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Effect of ependymal and pial surfaces on convection- enhanced delivery:

Laboratory investigation

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Abstract

Object—Convection-enhanced delivery (CED) is increasingly used to investigate new treatments for central nervous system disorders. Although the properties of CED are well established in normal gray and white matter central nervous system structures, the effects on drug distribution imposed by ependymal and pial surfaces are not precisely defined. To determine the effect of these anatomical boundaries on CED, the authors infused low MW and high MW tracers for MR imaging near ependymal (periventricular) and pial (pericisternal) surfaces.

Methods—Five primates underwent CED of Gd-diethylenetriamine pentaacetic acid (Gd-DTPA; MW 590 D) or Gd-bound albumin (Gd-albumin; MW 72,000 D) during serial real-time MR imaging (FLAIR and T1-weighted sequences). Periventricular (caudate) infusions were performed unilaterally in 1 animal (volume of infusion [Vi] 57 μ l) and bilaterally in 1 animal with Gd-DTPA (Vi = 40 μ l on each side), and bilaterally in 1 animal with Gd-albumin (Vi = 80 μ l on each side). Pericisternal infusions were performed in 2 animals with Gd-DTPA (Vi = 190 μ l) or with Gd-albumin (Vi = 185 μ l) (1 animal each). Clinical effects, MR imaging, and histology were analyzed.

Results—Large regions of the brain and brainstem were perfused with both tracers. Intraparenchymal distribution was successfully tracked in real time by using T1-weighted MR imaging. During infusion, the volume of distribution (Vd) increased linearly ($R^2 = 0.98$) with periventricular (mean Vd/Vi ratio $\pm$ standard deviation; 4.5 ± 0.5) and pericisternal (5.2 ± 0.3) Vi, but did so only until the leading edge of distribution reached the ependymal or pial surfaces, respectively. After the infusate reached either surface, the Vd/Vi decreased significantly (ependyma 2.9 ± 0.8 , pia mater 3.6 ± 1.0 ; $p < 0.05$) and infusate entry into the ventricular or cisternal cerebrospinal fluid (CSF) was identified on FLAIR but not on T1-weighted MR images.

Conclusions—Ependymal and pial boundaries are permeable to small and large molecules delivered interstitially by convection. Once infusate reaches these surfaces, a portion enters the adjacent ventricular or cisternal CSF and the tissue Vd/Vi ratio decreases. Although T1-weighted MR imaging is best for tracking intraparenchymal infusate distribution, FLAIR MR imaging is the

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Disclosure

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most sensitive and accurate for detecting entry of Gd-labeled imaging compounds into CSF during CED.

Keywords

cerebrospinal fluid; convection-enhanced delivery; ependyma; imaging; *Macaca fascicularis*; *Macaca mulatta*; pia mater; ventricle

Convection-enhanced delivery of infusate to the CNS was first described by Bobo et al.¹ in 1994. During convective delivery, infusate is delivered into the interstitial space of CNS tissue and distributed by a small hydrostatic pressure gradient. Because CED relies on bulk flow to distribute infusate within the interstitial space, small and HMW compounds can be delivered in a homogeneous manner to clinically relevant volumes of tissue in a manner that bypasses the blood–brain barrier.¹⁶ The recent development of CT and MR imaging surrogate tracers that can be coinjected with therapeutic compounds during CED now permits monitoring drug distribution in real time using serial imaging.^{4,8,9,17–20}

Because surrogate imaging tracers provide an accurate method for tracking infusate distribution during CED, imaging of these molecules during CED permits real-time evaluation of the effects on distribution imposed by a variety of in vivo conditions during convective delivery.^{8,16} Previously, the properties of CED had been established in normal gray and white matter, but the effects on convective distribution imposed by ependymal and pial surfaces have not been defined. Recent evidence indicates that infusion with the tip of the catheter close to either of these surfaces may influence convective drug distribution.^{8,19} To precisely define the effect of these anatomical boundaries on CED, we infused LMW and HMW tracers for MR imaging with the tip of the infusion catheter near ependymal (periventricular) and pial (pericisternal) surfaces while monitoring tracer distribution in real time.

