Direct convective delivery of macromolecules to the spinal cord

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Object. Because of the limited penetration of macromolecules across the blood–spinal cord barrier, numerous therapeutic compounds with potential for treating spinal cord disorders cannot be used effectively. The authors have developed a technique to deliver and distribute macromolecules regionally in the spinal cord by using convection in the interstitial space.

Methods. The authors designed a delivery system connected to a “floating” silica cannula (inner diameter 100 μm, outer diameter 170 μm) that provides for constant volumetric inflow to the spinal cord. A solution containing albumin that was either unlabeled or labeled with carbon-14 or gadolinium was infused at various volumes (3, 6, 10, 20, 40, or 50 ml) at a rate of 0.1 ml/minute into the spinal cord dorsal columns of nine swine and into the lateral columns of three primates (Macaca mulatta). Volume of distribution (Vd), concentration homogeneity, and percentage of recovery were determined using scintillation analysis, kurtosis calculation (K), and quantitative autoradiography (six swine), magnetic resonance imaging (one swine and three primates), and histological analysis (all animals). Neurological function was observed for up to 3 days in four of the swine and up to 16 weeks in the three primates.

The Vd of 14C-albumin was linearly proportional (R² = 0.97) to the volume of infusion (Vi) (Vd/Vi = 4.4 ± 0.5; [mean ± standard deviation]). The increases in Vd resulting from increases in Vi were primarily in the longitudinal dimension (R² = 0.83 in swine; R² = 0.98 in primates), allowing large segments of spinal cord (up to 4.3 cm; Vi 50 ml) to be perfused with the macromolecule. The concentration across the area of distribution was homogeneous (K = 1.1). The mean recovery of infused albumin from the spinal cord was 85.5 ± 5.6%. Magnetic resonance imaging and histological analysis combined with quantitative autoradiography revealed the albumin infusate to be preferentially distributed along the white matter tracts. No animal exhibited a neurological deficit as a result of the infusion.

Conclusions. Regional convective delivery provides reproducible, safe, region-specific, and homogeneous distribution of macromolecules over large longitudinal segments of the spinal cord. This delivery method overcomes many of the obstacles associated with current delivery techniques and provides for research into new treatments of various conditions of the spinal cord.

KEY WORDS • bulk flow • convection • drug delivery • macromolecule • spinal cord • pig • Macaca mulatta
Convective delivery into the spinal cord

space by convection. By using convective flow, infused solute can penetrate tissues homogeneously over a much larger volume than can be obtained by diffusion alone. Second, because convective flow in the spinal cord is anisotropic, with the preferred direction of flow running parallel to fiber tracts, the great distances over which the parallel organization of fibers is maintained suggests that white matter tracts of the spinal cord are an ideal location in which to attempt large scale longitudinal spread of molecular agents by convection-enhanced drug delivery. To determine whether convection could achieve such enhanced distribution, we examined the direct interstitial delivery of macromolecules into the spinal cords of swine and primates.

Materials and Methods

Animal Preparation

Nine female adult National Institutes of Health (NIH) minipigs received a volume of infusion (Vi) in increasing doses (3, 6, 10, and 20 μl) of 14C- (seven animals), gadolinium (Gd)- (one animal), or unlabeled albumin (one animal) solution into the dorsal columns of the cervical spinal cord. Three primates (Macaca mulatta) received an increasing Vi (20, 40, and 50 μl) of Gd-albumin into the lateral columns of the cervical segments of the spinal cord.

All animal investigation was conducted in accordance with the NIH guidelines on the use of animals in research and was approved by the Animal Care and Use Committee of the National Institute of Neurological Disorders and Stroke and by the NIH Radiation Safety Committees.

Delivery System

To distribute macromolecules into the spinal cord by using convection, we developed a noncompliant delivery system that is gas-tight with no dead volume. A syringe pump was used to generate continuous pressure throughout an infusion. During infusion, the pressure was transmitted from the pump to a glass, gas-tight, syringe solution into the dorsal columns of the cervical spinal cord. Three primates (Macaca mulatta) received an increasing Vi (20, 40, and 50 μl) of Gd-albumin into the lateral columns of the cervical segments of the spinal cord.

