Pharmacokinetic Strategies in CNS Drug Discovery

Our understanding of the design and functioning of the Central Nervous System has dramatically improved over the last two decades. In spite of this, the discovery and clinical development of drugs for many CNS disorders has remained elusive. The failure rate for new drugs targeting important CNS diseases in general have higher failure rates than the other diseases, both preclinically and clinically.

During the preclinical stage, it is relatively more difficult to make findings in CNS disease that can be translated into a successful clinical candidate than in most other areas. The reason for this difficulty is the presence of blood-brain barrier (BBB) which limits the entry of molecules into the CNS. Commonly used techniques to increase penetration by small molecules, such as enhanced lipophilicity, can dramatically reduce solubility, leading to difficulties in drug delivery. Many classes of large molecules, such as peptides and antibodies, will not readily access the CNS without some form of assisted transport. This is the reason pharmacokinetics of the drug along with the drug delivery mechanisms play an important role in determining the success of new CNS drug.

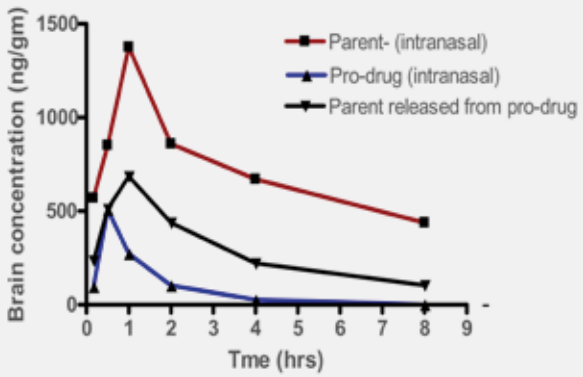
We shall discuss some successful PK approaches that we have employed in the recent past and may help in CNS targeted drug discovery and development efforts.

A. Prodrug Approach to Target CNS

A challenging issue in CNS drug discovery has been to target the brain without any systemic toxicities. Here, we focus on a case study where a drug of plant origin was found to improve cognitive functions but showed severe gastrointestinal (GI) toxicity. Therefore, a pro-drug approach was executed with the aim to circumvent the peripheral side-effects of the parent while imparting the required brain exposure to retain efficacy.

Studies were performed with the above approach via two routes of delivery, viz. intranasal and sublingual to avoid the GI related toxicity (Fig. 1A and 1B). The results corroborated that intranasal route achieved greater exposure compared to sublingual with no toxicity while retaining efficacy. This enabled the sponsor to decide on compound progression.

1A Brain concentration of Parent, Pro-drug and Parent- released from Prodrug



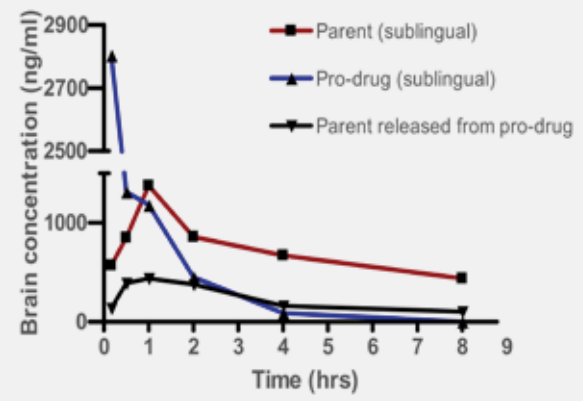
B. Cerebrospinal Fluid as a Surrogate for Brain Exposure

Drug targeting to the CNS is governed by sequential factors that include plasma-protein binding (PPB), blood-brain-barrier (BBB) permeability, brain protein binding, blood-cerebrospinal fluid barrier (BCSF) permeability and the transporters at the CNS barrier. While transporter liabilities and compound lipophilicity can be easily ascertained, the evaluation of free fraction in human brain can present a challenge.

This raises the question

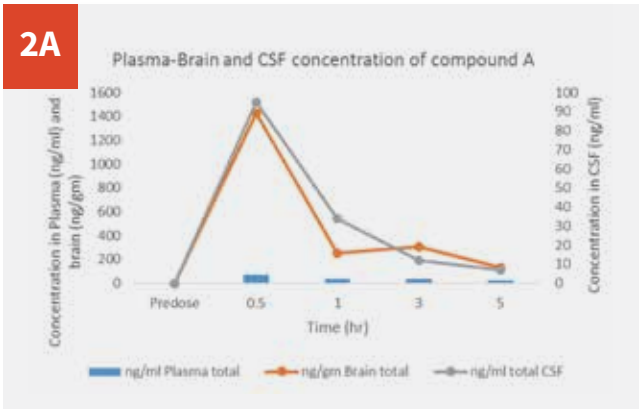
Can Cerebrospinal Fluid (CSF) be a surrogate in predicting brain drug exposure? Collecting human CSF is ethically accepted for biomarker evaluation in several disease conditions. Our expertise in collecting CSF from the cisterna magna of mice and rats has enabled the evaluation of PK/PD relationships in CNS drug discovery.

