Convection-enhanced delivery to the central nervous system

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Convection-enhanced delivery (CED) is a bulk flow–driven process. Its properties permit direct, homogeneous, targeted perfusion of CNS regions with putative therapeutics while bypassing the blood-brain barrier. Development of surrogate imaging tracers now permit accurate, noninvasive real-time tracking of convective infusate flow in nervous system tissues. The potential advantages of CED in the CNS over other currently available drug delivery techniques, including systemic delivery, intrathecal and/or intraventricular distribution, and polymer implantation, have led to its application in research studies and clinical trials. The authors review the biophysical principles of convective flow and the technology, properties, and clinical applications of convective delivery in the CNS.

http://thejns.org/doi/abs/10.3171/2014.10.JNS14229

KEY WORDS  convection-enhanced delivery; drug delivery; central nervous system; technique; bulk flow

BASEd on the rapid progression in understanding the precise pathobiology underlying various neurological diseases, a number of promising new putative therapeutics have been developed for specific disorders that have been ineffectually treated or are not currently treatable. While these agents have been successful in reversing disease-related pathology in vitro and/or in animal models, they have not been successfully translated into clinically effective therapies. One of the largest obstacles to the successful conversion of putative therapeutics into effective treatments is the inability to deliver these agents past the CNS blood-brain barrier (BBB) in a reliable, targeted, and homogeneous way. Convective flow, using currently available approaches for drug delivery, including systemic delivery, intrathecal and/or intraventricular distribution, and polymer implantation, have led to its application in research studies and clinical trials. The authors review the biophysical principles of convective flow and the technology, properties, and clinical applications of convective delivery in the CNS.

Biophysical Principles of Convective Flow

Within the extracellular space of the CNS, fluids and agents move either by diffusion or by bulk flow. Diffusive flux (J) depends on the concentration gradient (VC), as stated by Fick’s law, J = –DVC, where tissue diffusivity (D) is highly dependent on the molecular weight of the molecule. Unfortunately, effective diffusion times are long for macromolecular therapeutics, and transport depends on large concentration gradients, often requiring unacceptably high
concentrations near the drug source. As a result, extensive distribution by diffusion is not possible for macromolecular therapeutic agents of interest for most disorders, and practically, diffusive penetration in brain tissue is generally limited to a few millimeters.57

Bulk flow is extracellular fluid flow that can exist under either normal or abnormal (for example, edema) conditions. Within the CNS, these flows can be modeled by treating tissue as a hydrated porous medium consisting of fluid and solid phases, in which the fluid phase is the interconnected interstitial space and the solid phase is the aggregation of cellular, vascular, and extracellular matrix constituents. Bulk flow is driven by fluid pressure gradients that exist within tissues and can be modeled by Darcy’s law, which asserts that the velocity of fluid (v) is directly related to the tissue pressure gradient (∇p): v = –K∇p, where hydraulic conductivity (K) is a measure of flow conductance. Compared with diffusion, bulk flows are largely independent of molecular weight.

In CED, a cannula is discretely introduced directly into the nervous system interstitial spaces with its tip at the target site. Controlled infusions induce bulk flows, which distribute infusate over large volumes within the extracellular space and are capable of achieving micrometer depths of penetration. During CED, transport to surrounding tissue depends on bulk flow, as well as diffusion and clearance loss due to permeation and reaction. The balance between these sources and sinks determines the overall penetration distance. Theories for CED at a constant infusion rate into homogeneous brain tissues provide the simplest possible expression to describe concentration profiles and penetration distances. In this model, interstitial bulk velocity (v) varies radially around a spherical cannula source and is solved using the continuity equation (differential mass balance of water in brain tissue) and Darcy’s law: v(r) = q/(4pr²), where q is the infusion flow rate and r is the radius from the cannula tip. More complex analytical solutions for infusion from a cannula source have also been developed that account for water uptake in tissue and tissue swelling with pressurization.5,17,85,103

