Pharmacokinetic Comparison of Pemetrexed Administered via Lumbar Intrathecal vs. Cisterna Magna Intubation in Sprague-Dawley Rats

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Abstract

The central nervous system's unique defense mechanisms—the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB)—establish stringent pharmacological and toxicological defenses through selective regulation. In the study of central nervous system (CNS) diseases, commonly employed methods of invasive drug administration in rats include lumbar and/or cisterna magna puncture and intubation. However, repeated punctures can lead to inflammation or even infection at the puncture site, posing challenges for experiments that necessitate repeated drug administration. Intubation techniques can effectively mitigate these potential risks [1, 2]. Furthermore, anatomical differences between the lumbar and cisterna magna delivery routes critically influence the pharmacokinetic (PK) profiles of test articles [3].

Objective

To further evaluate how these delivery routes affect PK profiles, we conducted a study comparing the PK profiles of Pemetrexed (MW: 427 g/mol) administered via lumbar intrathecal intubation versus cisterna magna intubation in Sprague-Dawley (SD) rats.

Method

Ten animals were randomized into two groups, each receiving a single bolus dose of pemetrexed (1 mg/kg, 100 µL/animal) via one of the two routes. The plasma and cerebrospinal fluid (CSF) pemetrexed concentrations over 24 hours were quantified using LC-MS/MS, which led to the revelation of distinct pharmacokinetic (PK) parameters. WuXi AppTec DMPK has refined a streamlined cannulation method (Figure 1) enabling single-operator procedures, shorter surgery times, high post-operative catheter patency, and support for chronic/repeat dosing.

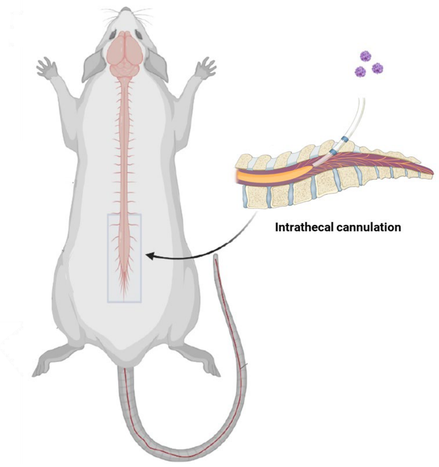
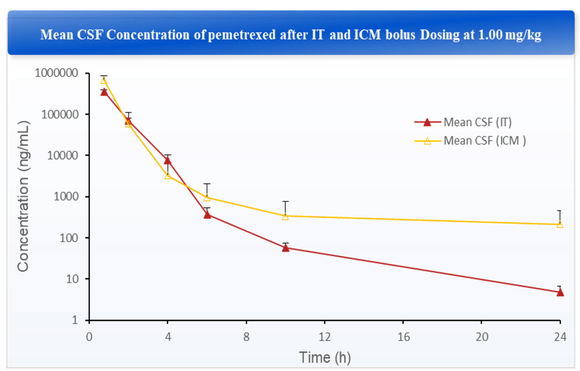


Figure 1. Schematic of Optimized Rat Intrathecal Catheterization Model.

Results

Table 1. Validation Study Design.

Group	Surgery	Volume (µL)	Administration	Time Points (h)	Sample Collection
1	ICM (intra cisterna magna) Catheter	100	Bolus	0.75, 2, 4, 6, 10, 24	Blood (jugular vein), CSF (cisterna magna)
2	Intrathecal Catheter	100	Infusion (20 min)		



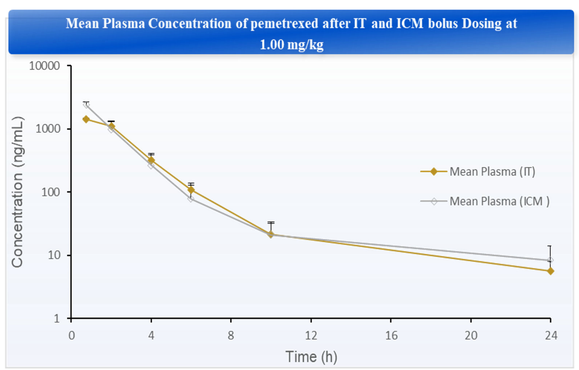


Figure 2. CSF and Plasma Concentration Profiles After Bolus (G1:ICM Catheter) vs. Bolus (G2: Intrathecal Catheter).

Table 2. PK Parameters of Pemetrexed in Plasma and CSF After Bolus (G1:ICM Catheter) vs. Bolus (G2: Intrathecal Catheter).(Mean ± SD).

Parameters	ICM Catheter	Intrathecal Catheter	ICM Catheter	Intrathecal Catheter
	Plasma		CSF	
C_{max} (ng/mL)	2380 ± 302	1425 ± 67.1	677678 ± 194676	349585 ± 36807
$T_{1/2}$ (h)	4.93 ± 1.32	3.58 ± 0.42	5.03 ± 1.68	3.15 ± 0.51
$AUC_{0\text{-last}}$ (ng.h/mL)	4608 ± 1212	4138 ± 567	602974 ± 242941	410045 ± 45696

Despite achieving higher peak concentrations (C_{max}), substantial inter-individual variability (CV > 35.9 %) was observed in the cisterna magna group, possibly attributable to the CSF sampling position near the injection site. Anatomical analysis indicates that the closed environment adjacent to the fourth ventricle in the cisterna magna may delay drug clearance, whereas lumbar administration allows for easier dilution and accelerated transport to systemic circulation due to the need for diffusion against the physiological flow of cerebrospinal fluid.

Conclusion

In summary, selecting the appropriate administration method based on specific study requirements is crucial for accurately evaluating the pharmacokinetic processes of drugs in the CNS. This approach provides a more reliable technical pathway for the discovery and development of novel CNS drugs.

References

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