Novel Rat Intrathecal Catheterization Model for Direct Antisense Oligonucleotide (ASO) Drugs Delivery to the Central Nervous System

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Abstract

Due to the existence and tight regulation of the blood-cerebrospinal fluid barrier (BCSFB) and the blood-brain barrier (BBB), over 98% of small-molecule and macromolecular drugs (e.g., proteins, nucleic acid-based agents) have difficulty effectively penetrating from the blood circulation system into the central nervous system (CNS). This has led to a significant common technical bottleneck in the development of CNS-targeted drugs. [1] During pre-clinical research, current CNS delivery methods mainly include systemic delivery, invasive local direct injection (such as intracerebral injection), and non-invasive delivery systems. However, these methods are often limited by low bioavailability in the CNS, the trauma caused to animals by the procedures, and/or technical complexity.[2] Clinically, due to the difficulty in penetrating the BCSFB-BBB caused by the high molecular weight of antisense oligonucleotides (ASOs), subarachnoid intrathecal injection is often used to achieve efficient drug delivery to the cerebrospinal fluid (CSF). [3] Our team experimented with different methods and developed a novel lumbar intrathecal catheterization technique in rats, characterized by high success rates and minimal invasiveness.

Objective

To further evaluate the consistency of data after multiple administrations of the drug, we conducted a study comparing the data of Nusinersen (MW: 7.5 kDa) administered via lumbar intrathecal intubation in Sprague-Dawley (SD) rats.

Method

We validated its reliability through pharmacokinetic (PK) studies of ASO drugs. The methodology employs a guidewire-assisted catheter implantation through the cauda equina space (L5-L6 intervertebral region), achieving a total incision length of <5 mm to substantially reduce physiological stress caused by surgical procedures. Procedural efficiency is demonstrated by an operation time of < 15 minutes per rat, a catheterization success rate > 95%, and a 100% postoperative survival rate.

Results

Table 1. Intrathecal Injection Validation Study Design.

Group	Animal NO.	Surgery	Volume (μL)	Administration	Time Points (h)	Sample Collection
1(Phase 1)	R01-R05	Intrathecal Catheter	50	Bolus	0.25, 1, 2, 6, 8, 24	Blood (jugular vein), CSF (cisterna magna)
2 (Phase 2)		Intrathecal Catheter	50	Bolus		

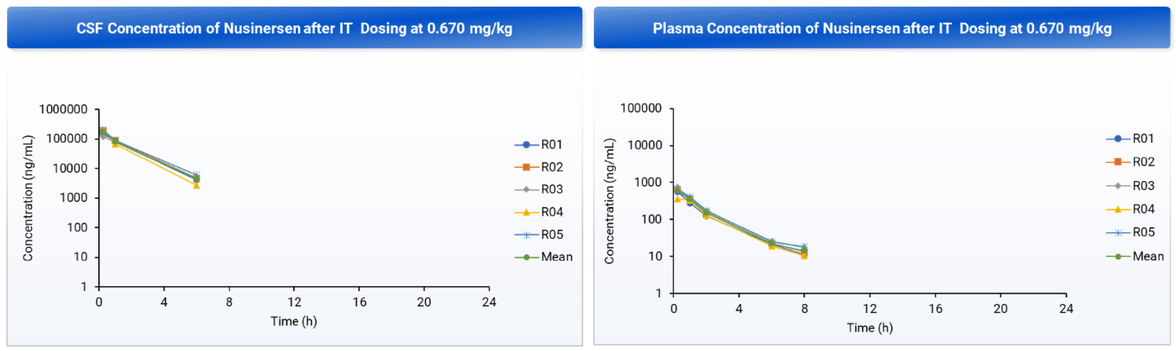

Figure 1. CSF and Plasma Concentration Profiles After Bolus (G1, phase 1) via Intrathecal Catheterization.

Table 2. Nusinersen CSF Concentration-Time Data After Bolus (G1) (Mean ± SD).

CSF concentration (ng/mL)									
Time (h)	R01	R02	R03	R04	R05	Mean	±	SD	CV (%)
0.25	149000	190000	117000	202000	202000	172000	±	37676	21.9
1	83400	91600	78000	68200	89000	82040	±	9348	11.4
6	4160	4800	4840	2760	6160	4544	±	1234	27.2
24	BQL	BQL	BQL	BQL	BQL	ND	±	ND	ND

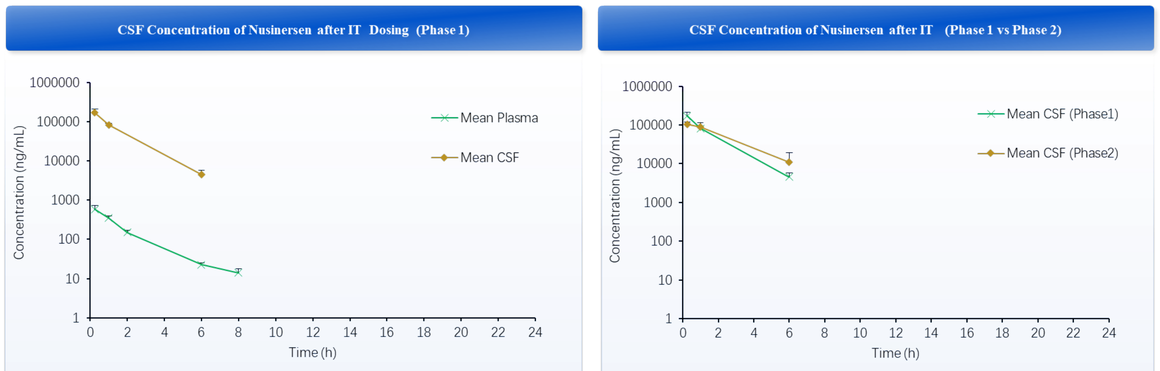

Figure 2. CSF and Plasma Concentration Profiles After Bolus (G1, phase 1) vs. Bolus (G1, phase 2) via Intrathecal Catheterization.

Conclusion

Importantly, this technique circumvents the neurological injury risks associated with traditional lumbar puncture while enabling persistent repeated dosing （more than 4 weeks）. By establishing a reliable preclinical platform for CNS drug screening, this advancement holds significant potential to accelerate CNS drug development.

References

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