Real-time image-guided direct convective perfusion of intrinsic brainstem lesions

Technical note

RUSSELL R. LONSER, M.D.,† KATHERINE E. WARREN, M.D.,‡ JOHN A. BUTMAN, M.D., PH.D.,§ ZENAIDE QUEZADO, M.D.,¶ R. AARON ROBISON, M.D.,† STUART WALBRIDGE, B.S.,† RAPHAEL SCHIFFMAN, M.D.,* MARSHA MERRILL, PH.D.,† MARION L. WALKER, M.D.,† DERIC M. PARK, M.D.,† DAVID CROUTEAU, M.D.,† ROSCEO O. BRADY, M.D.,† AND EDWARD H. OLDIELD, M.D.†

†Surgical Neurology Branch and ‡Developmental and Metabolic Neurology Branch, National Institute of Neurological Disorders and Stroke; †Neuro-Oncology Branch, National Cancer Institute; §Section of Neuroradiology, Diagnostic Radiology Department and ¶Department of Anesthesia and Surgical Services, Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland; *Division of Pediatric Neurosurgery, Department of Neurosurgery, Primary Children’s Medical Center, University of Utah Health Science Center, Salt Lake City, Utah; and †NeoPharm, Inc., Lake Forest, Illinois

✓Recent preclinical studies have demonstrated that convection-enhanced delivery (CED) can be used to perfuse the brain and brainstem with therapeutic agents while simultaneously tracking their distribution using coinfusion of a surrogate magnetic resonance (MR) imaging tracer. The authors describe a technique for the successful clinical application of this drug delivery and monitoring paradigm to the brainstem. Two patients with progressive intrinsic brainstem lesions (one with Type 2 Gaucher disease and one with a diffuse pontine glioma) were treated with CED of putative therapeutic agents mixed with Gd–diethylenetriamine pentaacetic acid (DTPA). Both patients underwent frameless stereotactic placement of MR imaging–compatible outer guide–inner infusion cannulae. Using intraoperative MR imaging, accurate cannula placement was confirmed and real-time imaging during infusion clearly demonstrated progressive filling of the targeted region with the drug and Gd-DTPA infusate. Neither patient had clinical or imaging evidence of short- or long-term infusate-related toxicity. Using this technique, CED can be used to safely perfuse targeted regions of diseased brainstem with therapeutic agents. Coinfused imaging surrogate tracers can be used to monitor and control the distribution of therapeutic agents in vivo. Patients with a variety of intrinsic brainstem and other central nervous system disorders may benefit from a similar treatment paradigm. (DOI: 10.3171/JNS-07/07/0190)

KEY WORDS • brainstem • convection-enhanced delivery • glioma • intraoperative imaging • magnetic resonance imaging

MANY intrinsic diseases of the brainstem result in complications or death because there are no effective surgical or medical therapies. Due to growing insights into the molecular biology of many of these disorders, an expanding number of putative therapeutic compounds are being developed for their treatment. Unfortunately the ineffective distribution of these therapeutic agents to the brainstem has prevented them from being effective. Currently, the delivery of drugs to the brainstem relies on systemic or intrathecal drug administration, both of which have a number of limitations. Systemic delivery (intravenous or intraarterial) is frequently restricted by the inability of drugs to cross the blood–brain barrier and may cause systemic toxicity and nontargeted distribution.20,29,52 Drug distribution to the tissues after intrathecal administration depends on diffusion, and as a result, penetration into the brainstem using this delivery technique is severely constrained. Moreover, intrathecal drug administration produces nontargeted heterogeneous dispersion throughout the CNS.1,29