Tissue transport of the infused species is described by a differential mass balance relation governing tissue concentration as a function of space and time, which is formulated to account for convection, diffusion, metabolism, binding, and net transport across the microvasculature: ∂C/∂t = D∇²C – ∇·(vC/∫f) – kₘₐ C/∫f – P × s(C/f – C₀), where kₘₐ is the first-order metabolic rate constant in tissue (the rate of degradation), f is the fluid volume fraction (porosity), C₀ is the plasma concentration of infused solute (usually 0), and P × s is the product of permeability coefficient and surface area per volume of tissue that accounts for the passive movement of infusate across vessels. When needed, f can be replaced by another constant accounting for weak binding of infusate species to tissue components.68

This equation is generally solved numerically. Simulations for nonbinding 180-kD macromolecules delivered at 3 μl/min from a spherical source into homogeneous tissue are associated with radial penetrations of 1.5 cm in 12 hours with relatively flat and uniform profiles (“square-shaped” concentration profile) that decline dramatically at the advancing front (Fig. 1).65,66 Initially, transport is dominated by convection, and the advancing front approaches a step function. With time, the steepness and bluntness of the advancing front decreases because of the superimposed contributions of diffusion and clearance. After the cessation of infusion, further transport of the drug will occur through tissue by continued convection (as long as a pressure gradient from the infused region persists) and by diffusion until clearance mechanisms clear the drug entirely from tissue. This phase should be considered in any dose-response estimation.

Recently, Sarntinoront and colleagues100–102 developed an integrated finite element formalism model that can be used to optimize the distribution of substance P–associated protein toxin to the spinal cord for chronic neuropathic pain treatment. This model accounts for the anisotropic transport in the spinal cord, the anatomical boundaries throughout the spinal cord substance, as well as substance P–associated protein toxin binding/uptake, metabolism, and dose response. Further, groups have used computational analyses based on diffusion tensor imaging (an MRI technique that measures the restricted diffusion of water in nervous system tissues and measures axonal alignment) that account for preferential fluid flow and diffusion transport directions, which can vary in the extracellular spaces within complex nervous system anatomical structures.39,40,55,89,101

Convective Delivery Technology

Infusion Apparatus

Direct transmission of a small controlled pressure differential is required for the steady flow of infusate into the extracellular CNS spaces. Constant and reliable pressure transmission during infusion demands a noncompliant infusion system. To minimize compliance in the infusion apparatus and reduce infusate binding, infusate reservoirs, tubing, and cannula are derived from noncompliant materials, including silicate, hardened plastic, and metals. The
minimization or elimination of system compliance allows precise delivery of the infusate in either continuous or bolus convective flow patterns. Large-animal (primate) data indicate that convective distribution of the infusate in the CNS is similar, feasible, and safe using either flow pattern if a noncompliant system is utilized.\textsuperscript{71}

**Infusion Cannula**

Mathematical modeling, preclinical animal data, and clinical data indicate that the infusion cannula design affects the success of convective delivery to the CNS by reducing infusate leakback around the cannula at higher infusion rates and by eliminating intraparenchymal air entrainment (associated with catheters with an inner stylet) during insertion.\textsuperscript{14,41,68,90,114} Specifically, the minimization of cannula tip diameter, which reduces tissue expansion, is a way to minimize leakback during infusion and has been demonstrated by mathematical modeling and animal data.\textsuperscript{66} Further, avoiding entrainment of intraparenchymal air that occurs with malleable infusion catheters upon removal of the rigid inner stylet needed for accurate placement of the tip is necessary to avoid preferential distribution in the tissue air pocket. These critical cannula properties have been achieved through the development of inner infusate cannula–outer guide cannula combinations.\textsuperscript{22,31,62} hollow fiber tubes,\textsuperscript{77,78} as well as step-design cannulae.\textsuperscript{41,54}

**Properties of Convective Delivery**

**Bypassing the BBB**

Because putative therapeutics are perfused directly into the CNS using CED, the delivery of infusate bypasses the BBB. Further, the compounds that do not cross the BBB are the ideal agents to distribute via CED. Therapeutic compounds that do not readily penetrate the BBB from the systemic circulation, when delivered by convection, remain sequestered on the abluminal side of the BBB within the perfused parenchyma for prolonged periods until they are metabolized and cleared from the interstitial spaces.\textsuperscript{17,21,60,69} Consequently, large-molecular-weight (>400 D) and/or hydrophilic compounds are best for CED. These features of CED in the CNS permit manipulation of precisely targeted regions or regulation of broader anatomical regions via upstream or downstream effects of infusate delivery.

