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Convection-Enhanced Delivery for the Treatment of Pediatric Neurologic Disorders

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Abstract

Direct perfusion of specific regions of the central nervous system by convection-enhanced delivery is becoming more widely used for the delivery of compounds in the research and treatment of various neural disorders. In contrast to other currently available central nervous system delivery techniques, convection-enhanced delivery relies on bulk flow for distribution of solute. This allows for safe, targeted, reliable, and homogeneous delivery of small- and large-molecular-weight substances over clinically relevant volumes in a manner that bypasses the blood-central nervous system barrier. Recent studies have also shown that coinjected imaging surrogate tracers can be used to monitor and control the convective distribution of therapeutic agents in vivo. The unique features of convection-enhanced delivery, including the ability to monitor distribution in real-time, provide an opportunity to develop new research and treatment paradigms for pediatric patients with a variety of intrinsic central nervous system disorders.

Keywords

blood-brain barrier; central nervous system; convection-enhanced delivery; drug delivery

Introduction

Effective drug delivery remains the single largest obstacle to the treatment of many pediatric central nervous system disorders. Despite the recent development of a number of putative therapeutic compounds that are effective in vitro, the application and efficacy of these agents in vivo have been restricted by limitations associated with currently available delivery techniques. Existing central nervous system delivery techniques consist of systemic delivery, intrathecal or intraventricular administration, and polymer implantation.^{1,2} Systemic delivery is restricted by systemic toxicity, nontargeted distribution, and the inability of many substances to cross the blood-nervous system barrier. Diffusion-dependent methods, including intrathecal or intraventricular administration and polymer implantation, are limited by nontargeted distribution, inhomogeneous dispersion, and ineffective volume of distribution.

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To overcome the obstacles associated with currently available central nervous system drug delivery methods, a number of centers have investigated the use of convection-enhanced delivery to distribute compounds in the nervous system.^{3–6} Data from these studies indicate that the direct perfusion of the central nervous system interstitial spaces using convective distribution allows for the safe, targeted, homogeneous delivery of agents into small and large tissue volumes in a manner that bypasses the blood-nervous system barrier. Moreover, convective coinfusion of a mixture of therapeutic agent and an imaging surrogate tracer can now be used to monitor drug distribution in real-time using computed tomography (CT) or magnetic resonance imaging (MRI). These unique features of convection-enhanced delivery permit the development of new drug delivery paradigms for the treatment of central nervous system disorders.

Convection-Enhanced Delivery

General properties

Convective distribution of infusate within the interstitial spaces of the central nervous system is driven by a small continuous pressure gradient that is generated by an infusion pump and transmitted to the point of delivery via a cannula inserted directly into the region of perfusion.³ This small hydrostatic pressure gradient permits the movement of solute through extracellular spaces over volumes and at speeds several orders of magnitude greater than those associated with simple diffusion. Typical rates of infusion for convective delivery range from 0.5 $\mu\text{L}/\text{minute}$ to 6 $\mu\text{L}/\text{minute}$. Based on the bulk flow properties of convection-enhanced delivery, a number of preclinical and clinical studies have investigated the unique distributive features of this central nervous system delivery method.

Bypasses the Blood-Nervous System Barrier

Therapeutic compounds are infused directly into the abluminal (intraparenchymal) side of the capillaries that form the blood-nervous system barrier using convection-enhanced delivery. Subsequently, the blood-nervous system barrier is circumvented and can be used to isolate infused agent from the systemic circulation and support sustained therapeutic concentrations of large and/or hydrophilic molecules.³

Reliability

Because the distribution of infusate occurs in the interstitial space, the volume of distribution associated with convection is larger than the volume of infusion and is inversely proportional to the interstitial fraction of tissue. Since the interstitial space constitutes 15% to 25% of the neural parenchyma, the volume of distribution resulting from convection is substantially larger than the volume of infusion.² Studies have shown that volume of distribution:volume of infusion ratios of 4:1 to 5:1 can be consistently achieved in normal brain, spinal cord, and peripheral nerve tissue, while higher ratios approaching 9:1 can be found in the brainstem.^{7–10} Consistent with an interstitial distribution process, the elevated volume of distribution:volume of infusion ratio in the brainstem (compared with other anatomic regions in the central nervous system) is a reflection of the highly compacted axons and nuclei in this area and a correspondingly reduced interstitial volume.