Methods

Experimental Animals

All animal investigations were conducted in accordance with the National Institutes of Health guidelines on the use of animals in research and were approved by the Animal Care and Use Committee of the National Institute of Neurological Disorders and Stroke. Two adult Cynomolgus (*Macaca fascicularis*) and 3 adult Rhesus primates (*Macaca mulatta*) were used in this study.

Preparation of Tracers

Gadolinium-Bound DTPA—A concentration of clinical grade Gd-DTPA (Bayer HealthCare Pharmaceuticals) was prepared in phosphate-buffered saline (5 mM).

Gadolinium-Bound Albumin—The 2-(p-isothiocyanatobenzyl)-6-methyldiethylenetriamine pentaacetic acid (1B4M)-DTPA was conjugated to human serum albumin (Sigma) using a previously described technique (3 mM).^{2,9,12,16}

Infusion Procedure

Infusion of Tracers—A total of 5 primates (Table 1) underwent infusion with the tip of the catheter either near an ependymal surface (caudate head [3 infusions of Gd-DTPA and 2 infusions of Gd-albumin]) or near a pial surface (the anterior portion of the pons [1 infusion each of Gd-DTPA and Gd-albumin]). Two of these animals underwent bilateral infusions into the caudate close to the lateral ventricle surface (Gd-DTPA, $V_i = 40 \mu\text{l}$ per infusion; Gd-albumin, $V_i = 80 \mu\text{l}$ per infusion), and 1 animal underwent a unilateral periventricular infusion

(Gd-DTPA, $V_i = 57 \mu\text{l}$). Two other animals underwent pericisternal infusions using a single cannula with the tip in the anterior margin of the pons (Gd-DTPA, $V_i = 190 \mu\text{l}$; Gd-albumin, $V_i = 185 \mu\text{l}$).

After the animals were sedated and intubated, general endotracheal anesthesia was administered using isoflurane. Animal temperature, heart rate, oxygen saturation, electrocardiographic response and end-tidal partial pressure of carbon dioxide were monitored during the procedure. The head of each animal was secured in a stereotactic frame (Crist Instrument Co.). Using sterile technique, a midline skin incision extending from the anterior to the posterior aspect of the vertex of the skull was made, and self-retaining retractors were used to expose the underlying skull. A 1-cm bur hole was placed over the stereotactically determined entry point(s), and the underlying dura mater was incised. Silicate cannulae were used to avoid artifact on the MR images, as previously described.⁹ An outer guide cannula (outer diameter 0.027 in, inner diameter 0.015 in) was stereotactically placed through the dural opening along the target trajectory to a level 0.5–1.5 cm above the desired caudate or pontine target. The guide cannula was then secured to the skull with methylmethacrylate. After the inner cannula (outer diameter 0.014 in, inner diameter 0.006 in) was connected to the infusion apparatus, it was placed through the outer guide cannula to the target.

To distribute infusate into the brain using convection, we used a previously described noncompliant system that is gas-tight with no dead volume.⁹ A PHD 2000 syringe pump (Harvard Apparatus) was used to generate continuous pressure throughout the infusion procedure. During infusion, pressure was transmitted from the pump to an infusate-filled, gas-tight, glass syringe (total volume 250 μl) that was connected to thick-walled polyethylene tubing (outer diameter 0.050 in, inner diameter 0.023 in). The tubing was connected to the inner infusion cannula and the tip was placed to target. Infusions were performed at 0.5–1 $\mu\text{l}/\text{minute}$. After the infusion was complete, the cannulae and methylmethacrylate were removed.

Clinical Observation—Three of the animals were killed immediately after surgery. Two animals (1 that received Gd-DTPA in the bilateral caudate, 1 that received Gd-albumin in the pons) were observed daily for 27 and 20 days, respectively, and then killed. An overdose of intravenous pentobarbital (90 mg/kg) was administered at the completion of the study period. Animals were perfused with intracardiac heparinized saline followed by STF tissue fixative (Streck).