**Targeted Delivery**

Because infusate is distributed directly into site-specific regions of the CNS from an infusion cannula, the distribution of therapeutic agents is targeted. Previous studies have demonstrated that deep brain nuclear targets can be selectively perfused with small- and large-molecular-weight compounds (Fig. 2).\textsuperscript{32,54,57} Moreover, large-animal data indicate retrograde or anterograde transport of delivered therapeutics, including proteins, and transgene expression of products delivered by viral capsids or bacteriophage can be distributed from the perfused CNS region to other distant nonperfused regions via interconnecting white matter tracts in a highly predictable manner.\textsuperscript{30,38,42,54} These features of CED in the CNS permit manipulation of precisely targeted regions or regulation of broader anatomical regions via upstream or downstream effects of infusate delivery.

**Homogeneous Distribution**

Unlike diffusion-driven distribution, which results in limited tissue penetration from the diffusive surface (1 to 2 mm) and a steep drop-off in concentration over that distance (250- to 1000-fold decrease),\textsuperscript{6,105} bulk flow of the infusate during CED permits homogeneous distribution of infusate throughout a perfused tissue region. Autoradiographic analysis of infusate distribution in a large-animal brain, brainstem, spinal cord, and peripheral nerve demonstrates the homogeneity of convective delivery.\textsuperscript{7,58,63,72} Analysis of the distribution of radiolabeled compounds in animals euthanized immediately after completing a brief infusion via CED demonstrates a homogeneous “square-shaped” distribution pattern in gray and white matter consistent with a uniform high concentration of infusate over a perfused CNS region. Thus, biological and pharmacological effects that depend on the concentration of a...
molecule of interest exceeding a certain threshold can be precisely targeted.

Reproducible Distribution
Convective delivery in the CNS is reliable. Because convective distribution of an infusate occurs in the interstitial space, the distribution volume achieved by CED of a given infusate volume is inversely proportional to the size of the extracellular space available in the target tissue. Specifically, greater tissue distribution (per infusion volume) occurs in regions of the CNS with a smaller interstitial space. Alternatively, infusion into CNS regions with an expanded extracellular space (for example, regions with vasogenic edema) results in a reduction in the volume of tissue distribution (per infusion volume). Distribution volume to infusion volume ratios in naïve gray or white matter of the brain, spinal cord, and peripheral nerves range from 4:1 to 7:1.5,22,34,58,63 Perfusion into the tightly compacted white matter fibers of the brainstem is associated with larger distribution volume to infusion volume ratios, generally in the range of 6:1 to 10:1.60,72,99 This property of CED allows large, clinically relevant volumes of CNS tissue to be perfused relatively rapidly.

Clinically Relevant Distribution
Small or large clinically relevant volumes of perfusion are possible with convective delivery in the CNS. While convective perfusion of nuclear targets is feasible during an acute infusion (over minutes to hours), prolonged infusion can be used to completely perfuse significant regions of a cerebral hemisphere, the brainstem, and the spinal cord (Fig. 3).48,68 A significant limitation of other conventional delivery techniques is the inability to distribute drug in high concentrations in a targeted manner over large regions of the CNS. Because CED relies on bulk flow to move small- and large-molecular-weight infusate throughout the nervous system, large regions of nervous system structures can be perfused with drug in a relatively short period of time, provided that the drug is not too rapidly cleared. This property permits treatment of large regional disorders.