Abbreviations used in this paper: CED = convection-enhanced delivery; CNS = central nervous system; CSF = cerebrospinal fluid; DTPA = diethylenetriamine pentaacetic acid; FLAIR = fluid-attenuated inversion-recovery; FOV = field of view; IL-13 = interleukin-13; IL13-PE = IL-13 bound to PE; MR = magnetic resonance; NIH = National Institutes of Health; PE = Pseudomonas exotoxin; Vd = volume of distribution; Vi = volume of infusion.
To overcome these limitations, we have previously investigated animal models to explore the use of CED to deliver therapeutic agents in a delivery paradigm that permits monitoring of drug distribution during the infusion and the use of real-time imaging to evaluate the potential of CED to deliver agents to deep brain structures. To determine if CED could be used to deliver therapeutic agents to lesions of the brainstem, while monitoring drug distribution in humans, we developed a technique that uses image-guided placement of an infusion cannula, coinfusion of a mixture of the therapeutic agent and Gd-DTPA, and real-time monitoring of agent distribution using intraoperative MR imaging.

Illustrative Cases

Case 1

**History and Examination.** This male infant was born with anemia, thrombocytopenia, and hepatosplenomegaly. Bone marrow biopsy results revealed Gaucher cells and a serum glucocerebrosidase activity 1.7% of the normal, consistent with the diagnosis of acute neuronopathic (Type 2) Gaucher disease. Beginning when he was 2 months of age, systemic Gaucher disease manifestations in this child were successfully treated with intravenous glucocerebrosidase infusions. Intermittent strabismus developed when he was 2.5 months of age, but his neurological examination was otherwise age-appropriate. By 8 months of age he was hypotonic, had constant strabismus, and had become deaf. When he was 9.5 months of age, he underwent a tracheostomy and placement of a feeding tube because he was no longer able to protect his airway or swallow.

**Treatment and Posttreatment Course.** The patient was admitted to the NIH at 10.5 months of age with medically intractable seizures and a right frontal paramedian epileptogenic focus observed on electrocorticography. At that time he underwent perfusion (without the administration of Gd-DTPA) of the right paramedian frontal lobe with glucocerebrosidase (70 U/ml; total Vi 1.5 ml) under an institutional approved protocol. Despite our attempts to monitor infusate distribution during infusion using T2-weighted and FLAIR MR imaging sequences sensitive to increases in interstitial fluid, we were unable to determine the region of perfusion because of the incompletely developed state of the patient's brain.

The patient returned to the NIH at 13 months of age with progressive right facial and abducens nerve paresis. Based on these clinical findings we selected the region of the right facial and abducens nuclei for enzyme perfusion. To track glucocerebrosidase distribution during infusion, we mixed Gd-DTPA with the glucocerebrosidase and monitored the infusate distribution using T1-weighted MR imaging under an institutionally approved protocol. Preinfusion in vitro analysis confirmed stable enzyme activity that was not altered by mixing it with Gd-DTPA. Using a right frontal bur hole centered at the coronal suture and lateral to the midpupillary line, we used frameless image guidance to secure a right paramedian frontal lobe glucocerebrosidase (70 U/ml; total Vi 1.5 ml) infusion cannula. After placement of the inner infusion cannula, the patient underwent direct CED (0.5 to 10 μl/min) of the glucocerebrosidase (70 U/ml) and Gd-DTPA (1 mM; total Vi 1.8 ml) mixture to the right pontine region. The patient has not shown clinical or radiographic signs of toxicity (follow-up duration 12 months). His condition is clinically stable with intravenous enzyme replacement therapy; he has gained weight, and no progression of the seizure focus has been shown on electrocorticography.

Case 2

**History and Presentation.** This previously healthy girl, 3 years and 10 months of age, presented with ataxia, headaches, and nausea and vomiting in May 2005. Results of MR imaging revealed a diffuse pontine glioma with associated hydrocephalus. The patient underwent ventriculoperitoneal shunt placement in May 2005 and radiation therapy in June 2005 (5600 Gy) resulting in alleviation of her neurological symptoms. Despite a course of chemotherapy (temozolomide), lesion progression on MR imaging was identified in January 2006 and imaging studies obtained 4 weeks later demonstrated continued tumor growth in a region that appeared hypointense on imaging and was associated with gait ataxia.