Assessment of Accuracy and Reliability of the Delivery System

To determine the accuracy and reliability of the infusion system we loaded a solution of 14C-labeled (specific activity 0.024 μCi/mg) bovine serum albumin (concentration 0.79 mg/ml) in a 0.01-M sodium phosphate buffer, pH 7.2, into either 10- or 25-μl glass Hamilton syringes. Four samples at various volumes (1, 2.5, and 5 μl) were infused, using the previously described infusion apparatus, into 20-ml glass scintillation vials filled with 5 ml scintillation fluid. A scintillation counter was used to obtain counts per minute for each of the sample volumes, which were converted to “decays per minute” by using the sensitivity of the counter. The percentage of expected decays per minute was derived by dividing the actual decays per minute by the calculated theoretical decays per minute delivered.

Delivery Rate

All infusions in this study were performed at the rate of 0.1 μl/minute until the desired infusion volume was achieved. This infusion rate was chosen to minimize retrograde flow along the cannula tract. The rate was selected on the basis of observations that flow rates several-fold higher are required to produce significant backflow during rat intrastratal infusions with comparable diameter needles and that the maximum infusion rate tolerated without backflow is generally higher in white than in grey matter (RR Lonser, et al., unpublished data).

Infusate Materials

The animals were infused with either stock 14C-labeled (specific activity 0.024 μCi/mg) bovine serum albumin (69 kD; concentration 0.79 mg/ml) in a 0.01-M sodium phosphate buffer (pH 7.2) that had been diluted with 10 × phosphate-buffered saline (PBS) (9.8:1 per volume ratio) so that the final osmolality was 280 to 290 mOsm; bovine serum albumin (68 kD) that had been diluted in PBS (concentration 0.79 mg/ml), or Gd-labeled biotinylated human serum albumin11 that had been diluted with PBS (1:15 volume ratio). Each human serum albumin molecule was covalently linked via a lysine residue to 15 Gd and 10 biotin molecules (calculated as 78 kD).

Macromolecule Delivery to the Porcine Spinal Cord

After anesthesia had been induced in the animals, they were intubated, given halothane general endotracheal anesthesia, and positioned prone. The animals’ temperature, heart rate, oxygen saturation, electrocardiographic responses, and end-tidal PCO2, were monitored. The head of each animal was secured in a stereotactic frame and flexed. Using sterile technique, a dorsal midline incision was made from the base of the skull to the spinous process of C-7. Laminectomies were performed at C-1, C-2, and C-3. With the aid of an operating microscope the dura was incised, exposing the underlying spinal cord. A small incision (0.5 mm) in the pia mater overlying the dorsal columns of the spinal cord was made at the level of the caudal end of the C-1 body. The silica infusion cannula was advanced caudally through the pial opening into the white matter tracts of the spinal cord so that the cannula coursed parallel to the posterior column fibers and the tip was in the center of the dorsal columns, 10 mm from the pial opening (in Animal 6, a second catheter was placed in a similar orientation in the dorsal column at...
the caudal end of the C-2 body, and infusate was administered via the two canulas). The cannula was secured to the pia near its entrance into the spinal cord with tissue adhesive. To allow the tissue to seal around it, the cannula was left in place for 90 minutes before starting the infusion. The proximal infusion apparatus (cannula, infusate-filled syringe, and PEEK tubing) was secured to a stereotactic arm attached to the stereotactic head holder. Fifteen minutes after completion of the infusion, the glue securing the cannula was carefully dissected from the pia and the cannula was slowly removed. The animals were killed by barbiturate overdose immediately after surgery or after a period of recovery and observation.

**Determination of the Distribution Volume of the 14C-Labeled Infusate**

The 14C-infused regions of six porcine spinal cords were frozen, stored at −70°C, and cut longitudinally at −20°C into 20-µm-thick serial sections on a cryostat. To determine the Vd, every fifth section was placed on silanated slides. The slides were exposed to autoradiographic film for 4 hours by using appropriate 14C standards. The area was measured using the NIH Image software program. A threshold of 15% of the maximum optical intensity over the infusion was used to determine the limits of the measured infusion. The Vd was calculated by summing the areas and multiplying by 0.1 mm.

**Determination of Recovery of 14C Infusate**

To determine the percentage of recovery of infusate we studied six pigs. Two 20-µm sections located between each of the sections used for autoradiography were removed and placed in 20-ml scintillation vials filled with 5 ml scintillation fluid. Decays per minute were obtained using a scintillation counter. Values for recovery of 14C activity were derived by multiplying the total number of decays per minute in the sections by 2.5 and then dividing the product by the calculated theoretical total activity of the delivered infusate.