Anisotropic and Isotropic Flow Patterns
While distribution of infusate in gray matter is isotropic (approximating a spherical distribution pattern around the tip of the infusion cannula), convective distribution of infusate into white matter is anisotropic and occurs preferentially along parallel white matter tracts.14,58,63 The preferential infusate flow along white matter tracts can be exploited to fill large regions of white matter from a single infusion point source.44,49,68 Specifically, infusion in the cerebral white matter tracts (for example, corona radiate) can be used to rapidly fill regions of the cerebral hemisphere and immediately subjacent cortical gray matter from a single infusion cannula.58 Similarly, convective infusion into the parallel lateral corticospinal tracts results in perfusion over several segments of the spinal cord.58

Effects of Anatomical Boundaries
Convective tissue perfusion efficiency near pial and ependymal surfaces can be adversely affected once the leading edge of infusion meets these anatomical surfaces. Primate and clinical infusion data demonstrate that once the leading edge of a convective infusion encounters a pial or ependymal surface, the tissue distribution volume to infusion volume ratios decline as leakage of the infusate (small and large molecular weight) into the CSF of the cistern or ventricle occurs.56 Once infusate begins to cross these surfaces, a portion of the total infusate is lost into the CSF and is not distributed to tissue, reducing the distribution. The distribution volume will continue to decline compared with the distribution that would otherwise occur as a larger portion of the infusion volume encounters a pial or ependymal surface and a larger fraction of the total infusate is lost to the CSF space.

Application Over a Wide Range of Compounds
Convective-enhanced delivery permits the distribution of compounds with a wide range of molecular weights in the CNS. Convective delivery has been used to deliver small compounds (< 1 kD), including chemotherapeutic agents, amino acids, and low-molecular-weight imaging tracers. Alternatively, CED has been used to distribute proteins, virus and/or virus-sized particles, liposomes, and nanoparticles.24,33,42,106 While small- and most large-molecular-weight compounds will distribute by convective flow in a similar manner, viruses, virus-sized particles, and nanoparticles have restricted flow (tissue distribution volume to infusion volume ratio of 2:1 to 3:1).13,42,106 This reduction in delivery efficiency is attributed to limits in the size of the extracellular space in the CNS, which has been estimated to be on the order of 100 nm.25,108 and to certain features of the infused nanoparticle.42

Imaging of Convective Distribution
Use of co-infused surrogate imaging tracers to track convective distribution in real time provides an opportunity to increase the effectiveness and safety of CED, to permit reliable assessment of therapeutic efficacy (by confirming successful delivery and distribution), and to better
define the properties of CED in the CNS. Preclinical data demonstrate that CT and MRI tracers can be co-infused to accurately assess convective infusate distribution (Fig. 3). Because CED relies on bulk flow and because most large- and many small-molecular-weight compounds distribute at a similar rate during the typical time course of CED, surrogate tracers that differ substantially in size from the putative therapeutic can often be used to track drug distribution over infusion volumes necessary to treat many neurological disorders.

There are small-molecular-weight (< 1 kD) contrast agents for CT and MRI that are approved for clinical use and that can be used as surrogate tracers to track distribution during CED. Real-time imaging of CED is possible and has been used safely in animal and clinical trials to track small- and large-molecular-weight therapeutic compounds. While the small-molecule surrogate imaging tracers iopamidol and Gd-DTPA will accurately track large therapeutic compounds over infusate volumes sufficient to perfuse discrete disease-specific regions, the use of these surrogate tracers for tracking macromolecular distribution over large volumes and with prolonged infusion times will not accurately reflect the distribution of the drug, because of the tracer’s long-term clearance by microvascular efflux and the long-term diffusional broadening associated with its low molecular weight.

In the case of the CT contrast agent iopamidol, experiments have shown that this small-molecule surrogate tracer accurately provides estimates of dextran (70 kD) distribution volumes (that is, less than 20% difference between imaged and actual distribution volumes) provided that infusion rates ($q_i$) are not too slow for a given total infusion volume ($V_i$). For these specific compounds, modeling has shown that for a desired $V_i$ (in $\mu\text{l}$), $q_i$ (in $\mu\text{l}/\text{min}$) must be chosen so that $q_i \geq V_i/600$. From such empirical relationships, it is likely that many neurological disorders can be investigated with the expectation that the infusate volume required would be accurately tracked using a small-molecular-weight contrast agent—provided that the therapeutic compound, large or small, is negligibly reactive and confined to the extracellular space.

