Published in final edited form as:

Neurosurg Clin N Am. 2017 October ; 28(4): 615–622. doi:10.1016/j.nec.2017.05.012.

Imaging of convective drug delivery in the nervous system

Russell R. Lonser, M.D.

Department of Neurological Surgery, Ohio State University Wexner Medical Center, 410 West 10th Avenue, Doan 1047, Columbus, Ohio 43210

Synopsis

Convection-enhanced delivery (CED) permits for the direct homogeneous delivery of small and large molecular weight putative therapeutics to the nervous system in a manner that bypasses the blood-nervous system barrier. The development of co-infused surrogate imaging tracers (for computed tomography and magnetic resonance imaging) allows for the real-time, non-invasive monitoring of infusate distribution during convective delivery. Real-time image monitoring of convective distribution of therapeutic agents, insures that targeted structures/nervous system regions are adequately perfused, enhances safety, informs efficacy (or lack thereof) of putative agents and provides critical information regarding the properties of CED in normal and various pathologic tissue states.

Keywords

convection-enhanced delivery; drug delivery; infusion; imaging; nervous system surrogate imaging tracer

Introduction

The rapidly expanding biologic understanding of the pathologic mechanisms underlying a variety of neurologic disorders has led to the development of numerous promising putative therapeutics to treat ineffectively or untreatable neurologic diseases. While these potentially therapeutic compounds have shown great promise during *in vitro* and in translational (animal) investigations, they have not realized clinical therapeutic success. A major obstacle to the safe and successful implementation of new therapeutic compounds for neurologic disease treatment has been the inability to provide their targeted and effective distribution to the nervous system across the blood-nervous system barrier (BNSB) using currently available delivery techniques (including systemic, intrathecal/intraventricular or drug-impregnated polymer delivery).^{1–6}

Phone: 614-685-6985, russell.lonser@osumc.edu.

Disclosure Statement: The author holds a patent for imaging of convection-enhanced delivery.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Systemic drug delivery is limited by the BNSB, which permits only small (less than 400 Da molecular weight) and lipophilic molecules into the nervous system parenchyma.^{5,7} Intrathecal/intraventricular and polymer implantation delivery are driven by diffusion that limits drug distribution to 2 to 4 millimeters (with a steep exponential drop in concentration) from the drug exposed surface.^{1,6} Convection-enhanced delivery (CED) relies on infusate bulk flow and can be used to overcome the limitations of other delivery techniques to directly distribute therapeutic compounds to target regions in the nervous system in a manner that bypasses the BNSB. Recently, co-infused surrogate imaging tracers (computed tomography [CT] and magnetic resonance [MR]-imaging) have been developed to monitor convective delivery in real-time.^{8–24}

Convection-Enhanced Delivery

The characteristics of convective delivery of infusate in the nervous system are based on bulk flow properties.^{25–27} The bulk flow (or convective flow) that drives CED is derived from a syringe pump that generates a small infusate hydrostatic pressure gradient that is transmitted through a non-compliant infusion apparatus to an infusion cannula.^{26,27} Based on its bulk flow properties, convective delivery reliably (with region dependent volume of infusion to volume of tissue distribution ratios in the range of 2:1 to 10:1) and homogeneously (“square-shaped” distribution pattern) distributes infusate to targeted regions of the peripheral or central nervous system.^{8–10,27–32} Because infusate is distributed directly to the nervous system parenchyma via a cannula using CED, the BNSB is bypassed and agents that do not penetrate this vascular barrier are ideally suited for CED, as they do not readily efflux back into the vascular system and remain sequestered on the abluminal (parenchymal) side of the BNSB for prolonged periods of time.

Imaging Convective Delivery

Surrogate Tracers

Real-time imaging convective drug delivery—Effective real-time imaging of convective drug delivery in the nervous system is critical for several reasons. First, it can confirm adequate and accurate drug distribution, which ensures that a targeted anatomic structure or region is sufficiently treated.³³ Second, it informs understanding of drug efficacy (or lack thereof). Only by understanding if drug was effectively delivered, can efficacy be determined.^{34,35} Third, it enhances safety by making certain that drug delivery is limited to the targeted site. Fourth, data derived from infusions can be used to directly inform predictive infusate modeling, which could optimize cannula placement in the future.¹⁷ Finally, real-time imaging provides understanding of convective delivery properties in normal or diseased nervous system tissues.^{17,36} Better understanding of the properties of CED, including optimal rate of delivery, as well as the effects of edema, volume loss in degenerative conditions and anatomic boundaries/surfaces, will enhance delivery reproducibility and reliability.

