CSF SAMPLING METHODS TO EVALUATE DRUG PHARMACOKINETICS IN THE CNS

The drug development process has several critical milestones. One of the milestones is pharmacokinetics (PK) studies, which is the study of how a given drug interacts with the body. PK studies typically evaluate the ADME or absorption, distribution, metabolism and excretion of a new therapy. Crossing the BBB poses a significant challenge for several therapies that target brain diseases including neurodegenerative diseases and brain tumors. PK studies performed in the CNS are especially important to ascertain how much of a given drug crosses the blood brain barrier (BBB)[1] to have a therapeutic effect on brain tissues. If the drug cannot cross the BBB efficiently, then it is likely to have limited therapeutic efficacy at an acceptable dosage. It is important to understand the barriers between blood, CSF and the extracellular fluid (ECF) to appreciate the complexities of drug transport into the brain. The BBB separates blood flow from brain tissue and is a tight barrier with no gap junctions or pores, while the BCSFB (blood CSF barrier) is more porous and supports vesicular pinocytosis for the transport of biomolecules including drugs[2]. Since CSF freely interacts with blood and is in fact produced from blood plasma, drugs that are administered systemically are detected in CSF[2]. Studies in large animal models such as nonhuman primates and canines have shown that direct administration into the CSF can deliver drugs to specific areas of the brain[3]. The most common administration methods are lumbar puncture and ICV or intracerebroventricular injection3. Measurement of the available drug concentration and metabolites in CSF after administration are typical readouts to assess ADME characteristics.

Typically, PK studies are performed in primate models that have similar brain anatomy and physiology as humans. PK studies are complex and require analysis at multiple time points to map out the effect of the drug on the body, so it is essential to use minimally invasive methods for repeated sampling of biofluids. There are a couple of different methods to access biofluids in the CNS. One approach is CSF sampling through lumbar puncture or through the cisterna magna, and another approach is through microdialysis where a probe is placed in the tissue of interest to facilitate sampling[4]. Both approaches have their uses and limitations. CSF sampling typically uses lumbar puncture for repeated sampling of the spinal CSF, while microdialysis samples ECF around the tissue of interest[4]. Secondly, microdialysis is more widely performed in rodent models with limited use in nonhuman primates, while CSF sampling is well established in nonhuman primates. Microdialysis methods are useful to analyze the immediate environment surrounding a brain tumor or brain region of interest while CSF sampling provides a more global picture of free or unbound drug concentrations. Typically, samples from a microdialysis probe are used to evaluate changes in secreted proteins and neurotransmitters and locally expressed biomarkers. On the other hand, CSF sampling can be used to evaluate global biomarker changes as the sampling is typically done at a site that is distal to the tissue of interest. Interestingly, some reports have shown no significant differences in drug PK characteristics between CSF samples and ECF samples acquired through microdialysis[5]. Therefore, it is important to select the appropriate sampling method depending on the experiment objective and animal model of choice. In summary, sampling and analyzing the CSF are essential to evaluate both direct drug delivery and drug pharmacokinetics in the CNS.

References:

[1] https://pubmed.ncbi.nlm.nih.gov/15381336
[2] https://link.springer.com/article/10.1007/s10928-013-9301-9
[3] https://www.sciencedirect.com/science/article/pii/S0169409X21000685
[4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6388052
[5] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4151035