**Treatment and Posttreatment Course.** The patient was admitted to the NIH in March 2006 with progressive gait ataxia, bilateral abducens weakness (worse on the left side) and left facial nerve weakness. The patient underwent coinfusion of the brainstem glioma with a mixture of the antiglioma cytotoxin IL13-PE and Gd-DTPA (1 mM) under an institutionally approved protocol. Preinfusion in vitro analysis confirmed that the potent activity of IL13-PE against glioma cells was not altered by mixing it with Gd-DTPA. We made a left frontal bur hole centered at the coronal suture and lateral to the midpupillary line and used frameless image guidance to secure an outer guide cannula on a trajectory that permitted placement of an inner infusion cannula to access the target region (the area of hypointensity in the posterior pons observable on MR imaging). After placement of the inner infusion cannula, the patient received direct convective coinfusion of IL-13 (0.5 to 10 μl/min) with PE (0.125 μg/ml) and Gd-DTPA (1 mM), with a total Vi of 1.4 ml to the pontine region. For 48 hours after the infusion the patient experienced mild transient lethargy and exacerbation of the preexisting bilateral abducens nerve weakness (5 days) that resolved with a 5-day course of steroid medication. Follow-up MR imaging studies obtained 3 and 4 weeks after infusion revealed no evidence of tumor progression or toxicity; however, imaging studies obtained 8 weeks posttreatment demonstrated tumor progression. This development was also associated with progressive gait ataxia, bilateral abducens nerve paralysis, left facial nerve paralysis, and swallowing difficulties. The patient died of progressive tumor growth 4 months after infusion.

**Operative Technique.**

To infuse regions within the brainstem using CED, we use a transfrontal approach similar to that described for obtaining biopsy samples of brainstem lesions. Preoperative (pre- and/or postcontrast enhanced) T1-weighted MR images of the brain are obtained with the aid of a 1.5-tesla MR scanner making 1-mm cuts in the axial plane (no spacing). The imaging data set is then transferred to a commercial neurosurgical image guidance workstation (StealthStation TRIA plus System; Medtronic). Reconstructed images in three planes (coronal, axial, and sagittal) are used to target a...
specific site in the brainstem for infusion cannula tip placement. Based on the desired site for placement of the infusion cannula tip, a frontal calvarial entry point is selected that provides an optimal extraventricular path for the cannula to the preselected target.

The patient is brought to the intraoperative MR imaging suite for surgery, and general anesthesia is induced. The patient is placed supine and the head is immobilized with three-point pin fixation after gentle flexion of the neck. Scalp reference fiducial points are registered with the image-guidance system (StealthStation TRIA plus System). The left or right frontal region is prepared and draped in a sterile fashion. A 3.5-cm linear incision is made in the sagittal plane after infiltration of the subcutaneous tissues with 2 to 4 ml of 1% lidocaine with epinephrine (1:200,000). A bur hole is made at the predetermined calvarial entry point. Two or three nylon screws are fixed into the outer table of the skull adjacent to the bur hole, and the underlying dura mater is coagulated with bipolar cautery and opened in a cruciate pattern with a No. 11 blade. Using active and passive image guidance (SureTrak II, StealthStation TRIA plus System), a 16-gauge silicate outer guide cannula is stereotactically placed along the predetermined target trajectory to a level 1.5 to 3.0 cm above the desired target. Gel foam is placed in the bur hole over the surface of the exposed brain and around the outer guide cannula. The outer guide cannula is secured in place to the calvarium with a thin layer of methylmethacrylate (5 mm) that is anchored by the nylon screws (Fig. 1). The methylmethacrylate in turn holds the outer guide cannula in place by adhering to the threaded collar on its proximal end. After being connected to the infusion apparatus, a 21-gauge silicate inner infusion cannula is placed through the outer guide cannula to the target (Fig. 1). The wound is sutured closed around the cannulae and a sterile dressing is applied.