Homogeneity of infusion

Because convection-enhanced delivery relies on bulk flow, not diffusion, homogeneous distribution of infusate is possible. Preclinical studies using radiolabeled infusate have consistently shown that the concentration of infusate is similar over the entire perfused region, with a steep drop-off at the margins of the infusion.^{7–10} This “square-shaped” distribution pattern underscores the homogeneous perfusion of tissue that is possible with convective delivery (Figure 1). This property permits for the targeting of specific regions of

the central nervous system with high concentrations of a therapeutic compound, while exposing the immediately surrounding tissues to exponentially less infusate.

Clinically relevant distribution

Because of the large volume of distribution:volume of infusion ratio associated with convection-enhanced delivery, a relatively small volume of infusion can be distributed over a clinically relevant volume of distribution. Moreover, because convection-enhanced delivery relies on bulk flow for infusate distribution, a significantly larger volume of distribution can be achieved with convection than with simple diffusion-driven processes such as intrathecal or intraventricular delivery or polymer implantation. Studies have shown that large regions (ie, holohemispheric, brainstem, and multiple vertebral levels of the spinal cord) of the central nervous system and peripheral nervous system (ie, segments of nerves the length of a limb) can be perfused using convection-enhanced delivery.^{8,9,11}

Safety

Animal and clinical studies have demonstrated that large volumes within the central nervous system can be safely perfused via convection-enhanced delivery. Histopathologic analyses in animal studies after convective delivery of agents have revealed only mild gliosis in the vicinity of the infusion cannula tract within a 50 μ radius.^{7,9} At the infusion rates typically used in convective delivery, perfusion of large, clinically relevant volumes in the central nervous system can be achieved safely and without significant increases in the interstitial or intracranial pressures within normal or tumor tissues.^{4,11–14}

Real-time imaging of distribution

Since the volume of distribution and the anatomic distribution will vary with the site of treatment and because the distribution of flow in the extracellular space of the brain is influenced by tissue heterogeneity, direct visualization of the distribution of the infused agent in the central nervous system during infusion will be crucial for further development and optimal clinical use of convective delivery. Recently, small- and large-molecular-weight CT and MRI tracers that can be coinjected with therapeutic compounds during convection-enhanced delivery have been developed and investigated.^{7,15–20} Studies have shown that mixing therapeutic agents and imaging surrogate tracers or encapsulating drugs in labeled liposomes²⁰ allows for the precise monitoring of small or large molecule distribution in real-time using serial CT or MRI. The ability to noninvasively monitor distribution of infusate in real-time enhances the accuracy of infusion, ensures adequate target perfusion, and permits for the accurate determination of the efficacies of various therapeutic agents.

Clinical Applications of Convection-Enhanced Delivery

Convective delivery of therapeutic agents has the potential for clinical use in the treatment of a broad spectrum of neurological disorders that include malignant brain tumors, metabolic disorders, neurodegenerative diseases, epilepsy, stroke, and trauma. Subsequently, convective delivery of putative therapeutic compounds has been used to target central nervous system conditions that otherwise lack any effective medical or surgical treatments in the pediatric and adult populations. We describe the use of convection to distribute agents into the brainstem to treat two pediatric intrinsic central nervous system disorders (diffuse pontine glioma and Gaucher disease).

Diffuse pontine glioma

Diffuse pontine gliomas are aggressive brainstem tumors that are universally fatal. They represent the leading cause of death by brain tumors in children and have a median survival of less than 12 months from the time of diagnosis.²¹ Patients frequently present with cranial

nerve dysfunction, ataxia, motor or sensory deficits, and long-tract signs. Because of the location and the highly infiltrative nature of these tumors, surgical excision is not possible. Current therapy includes radiation and chemotherapy, which is palliative at best. While putative therapeutic compounds exist for treatment of diffuse brainstem gliomas, they have not been effective in part because of the inability of systemically administered compounds to cross the blood-nervous system barrier in therapeutic amounts. To determine whether a targeted glioma cytotoxin could be delivered to brainstem gliomas via convection-enhanced delivery while monitoring its distribution, we coinjected interleukin-13 bound to *Pseudomonas* toxin and an imaging surrogate tracer into a diffuse brainstem glioma and used real-time MRI to track the distribution of the coinjection.

