Poster 436

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Antiretroviral Concentrations in Brain Tissue Are Similar to or Exceed Those in CSF

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Objective

Measure ART drug concentrations in brain tissue collected from adults dying with HIV disease and compare them to published values for ART drug concentrations in cerebrospinal fluid (CSF).

Background

Limited distribution of many antiretroviral therapy (ART) drugs into the central nervous system (CNS) results in much lower drug concentrations in CSF than in blood. Estimates of CSF distribution have been linked to HIV RNA levels in CSF and neurocognitive performance but results can be inconsistent.

One possible reason for this inconsistency is that ART drug concentrations in CSF may not accurately reflect those in brain tissue. The objective of this analysis was to measure ART drug concentrations in brain tissue collected from adults dying with HIV disease and to compare them to CSF values.

References

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2. Best et al, J Antimicrobial Chemotherapy. 2011; 66(2): 354-7
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Results

	n	Overall	WM	GP	CGM
Atazanavir	2	< 25	< 25	< 25	< 25
Efavirenz	2	38.6	45.2	34.8	35.9
Emtricitabine	4	181.3	230.4	173.2	140.3
Lamivudine	3	196.9	205.5	209.8	175.4
Lopinavir	4	153.3	410.6	< 25	< 25
Tenofovir	6	206.0	220.0	212.1	185.8

Table. Summary of mean ART drug concentrations in samples from 3 brain regions (white matter (WM), globus pallidus (GP), and cortical gray matter (CGM)) as well as across all brain regions (Overall). Concentration units are ng/mL.

- **Demographics, disease, and treatment characteristics:** Subjects were mostly men (89%) of European ancestry (56%) with a mean age of 40.8 (SD 5.5). At the time of the last antemortem assessment, the duration of the current ART regimen was 2.2 years (SD 3.0).

  All subjects had AIDS at the time of death with an estimated duration of HIV disease of 14.6 years (SD 5.2) and a mean nadir CD4+ T-cell count of 34.6/μL (SD 39.5). The most common cause of death was pneumonia. The mean duration between death and tissue collection was 12.3 hours (SD 9.1).
- **Drug Concentrations:** ART drug concentrations in brain tissue are summarized in the Table. Concentrations of ATV[1], EFV[2], FTC[3], and 3TC[4] were similar to published concentrations in CSF but concentrations of TFV were higher than reported values in CSF[5]. LPV concentrations in brain tissue were also higher than reported in CSF[6] but only in WM.

  Drug concentrations appeared to vary by brain region: Across all drugs, concentrations were lower in CGM than in the other two regions (p=0.01, paired signed rank test).

Conclusions

- This is the first analysis of ART drug concentrations in human brain tissue.
- Concentrations of most drugs in this small analysis were similar to reported concentrations in CSF but tenofovir had higher concentrations than expected based on published reports of CSF concentrations.
- Regional variation in ART drug concentrations may be important for antiviral efficacy and toxicity.

Methods

Design: 9 HIV+ adults were evaluated in the California NeuroAIDS Tissue Network (CNTN) within 6 months of death; reported taking ART at that antemortem visit; and had detectable concentrations of at least one ART drug in serum at autopsy. Autopsies were performed within 30 hours of death. Brain tissue was collected and stored at -80°C.

Drug Concentration Assays: Concentrations of 6 ART drugs (atazanavir (ATV), efavirenz (EFV), emtricitabine (FTC), lamivudine (3TC), lopinavir (LPV), tenofovir (TFV)) were measured in 3 brain tissue regions (globus pallidus (GP), cortical gray matter (CGM), white matter (WM)) by high performance liquid chromatography-mass spectrometry with a lower limit of quantitation of 25 ng/mL.

Analysis: Drug concentrations were compared across brain regions using paired signed-rank tests.