The patient is transferred from the operating table in the intraoperative MR imaging suite and placed in the intraoperative MR scanner (Achieva 1.5 T; Phillips). The patient is maintained in a state of general anesthesia, kept on the intraoperative MR imaging table, and observed by an anesthesiologist and surgeon throughout the entire infusion process. Magnetic resonance imaging studies are performed throughout the entire infusion. Accurate cannula placement is confirmed on MR imaging. To distribute infusate to the brainstem using convection, a Harvard syringe pump (PHD 2000) is used to generate continuous convective pressure throughout the infusion. During the infusion, the pressure is transmitted from the pump to an infusate-filled syringe (5-ml total volume) connected to polyethylene tubing (outer diameter 0.050 in; inner diameter 0.023 in). The tubing is attached directly to the inner infusion cannula, which is placed into the targeted region of the brainstem. Infusions are started (0.5 μl/min and increased in stages up to 10 μl/min) and monitoring is continued until the infusions are completed. Magnetic resonance images (T1-weighted: TR 400 msec, TE 10 msec, 220 mm FOV) in the axial plane (slice thickness 5 mm, no spacing) are obtained at 15- to 45-minute intervals. Fluid-attenuated inversion-recovery MR images (TR 10,000 msec, TI 2200 msec, TE 152 msec, TSE 52, 220 mm FOV) are obtained in the axial plane (slice thickness 5 mm, no spacing) at variable intervals as a highly sensitive assessment of leakage of drug mixed with Gd-DTPA into the CSF spaces.

After the infusion is completed, the inner infusion cannula is withdrawn. The methylmethacrylate is drilled away from the anchor screws with a high-speed drill. The outer guide cannula is removed en bloc along with the immediately surrounding methylmethacrylate. The anchor screws and any remaining methylmethacrylate are removed. The wound is closed in layers using absorbable sutures. The patient is awakened and returned to the surgical intensive care unit for immediate postoperative care.

Results

Placement of Infusion Cannula

Both patients underwent successful preoperative stereotactic MR imaging and cannula placement targeting 1 day before surgery. Using the described frameless stereotactic technique, the outer guide cannulae were placed accurately along the desired trajectory. The inner infusion cannulae were placed through the outer guide cannulae to the desired target as determined by intraoperative MR imaging. Active image guidance of both the outer guide and inner infusion cannulae made accurate tracking possible during placement.

Intraoperative Imaging

Real-time imaging during the infusions demonstrated that the anatomical region infused with the mixture of Gd-DTPA and the chosen drug was clearly distinguishable from the surrounding noninfused tissue in both patients (Figs. 2 and 3). Volumetric analysis of the Gd-DTPA and glucocerebrosidase distribution in the pons of the patient with Gaucher disease (Case 1) revealed that the Vd increased linearly with the Vi until the targeted region was perfused (Figs. 2 and 4) (mean overall Vd/Vi ratio of 3.1 ± 1.6). During the initial part of the infusion (first 160 μl) in this patient, the mean Vd/Vi ratio was 5.6 ± 1.3. The mean Vd/Vi ratio decreased to 2.4 ± 0.7 as the Vi increased (Fig. 4). The timing of the
decrease corresponded radiographically with the timing of the imaged infusion margin reaching the posterior edge of the brainstem. Fluid-attenuated inversion-recovery MR imaging performed at this point revealed extravasation of coin fused Gd-DTPA from the tissue surface (Fig. 4).

Sequential imaging during infusion of the diffuse pontine glioma in the patient in Case 2 with IL13-PE and Gd-DTPA demonstrated perfusion of the hypointense tumor in the pons, as shown by the region filled with Gd-DTPA (white areas) (Fig. 3).

Volumetric analysis of the IL13-PE and Gd-DTPA distribution in the diffuse pontine glioma patient revealed that the Vd increased linearly with the Vi ($R^2 = 0.92$) until the hypointense region of the tumor was perfused (Figs. 3 and 5). The Vd/Vi ratio was $3.7 \pm 0.4$ (Fig. 5). Fluid-attenuated inversion-recovery MR imaging revealed no evidence of extravasation of coin fused Gd-DTPA into the CSF. There was no evidence of infusate leakback along the needle track in either patient.

