Low Atazanavir Concentrations in Cerebrospinal Fluid

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Abstract

BACKGROUND: HIV Neurocognitive Impairment (HNC) is prevalent despite the use of antiretroviral therapy. Protease inhibitors (PI) are potent antiretrovirals but may have limited CNS penetration due to high plasma concentrations, which may allow ongoing replication and injury. Atazanavir (ATAV) is a commonly used PI, 100-fold lower than plasma concentrations, and therefore available to penetrate into the CNS. The objective of this study was to determine the penetration of ATV into cerebrospinal fluid (CSF). METHODS: CHARTER is an on-going, multi-center, observational study to determine the effects of potent antiretroviral therapy on HIV-associated neurological disease. Single random plasma and CSF samples were drawn within an hour of each other from subjects taking ATV-ritonavir between October 2003 and October 2005. Plasma samples were analyzed by sensitive enzyme immunoassay; lower limit of detection 45 ng/mL. CSF samples were assayed by immunoassay (ARK ATV-TestTM); lower limit of detection 5 ng/mL. Data were analyzed using summary statistics and linear regression. RESULTS: 57 participants (age 43 ± 8 years; 62 ± 13 % female; 26, Black; 14, Hispanic; 4, Asian; 4, Other; BQL per drug); 97 paired plasma and CSF samples were below detection. Eleven additional patients with plasma concentrations below 400 ng/mL had CSF samples below detection, as expected based on the observed plasma:CSF ratio. Plasma concentrations correlated with CSF concentrations (r=0.68). Plasma and CSF viral loads at the time of sampling were 2.5 ± 1 (1.9 ± 0.4) log10 copies/mL. CONCLUSIONS: ATV plasma and CSF concentrations are highly variable and are 100-fold lower than plasma concentrations, even with ritonavir boosting. Observed CSF concentrations were less than the estimated free concentration in plasma (~210 ng/mL), suggesting active transport out of the CSF. Increasing plasma exposure to ATV may increase ATV penetration.

Background and Objective

• HIV Neurocognitive Impairment is prevalent despite the use of combination antiretroviral therapy.
• Potent protease inhibitors (PI) may not penetrate into the CNS in therapeutic concentrations, which may allow ongoing replication and injury.
• In the ATARITMO-Study, 2 of 12 patients whose virus was suppressed in plasma developed measurable virus in CSF while on ATV maintenance therapy.

Methods

• CHARTER is an on-going, multi-center, observational study to determine the effects of potent antiretroviral therapy on HIV-associated neurological disease.
• Single random plasma and CSF samples were drawn within an hour of each other from subjects taking atazanavir (ATV) with or without ritonavir (RTV) between October 2003 and October 2005.
• Daily doses of ATV included 300–400 mg alone, and 300–400 mg with RTV
• Samples were assayed by rapid, automated enzyme immunoassays (ARK ATV-Tests™, ARK Diagnostics, Inc. Sunnyvale, CA).

Results

• 80 plasma and 76 CSF samples were evaluated from 57 participants (Table 1).
• CSF atazanavir concentrations were approximately 1% of the corresponding plasma concentrations (Table 2 & Figure 2).

Table 1. n (females/males)

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<tr>
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<th>Without RTV</th>
<th>With RTV</th>
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<tr>
<td>n</td>
<td>9 (8/1)</td>
<td>48 (48/0)</td>
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Table 2. Concentration of Atazanavir in CSF

<table>
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<tr>
<th>CSF Plasma Concentration</th>
<th>Atazanavir (ng/mL)</th>
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<tr>
<td>10, 20, 30, 40, 50</td>
<td>ATV in Plasma (ng/mL)</td>
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Figure 2. Figure 3.

• Atazanavir concentrations in the CSF are 100-fold lower than plasma concentrations, even with ritonavir boosting.
• Observed CSF concentrations are less than the estimated free concentration in plasma (~210 ng/mL), suggesting active transport out of the CSF.
• Increasing atazanavir plasma exposure may increase CSF penetration.
• Atazanavir CSF concentrations do not consistently exceed the wild-type IC50, and may not protect against HIV replication in CSF.

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