented by a solid (plasma) or dashed (CSF) line. Dotted lines represent the modeled curves for the 1st and 3rd quartiles.

The pharmacokinetic parameters and variability derived from the model were consistent with prior studies: CSF IDV levels varied little over the dosing interval and approximated the modeled minimum IDV concentration ($C_{min}$) in plasma at a dose of 800 mg every 8 h. Table 1 summarizes the pharmacokinetic parameters and intersubject variability for the model. The fraction of IDV that penetrated into CSF from plasma, an estimate of the AUCCSF/AUCplasma ratio, was 6% (95% confidence interval, 5 to 9%).

The data were well described by the model with no significant biases, and modeled estimates were similar to published data (9, 14), including substantial intersubject variability. Considering possible sources of biological, assay, and modeling variation, the calculated residual model errors were 25% for concentrations in plasma and 52% for concentrations in CSF.

All CSF IDV levels exceeded 25 nM and 12 of 22 (54%) exceeded 100 nM, the limits of the clinical IC95 range. CSF HIV RNA levels were less than 50 copies/ml in 15 of 22 samples (68%) at the time of collection. CSF HIV RNA detection was not associated either with the specific antiretroviral regimen or with CSF IDV levels in individual patients exceeding the upper limit of the clinical IC95 range.

Our findings are consistent with prior studies: CSF IDV levels varied little over the dosing interval and approximated both trough levels in plasma and the clinical IC95 range. Specifically, the modeled CSF PPK curve was flat at approximately 155 nM, a level that exceeds the upper limit of the clinical IC95 range by 55%. Despite this, the measured IDV concentrations in 10 of 22 (45%) patients were less than 100 nM. However, the clinical significance of this finding cannot be interpreted without directly measuring the IDV susceptibility of each patient’s CSF viral population.

Although our HPLC-based assay measured both free and protein-bound drug, only the unbound fraction has antiviral activity. However, the low CSF-to-plasma protein ratio (1:200) probably reflects a similar ratio of drug-binding proteins, such as α1-acid glycoprotein. With low levels of drug-binding proteins in CSF, the unbound fraction of IDV approximates the total measured concentration and may sometimes exceed the unbound fraction in plasma. For example, although the median concentration in CSF and the $C_{min}$ in plasma were both estimated in our model, the estimated unbound fraction in CSF (~100%, or 155 nM) exceeded the estimated $C_{min}$ in plasma (40% of 155 nM, or 62 nM) 2.5-fold.

We found that isolated CSF IDV/plasma IDV ratio measurements inadequately described CSF penetration since the ratios vary more than 100-fold depending on the postdose collection time. By estimating the AUCCSF/AUCplasma ratio through PPK modeling, we avoided the sampling bias inherent in this measure and demonstrated that CSF IDV concentrations exceed the clinical IC95 range even though only 6% of levels in plasma enter this compartment. These CSF levels are sustained throughout the dosing interval and may contribute to the antiretroviral activity of combination regimens that contain better-penetrating agents.

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TABLE 1. Pharmacokinetic parameters and intersubject variability

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Estimated value</th>
<th>Intersubject variability (%)</th>
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<tbody>
<tr>
<td>Volume of distribution (liters)</td>
<td>195</td>
<td>47</td>
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<tr>
<td>Elimination constant (h)</td>
<td>0.30</td>
<td>81</td>
</tr>
<tr>
<td>AUCCSF/AUCplasma (%)</td>
<td>6</td>
<td>14</td>
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<tr>
<td>Half-life (h)</td>
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<td>Apparent clearance (liters/h)</td>
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<tr>
<td>Plasma-to-CSF transfer constant (h)</td>
<td>&gt;0.35</td>
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<tr>
<td>CSF-to-plasma transfer constant (h)</td>
<td>&gt;0.35</td>
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</tbody>
</table>

* The pharmacokinetic parameters and variability derived from the model were within expected ranges.

REFERENCES