Rationale for surrogate imaging tracers—Currently, the most developed, readily applicable and effective method for real-time imaging of CED is the use of surrogate imaging tracers. Surrogate imaging tracers are co-infused (rather than directly attached to

drug) with putative therapeutics. These surrogate agents can be detected by CT-scanning, MR-imaging or both methods during convective delivery.^{8–21,37} Features of surrogate imaging agents that are ideal and/or critical include an excellent safety profile, can accurately track a wide range of co-infused therapeutic agents, are detected by non-invasive imaging methods, provide clear well-defined imaging with high spatial resolution, are readily available/developed, can be detected by widely available imaging techniques and have no effect on co-infused drug action. Data from preclinical and clinical investigations have defined several CT and MR-imaging surrogate agents.

CT-scanning surrogate imaging tracers—Small (iopamidol) and large (iopanoic acid–labeled albumin; greater than 70,000 Da) molecular weight surrogate CT-scanning tracers have been studied in rodent and non-human primate models using convective delivery.^{11,38} These surrogate imaging agents provided clear real-time well-defined imaging using CT-scanning (Figure 1) without evidence of clinical or tissue toxicity. The tracking accuracy of the small (iopamidol) commercially available tracer, based on quantitative autoradiography, for a small (sucrose, 359 Da) and large molecule (dextran, 70,000 Da) infusate was excellent (19.7% and 7.5% difference in imaged volume versus actual distribution, respectively) (Figure 2). These studies demonstrated the safety, feasibility, accuracy and utility of using a CT-scanning tracer paradigm for convective drug delivery.

MR-imaging surrogate tracers—Because small molecular weight MR-surrogate imaging tracers (gadolinium [Gd]-diethylenetriamine pentaacetic acid [Gd-DTPA]; 983 Da and gadoteridol; 559 Da) are commercially available and because these tracers can be used to track a wide range of putative therapeutic agent, they have been the best studied surrogate imaging tracers. These compounds have been investigated extensively in rodent and non-human primate models.^{10,16,39–42} These surrogate MR-imaging agents provided clear real-time, well-defined, high resolution, imaging using MR-scanning (Figure 3) without evidence of clinical or tissue toxicity. The tracking accuracy of these small molecular weight Gd-based compounds co-infused with small (muscimol, 114 Da) and large molecules (proteins; adeno-associated viruses, 24 nm; M13 bacteriophage, 900 nm)^{43–45} is excellent (Figure 4).

To optimize tracking accuracy of convective drug delivery over a wide size range of putative therapeutic agents using small commercially available Gd-based surrogate tracers (Gd-DTPA and gadoteridol), the effect of varying the concentration of these Gd- surrogate tracer concentrations has been investigated. Asthagiri and colleagues⁴⁶ demonstrated that a 5 mM concentration of Gd-DTPA most accurately tracked a wide size range of putative therapeutic agents from small molecules (less than 400 Da) to large proteins (70,000 Da).^{12,15} However, tracking of nanometer-sized molecules, including adeno-associated virus and bacteriophage, was most accurate using a lower concentration of Gd-DTPA or gadoteridol (1 mM).^{21,43,44} These findings have been the basis for determining the most accurate concentrations of surrogate imaging tracers in clinical trials employing various therapeutic compounds.

Other MR-imaging surrogate tracers—Several large molecular weight imaging surrogate tracers (Gd-based compounds conjugated to proteins, including albumin; 70,000 Da or more) have been investigated in animal models.^{10,13,47,48} Like low molecular weight Gd-based imaging surrogate tracers, these high molecular weight surrogate MR-imaging

compounds have been shown to provide clear well-defined high resolution imaging in real-time with conventional MR-scanning. Further, these agents, in some cases, have been shown to accurately track a wide size range of putative therapeutic compounds. However, these surrogate imaging agents have not been used in CED clinical trials. Unlike Gd-DTPA and gadoteridol, these large molecule imaging agents are not commercially available. Nevertheless, large molecular weight surrogate MR-imaging agents may be useful to most accurately track very large infusion volumes of high molecular weight therapeutic compounds.