**Discussion**

**Convection-Enhanced Delivery**

Convection-enhanced delivery relies on bulk flow driv-
by a small hydrostatic pressure derived from a syringe pump to distribute molecules within the extracellular spaces of the CNS. Since CED does not rely on diffusion for distribution of the infused agents, it is not limited by the molecular weight, concentration, or diffusivity of these agents. Because the use of CED permits distribution of molecules directly within nervous tissues via the tip of a cannula, the blood–brain barrier can be bypassed and regions in the CNS can be targeted, including the brainstem. Based on the properties of bulk flow of infusate in the CNS, CED can be used to distribute both small and large molecules reliably, safely, and homogeneously over a range of volumes. Given that CED distributes infusate within the extracellular spaces of tissue, the volume of perfused tissue is inversely related to the extracellular fluid fraction in the infused region of the CNS.

**Brainstem Lesions**

The patients treated by direct convective brainstem infusion in the present study harbored intrinsic brainstem lesions for which there are no known effective medical or surgical therapies. The conditions in both patients are rapidly progressive and universally fatal.

**Gaucher Disease.** The patient in Case 1 had acute neuronopathic (Type 2) Gaucher disease. Gaucher disease is caused by an inherited insufficiency of glucocerebrosidase. Deficiency of glucocerebrosidase results in the pathologic accumulation of glucocerebroside in the lysosomes of Gaucher cells (monocyte-derived macrophages) and occasionally in neurons of the CNS. The abnormal accumulation of Gaucher cells and intracellular glucocerebroside results in anemia and thrombocytopenia, hepatosplenomegaly, skeletal abnormalities, and in some patients, neuronal damage.

Based on the pace of progression and presence of neuronal involvement, Gaucher disease is classified into Types 1, 2, and 3. Type 1 (nonneuronopathic variant) is the most common form of Gaucher disease and the nervous system is not involved. Type 2 (acute neuronopathic variant) has extensive CNS involvement. It is rapidly progressive and fatal (mean age at death is less than 1 year). In addition to
Brainstem convection

systemic effects, it is associated with rapid brainstem dys-
function that is often the underlying cause of death. Type 3
(subacute or chronic neuronopathic variant) patients exhib-
it variable degrees of systemic and neurological involve-
ment, the progression of which is more insidious.

While intravenous glucocerebrosidase replacement ther-
apy halts and reverses the progression of Gaucher disease in
 tissues outside the CNS, it does not slow the progres-
sive neurological deterioration in patients with Type 2 or 3
Gaucher disease because of the inability of intravenously
administered glucocerebrosidase (molecular weight 60 kD)
to cross the blood-brainstem barrier. To overcome this de-
livery limitation, we previously showed that CED can be
used to safely and effectively perfuse the brain and brain-
stem of animals with supraphysiologic levels of glucocere-
brosidase.25

Diffuse Pontine Glioma. The patient in Case 2 had a dif-
fuse pontine glioma. Diffuse brainstem gliomas are the
main cause of death by brain tumors in children and are uni-
formly fatal (median survival < 1 year).2,3 These tumors
most frequently cause ataxia, cranial nerve deficits, and mo-
tor and sensory deficits in the extremities. Because of the
location and infiltrative nature of these tumors, excision is
not possible.11 Therapy includes radiation and chemothera-
py, which is palliative at best.11,12

Because of their large molecular size, poor diffusivity,
and inability to cross the blood-brainstem barrier, promising
antiglioma therapeutic proteins developed for the treatment
of gliomas have not been successfully delivered to these tu-
mors using conventional delivery techniques. Human IL-13
fused to a mutated form of PE, has shown promising anti-
tumor properties against gliomas.14–18 Although IL13-PE is
a large protein (52 kD) and does not penetrate the blood–
brain barrier, it is selectively cytotoxic to glioma cells,10,15
and is a potentially ideal agent for brainstem distribution
and treatment of brainstem gliomas using CED.31

Brainstem Perfusion

Infusion Target Sites. The CNS sites of treatment in these
patients were chosen because they represented anatomical
regions linked to radiographic and/or neurological worsen-
ing. The pontine region was chosen for infusion in the Type
2 Gaucher disease patient because he presented with pro-
gressive facial and abducens weakness. The hypointense re-
region of tumor in the diffuse pontine glioma patient was tar-
geted because it represented a region of obvious tumor on
MR imaging that had demonstrated progressive growth in
the months before infusion.