**Determination of the Homogeneity of Delivery**

Using autoradiographs obtained in the 14C-infused animals, longitudinal and cross-sectional concentration profiles of infusate were determined from representative rectangles (width 0.03 mm) whose lengths spanned the infused region in the appropriate direction. The tissue concentration, in sequential 0.125-mm increments, was derived by converting the optical density of the infused region on the autoradiographs to tissue equivalents (µCi/g tissue) by using appropriate 14C standards and the NIH Image software.

To characterize the uniformity of solute distribution associated with convection-enhanced infusion, we determined the kurtosis (K) value for concentration profiles obtained from a 10-µm 14C-albumin infusion (Animal 6). The concentration profile of radioactivity was determined along the longitudinal dimension of the infusion volume in 0.03-mm increments, converted to an equivalent mass distribution, and used to calculate K (Equation 1) where X^n is the nth moment of the longitudinal distribution.

\[
K = \left[ \frac{\langle X^4 \rangle}{\langle X^2 \rangle^2} - 3 \right]
\]

We then determined the expected values of K for two limiting cases of transport: pure diffusion and bulk flow. We modeled purely diffusive distribution of albumin along the axis of a thin cylindrical rod (approximating a dorsal column) by a probability density function (p(x); Equation 2) based on the assumption that a mass delivered at the same rate as by infusion moves axially outward from a central cross section in the rod solely by diffusion. The t_0 is identical to the total infusion time; x is the axial distance from the central cross-section, erf is the complementary error function, and D is the albumin diffusion coefficient (D = 6.9 × 10−9 cm²/s) in the extracellular space.

\[
p(x) = \left[ \frac{t_0}{\pi D x} \right]^\frac{1}{2} e^{-\frac{x^2}{2Dt_0}} \text{erfc} \left( \frac{x}{\sqrt{2Dt_0}} \right)
\]

In the case of the thin cylindrical rod model of pure diffusion, the K value is 1. In contrast, pure bulk flow, described by a homogeneous square wave distribution, has a K value of −1.2.

**Determination of Anatomical Location and Histological Analysis of Infusion**

The anatomical location of the infusions was determined by precise anatomical alignment of autoradiographs over corresponding spinal cord sections obtained in the longitudinal or cross-sectional plane. Longitudinal sections were obtained from the six minipigs used to determine Vd and recovery, and cross-sectional slides were obtained from the spinal cord of an animal infused with 10 µl of 14C-albumin. The specimens were stained with hematoxylin and eosin, Nissl’s, or Luxol fast blue. Twenty-micron sections obtained in swine infused with 10 µl biotinylated Gd-albumin were stained histochemically for GABA according to the manufacturer’s protocol and then counterstained with Luxol fast blue.

**In Vivo Magnetic Resonance Imaging of Swine Infusion**

After a 10-µl infusion of biotinylated Gd-albumin and removal of the infusion cannula, magnetic resonance (MR) imaging of the infused region was performed. A 1.5-tesla imaging system was used. Axial, coronal, and sagittal T1-weighted 3-mm sections were obtained through the region of infusion. The animal was permitted to recover from sedation, and it was observed for neurological deficits. Afterward, the animal was killed, and the infused spinal cord was removed, frozen, and serially sectioned at 20-µm intervals for GABA and Luxol fast blue staining.

**In Vivo MR Imaging, Neurological Observation, and Histological Analysis of Primate Infusion**

The infusion technique used for the three primates was similar to that used for the pigs. Laminctomies were performed from C-3 to C-7. With the aid of an operating microscope, the dura was incised. A small incision (0.5 mm) in the pia overlying the left lateral corticospinal tract was made at the level of the caudal end of the C-4 body. The silica infusion cannula was advanced caudally through the pial opening into the spinal cord so that the cannula coursed parallel to the lateral column fibers for 20 mm and the tip was in the center of the lateral white matter tracts. The cannula was secured to the pia near its entrance into the spinal cord as described earlier. Fifteen minutes after completing the infusion, the glue securing the cannula was carefully dissected from the pia and the cannula was slowly removed. The dura, deep fascial, and superficial tissue layers were closed in the standard fashion. The animals underwent MR imaging of the infused region. Sagittal and cortical T1-weighted 3-mm sections and axial 7-mm sections were obtained through the region of infusion 45 to 60 minutes after the infusion was completed. When MR imaging was completed, the animals were allowed to recover and were serially examined over extended observation periods (1.5, 5, and 16 weeks). At the end of the observation period, the animals were killed by barbiturate overdose, and their spinal cords were removed, frozen, and sliced in 20-µm sections. Staining with Nissl’s and Luxol fast blue dyes, as well as for glial fibrillary acidic protein, was performed.