Other MR-imaging methods—Because CED relies on bulk flow perfusion of infusate into the interstitial spaces, T2-weighted and diffusion-weighted MR-imaging sequences have been used to track and approximate the volume of drug distribution.^{49–52} Based on the increase in extracellular fluid in the infused region, T2-weighted and diffusion-weighted sequences will frequently demonstrate a region of high intensity on MR-imaging that corresponds to the region of infusion. However, quantitative autoradiographic analysis using variably-sized radiolabeled compounds revealed that these sequences significantly underestimated the volume of infusion of both small (¹⁴C-sucrose) and large (¹⁴C-dextran) molecular weight compounds.⁵¹ Specifically, both T2-weighted and diffusion-weighted sequences underestimated the volume of distribution of the co-infused molecule by 49 to 60%.

Clinical application of surrogate imaging tracers—Based on the findings from animal studies,^{15,16,21,36,39} small molecular weight surrogate MR-imaging tracers (Gd-DTPA and gadoteridol) have been recently used in clinical trials that employ CED across a variety of neurologic disorders (e.g., tumor, neurodegenerative disease, metabolic disorders). Consistent with animal safety and feasibility studies, these surrogate imaging agents provide clear well-defined high-resolution imaging using MR-scanning (Figure 5) without evidence of clinical toxicity. Real-time MR-imaging demonstrates progressive filling of the target regions in patients. The ability to image in these cases enhances the reliability of convective infusion, permits infusion cessation after target perfusion, allows for on-the-fly adjustments that enhance the effectiveness of delivery, reveals the effect of normal/diseased structures on CED, allows for analysis of effective drug therapy using biologic markers and provides insight into rate optimization.^{14,16,17,41}

Potential limitations of surrogate tracers—Currently, low molecular weight CT-scanning (iopamidol) and MR-imaging (Gd-DTPA and gadoteridol) surrogate tracers are commercial available. Subsequently, these surrogate tracers have been the most studied and are currently employed for clinical use (i.e., MR-imaging surrogate tracers). Because of the bulk flow properties of CED, these small molecule surrogate tracers will move radially out from the infusate cannula through the nervous system interstitial spaces at similar rates to other small, as well as large molecules over a range of clinically-relevant tissue perfusion volumes. However, during large volume infusions, the diffusional rate of movement of a small molecule imaging tracer at the leading edge of the infusion may be faster than the rate of the large therapeutic molecule moving radially from the point of infusion by convection.

Consequently, a small molecule imaging tracer would over estimate distribution in this scenario.

The estimated tracking accuracy (20% or less volumetric difference between drug distribution estimated by imaged surrogate tracer and actual drug distribution) of a small surrogate imaging agent (iopamidol; 777 Da) for a large protein (dextran; 70,000 Da) over a range of volumes is defined by the equation,¹¹

$$V_i (\text{microliters}) = 600 \times q_v (\text{microliter/minute}),$$

where V_i is the infusion volume in microliters and q_v is the rate of convective infusion in microliters/minute. Consequently, increasingly larger volumes of a large molecular weight therapeutic infusion can be accurately tracked by a small molecular weight surrogate imaging tracer using increasingly higher rates of infusion. Nevertheless, most clinically relevant infusion volumes can be accurately tracked using rates of infusion employed in clinical trials.

The accuracy of surrogate imaging tracers to track CED in the nervous system is also based on several other criteria. Other features that could underlie a real-time tracer imaging mismatch with actual drug distribution include differences in rates of efflux, rates of degradation, interstitial tissue binding and metabolic rates.^{11,25} Finally, after infusion cessation, convective forces will be diminished and eventually disappear. Alternatively, diffusional forces will become more prominent and a small molecule tracer could diffuse faster than a large molecule therapeutic creating an overestimation of volume of drug distribution after completion of infusion (using a small molecule surrogate tracer and large molecule drug).

Conclusions

Real-time MR-imaging of surrogate imaging tracers to track convective delivery of putative therapeutics is now being employed in clinical trials. Imaging of CED ensures effective drug distribution, enhances safety and provides critical insights into the properties of convective delivery in normal and diseased nervous system tissues.