Cannula Placement. Using the described frameless ste-
roteactinic technique, the outer guide–inner infusion cannulae
system was placed accurately to the desired target. The use
of this type of cannulae system has potential advantages for
infusion of deep CNS structures. The outer guide cannula
provides a trajectory guide for the inner infusion cannula
and permits easy replacement of the infusion cannula if nec-
essary and allows for infusion through the same cannula at
varying depths of penetration. The increased strength of the
larger outer infusion cannula provides additional support to
the smaller (diameter) infusion cannula. Using a smaller in-
fusion cannula reduces the potential for infusate leakback
and permits infusion at higher rates,24 as well as reduces the
risk of mechanical tissue injury.

Infusion Imaging. Using T1-weighted intraoperative MR
imaging studies, we confirmed accurate placement of the
cannula tip before beginning the infusion and monitored the
infusate distribution in the brainstem during delivery with
real-time imaging. During coinfusion of drug mixed with
Gd-DTPA, MR imaging revealed that the anatomical re-
gion infused with Gd-DTPA could be clearly distinguished
from the surrounding uninfused tissue (Figs. 2 and 3). The
targeted region surrounding the tip of the cannula steadily
filled with increasing Vi during infusion.

The importance of tracking drug delivery during CED to
not only ensure the accuracy and adequacy of convective
distribution, but to gain critical insights into the properties
of CED in the CNS was demonstrated clearly in these pa-
tients and other patients with supratentorial malignant gli-
omas that have undergone CED imaging analysis paradigms
(that is, single photon emission computed tomography im-
aging of radiolabeled surrogate tracers and radiolabeled
drug, or diffusion weighted MR imaging).27,33,34 The lack of
a confused surrogate tracer for the frontal lobe infusion in
the first patient made it impossible to accurately track infu-
sion distribution. The use of a surrogate imaging tracer per-
mits the determination of the infusion distribution charac-
teristics and properties and makes it possible to assess the
adequacy of infusion, to more sensitively determine region-
al toxicity, as well as to gain insight into the properties
of CED in humans and in various disease states. Moreover,
the ability to track drug distribution during delivery should
enhance safety, as the infusions could be stopped earlier once
the desired region is known to be perfused.

The potential effects of convective infusion near a tissue
surface were demonstrated in the infusion of the patient in
Case 1. Over the initial 160 μl of infusion in the patient with
Gaucher disease, the mean Vd/Vi ratio was similar to the
distribution predicted by preclinical experiments (5.6 ± 1.3
versus 7.0 ± 0.4),25 but as the Vi increased (beyond 160 μl)
the mean Vd/Vi ratio decreased. The mean Vd/Vi ratio when
Vi was greater than 160 μl was 2.4 ± 0.7. Magnetic reso-
nance imaging revealed that the reduction in Vd/Vi ratio oc-
curred as the posterior front of advancing infusate reached
the posterior pial boundary of the pons. At this time, leakage
of Gd-DTPA from the pial boundary of the posterior pons
into the fourth ventricle and surrounding cisterns (Fig. 4)
was revealed on FLAIR MR imaging and a portion of the
intraparenchymally delivered infusate was being lost across
the posterior surface of the brainstem. These findings indi-
cate that placement of a cannula tip further from the pial
boundary could have been used in this patient (and future
patients) to avoid this problem.