Magnetic Resonance Imaging

Using a 1.5-T imaging unit, T1-weighted MR imaging sequences (slice thickness 1 mm, voxel size 1 mm^3) were obtained to track the Vd of the infusate and to detect entry of the infusate into the CSF spaces. The T1-weighted sequences, alternating with FLAIR sequences, were obtained continuously (every 20–40 minutes) throughout the entire infusion.

Imaging Analysis

The MR images were analyzed using Image J software (Sun Microsystems, Inc.). The 3D Vds in the region infused were calculated using an MR imaging signal intensity value of 2 standard deviations above the mean MR imaging signal of the surrounding noninfused brain, which served as a threshold for segmentation.¹⁸ The Vd of the MR imaging tracer was compared with the corresponding V_i to determine the Vd/ V_i ratio.

Statistical Analysis

Statistical studies were used as defined in text. Significance was determined by a probability value < 0.05 .

Results

Ependymal Surface Effects

To evaluate the effects of CED on LMW and HMW tracers near an ependymal surface, Gd-DTPA (MW 590 D) or Gd-albumin (MW 72,000 D) were infused in the caudate head with the catheter tip 2–4 mm from the ependymal surface of the frontal horn of the ventricular system. Real-time, T1-weighted MR images obtained during infusion revealed that the region of the caudate surrounding the cannula tip filled progressively with either Gd-DTPA or Gd-albumin. Although there was no evidence of infusate entry into the ventricular system on T1-weighted imaging during infusion, FLAIR sequences demonstrated leakage of Gd-DTPA and Gd-albumin into ventricular CSF (Figs. 1 and 2) after the leading edge of the infusion reached the ependymal surface (as displayed on T1-weighted images). Volumetric analysis of the infused tissue region on T1-weighted imaging at various time points during the infusion revealed that the Vd of Gd-DTPA and Gd-albumin increased linearly ($R^2 = 0.98$) with Vi. The mean Vd/Vi ratio for both tracers was 4.5 ± 0.5 (mean Gd-DTPA 4.6 ± 0.9 ; Gd-albumin 4.5 ± 0.4) (ratio range 3.9–5.7) before leakage into the ventricle was observed (Figs. 1 and 2). After the infusate reached the ventricular wall and leakage into the ventricle was evident on FLAIR-imaging, the mean Vd/Vi ratio for both tracers (2.9 ± 0.8 [Gd-DTPA 3.1 ± 0.7 and Gd-albumin 2.6 ± 1.2]) ($R^2 = 0.85$) decreased significantly ($p < 0.05$, Student t-test) (Figs. 1 and 2). Differences between the Vd/Vi ratios between Gd-DTPA and Gd-albumin were not significant ($p > 0.05$, Student t-test).

Pial Surface Effects

To evaluate the effects of CED on LMW and HMW tracers near a pial surface, Gd-DTPA or Gd-albumin was infused with the catheter tip in the anterior portion of the pons 3 mm from the pial surface, immediately adjacent to the prepontine cistern. Real-time, serial T1-weighted, MR imaging during infusion revealed that the region of the pons surrounding the cannula tip filled progressively with either Gd-DTPA or Gd-albumin. Although there was no evidence of infusate entry into the cistern on T1-weighted imaging during infusion, FLAIR sequences demonstrated leakage of Gd-DTPA and Gd-albumin into cisternal CSF (Figs. 1 and 2) after the leading edge of the infusion reached the pial surface as seen on T1-weighted images. Volumetric analysis of the infused tissue region on T1-weighted imaging at various intervals during the infusion revealed that the Vd of Gd-DTPA and Gd-albumin increased linearly ($R^2 = 0.99$) with Vi. The mean Vd/Vi ratio for both tracers was 5.2 ± 0.3 (mean Gd-DTPA 5.5 ± 0.3 and Gd-albumin 4.8 ± 0.2 ; ratio range 4.6–5.8) before leakage into the ventricle was observed (Figs. 1 and 2). After the infusate reached the pial surface and leakage into the cistern was evident on FLAIR imaging, the mean Vd/Vi ratio diminished for both tracers (3.6 ± 1.0 [Gd-DTPA 3.8 ± 0.9 and Gd-albumin 3.4 ± 1.1]) ($R^2 = 0.74$) decreased significantly ($p < 0.05$, Student t-test) (Figs. 1 and 2). Differences between the Vd/Vi ratios between Gd-DTPA and Gd-albumin and between regions (caudate and brainstem) were not significant ($p > 0.05$, Student t-test).