References

1. Blasberg RG, Patlak C, Fenstermacher JD. Intrathecal chemotherapy: brain tissue profiles after ventriculocisternal perfusion. *The Journal of pharmacology and experimental therapeutics*. 1975; 195(1):73–83. [PubMed: 810575]
2. Chen PY, Ozawa T, Drummond DC, et al. Comparing routes of delivery for nanoliposomal irinotecan shows superior anti-tumor activity of local administration in treating intracranial glioblastoma xenografts. *Neuro-oncology*. 2012
3. Langer R. New methods of drug delivery. *Science*. 1990; 249(4976):1527–1533. [PubMed: 2218494]
4. Morrison, PF. Distributed Models of Drug Kinetics. In: Atkinson, AJ., editor. *Principles of Clinical Pharmacology*. San Diego: Academic Press; 2001.

5. Pardridge WM. Drug delivery to the brain. *J Cereb Blood Flow Metab.* 1997; 17(7):713–731. [PubMed: 9270488]
6. Strasser JF, Fung LK, Eller S, Grossman SA, Saltzman WM. Distribution of 1,3-bis(2-chloroethyl)-1-nitrosourea and tracers in the rabbit brain after interstitial delivery by biodegradable polymer implants. *The Journal of pharmacology and experimental therapeutics.* 1995; 275(3):1647–1655. [PubMed: 8531140]
7. Muldoon LL, Alvarez JI, Begley DJ, et al. Immunologic privilege in the central nervous system and the blood-brain barrier. *J Cereb Blood Flow Metab.* 2013; 33(1):13–21. [PubMed: 23072749]
8. Lonser RR, Gogate N, Morrison PF, Wood JD, Oldfield EH. Direct convective delivery of macromolecules to the spinal cord. *Journal of neurosurgery.* 1998; 89(4):616–622. [PubMed: 9761056]
9. Lonser RR, Weil RJ, Morrison PF, Governale LS, Oldfield EH. Direct convective delivery of macromolecules to peripheral nerves. *Journal of neurosurgery.* 1998; 89(4):610–615. [PubMed: 9761055]
10. Lonser RR, Walbridge S, Garmestani K, et al. Successful and safe perfusion of the primate brainstem: in vivo magnetic resonance imaging of macromolecular distribution during infusion. *Journal of neurosurgery.* 2002; 97(4):905–913. [PubMed: 12405380]
11. Croteau D, Walbridge S, Morrison PF, et al. Real-time in vivo imaging of the convective distribution of a low-molecular-weight tracer. *Journal of neurosurgery.* 2005; 102(1):90–97. [PubMed: 15658101]
12. Murad GJA, Walbridge S, Morrison PF, et al. Real-time, image-guided, convection-enhanced delivery of interleukin 13 bound to *Pseudomonas* exotoxin. *Clin Can Res.* 2006; 12(10):3145–3151.
13. Szerlip NJ, Walbridge S, Yang L, et al. Real-time imaging of convection-enhanced delivery of viruses and virus-sized particles. *Journal of neurosurgery.* 2007; 107(3):560–567. [PubMed: 17886556]
14. Lonser RR, Warren KE, Butman JA, et al. Real-time image-guided direct convective perfusion of intrinsic brainstem lesions. Technical note. *Journal of neurosurgery.* 2007; 107(1):190–197. [PubMed: 17639894]
15. Murad GJ, Walbridge S, Morrison PF, et al. Image-guided convection-enhanced delivery of gemcitabine to the brainstem. *Journal of neurosurgery.* 2007; 106(2):351–356. [PubMed: 17410722]
16. Lonser RR, Schiffman R, Robison RA, et al. Image-guided, direct convective delivery of glucocerebrosidase for neuronopathic Gaucher disease. *Neurology.* 2007; 68(4):254–261. [PubMed: 17065591]
17. Chittiboina P, Heiss JD, Warren KE, Lonser RR. Magnetic resonance imaging properties of convective delivery in diffuse intrinsic pontine gliomas. *Journal of neurosurgery Pediatrics.* 2014; 13(3):276–282. [PubMed: 24410126]
18. Saito R, Krauze MT, Bringas JR, et al. Gadolinium-loaded liposomes allow for real-time magnetic resonance imaging of convection-enhanced delivery in the primate brain. *Experimental neurology.* 2005; 196(2):381–389. [PubMed: 16197944]
19. Krauze MT, McKnight TR, Yamashita Y, et al. Real-time visualization and characterization of liposomal delivery into the monkey brain by magnetic resonance imaging. *Brain research Brain research protocols.* 2005; 16(1–3):20–26. [PubMed: 16181805]
20. Fiandaca MS, Varenika V, Eberling J, et al. Real-time MR imaging of adeno-associated viral vector delivery to the primate brain. *NeuroImage.* 2009; 47(Suppl 2):T27–35. [PubMed: 19095069]
21. Su X, Kells AP, Salegio EA, et al. Real-time MR imaging with Gadoteridol predicts distribution of transgenes after convection-enhanced delivery of AAV2 vectors. *Molecular therapy: the journal of the American Society of Gene Therapy.* 2010; 18(8):1490–1495. [PubMed: 20551915]
22. Sampson JH, Brady ML, Petry NA, et al. Intracerebral infusate distribution by convection-enhanced delivery in humans with malignant gliomas: descriptive effects of target anatomy and catheter positioning. *Neurosurgery.* 2007; 60(2 Suppl 1):ONS89–98. discussion ONS98–89. [PubMed: 17297371]