We have previously described a female (age, 3 years and 10 months) who presented with ataxia, headaches, nausea, and vomiting and was diagnosed with a diffuse pontine glioma on MRI.¹¹ The patient underwent ventriculoperitoneal shunt placement and radiation therapy after diagnosis, which alleviated her neurologic symptoms. Despite chemotherapy initiated 8 months after diagnosis, MRI 4 weeks later demonstrated progressive tumor growth in a region of imaging hypointensity. The patient was admitted to the National Institutes of Health (NIH) 10 months after diagnosis with progressive gait ataxia, bilateral abducens weakness (left greater than right), and left facial nerve weakness. Under an institutional-approved protocol, she underwent direct convective coinjection of interleukin-13 bound to *Pseudomonas* toxin and a surrogate MRI tracer, gadolinium-diethylenetriamine penta-acetic acid (total infusion volume, 1.4 mL), into the tumor.

Real-time, intraoperative MRI performed during the infusion demonstrated that the anatomic region perfused with interleukin-13 bound to *Pseudomonas* toxin and gadolinium-diethylenetriamine penta-acetic acid was clearly distinguishable from the surrounding noninfused tissue. The region surrounding the tip of the cannula steadily filled with infusion on serial MRI (Figure 2). MR volumetric analysis of the infused region at intervals revealed that volume of distribution increased linearly with volume of infusion. Consistent with an interstitial distribution process, the volume of distribution:volume of infusion ratio was 3.7 ± 0.4 (Figure 3).

After the infusion, the patient experienced mild transient lethargy for 48 hours and exacerbation of the preexisting bilateral abducens nerve weakness for 5 days that resolved. Follow-up MRI performed at 3 weeks and 4 weeks after infusion revealed no evidence of tumor progression or toxicity. Imaging 8 weeks after treatment revealed tumor progression associated with progressive gait ataxia, bilateral abducens nerve paralysis, left facial nerve paralysis, and swallowing difficulties. The patient died of progressive disease 4 months after the infusion.

The clinical and imaging findings from this case highlight potential features of convection-enhanced delivery in certain pathologic states. First, exacerbation of pre-existing neurologic dysfunction or development of a new neurologic deficit during infusion is a potential difficulty related to convection-enhanced delivery of agents into tumors or edematous tissue. This patient developed transient lethargy and worsening of pre-existing bilateral abducens nerve weakness. This was likely due to an increase in fluid associated with infusion into a region with tumor and associated edema. Similar to findings from previous convection-enhanced delivery clinical studies, the effects were transient and reversed with steroid treatment and infusion cessation. Second, the volume of distribution:volume of infusion ratio in this patient (3.7:1) was lower than the ratio (9:1) described in naive primate brainstem studies.⁷ This decrease in the volume of distribution:volume of infusion ratio likely represents an expansion of the extracellular space secondary to tumor-related vasogenic edema. Finally, to optimize convection-enhanced delivery of drugs in various

disease states, further investigation into the effect that pathologic tissues have on distribution will be required using real-time imaging. Real-time imaging of convective distribution will better elucidate the effects that variables including infusion rate, catheter design/placement, tissue edema, and anatomic boundaries have on volume of distribution.

Gaucher disease

Acute neuronopathic (type 2) Gaucher disease is a rare inherited sphingolipidosis that is caused by a deficiency in glucocerebrosidase. The accumulation of glucocerebroside within lysosomes of specialized macrophages (Gaucher cells) and in central nervous system neurons leads to neurologic, hematologic, skeletal, visceral, and pulmonary abnormalities.²² The disease presents in infancy and is characterized by myoclonic epilepsy and progressive brainstem deterioration that manifests as opisthotonic posturing, strabismus, swallowing impairment, and apnea.²² Although intravenous glucocerebrosidase replacement therapy can reverse disease progression in non-central nervous system tissues, the 60 kilodalton enzyme cannot pass through the blood-nervous system barrier and acute neuronopathic Gaucher disease remains untreatable.^{11,18} Death usually occurs by 1 year of age due to complications of brainstem involvement.¹⁸ To determine whether glucocerebrosidase could be delivered to central nervous system targets affected in neuronopathic Gaucher disease via convection-enhanced delivery while monitoring distribution, glucocerebrosidase and gadolinium-diethylenetriamine penta-acetic acid were coinfused into affected brainstem nuclei while distribution was monitored in real-time using MRI.

