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Review Article

Intracerebroventricular Delivery as a Safe, Long-Term Route of Drug Administration

Jessica L. Cohen-Pfeffer MD [a], Sridharan Gururangan FRCP [b], Thomas Lester MBS [a], Daniel A. Lim MD, PhD [c], Adam J. Shaywitz MD, PhD [a], Manfred Westphal MD, PhD [d], Irene Slavc MD [e,*]

[a] *BioMarin Pharmaceutical Inc, Novato, California*
[b] *McKnight Brain Institute, University of Florida, Gainesville, Florida*
[c] *Department of Neurological Surgery, University of California, San Francisco, San Francisco, California*
[d] *Department of Neurosurgery, University Clinic Hamburg-Eppendorf (UKE), Hamburg, Germany*
[e] *Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria*

ABSTRACT

Intrathecal delivery methods have been used for many decades to treat a broad range of central nervous system disorders. A literature review demonstrated that intracerebroventricular route is an established and well-tolerated method for prolonged central nervous system drug delivery in pediatric and adult populations. Intracerebroventricular devices were present in patients from one to 7156 days. The number of punctures per device ranged from 2 to 280. Noninfectious complication rates per patient (range, 1.0% to 33.0%) were similar to infectious complication rates (0.0% to 27.0%). Clinician experience and training and the use of strict aseptic techniques have been shown to reduce the frequency of complications.

Keywords: intracerebroventricular, ICV, intrathecal, drug delivery, Ommaya reservoir, Rickham reservoir, complications, infections
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Introduction

Intrathecal delivery methods enable the administration of soluble therapeutics directly into the central nervous system (CNS). As an intrathecal delivery method, the intracerebroventricular (ICV) route of administration instills therapy into the cerebral ventricles via an ICV port implanted under the scalp. This route of administration, also referred to as intraventricular administration, has been used for several decades to provide treatments for pediatric and adult patients who suffer from a broad range of diseases, including infectious meningitis, intractable pain, and various types of cancer.[1-5] In addition to the ICV route, intrathecal delivery methods include single or repeated intrathecal lumbar (IT-L) injections, in which agents are directly administered into the cerebrospinal fluid (CSF) by puncturing the membranes surrounding the spinal cord (Fig 1). Intrathecal routes of administration allow therapies to bypass the blood–brain barrier (BBB) and are commonly used to treat a variety of diseases in pediatric and adult patients.[4,7-10]

As part of the neurovascular unit, the BBB is composed of tight endothelial junctions that are surrounded by a basal membrane that separates the endothelium from pericytes, astrocytes, and neurons.[7] This physiological barrier restricts the movement of large molecules between the blood, CSF, and interstitial fluid of the brain.[7,11,12] Direct delivery into the CNS is required in many circumstances when, due to the selectivity of the BBB, systemically administered therapies may fail to reach therapeutic levels in the CNS.[4,13] In some cases, intravenous therapy may be augmented or even

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* Communications should be addressed to: Prof. Dr. Slavc; Department of Pediatrics and Adolescent Medicine; Medical University of Vienna; Waehringer Guertel 18-20; 1090 Vienna, Austria.
E-mail address: irene.slavc@meduniwien.ac.at

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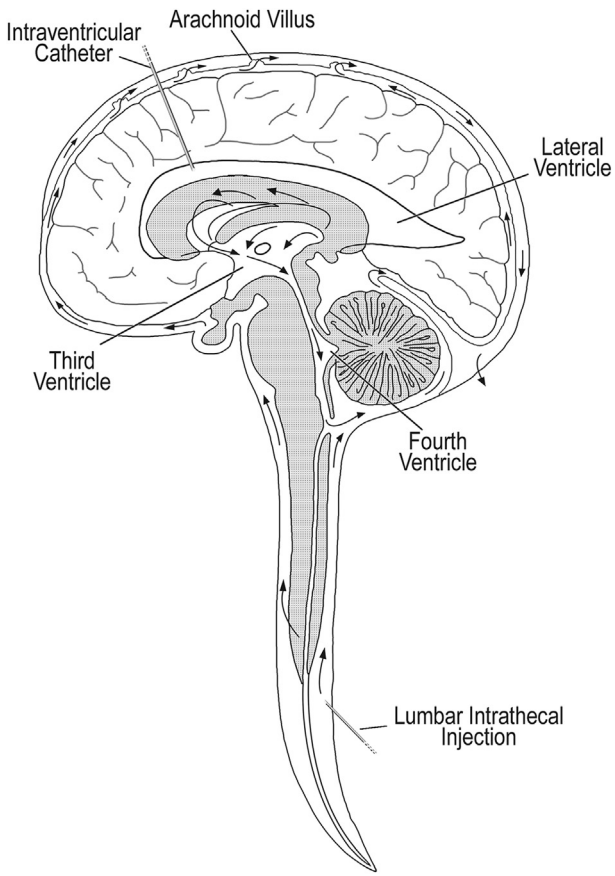