**Sources of Supplies and Equipment**

The syringe pump (model 22) was obtained from Harvard Apparatus (S. Natick, MA), and the Hamilton syringe, gas-tight syringe, PEEK tubing, fused silica, and Teflon Luer fitting from Thompson Instruments (Springfield, MA). The 14C-labeled bovine serum albumin solution was purchased from New England Nuclear.
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Assessment of the reliability and accuracy of the infusion apparatus

<table>
<thead>
<tr>
<th>Vi (μl)</th>
<th>No. of Samples</th>
<th>Percentage of Expected Decays*</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>98.6 ± 0.9</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>100.8 ± 1.3</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>99.5 ± 1.0</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>99.9 ± 1.6</td>
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</table>

* Values are expressed as mean ± standard deviation.

Assessment of Delivery System Accuracy and Reliability

The high degree of reliability and accuracy of the mechanical system for delivery was demonstrated over the various volumes (1, 2, 5, and 10 μl) of 14C-albumin infused in vitro at 0.1 μl/minute. The reliability of delivery was evident by the linear relationship between the volume of infusate delivered and the total decays per minute (R² = 0.99). The high accuracy of this system was revealed by a mean percentage of expected decays per minute of 99.7 ± 1.4% (range 98.6–100.8%) over all infused volumes (Table 1).

Distribution Volume of 14C-Albumin and Recovery

After infusion of 14C-albumin into the NIH minipig spinal cord, the Vd was linearly proportional (R² = 0.97) to the Vi with a mean Vd/Vi of 4.4 ± 0.5 (Table 2 and Fig. 2A). The anisotropic flow of infusate in the spinal cord was demonstrated by the autoradiographs (Fig. 3 and Fig. 2B and C). Increases in Vd, resulting from corresponding increases in Vi, were attributable to increases in the longitudinal dimension (R² = 0.83), whereas the cross-sectional dimensions remained relatively constant (Table 3). The calculated radioactive albumin recovered from within the spinal cord was 85.5 ± 5.6% of the total 14C-albumin activity infused over the range of Vi (Table 2).

Anatomical Distribution of 14C-Albumin

The anatomical distribution of 14C-albumin in the spinal cord was examined using quantitative autoradiography, image analysis, and histological analysis. A comparison of autoradiographs and corresponding tissue sections stained with Luxol fast blue, which had been obtained in the NIH minipigs infused with 14C-albumin, confirmed that the region of infusion was exclusively within the white matter tracts of the dorsal columns in the longitudinal (six animals) and cross-sectional (10 μl; one animal) planes (Fig. 2B and C).

Homogeneity of Infusion

Delivery by convection into the white matter of swine approximated a square wave distribution of radioactivity in the infused area (Fig. 2D and E). The K value for the experimental longitudinal distribution of −1.1 compared closely with the −1.2 value expected for a uniform square wave distribution generated by pure bulk flow. In contrast, the distribution of albumin by pure diffusion would be expected to result in a nonuniform distribution with a K value of 1.

Infusion of Gd-Albumin Into Swine

Magnetic resonance imaging of the region of porcine spinal cord infused with biotinylated Gd-albumin (Vi 10 μl; Fig. 2F) corresponded closely with the anisotropic distribution of infusate that occurred in the animals infused with 14C-albumin (Fig. 2B and C). Biotin staining of tissue sections obtained from the region of infusion further confirmed that the infusion was limited to the white matter tracts of the dorsal columns and revealed the preferential longitudinal distribution of the infusate (Fig. 2G).