Because CED relies on infusate delivery into the interstitial spaces of the CNS, T2- and diffusion-weighted real-time MRI has been used to track drug distribution. Qualitative T2- and diffusion-weighted changes have been shown surrounding the infusion cannulae and areas of infusate distribution in these studies. Nevertheless, when qualitative autoradiographic assessment of the accuracy of the T2- and diffusion-weighted sequences was performed, it was revealed that these MRI sequences significantly underestimated the distribution of both small and large molecules. Specifically, these imaging techniques underestimated the volume of distribution of small-sucrose) and large- (albumin) molecular-weight distribution using CED by 49%—60%.

Safety of Convective Delivery

Increasing the fluid content of the interstitial space leads to edema in the perfused region. Previous studies have shown, however, that even when 180 $\mu\text{l}$ was infused into a rat brain over 2 hours (a volume sufficient to fill more than an entire rat hemisphere), intracranial pressure never rose above 8 mm Hg. While brain edema in eloquent areas can cause transient neurological symptoms, the deficits are reversible if intracranial pressure is maintained in the normal range and the vascular supply to the brain is not impaired. Since intratissue pressure remains in the normal range with CED, the infusion of large volumes (even with near hemisphere filling) has no effect on blood flow to the perfused regions. This explains why permanent neurological injury has not occurred as a result of large-volume infusions. These clinical findings are also confirmed by histological studies showing no tissue damage in infused regions after CED.

It is possible that convective delivery could cause expansion of the interstitial space and symptomatic edema infusion at high rates, prolonged infusion (for example, chronic infusions), and infusion of very large volumes (for example, holohemispheric). The excess fluid, especially with rapid or high-volume infusions, in the region of a preexisting mass, such as a tumor, could induce herniation with its attendant serious effects. Despite these concerns, irreversible neurological deficits and significant intracranial pressure increases associated with convective delivery rarely occur in small animals, nonhuman primates, or humans (over 200-ml infusions into the brain in patients with brain tumors). If deficits occur, they rapidly reverse with the cessation of infusion and/or glucocorticoid administration.

Despite the well-defined safety of CED of therapeutics in the CNS, there have been reported cases of lasting or irreversible neurological changes in animal studies and human clinical trials. These neurological changes have been attributed to prolonged edema or effects of the drug on tumor (in tumor-specific trials and/or the putative therapeutic infused at doses in a potentially tissue toxic range). Lasting or irreversible neurological changes directly attributed to the convective infusion of substances in the CNS have not occurred over a range of infusate rates, including rates up to 10 $\mu\text{l}/\text{min}$.

Clearance of Solutes After CED

During the postinfusion phase, solute (particularly small molecules) continues to redistribute, both via natural bulk flow and diffusion. However, as a result of continuing local clearance of the infusate, diffusional expansion of the perfused region is limited for most agents. Further, because of the square-shaped distribution curve associated with most CED protocols, postinfusion diffusion is confined to the steep edge of the distribution, and this generally contributes negligible extension to the tissue penetration depth already achieved at the end of the infusion proper. Only in the case of small infusion volumes would such diffusion significantly increase the tissue distribution volume.

Clinical Application of Convective Delivery

Convective Delivery Paradigms

Targeted Therapeutics

A number of new targeted therapeutics have been developed to address a wide variety of neurological disor-
The properties of CED are being exploited to deliver therapeutic agents to site-specific regions of the CNS to investigate a variety of disorders that are currently untreatable or cannot be addressed using other available CNS drug delivery methods. Ideal agents for delivery by convection include those that are pathologically selective, have a targeted CNS region for application, are metabolized at rates that permit them to be therapeutic, and do not effectively cross the BBB. Therapeutic approaches can selectively lesion or augment diseased CNS cell populations, regulate abnormal metabolic disease pathways, transiently alleviate pathophysiology, and/or target tumor cells for selective destruction. Neurological disorders and agents that have been investigated using CED are described in Table 1.