23. Yin D, Valles FE, Fiandaca MS, et al. Optimal region of the putamen for image-guided convection-enhanced delivery of therapeutics in human and non-human primates. *NeuroImage*. 2011; 54(Suppl 1):S196–203. [PubMed: 19761848]
24. Richardson RM, Kells AP, Martin AJ, et al. Novel platform for MRI-guided convection-enhanced delivery of therapeutics: preclinical validation in nonhuman primate brain. *Stereotactic and functional neurosurgery*. 2011; 89(3):141–151. [PubMed: 21494065]
25. Lonser RR, Sarntinoranont M, Morrison PF, Oldfield EH. Convection-enhanced delivery to the central nervous system. *Journal of neurosurgery*. 2015; 122(3):697–706. [PubMed: 25397365]
26. Morrison PF, Laske DW, Bobo H, Oldfield EH, Dedrick RL. High-flow microinfusion: tissue penetration and pharmacodynamics. *The American journal of physiology*. 1994; 266(1 Pt 2):R292–305. [PubMed: 8304553]
27. Bobo RH, Laske DW, Akbasak A, Morrison PF, Dedrick RL, Oldfield EH. Convection-enhanced delivery of macromolecules in the brain. *Proceedings of the National Academy of Sciences of the United States of America*. 1994; 91(6):2076–2080. [PubMed: 8134351]
28. Wood JD, Lonser RR, Gogate N, Morrison PF, Oldfield EH. Convective delivery of macromolecules into the naive and traumatized spinal cords of rats. *Journal of neurosurgery*. 1999; 90(1 Suppl):115–120. [PubMed: 10413135]
29. Ratliff JK, Oldfield EH. Convection-enhanced delivery in intact and lesioned peripheral nerve. *Journal of neurosurgery*. 2001; 95(6):1001–1011. [PubMed: 11765815]
30. Weber FW, Floeth F, Asher A, et al. Local convection enhanced delivery of IL4-Pseudomonas exotoxin (NBI-3001) for treatment of patients with recurrent malignant glioma. *Acta neurochirurgica Supplement*. 2003; 88:93–103. [PubMed: 14531567]
31. Lopez KA, Tannenbaum AM, Assanah MC, et al. Convection-enhanced delivery of topotecan into a PDGF-driven model of glioblastoma prolongs survival and ablates both tumor-initiating cells and recruited glial progenitors. *Cancer research*. 2011; 71(11):3963–3971. [PubMed: 21464045]
32. Laske DW, Morrison PF, Lieberman DM, et al. Chronic interstitial infusion of protein to primate brain: determination of drug distribution and clearance with single-photon emission computerized tomography imaging. *Journal of neurosurgery*. 1997; 87(4):586–594. [PubMed: 9322847]
33. van Putten EH, Wembacher-Schroder E, Smits M, Dirven CM. Magnetic Resonance Imaging-Based Assessment of Gadolinium-Conjugated Diethylenetriamine Penta-Acetic Acid Test-Infusion in Detecting Dysfunction of Convection-Enhanced Delivery Catheters. *World neurosurgery*. 2016; 89:272–279. [PubMed: 26862025]
34. Sampson JH, Archer G, Pedain C, et al. Poor drug distribution as a possible explanation for the results of the PRECISE trial. *Journal of neurosurgery*. 2010; 113(2):301–309. [PubMed: 20020841]
35. Jahangiri A, Chin AT, Flanigan PM, Chen R, Bankiewicz K, Aghi MK. Convection-enhanced delivery in glioblastoma: a review of preclinical and clinical studies. *Journal of neurosurgery*. 2017; 126(1):191–200. [PubMed: 27035164]
36. Jagannathan J, Walbridge S, Butman JA, Oldfield EH, Lonser RR. Effect of ependymal and pial surfaces on convection-enhanced delivery. *Journal of neurosurgery*. 2008; 109(3):547–552. [PubMed: 18759589]
37. Regino CA, Walbridge S, Bernardo M, et al. A dual CT-MR dendrimer contrast agent as a surrogate marker for convection-enhanced delivery of intracerebral macromolecular therapeutic agents. *Contrast media & molecular imaging*. 2008; 3(1):2–8. [PubMed: 18335478]
38. Nguyen TT, Pannu YS, Sung C, et al. Convective distribution of macromolecules in the primate brain demonstrated using computerized tomography and magnetic resonance imaging. *Journal of neurosurgery*. 2003; 98(3):584–590. [PubMed: 12650432]
39. Gimenez F, Krauze MT, Valles F, et al. Image-guided convection-enhanced delivery of GDNF protein into monkey putamen. *NeuroImage*. 2011; 54(Suppl 1):S189–195. [PubMed: 20080195]
40. Salegio EA, Kells AP, Richardson RM, et al. Magnetic resonance imaging-guided delivery of adeno-associated virus type 2 to the primate brain for the treatment of lysosomal storage disorders. *Human gene therapy*. 2010; 21(9):1093–1103. [PubMed: 20408734]
41. Voges J, Reszka R, Gossmann A, et al. Imaging-guided convection-enhanced delivery and gene therapy of glioblastoma. *Annals of neurology*. 2003; 54(4):479–487. [PubMed: 14520660]