We have previously described a male infant with type 2 Gaucher disease who was born anemic, thrombocytopenic, and with hepatosplenomegaly.^{11,18} When he was 2 months of age, the systemic manifestations of the disease were successfully treated with intravenous glucocerebrosidase infusions. The patient developed intermittent strabismus at 2.5 months of age, but otherwise had an age-appropriate neurological exam. By 8 months of age he was hypotonic, the strabismus was constant, and he was deaf. At 9.5 months of age, he was no longer able to protect his airway or swallow, and he underwent placement of a feeding tube and tracheostomy. The patient was admitted to the NIH at 13 months of age with progressive right facial and abducens nerve paresis. On the basis of these clinical findings, we selected the region of the right facial and abducens nuclei for enzyme perfusion.

To track glucocerebrosidase distribution during infusion, we mixed gadolinium-diethylenetriamine penta-acetic acid with the glucocerebrosidase and monitored infusate distribution using T1-weighted and fluid-attenuated inversion recovery MRI under an institutional-approved protocol. After placement of the infusion cannula, the patient underwent direct convective coinfusion (0.5 μ L/minute to 10 μ L/minute) of the glucocerebrosidase and gadolinium-diethylenetriamine penta-acetic acid (total infusion volume, 1.8 mL) in the right pontine region. Volumetric analysis of the gadolinium-diethylenetriamine penta-acetic acid and glucocerebrosidase distribution revealed that volume of distribution increased linearly with volume of infusion until the targeted region was perfused (Figure 4; mean overall volume of distribution:volume of infusion ratio, 3.1 ± 1.6). During the initial part of the infusion (first 160 μ L), the mean volume of distribution:volume of infusion ratio was 5.6 ± 1.3 but decreased to 2.4 ± 0.7 as the volume of infusion increased (Figure 4). The timing of the decrease corresponded radiographically with the timing of the imaged infusion margin reaching the posterior edge of the brainstem on T1-weighted MRI. Fluid-attenuated inversion recovery MRI performed at this point revealed extravasation of coinfused gadolinium-diethylenetriamine penta-acetic acid from the tissue surface (Figure 4) that was not detectable on T1-weighted MRI.

The patient did not show clinical or radiographic signs of toxicity at 12-month follow-up. He remained clinically stable on intravenous enzyme replacement and gained weight. At 22.5 months of age, he died from a systemic fungal infection of his vascular access port.

This case underscores the therapeutic applicability of convective delivery for the targeted treatment of intrinsic neurologic disorders and the critical importance of real-time imaging to track infusate distribution. It also raises several issues to consider when applying convection-enhanced delivery to pathological disease states. First, tissue interfaces such as those that arise at the ependyma, pia, and at the boundaries of pathological lesions may affect convective distribution. In this case, perfusion of the right pontine target was successfully achieved during the infusion, but continued perfusion after the leading edge of the infusion reached the pial boundary of the posterolateral pons resulted in extravasation of the infusate. Extravasation of the infusate beyond the pontine pial border corresponded to a decrease in the volume of distribution:volume of infusion ratio (Figure 4). Second, while the extravasation of infusate was not detected on T1-weighted MRI, fluid-attenuated inversion recovery sequences clearly showed leakage of gadolinium-diethylenetriamine penta-acetic acid (infusate) into the 4th ventricle and adjacent cerebrospinal fluid cisterns that was not detected on T1-weighted MRI. Fluid-attenuated inversion recovery MRI is a very sensitive sequence that can be used to detect gadolinium-based surrogate tracers in the cerebrospinal fluid that may not be detected by other sequences such as T1-weighted MRI. This case highlights the need to further investigate the effects of anatomic boundaries such as pial and ependymal borders and resection cavities on convective delivery, and on technical factors such as optimum cannula placement. Lastly, while the clinical cases presented demonstrate perfusion of brainstem targets, convection-enhanced delivery can be used to effectively access other eloquent central nervous system structures, including deep brain nuclei, white matter tracts, and the spinal cord.^{6-7, 9-11}