FIGURE 1.
Illustration of cerebrospinal fluid flow and typical placement of intracerebroventricular (intraventricular) and intrathecal lumbar catheters.[6] This image was adapted with permission and published in *Annals of Pharmacotherapy*, Vol. 27, Luer MS, Hatton J, Vancomycin administration into the cerebrospinal fluid: a review, 912-921, Copyright SAGE Publications (1993).

replaced with delivery systems that target the CNS to provide safe and effective doses of therapy to the CNS while minimizing systemic toxicity.[9,14,15]

To circumvent the selectivity of the BBB, therapies can be administered via ICV devices directly into the CSF.[16-18] An ICV device (e.g., Ommaya reservoir or Rickham reservoir) consists of a port that is implanted by neurosurgeons in the subgaleal space under the scalp and connected to the ventricles within the brain via an outlet catheter.[19] Drug administration via an ICV device provides greater convenience and comfort for patients compared with repeated IT-L punctures.[20,21] However, the potential for increased intracranial pressure remains a theoretical concern during administration of medications via the ICV route, especially when larger volumes are administered over a short period of time.[21] To address this concern, many studies have included the use of isovolumetric injection, noting that withdrawal of CSF before administration of the medication can help to avoid volume overload.[22-25] In addition, ICV infusion can deliver therapies in the long term and at a constant rate that does not result in increased intracranial pressure.[21,26] Once the devices are no longer therapeutically needed, they can be explanted, although oncologists routinely recommend that, in the absence of complications, these devices remain in place indefinitely.[27-29]

The distribution of intrathecally administered therapies throughout the CNS has been investigated in a number of recent publications.[4,19,22,24,26,30-35] Although one review hypothesized that the low rate of interstitial fluid secretion by microvessels of the brain can work against drug diffusion into brain tissue, and that the ICV delivery route may be a suitable strategy only for areas close to the ventricles,[19] many studies have demonstrated that ICV and IT-L administered therapies can be distributed throughout the brain and other regions of the CNS.[4,22,24,26,30-35]

Successful early stage studies of ICV-delivered therapies for new therapeutic indications (beyond oncology and pain)[24,26,30-32,34,36,37] have led to several clinical trials. These trials include recombinant human tripeptidyl-peptidase 1 administered to patients aged three to 16 years with late-infantile neuronal ceroid lipofuscinosis type 2 disease[38]; recombinant human heparan-N-sulfatase administered to patients aged 12 to 48 months with mucopolysaccharidosis IIIA[39]; and recombinant human iduronate-2-sulfatase administered to patients aged three to 18 years with mucopolysaccharidosis II.[40] In addition, at least 2 other clinical trials have used ICV devices to administer therapy: a vascular endothelial growth factor assessed in patients aged 18 to 75 years with amyotrophic lateral sclerosis[41] and a product containing platelet-derived growth factor in patients with Parkinson disease aged 30 to 75 years.[42]

The ICV route of administration is an established and globally used method of drug delivery; individual clinics' procedures and recommended guidelines on the use of ICV access devices (e.g., Ommaya and Rickham reservoirs) have been published (summarized in Fig 2).[27,43,44] Numerous studies have demonstrated that employing strict aseptic techniques when accessing ICV devices can dramatically reduce infectious complication rates,[27,44-47] and following best practices for ICV device use can prevent infectious and noninfectious complications.

The increased use of chronic ICV delivery warrants an analysis of the long-term safety and tolerability of the ICV route in both pediatric and adult patients. Because the placement of ICV devices uses common neurosurgical techniques,[48] this literature analysis does not include device implantation; rather, this review examines long-term management of the ICV access point, the duration of safe ICV device use, and the nature and rate of complications (infectious and noninfectious) associated with the ICV administration of therapies targeting the CNS.

Methods

A literature search was conducted using Embase, Scopus, and PubMed to identify articles and conference abstracts published through October 17, 2014, that included ICV as a route of administration across a range of disease states. Similar search strategies and terms were used within each database. Published articles and abstracts were searched using the following keywords: ("intracerebroventricular" or "ventricular" or "intraventricular" with "infusion" or "injection" or "drug" or "therapy" or "treatment" or "delivery") AND ("intrathecal" or "pump" or "ommaya" or "reservoir" or "rickham" or "mccomb" or "salmon" or "siphonguard" or "port" or "catheter" or "brain" or