42. Ding D, Kanaly CW, Bigner DD, et al. Convection-enhanced delivery of free gadolinium with the recombinant immunotoxin MR1-1. *Journal of neuro-oncology*. 2010; 98(1):1–7. [PubMed: 19898744]
43. Ksendzovsky A, Walbridge S, Saunders RC, Asthagiri AR, Heiss JD, Lonser RR. Convection-enhanced delivery of M13 bacteriophage to the brain. *Journal of neurosurgery*. 2012; 117(2):197–203.
44. Richardson RM, Kells AP, Rosenbluth KH, et al. Interventional MRI-guided putaminal delivery of AAV2-GDNF for a planned clinical trial in Parkinson's disease. *Molecular therapy: the journal of the American Society of Gene Therapy*. 2011; 19(6):1048–1057. [PubMed: 21343917]
45. Heiss JD, Walbridge S, Asthagiri AR, Lonser RR. Image-guided convection-enhanced delivery of muscimol to the primate brain. *Journal of neurosurgery*. 2010; 112(4):790–795. [PubMed: 19715424]
46. Asthagiri AR, Walbridge S, Heiss JD, Lonser RR. Effect of concentration on the accuracy of convective imaging distribution of a gadolinium-based surrogate tracer. *Journal of neurosurgery*. 2011; 115(3):467–473. [PubMed: 21619409]
47. Saito R, Bringas JR, McKnight TR, et al. Distribution of liposomes into brain and rat brain tumor models by convection-enhanced delivery monitored with magnetic resonance imaging. *Cancer research*. 2004; 64(7):2572–2579. [PubMed: 15059914]
48. Krauze MT, Vandenberg SR, Yamashita Y, et al. Safety of real-time convection-enhanced delivery of liposomes to primate brain: a long-term retrospective. *Experimental neurology*. 2008; 210(2): 638–644. [PubMed: 18295759]
49. Sampson JH, Raghavan R, Provenzale JM, et al. Induction of hyperintense signal on T2-weighted MR images correlates with infusion distribution from intracerebral convection-enhanced delivery of a tumor-targeted cytotoxin. *AJR American journal of roentgenology*. 2007; 188(3):703–709. [PubMed: 17312057]
50. Rosenbluth KH, Martin AJ, Bringas J, Bankiewicz KS. Evaluation of pressure-driven brain infusions in nonhuman primates by intra-operative 7 tesla MRI. *Journal of magnetic resonance imaging: JMRI*. 2012; 36(6):1339–1346. [PubMed: 22887937]
51. Iyer RR, Butman JA, Walbridge S, Gai ND, Heiss JD, Lonser RR. Tracking accuracy of T2- and diffusion-weighted magnetic resonance imaging for infusate distribution by convection-enhanced delivery. *Journal of neurosurgery*. 2011; 115(3):474–480. [PubMed: 21663409]
52. Richardson RM, Gimenez F, Salegio EA, et al. T2 imaging in monitoring of intraparenchymal real-time convection-enhanced delivery. *Neurosurgery*. 2011; 69(1):154–163. discussion 163. [PubMed: 21430597]

