Pharmacology of Antiretrovirals in Cerebrospinal Fluid

Dr. Letendre started his talk by analysing the principles of neuropathogenesis inducted by HIV infection and particularly the involvement of different types of cell (mainly perivascular macrophages and microglia). This last element and the protected anatomical site of central nervous system (CNS) can alter the response to antiretroviral drugs. Blood-brain barrier (BBB), blood-CSF barrier and low levels of drug binding proteins are the affecting element in the CNS and thus limit the passage of many drugs into this compartment. Furthermore pharmacokinetic studies are difficult to perform due to the limited accessibility of CSF and therefore population based PK studies (with sparse sampling strategies) are very useful in this setting. Dr. Letendre specifically showed the determinants of drug penetration across the BBB (figure 1).

Unbound concentrations in blood are one of the major determinants of drug available for action and transport and the data about darunavir were highlighted: unbound concentrations were lower than the total ones but were highly related to drug levels in the cerebrospinal fluid. Dr. Letendre then compared the free fractions of different drugs (and the protein binding of each one) to CSF-to-plasma-ratios: University of San Diego unpublished data are shown in figure 2 where drugs less bound have the highest ratios in the CSF.

The speaker reviewed literature data about the passage of different compounds. Abacavir (ABV) and Tenofovir (TDF) exposures were shown and compared to their in vitro IC50s: ABV penetration was 36% while TDF one was 5% of their respective plasma exposures. NNRTIs were then discussed: efavirenz low CSF penetration (0.5%) was compared to the drug IC50 (0.5ng/ml) thus revealing effective levels in most of the patients. Nevirapine passage ranged, in different studies, from 29 to 63% of plasma concentrations being one of the most penetrant drug in the antiretroviral armamentarium; Cmax and Cmin were several times above the IC50 (respectively 120 and 10 times the value) thus assuring a good pharmacokinetic profile. The same issue emerged for some ritonavir boosted protease inhibitors: as an example data about lopinavir were discussed. The drug passage is quite low (0.23%) but it seemed enough to guarantee CSF concentrations above the IC50 in most of the patients. Atazanavir (boosted or unboosted) was shown by Best and colleagues (AIDS 2009) to have a small CSF-to-plasma ratio (around 1%) and that many patients experienced suboptimal levels (and below the IC50 of 11...
ng/ml). The speaker then analysed some of the determinants of inter-individual variability in CSF concentrations referring to efavirenz (whose plasma concentrations seem to affect its tolerability and that are related to CSF ones) and raltegravir. In the last drug the passage through the blood brain barrier seem to be conditioned by the barrier integrity and thus to the albumin ratio.

The core of Dr. Letendre’s talk was the analysis of the CNS penetration-effectiveness score (CPE) that was published in 2008; the criteria underlying the ranking were discussed and pharmacokinetic, pharmacodynamic and clinical data were used. He showed the revised CPE score that has been modified, with larger patient included and new data available, to have 4 ranks (from 1 to 4) (figure 3).

This new ranking has a strong correlation with the proportion of detectable CSF viral loads thus being an useful tool to describe the effectiveness of HAART regimens in the central nervous compartment (figure 4); such a correlation was stronger when considering patients with undetectable viral load in plasma only.

Dr. Letendre explained the multiple mechanisms of brain damage that can be found in the HIV infection...
and the effect of antiretrovirals. The reduction of HIV replication in the CNS reduce the formation of neurotoxins and improve neuroprotection thus improving the cognitive health of patients; many comorbidities can contribute to the worsening of this damage. Several strategies (anti-inflammatory molecules, antioxidants, growth factors, natural progenitor cells) have been studied in order to improve neuroprotection but, so far, they have not shown any consistent advantage. The improvement of neuroeffectiveness of HAART regimens have been proven to be effective in some, but not all, studies and differences (prospective vs. retrospective) can partially explain these different outcomes. Nevertheless the CHARTER group has collected data, still unpublished, about higher neuropenetration and improved mood (even taking into account antidepressant use) and other groups on its association with better survival (among perinatally infected children and patients with opportunistic infections of the CNS).

The challenges of the study of antiretrovirals in the CNS were then elucidated. The measurement of concentrations in CSF with adequate sample size and the evaluation of new PK enhancers will help in determining the relationship between CSF and brain concentrations (both intracellular and extracellular) and the correlates of inter-individual variability. The most accurate inhibitory concentrations for estimating nervous system efficacy have to be studied as well as clinical tools to assess it (CSF viral loads, neuropsychological testing, etc). This element should be evaluated for single drugs and for combination of antiretrovirals taking into account the neurotoxicity of such compounds. Expert panels should then meet regularly with these precise definitions to update and modify the CPE score and the fields of its application.

Figure 4:

![CNS Penetration-Effectiveness Ranks & HIV RNA in CSF](image)
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