Clinical Analysis

The 2 animals that survived showed no signs of clinical toxicity from the infusion or infusate during the follow-up period.

Discussion

Imaging of CED

Because tracking convective delivery of infusate will be critical to determine the adequacy of drug delivery, to gain insight into effects on Vd by different tissue/surface properties, and to

establish the efficacy of putative therapeutic agents, we and others have investigated the applicability and feasibility of using surrogate imaging tracers, coinjected with therapeutic agents, to monitor drug distribution in real time. Investigation of a variety of CT and MR imaging agents has shown that surrogate tracers can be used to safely and accurately monitor distribution of a wide range of LMW and HMW compounds.^{4,8,9,19,20} Because surrogate-imaging tracers can provide an accurate method that represents infusate distribution during CED, real-time imaging of these molecules during CED permits evaluation of the effects imposed on drug distribution by a variety of in vivo conditions on convective delivery.

Previous Studies

Pilot clinical studies describing imaging of surrogate tracers coinjected with putative therapeutic agents provide early insight into the effect on convective distribution that infusion near ependymal and pial surfaces may have. Lonser et al.⁸ previously coinjected Gd-DTPA with glucocerebrosidase into the brainstem of an infant with Type 2 Gaucher disease. Real-time MR imaging throughout the infusion (at 20–40-minute intervals) demonstrated that a clinically relevant Vd of therapeutic agent could be delivered safely to the brainstem in a targeted manner. This single patient study also suggested that the pia was permeable to infusate delivered by CED and that infusions near a pial surface could potentially lead to reduced distribution efficiency once the leading edge of infusate encounters this anatomical surface, given that further infusion resulted in a portion of the infusate crossing into the immediately adjacent CSF space. Correspondingly, imaging evidence of infusate (Gd-DTPA) leakage across a pial boundary in this case was concurrent with the onset of a decrease in the mean Vd/Vi ratio (from 6:1 to 3:1).

Recently, Sampson et al.¹⁹ infused ¹²³I-human serum albumin mixed with a tumor-targeted cytotoxin (interleukin 13 bound to *Pseudomonas* exotoxin) in 7 patients with malignant supratentorial gliomas and imaged the distribution of infusate with SPECT scanning. The findings from this study provide several important insights into convective delivery of HMW compounds in humans. First, consistent with findings from normal and near-normal brains in large animal and human studies,^{1,6,8,10} this study confirmed with a direct imaging technique that clinically relevant Vds are achievable with CED, including in supratentorial brain involved with tumor. Second, leakage of infusate across ependymal surfaces or along an infusion catheter track into ventricular or subarachnoid CSF spaces was observed to have a detrimental effect on the tissue Vd/Vi ratio. Third, there is a high incidence of infusate leakage around large (2-mm-diameter) infusion catheters, such as the ones used in their study and in prior clinical trials. Although previous modeling and animal studies predicted that catheter size would be directly related to the likelihood and degree of infusion leakback,^{3,14} Sampson et al. demonstrated the powerful effect of this catheter property on leakback and Vd in humans. Finally, the findings of Sampson et al. supported prior data by Laske et al.⁷ that indicated tumor and tumor-associated tissue alterations can significantly affect convective distribution patterns.