Key Points

- Direct convective delivery bypasses the blood-nervous system barrier and homogeneously distributes small and large molecular weight compounds to the nervous system.
- Surrogate imaging tracers (computed tomography and magnetic resonance imaging) permit real-time monitoring of convection-enhanced delivery to the nervous system.
- Real-time imaging ensures adequate convective delivery of therapeutics, enhances safety, informs efficacy and provides insight into convective delivery properties.

Figure 1.

Real-time coronal computed tomography scanning of iopamidol infusion into the right frontal lobe (white matter) of a non-human primate. Imaging reveals progressive well-defined distribution of iopamidol at various time points during infusion including 15 (A), 30 (B), 45 (C), 60 (D) and 75 microliters (E). *From Croteau D, Walbridge S, Morrison PF, et al. Real-time in vivo imaging of the convective distribution of a low-molecular-weight tracer. Journal of neurosurgery. 2005;102(1):90–97; with permission.*

Figure 2.

Coronal computed tomography scan (*left*) and corresponding quantitative autoradiogram (*right*) demonstrating the high anatomic and distribution accuracy of iopamidol (777 Da) as a surrogate tracer for ^{14}C -dextran (70,000 Da). *From Croteau D, Walbridge S, Morrison PF, et al. Real-time in vivo imaging of the convective distribution of a low-molecular-weight tracer. Journal of neurosurgery. 2005;102(1):90–97; with permission.*

Figure 3.

T1-weighted coronal magnetic resonance (MR)-imaging during infusion of gemcitabine (100 microliters) with surrogate tracer, gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA, white area), into a non-human primate brainstem. The region of infusion can be clearly seen progressively filling with infusate from the cannula tip (A; arrow) using MR-imaging of the pons every 30 minutes (A to E) until infusion completion. *From Murad GJ, Walbridge S, Morrison PF, et al. Image-guided convection-enhanced delivery of gemcitabine to the brainstem. Journal of neurosurgery. 2007;106(2):351–356; with permission.*

Figure 4.

Thalamic immunostaining for M13 bacteriophage (900 nm) and corresponding magnetic resonance imaging studies of thalamic infusion. (*Left*) Immunostaining for M13 bacteriophage demonstrates perfusion of the thalamus. (*Right*) Coronal T1-weighted MR-imaging of gadolinium-DTPA co-infused with M13 bacteriophage. The Gd-DTPA distribution and corresponds to immunostaining for M13 bacteriophage. *From Ksendzovsky A, Walbridge S, Saunders RC, et al. Convection-enhanced delivery of M13 bacteriophage to the brain. Journal of neurosurgery. 2012;117(2):197–203; with permission.*

Figure 5.

Sagittal (left) and axial (right) T1-weighted magnetic resonance imaging of infusion of gadolinium-diethylenetriamine pentaacetic acid co-infused with interleukin-13 *Pseudomonas* exotoxin into the pons (white area) of a patient with a diffuse intrinsic pontine glioma. From Lonser RR, Sarntinoranont M, Morrison PF, Oldfield EH. Convection-enhanced delivery to the central nervous system. *Journal of neurosurgery*. 2015;122(3):697–706; with permission.