1B Brain concentration of Parent, Pro-drug and Parent- released from Prodrug

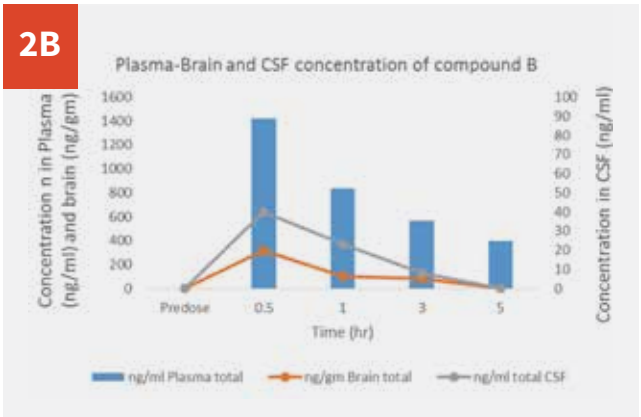


The plasma, brain and CSF exposures of two representative compounds in male rats have been exemplified in Fig.2. Pharmacokinetics for Compound A showed high brain and CSF exposure with low Plasma concentration (Fig. 2A). Compound B on the other hand showed high plasma exposure with low brain and CSF concentrations. With the understanding that the free -brain fraction of compound flows into the CSF, parallel ex vivo protein binding studies were conducted for both compounds with brain homogenate and plasma. A direct correlation was confirmed between total drug concentration in CSF and free-brain fraction (Fig. 2C). This evaluation suggests that CSF can act as a surrogate for brain exposure.

2A



2B



2C

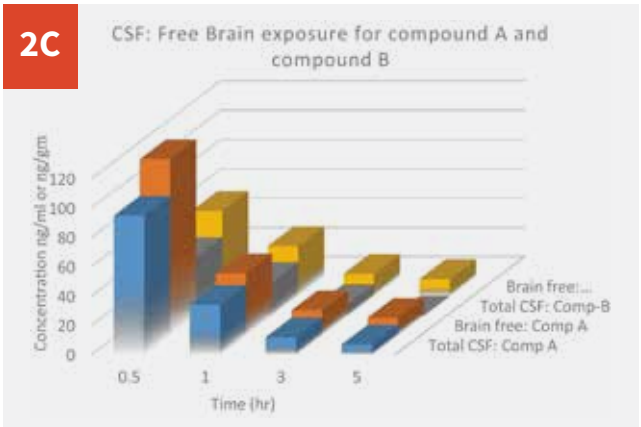


Fig.2: Plasma, Brain and CSF exposures of two representative compounds (2A, 2B) and correlation of total CSF to free-brain concentration (2C)

Conclusion

A prodrug approach to release of active CNS drugs at the site of action is an effective strategy to reduce toxic side effects. Furthermore, drug delivery via intranasal route maximizes drug absorption by diffusion, thus bypassing the first-pass effect related to GI-toxicity. Once the drug reaches the site of action, another challenge in CNS drug discovery is assessing brain exposure and this has been eased by measuring CSF levels that reflect free brain concentrations.

CSF also lends itself as a readily accessible matrix for biomarker / metabolite measurements supporting PK/PD assessment. of free fraction in human brain can present a challenge.

Aragen's DMPK Capabilities

Aragen provides comprehensive, cost-effective pharmacokinetics support across the drug discovery paradigm for evaluating and optimizing the drug-like properties of new chemical entities. Our unique PK expertise lies in incorporating customized innovative approaches and advanced technologies such as high throughput screening to provide decision-enabling high-quality data with rapid turnaround times. Our highly efficient onsite bioanalytical setup, has no bottlenecks in producing large volume of data.

1300 PK studies/month

1000 ADME studies/month

300000 bioanalysis /month

High quality, reproducible, decision-enabling data and no bottlenecks in bioanalysis

Very competitive pricing with volume discounts

Key Differentiators of Our PK Studies

- **Consultative Approach:** Our team provides consultative client support from study design, execution, data interpretation and suggestions of path forward.
- **Turnaround Time:** Turn Around Time for our core PK services is within 7 working days without compromising on quality. This is one of the quickest in the industry.
- **Experienced Team:** Our team has experience in addressing challenging sponsor requirements, working with Big Pharma, Mid-Sized Pharma, Virtual Companies and Academic institutions.
- **High Quality Animals:** Local presence of Charles River and Taconic for rodents and Isoquimen for beagle dogs helps us in providing the highest quality PK data.
- **Project Management:** XLRATE™ project management platform to support integrated drug discovery programs helps in delivering quicker DMPK screening data.

About Aragen

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Let's begin the Conversation

E: bd@aragen.com
W: aragen.com
in /company/aragen-life-sciences
f /AragenLifeSciences

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