Despite the early insights provided by the contributions of Lonser et al.⁸ and Sampson et al.,¹⁹ there are several and significant limitations in the understanding of the effects that ependymal and pial tissue boundaries have on CED. First, because an LMW imaging tracer (Gd-DTPA) was used in the study by Lonser et al., there was no information on the effect that pial surfaces may have on CED of HMW compounds or the effect that an ependymal surface may have on CED of either LMW or HMW compounds. Moreover, that study involved only 1 individual. Similarly, the report by Sampson et al. described the effect that ependymal and pial surfaces may have on the distribution of an HMW compound (labeled albumin) during CED, but did not provide information on LMW compounds. Because both LMW and HMW compounds will be delivered by convection in clinical trials, it is important to understand the effects of tissue boundaries in compounds over a wide range of molecular sizes. The current study shows that

both LMW and HMW compounds delivered by convection are similarly permeable to ependymal and pial surfaces and that the efficiency of convective distribution is affected by loss of infusate across these permeable boundaries. Second, the SPECT imaging used to determine infusate distribution in the study of Sampson et al. predicted that pial surfaces were impermeable to HMW infusate (including catheters placed within 1 mm of a pial surface). This contrasts with the findings in the current study. This disparity is probably related to differences in the sensitivity of the imaging techniques (SPECT vs MR imaging), the frequency of imaging (every 20–40 minutes in the current study vs every 24 hours in the study by Sampson et al.), and/or dissimilarities between tissue types (tissue invaded by tumor vs normal tissue). Furthermore, SPECT imaging has limited resolution (voxel size 64 mm³) compared with the resolution of MR imaging used in the current study (voxel size 1 mm³). The MR imaging used in the current study also used a sensitive MR imaging sequence (FLAIR) to detect infusate leakage when it first began to reach the CSF, as the imaging was performed continuously throughout the infusion. Using high-resolution and continuous imaging, the results of the current study establish that not only are the ependyma and pia permeable to both LMW and HMW compounds delivered by convection, but also demonstrate that once the leading edge of infusion reaches these surfaces increasing leakage of infusate occurs with continued infusion. This results in leakage of an increasing portion of the infusate into the CSF (as a larger portion of the infusate front comes in contact with the surface) and a corresponding decrease in the efficiency of tissue distribution (that is, the Vd/Vi ratio). Finally, the study by Sampson et al. was performed in CNS tissues substantially altered by tumor, tumor-related changes (for example, edema, intratumoral necrosis, and peritumoral necrosis), or treatment-related changes (for example, radiation, chemotherapeutic wafers, and surgical changes). Many of the most promising uses of CED will be into normal or near-normal CNS tissue, and it will be essential that the effect of a variety of tissue boundaries are accounted for under variable conditions. Although the study by Lonser et al.⁸ examined the effects of a pial surface in a patient with near-normal tissues, further investigation was required to substantiate that finding and to examine the effect of ependymal surfaces on CED of LMW and HMW infusate in normal tissues. To establish the effects of normal ependymal and pial boundaries on CED, we infused in normal nonhuman primate brains near ependymal and pial surfaces with LMW (Gd-DTPA) and large (Gd-albumin) HMW compounds while imaging distribution in real time.

Impact of Ependymal and Pial Surfaces on CED

Because tight junctions do not connect ependymal or pial cells, surfaces formed by these cells can allow exchange between interstitial fluid and CSF. Previously, studies using LMW and HMW tracers injected into the ventricular or the intrathecal CSF have demonstrated that compounds can cross ependymal and pial surfaces into the surrounding tissue.^{13,15} Alternatively, in this study, we have demonstrated leakage of LMW and HMW MR imaging tracers delivered by convection from the interstitial space into the CSF. The entry of these infused molecules into CSF resulted in decreasing efficiency of distribution within the tissue. This was demonstrated by a decrease in the slope of Vd/Vi after the imaging tracer crossed the ventricular and pial surfaces.