Clinical and Histological Effects of Infusion on Swine

The effects of infusion on neurological function on tissue response in the pigs were studied by observation and histological analysis. None of the four animals infused with 10 or 20 μl of 14C-albumin (two pigs), Gd-albumin (one pig), or unlabeled albumin (one pig) had signs of neurological deficit after examination for up to 3 days after infusion. Spinal cord sections stained with Luxol fast blue, Nissl’s, and hematoxylin and eosin revealed normal tissue architecture.

Magnetic Resonance Imaging Findings and Clinical and Histological Effects of Infusion on Primates

Similar to MR imaging and autoradiographic findings in the swine, the preferred anisotropic distribution was parallel to the fibers of passage in the lateral columns. This permitted filling of long longitudinal segments of the spinal cord over 1.7 (20 μl), 3.1 (40 μl), and 4.3 (50 μl)
Fig. 2. Convection-enhanced delivery of labeled albumin into the spinal cord of the NIH mini-pig. A: Graph showing that the relationship between the volume of infusion and volume of distribution was linear when $^{14}$C-albumin was infused into the dorsal columns of the cervical segments. B: Photomicrograph showing a cross section of a cervical segment of spinal cord infused with 10 $\mu$l $^{14}$C-albumin. The figure shows a Luxol fast blue-stained section superimposed over the corresponding autoradiograph. The area of infusion (black) is limited to the white matter tracts of the dorsal columns. Original magnification $\times$ 2.4. C: Photomicrograph displaying a longitudinal section of spinal cord infused with 10 $\mu$l $^{14}$C-albumin. The figure shows a Luxol fast blue-stained section with the superimposed corresponding autoradiograph. The distribution of $^{14}$C-albumin (black region) is restricted exclusively to the white matter tracts throughout the length of the infusion. Original magnification $\times$ 2.4. D and E: Graphs showing longitudinal and cross-sectional profiles of the concentration ($\mu$Ci/g tissue) across a typical autoradiograph after an infusion of 10 $\mu$l $^{14}$C-albumin. The square profiles and the distinct edges of the perfused region reveal the homogeneity of concentration across the infusion. F: Midsagittal T1-weighted MR image obtained in an animal infused with 10 $\mu$l biotinylated Gd-albumin. Imaging was performed in the animal immediately after completion of the infusion. The infused region (dorsal edge denoted by black arrows) is located in the dorsal columns of the spinal cord (ventral surface of spinal cord denoted by white arrows) and exhibits the preferential longitudinal distribution. A vertebral body is labeled “V.” G: Photomicrograph displaying a longitudinal section of the cervical region of the spinal cord from the same animal as shown in F. Consistent with the $^{14}$C-albumin infusions and MR imaging, the area of infusion (brown) is confined to the white matter tracts of the dorsal columns. The section was stained for biotin and counterstained with Luxol fast blue. Original magnification $\times$ 2.4.
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**TABLE 3**

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>$V_i$ (μL)</th>
<th>Longitudinal Distribution (mm)</th>
<th>Lateral Distribution (mm)</th>
<th>Ventrodorsal Distribution (mm)</th>
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<td>2.7</td>
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</tr>
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<td>10</td>
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<td>6*</td>
<td>10</td>
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<td>2.1</td>
<td>3.2</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>12.3</td>
<td>2.1</td>
<td>3.1</td>
</tr>
</tbody>
</table>

* This animal was infused via two cannulas at distinct sites in the dorsal columns.

**Discussion**

Convective Delivery

Convective-enhanced delivery uses bulk flow in the interstitial space to distribute macromolecules. Previous experience with convection in the brain has shown it to be a method by which macromolecules are infused homogeneously over large volumes of tissue to specific regions in the gray matter in a reproducible and clinically safe manner. In this study we examined convection-enhanced delivery of macromolecules to the white matter of the spinal cord and characterized the properties of bulk flow distribution in this region of the central nervous system.

Examination of $^{14}$C-albumin activity within the porcine spinal cord revealed a $V_d$ that increased linearly as the $V_i$ increased with a mean $V_d/V_i$ ratio of 4.4 ± 0.5. This ratio reflects the distribution expected with delivery of macromolecules within the extracellular spaces of the central nervous system. The preferential spread of macromolecular infusate along the longitudinal axis of fibers reflects the low resistance pathways in the extracellular spaces surrounding axons. The anisotropic distribution follows the highly uniform, parallel arrangement of fibers, as has been shown previously in convection-enhanced delivery of large molecules in the brain, as well as in studies of bulk flow including studies with quantitative-diffusion-tensor MR imaging. By taking advantage of these low resistance pathways in the spinal cord, we distributed macromolecular infusate longitudinally over long segments of spinal cord (4.3 cm when 50 μL was infused in the primate). Although clinically significant lengths of spinal cord were perfused with infusate in this study, the maximum length of cord perfusion was not determined and it is likely to be greater because we observed a linear increase in longitudinal distribution with increasing $V_i$ in the swine ($R^2 = 0.83$), as well as with the larger $V_i$ in the primates ($R^2 = 0.98$).

