

Serial CSF and Plasma Collection in Freely Moving Rats

Background

Despite that valuable insight is obtained from *in vitro* ADME (absorption, metabolism, distribution and excretion) screening assays, *in vivo* drug exposure is still emphasized by drug discovery teams when making decisions about molecules within a structural class. Plasma concentration *versus* time profiles are essential for deriving a more detailed analysis of drug exposure in terms of both PK and toxicokinetics.

Drug penetration into the central nervous system (CNS) is of vital importance in characterizing a CNS-targeted compound for potential efficacy and/or toxicity. CNS penetration is beneficial for drugs intended to treat neurological or psychiatric disorders where therapeutic targets reside mainly within the CNS, whereas it is not desirable for drugs intended to treat peripheral diseases. Presently, there are few rapid throughput *in vitro* models that can be used to test compounds for their ability to penetrate the CNS. Of the available *in vitro* assays, bovine brain endothelial cell (BBEC) cultures are the most predictive of blood brain barrier (BBB) penetration, however, the barrier is relatively leaky. *In vivo* models of CNS penetration are still the most reliable.

***In Vivo* Serial Cerebrospinal Fluid (CSF) and Plasma Collection**

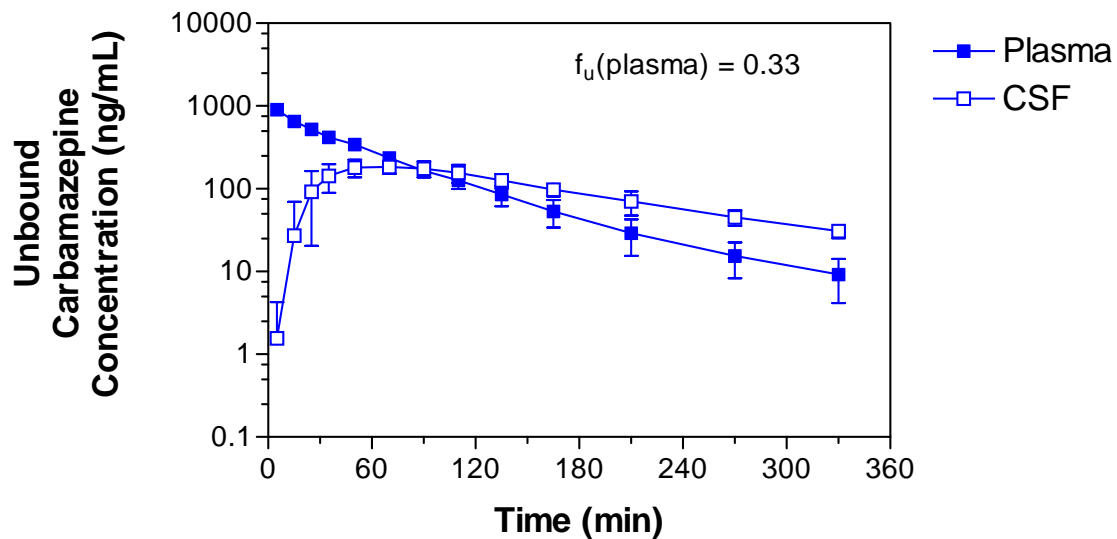
The CNS contains two regulated fluid compartments, the interstitial fluid that surrounds the neurons and glia and the CSF that fills the ventricles and cushions the external surfaces of the brain. In many instances, the CSF concentration of a drug candidate is indicative of its brain concentration. Since the time course of drug in the CSF and plasma following *i.v.* administration may be readily examined, NoAb has developed a model where both CSF and plasma are collected continuously from a single rat over an extended time (~6 to 8 hrs) period. The ratio of the areas under the CSF and plasma concentration *versus* time curves (AUC_{CSF}/AUC_{PLASMA}) gives an estimation of brain penetration of the drug candidate.

This model consists of freely moving rats, which have had cannulas placed into the femoral vein and artery for drug candidate administration and blood sample collection, respectively, and a third cannula is inserted into the cisterna magna for CSF collection. Using a peristaltic pump CSF is collected serially, at a flow rate of ~2 $\mu\text{L}/\text{min}$, for up to 8 hours following drug candidate administration. Depending on the sensitivity of the bioanalytical method for the drug candidate, CSF can be collected over 10 – 30 min intervals. At the same time, blood samples are collected at the mid-point of each CSF collection interval. Drug candidate concentrations in plasma and CSF are determined by LC-MS/MS methods.

As an example, plasma and CSF concentrations of carbamazepine were determined as a function of time following 4 mg/kg *i.v.* administration to 7 rats. The data are depicted graphically in the figure below.

CSF Penetration by Carbamazepine

(4 mg/kg *i.v.* n=7 rats)



This study design is an important tool for preclinical screening of novel drug candidates in neuropharmacotherapy, brain chemotherapy and antimicrobial therapy for CNS intended use.

www.noabbiodiscoveries.com

For more information contact:

David K. H. Lee, Ph.D.

Chief Scientific Officer

NoAb BioDiscoveries Inc.

905.814.5238, Ext. 222

dkhlee@noabbiodiscoveries.com