Imaging of Convective Drug Delivery in the Nervous System

Russell R. Lonser, MD

KEYWORDS

• Convection-enhanced delivery • Drug delivery • Infusion • Imaging • Nervous system
• Surrogate imaging tracer

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 MRI) 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.

INTRODUCTION

The rapidly expanding biological 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. Although 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]

Systemic drug delivery is limited by the BNSB, which permits only small (<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 mm (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 MRI) 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 noncompliant infusion apparatus to an infusion cannula.[26,27] Based on its bulk flow properties,

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

Department of Neurological Surgery, Ohio State University Wexner Medical Center, 410 West 10th Avenue, Doan 1047, Columbus, OH 43210, USA
E-mail address: russell.lonser@osumc.edu

Neurosurg Clin N Am ■ (2017) ■–■
http://dx.doi.org/10.1016/j.nec.2017.05.012
1042-3680/17/Published by Elsevier Inc.

convective delivery reliably (with region-dependent volume of infusion/volume of tissue distribution ratios in the range of 2:1–10:1) 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.

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, 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, MRI, or both methods during convective delivery.[8–21,37] Features of surrogate imaging agents that are ideal or critical are that they include an excellent safety profile, can accurately track a wide range of co-infused therapeutic agents, are detected by noninvasive 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 MRI surrogate agents.

CT scanning surrogate imaging tracers

Small- (iopamidol) and large- (iopanoic acid–labeled albumin; >70,000 Da) molecular-weight surrogate CT scanning tracers have been studied in rodent and nonhuman primate models using convective delivery.[11,38] These surrogate imaging agents provided clear real-time well-defined imaging using CT scanning (**Fig. 1**) without evidence of clinical or tissue toxicity. The tracking

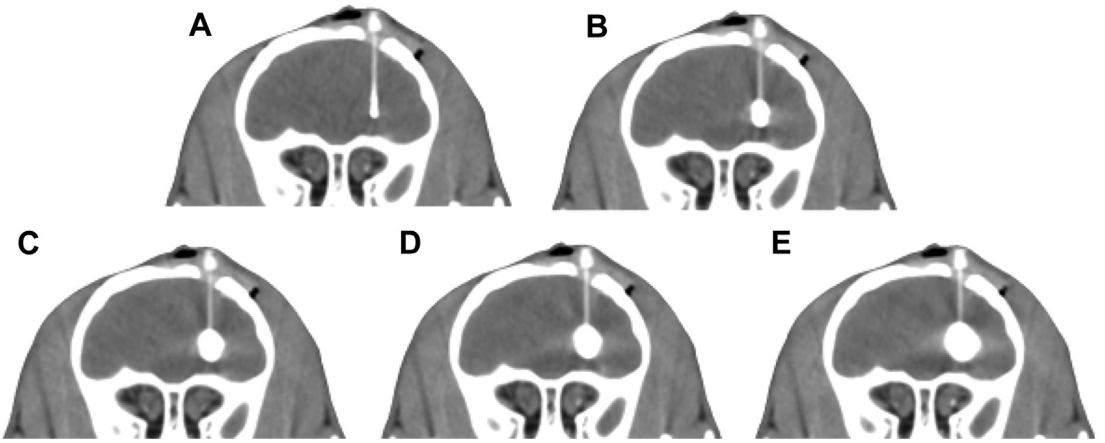

Fig. 1. Real-time coronal CT scanning of iopamidol infusion into the right frontal lobe (white matter) of a nonhuman primate. Imaging shows progressive well-defined distribution of iopamidol at various time points during infusion including 15 (*A*), 30 (*B*), 45 (*C*), 60 (*D*) and 75 μL (*E*). (*Courtesy of* National Institutes of Health.)