Summary

Convection-enhanced delivery can be used to safely bypass the blood-nervous system barrier to deliver therapeutic agents of varying sizes to specific targets within the central nervous system. Convective delivery produces a homogeneous distribution of solute that perfuses clinically relevant volumes of the central nervous system at therapeutic concentrations. The development and use of surrogate imaging agents have allowed for the tracking of convective delivery via real-time imaging. The clinical uses of convective delivery in the treatment of neurological disease are expanding. In the pediatric population, convection-enhanced delivery may hold promise in the treatment of a variety of intrinsic neurologic disorders.

Acknowledgments

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Figure 1.

Concentration profile of convection-enhanced delivery of labeled viral capsids into the striatum. Concentration (mCi/gram tissue) profile across a representative autoradiograph following convection-enhanced delivery of ^{35}S -radiolabeled adeno-associated virus capsid into the rodent striatum. The square-shaped profile reflects the homogeneity of concentration across the infusion, while the surrounding tissues are exposed to exponentially less infusate. From Szerlip NJ, Walbridge S, Yang L, et al. Real-time imaging of convection-enhanced delivery of viruses and virus-sized particles. *J Neurosurg.* 2007;107:560–567.

Figure 2.

(A) Schematic coronal representation of the placement of the outer guide-inner cannulae system used in convection-enhanced delivery. The outer guide cannula is placed under stereotactic guidance, and the inner infusion cannula is placed through the outer guide to the desired target as determined by intraoperative MRI. A specialized syringe pump infusion apparatus (not shown) is connected to the infusion cannula. (B–E): Real-time, serial, coronal T1-weighted MR images obtained during convection-enhanced delivery of interleukin 13 bound to *Pseudomonas* to a diffuse pontine glioma. Gadolinium-diethylenetriamine penta-acetic acid surrogate tracer was coinjected with the drug. The hypointense tumor (arrowheads) in the pons is perfused with the agent and surrogate tracer. From Lonser RR, Warren KE, Butman JA, et al. Real-time image-guided direct convective perfusion of intrinsic brainstem lesions. Technical Note. *J Neurosurg.* 2007;107:190–197.

Figure 3.

Volumetric analysis of infusate distribution during convection-enhanced delivery into a diffuse pontine glioma of a 3-year-10-month-old female. The volume of distribution increases linearly with volume of infusion until the hypointense region of tumor is perfused. The overall volume of distribution:volume of infusion ratio is 3.7 ± 0.4 . From Lonser RR, Warren KE, Butman JA, et al. Real-time image-guided direct convective perfusion of intrinsic brainstem lesions. Technical Note. *J Neurosurg*. 2007;107:190–197.

Figure 4.

Extension of infusate beyond pial boundary of the target area during convection-enhanced delivery to the pons in a child with acute neuronopathic Gaucher disease. (A) Graph of volumetric analysis of glucocerebrosidase distribution based on MRI of a coinjected surrogate tracer during convection-enhanced delivery. Volume of distribution increases linearly with volume of infusion, but as the volume of infusion increases further the volume of distribution:volume of infusion ratio decreases. The mean volume of distribution:volume of infusion is 5.6 ± 1.3 over the first 160 μL infused; thereafter the volume of distribution:volume of infusion ratio is 2.4 ± 0.7 . (B) Axial MR image of the coinjected tracer, gadolinium-diethylenetriamine penta-acetic acid, at the posterior pial surface of the brainstem (arrows). (C) Axial fluid-attenuated inversion recovery MR image demonstrating extravasation of the coinjected gadolinium-diethylenetriamine penta-acetic acid tracer from the edge of the posterolateral aspect of the right pons into the adjacent cerebrospinal fluid space. Leakage of the tracer beyond the pial border corresponds to the decrease in the volume of distribution:volume of infusion ratio. From Lonser RR, Warren KE, Butman JA, et al. Real-time image-guided direct convective perfusion of intrinsic brainstem lesions. Technical Note. *J Neurosurg.* 2007;107:190–197.