Excellent recovery (74.2–90.1%) of infusate occurred across all $V_i$ in the $^{14}$C-albumin-infused swine. These high recovery rates of infusate in the target tissue immediately after infusion are achieved as a result of preventing leakage of infusate back along the cannula track. We have found that a retrograde leak can be prevented using lower rates of infusion and allowing the tissue surrounding the cannula or needle time to seal before starting the infusion. Initially, we attempted infusion into the spinal cord with a stationary, rigid, 32-gauge needle (NIH minipig; four animals); however, we were unsuccessful because the physiological movements of the spinal cord would not permit sealing of tissue around the needle and significant retrograde leakage back around the needle occurred. In these animals, the recovery of infusate within the cord was less than 5%, and the $V_d$ was insignificant and confined to the needle tract and the cord surface (RR Lonser, et al., unpublished data). The development of a “floating” cannula (Fig. 1) avoided this problem and allowed the tissue to form a seal around the intraparenchymal portion of the cannula.

The distribution across the region of infusion, as quantified by $^{14}$C-albumin activity, was homogeneous. To characterize the homogeneity of the infusion, we calculated $K$ values. Kurtosis is a statistic used to describe numerically the shape of a distribution curve. We then compared the experimental result with two theoretical $K$ values used to describe the limiting cases of longitudinal distribution in...
the white matter tracts of the dorsal columns of the spinal cord (modeled as a thin rod); pure axial diffusion and pure bulk flow. Our observed $K$ value of $-1.1$ corresponds closely with the value of $-1.2$ for ideal bulk flow delivery and contrasts with the expected $K$ value of 1 for diffusion. This finding underscores the striking uniformity of infusate distribution achievable using convective delivery. Moreover, the uniformity and sharp dropoff of infusate concentration at the infusion edges is evident by the square-shaped concentration profile of radioactivity along the longitudinal axis (Fig. 2D) and is consistent with previous studies of convective delivery to the central nervous system. The highly uniform distributions allow for delivery of nearly equimolar concentrations of infusate over specific regions of spinal cord and obviate much of the heterogeneous, nontargeted delivery of compounds associated with systemic and intrathecal delivery.

Finally, convective delivery of macromolecules to the spinal cord was tolerated without evidence of neurological injury. None of the observed animals (four swine and three primates) exhibited neurological deficits after infusion, either in the immediate postoperative period or after longer observation (up to 16 weeks) with serial examinations (three primates). This is consistent with results from previous studies in which convective delivery was used in the brain as well as studies of rat intrastriatal infusions in our laboratory, which showed that at a conservative rate of 0.1 $\mu$L/minute infusate can reliably distribute molecules over a significant Vd without damaging surrounding tissues (RR Lonser, et al., unpublished data).

**Potential Applications**

Convexion-enhanced delivery of macromolecules to the spinal cord may have wide application in the investigation of new treatments of spinal cord conditions. By taking advantage of the anisotropy of the hydraulic conductivity of the parallel white matter tracts, large molecules can be distributed for treatment over long longitudinal segments of spinal cord. These features make convective delivery of drugs, particularly macromolecules, an attractive method for the treatment of many spinal cord disorders. The regional delivery of therapeutic agents over short or prolonged time courses may prove useful in a variety of spinal disorders, such as prevention of delayed apoptosis after spinal cord injury, attenuation of neurodegenerative diseases, treatment of pain disorders, and the delivery of compounds to enhance spinal cord repair and neuron survival.

**Conclusions**

This technique for delivery of agents to targeted regions of the spinal cord is easy to use and appears clinically safe. Such properties make convexion-enhanced intraspinal delivery an ideal method for investigation of potential treatments of traumatic injury or other focal intrinsic disorders of the spinal cord.

**References**


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