Physiological Manipulation

The ability to transiently augment or suppress the activity of targeted components of diseased neuronal circuits by selectively delivering neuroactive compounds presents a new opportunity to derive deeper insight into disease pathophysiology. Specifically, the ability to directly correlate the effects of the physiological manipulation of diseased brain structures with clinical effects represents an opportunity for understanding mechanisms of disease, introducing new methods of diagnosis, developing new treatments, as well as introducing and using new therapeutic agents. There are immediate opportunities to better understand disorders that have site-specific pathophysiological features, including Parkinson’s disease, essential tremor, obesity, anorexia nervosa, epilepsy, and behavioral disorders.

Future of Real-Time Imaging to Clinical Treatment Paradigm

Previously, CED using new putative therapeutic agents was clinically applied in isolated cases or Phase I/II trials (Table 1). The only CED Phase III trial performed to date involved the infusion of the glioma toxin interleukin-13 bound to Pseudomonas exotoxin in patients with glioblastoma multiforme. This treatment did not show a significant increase in patient survival compared with treatment with bis-chlorethylNitrosourea (BCNU)–impregnated Gliadel wafers. Because real-time imaging of co-infused surrogate MRI agents was not used routinely and drug distribution could not be accurately established, coverage of the targeted tissues was not confirmed. Moreover, in most of the clinical trials, the investigation has combined a new (experimental) therapeutic agent with CED, a new drug delivery approach. The advantages and limitations of convective delivery in various clinical circumstances, as well as the efficacy of various agents, are not known. These circumstances underscore the need for real-time imaging of drug distribution, or surrogates of drug distribution, during CED in clinical studies and/or applications to verify targeting.

With improved CED procedures and infusion systems, emerging clinical data from real-time imaging has demonstrated that CED can treat clinically relevant regions and volumes in a targeted manner. Further, these early clinical data underscore the properties described in preclinical studies, enhance safety by permitting controlled distribution, and give direct insight into therapeutic efficacy. Moreover, data from real-time imaging of convective delivery in the CNS provide understanding of the properties of CED in various clinical circumstances. Specifically, critical information about the optimal infusion rate, effect of pial/ependymal surfaces, effect of previous surgery, vaso- genic edema (when present), and preferred pathways of infusate flow can be derived from these studies.

Limitations of CED

While there are a number of advantages of CED in distributing therapeutic compounds to the CNS, there are also potential limitations. First, because CED requires cannula placement, it is more invasive than systemic delivery techniques. Second, drugs that easily cross the BBB will probably not be good drugs to deliver via CED, as they can readily leak through the CNS vasculature and into the systemic circulation. Third, therapeutics that are rapidly metabolized or taken up by CNS cellular components may limit the spread of infusate. Finally, improved targeting technologies that account for anatomical boundaries (that is, ependymal surfaces, pial surfaces, resection cavities, gray-white junctions) or pathological structural changes (that is, vasogenic edema or necrotic areas) will alter infusate flow and distribution and require longer infusion or multiple cannula placements to achieve therapeutic infusate coverage.

### Table 1. Convective delivery for the treatment of neurological disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Therapeutic Agent</th>
<th>References</th>
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<td>Metabolic disorder</td>
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<td>Neuronal ceroid lipofuscinosis</td>
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AADC = aromatic L-amino acid decarboxylase; AAV = adenovirus-associated virus; CLN2 = neuronal ceroid lipofuscinosis; CNTF = ciliary neurotrophic factor; GAD = glutamic acid decarboxylase; GDNF = glial-derived neurotrophic factor.
Predictive Modeling for Clinical Application

As the biomechanical principles of CED are better understood and confirmed via real-time imaging under a variety of pathological conditions, defined and accurate preclinical predictive modeling based on imaging should be feasible across a wide spectrum of neurological disease states. The ability to accurately predict optimal cannula placement and the capability to precisely anticipate infusate distribution based on preinfusion CT and MRI planning will be important for clinical trial development.40,55,56,89,102

References

32. Heiss JD, Walbridge S, Asthagiri AR, Lonser RR: Image-guided convection-enhanced delivery of muscitom to the


97. Sampson JH, Brady M, Raghavan R, Mehta AJ, Friedman...


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Conception and design: Lonser, Sarntinoranont, Oldfield. Acquisition of data: all authors. Analysis and interpretation of data: Sarntinoranont, Morrison, Oldfield. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lonser. Administrative/technical/material support: Lonser.

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