The potential effects of convective infusion in edematous
tissue were demonstrated in the infusion in Case 2. During
infusion of IL13-PE into the diffuse brainstem glioma, the
Vd/Vi ratio increased linearly (R² = 0.92) over the entire in-
fusion volume (total Vi 1.4 ml) (Fig. 5). The overall mean
Vd/Vi ratio for the infusion was 3.7 ± 0.4, which is less
than that achieved in our earlier primate brainstem infusion
studies (Vd/Vi 7.0 ± 0.4).25 Because the tissue distribution
of infusate by CED is inversely proportional to the extra-
cellular space and because there was no imaging evidence
of leakage of infusate into the CSF spaces, the most likely
explanation for reduction in Vd/Vi ratio is that the intra- and
peritumoral extracellular spaces are expanded by tumor-re-
lated vasogenic edema.27
Although imaging evidence of leakback along the cannula track was not observed over the range of infusion rates used in these patients, monitoring for leakback and determining the maximal rates of infusion during delivery will be a critical CED parameter that will be better defined after more patients have undergone treatment with confounded surrogate tracers. A maximum rate of 5 μL/minute was used in the patient with diffuse brainstem gliomas (Case 2) and a maximum infusion rate of 10 μL/minute was used in the patient with Gaucher disease (Case 1). Future investigations using surrogate tracers should resolve the issues regarding maximal infusion rates under various tissue conditions, as well as other factors that may affect leakback, such as cannula size and design.

**Gadolinium-DTPA as Surrogate Tracer.** Critical to the practical application of these findings is the determination of the CED conditions under which Gd-DTPA accurately traces solute spread and when it begins to fail in this role. As we have discussed previously, because of its small molecular weight (938 D), there are significant constraints on the usefulness of Gd-DTPA as a surrogate tracer during CED in humans. This is because at larger infusion volumes (≥2 ml) or slower infusion rates (<0.5 μL/min), diffusion becomes the dominant transport mechanism for small molecules such as Gd-DTPA, such that the convective transport behavior of larger molecules, such as dextran or glucocerebrosidase, will no longer correlate with that of Gd-DTPA. Thus, in most clinical situations in which compounds with a large molecular weight will be used, a surrogate tracer of higher molecular weight, such as Gd conjugated to albumin will be a more useful choice. However, at the volumes and infusion rates used here, convection of Gd-DTPA predominates, and our calculations indicate that Gd-DTPA tracked the distribution of both large and small molecules accurately.

**Safety of Brainstem Infusion.** While the efficacy of direct brainstem infusion in both of these disorders cannot be determined until more patients are treated, both patients tolerated convective infusion of the brainstem without irreversible toxicity. Neither patient had radiographic or clinical evidence of acute or long-term toxicity. Consistent with previous reports in patients undergoing CED of antitumor agents for supratentorial gliomas, the patient with diffuse brainstem glioma experienced mild transient lethargy and exacerbation of the preexisting abducens weakness that completely resolved when the infusion ended and she was started on a course of steroid therapy. This transient exacerbation of preexisting deficits and lethargy may be related to an increase in fluid associated with infusion in a region of tumor-related edema and is consistent with its reversibility upon infusion cessation and the inception of steroid therapy.

**Conclusions**

Convective delivery and distribution can be used to distribute therapeutic agents safely to the brainstem. Coinfused surrogate imaging tracers can be used to monitor and control distribution of putative therapeutic agents. A similar treatment approach may be useful for other disorders affecting large regions of the CNS, including other metabolic storage diseases, tumors, and degenerative diseases.

**References**


R. R. Lonser et al.
Brainstem convection


37. Wood JD, Lonser RR, Gogate N, Morrison PF, Oldfield EH: Convective delivery of macromolecules into the naive and traumatized spinal cords of rats. J Neurosurg 90 (1 Suppl):115–120, 1999


This research was supported by the Intramural Research Program of the National Institute of Neurological Disorders and Stroke at the NIH. A portion of this work was conducted under a material transfer agreement (IL13-PE) between the Surgical Neurology Branch of the National Institutes of Health and NeoPharm, Inc.

Address reprint requests to: Russell R. Lonser, M.D., Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Building 10, Room 5D37, Bethesda, Maryland 20892-1414. email: lonser@ninds.nih.gov.