Imaging Detection of Gd Leakage Into CSF

Our findings indicate that FLAIR MR imaging sequences are helpful in situations in which Gd-based imaging tracers are used to monitor CED, particularly when leakage of infusate into CSF is possible. Even though intraparenchymal distribution of infusate (Gd-DTPA or Gd-albumin) was best appreciated on T1-weighted MR imaging, it did not appear to cross the ependymal or pial surfaces on this imaging sequence. FLAIR MR imaging is designed to suppress the signal from CSF based on its T1 relaxation time. Therefore, slight alterations of the T1 relaxation time of CSF cause large signal changes on FLAIR.⁵ Given that Gd-based contrast agents act by shortening T1 relaxation times, FLAIR is extremely sensitive to low

concentrations of these agents in CSF. In fact, Mamourian and colleagues¹¹ found that FLAIR is ~ 10 times more sensitive than T1-weighted MR imaging for the detection of intravenously administered Gd-based contrast leakage into the CSF. This property of FLAIR allowed the leakage of Gd-based compounds into the CSF, through pial and ependymal surfaces, to be detected at a time when conventional T1-weighted MR imaging could not detect this leakage of Gd infusate. Sensitive detection of leakage of Gd-based compounds into the CSF during CED will be critical in clinical situations to accurately assess for leakage of infusate into CSF, not only across ependymal or pial surfaces, but also along the infusion catheter (leakback) and existing catheter tracks.

Conclusions

Ependymal and pial boundaries are permeable to small and large molecules delivered by convection. Once infusate reaches these surfaces, a portion leaks into the adjacent ventricular or cisternal CSF resulting in a decrease in the tissue Vd/Vi ratio. Although T1-weighted MR imaging is best for tracking intraparenchymal infusate distribution, FLAIR MR imaging is the most sensitive and accurate technique for detecting entry of Gd-labeled imaging compounds into CSF during CED.

Abbreviations in this paper

CED	convection-enhanced delivery
CNS	central nervous system
CSF	cerebrospinal fluid
DTPA	diethylenetriamine pentaacetic acid
HMW	high MW
LMW	low MW
Vd	volume of distribution
Vi	volume of infusion

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Fig. 1.

A: Graph depicting the V_i and V_d of the LMW tracer, Gd-DTPA, when infused near the primate ependymal surface (total V_i 57 μ l). The slope of the V_d/V_i ratio was a constant linear function (solid black line) until FLAIR sequencing detected Gd-DTPA leakage into the ventricle (gray line). At that point the V_d/V_i ratio significantly decreased ($p < 0.05$; dashed black line) indicating loss of infusate into the ventricle. B: At a V_i of 24 μ l, signal change was evident in the ventricle on coronal FLAIR imaging (white arrow). C: Although intraparenchymal tracer distribution (white arrow) was clearly visible in the caudate head on the corresponding coronal T1-weighted MR image, no contrast could be seen in the ventricular CSF using this MR imaging sequence.

Fig. 2.

A: Graph depicting Vi and Vd of the HMW tracer, Gd-bound albumin when infused with the catheter tip near the pial surface (total Vi 185 μ l). The slope of the Vd/Vi ratio was a constant linear function (*solid black line*) until FLAIR imaging detected Gd-bound albumin leakage into the cistern (*gray line*). At that point the Vd/Vi ratio significantly decreased ($p < 0.05$, *dashed black line*) indicative of infusate loss into the cisternal CSF. B: At a Vi of 75 μ l, signal change could be visualized in the prepontine cistern on axial FLAIR imaging (*arrowheads*). C: Although intraparenchymal tracer distribution was clearly visible in the anterior portion of the pons (*arrowheads*) on the corresponding axial T1-weighted MR image, no contrast was detected in the cisternal CSF using this MR imaging sequence.

TABLE 1

Summary of infusions in 5 animals

Infusion Agent & Location	No. of Infusions	Mean Vd/Vi Preleakage	Mean Vd/Vi Postleakage
Gd-albumin (periventricular)	2	4.5	2.6
Gd-DTPA (periventricular)	3	4.6	3.1
Gd-albumin (pericisternal)	1	4.8	3.4
Gd-DTPA (pericisternal)	1	5.5	3.8