A sophisticated understanding of the fate of drug molecules released into the brain following implantation can only be realized by developing a theoretical framework of transport in the brain. This could be used to provide a sound basis for applying new treatments in different clinical situations. To date, transport studies of drug delivery to the brain have mostly focused on the transcapillary transfer from blood to brain (3, 9, 23) or in the reverse direction (1, 21). The number and extent of mathematical models describing drug transport in brain tissue are mostly limited to dealing with transport within a small region of brain tissue. Diffusion or advection-diffusion models have been used to analyze data obtained from ventriculo-cisternal perfusion experiments (21, 27). The influence of metabolism and binding have been elucidated by microdialysis experiments (8, 16). Some models have dealt with the distribution of compounds released locally into a small region of brain tissue (19, 28).

There have been a few studies that indicate that bulk flow can be used to augment the transport of drugs in tissue by high-flow microinjection (2, 17). Fluid generated within the brain capillaries filters into the interstitial space, producing a positive net pressure in the parenchyma relative to that present in the subdural space (6). Rosenberg et al. (27) assumed a constant velocity in the interstitium and used an advection-diffusion analysis to infer that bulk flow was directed from the brain parenchyma toward the ventricles.

In most of the previous transport models, the drug distribution has been assumed to be one dimensional, and the influence of anatomic boundaries has not been considered. Experimental evidence (24) indicates that this assumption is incorrect at all but the earliest time points after local drug delivery. Other experiments have shown that mass transport in early times postimplantation is strongly influenced by edema (unpublished observations). Surgical trauma induces a local vasogenic edema, creating a region of high interstitial pressure around the implant, which has been observed to last until as much as 3 days post surgery (29). Researchers have modeled the increase of water content in the brain during a vasogenic edema using a consolidation theory approach (18). A finite element model taking into account the boundaries was applied to the formation dynamics of edema induced by a cold lesion to the cortex. But to date, there has been no...
attempt at analyzing the effect of edema on the transport of any drug delivered to the brain.

In a previous study (26), we developed a mathematical model for predicting distribution and clearance of a drug delivered to the brain by intracranial implantation. The model includes realistic brain geometry and salient anatomic features and allows for two-dimensional transportation of chemical species, including both diffusive and convective contributions. We have now extended that study to incorporate the differences in transport properties of the white and gray matter, the boundary effect of the ventricles, and the effect of edema on transport. Various controlled release scenarios have been considered in addition to bolus administration.

MATHEMATICAL MODEL

The transport of a drug released from the surface of a polymeric carrier into the brain can be viewed as affected by diffusion and bulk flow in a porous medium. The distribution of the drug compound may be described by a species mass balance over a volume of the brain tissue

$$\frac{\partial C}{\partial t} + \nabla \cdot CV = \nabla \cdot \left( \frac{D}{\tau} \nabla C \right) - kC$$

where $C$ is the species concentration defined over the tissue volume (g/cm$^3$), $t$ is time (s), $\nabla$ is the gradient operator (cm$^{-1}$), $V$ is the interstitial fluid velocity vector (cm/s), $D$ is the diffusion coefficient of the drug molecule in free water (cm$^2$/s), $\tau$ is the spatially varying tortuosity of the tissue, and $k$ is a lumped drug consumption constant that accounts for drug clearance into the capillaries and enzymatic metabolism of the drug molecule (s$^{-1}$). Consumption kinetics can be assumed to be first order when drug concentration in the blood plasma is low and when the concentration of drug in the tissue is low enough that any enzymatic reactions may be considered first order.

The interstitial fluid velocity field in a saturated porous medium is obtained by extending Darcy’s law through a whole tissue volume averaging of the balance of linear momentum

$$\frac{\rho}{\Phi} \frac{\partial V}{\partial t} + \frac{\mu V}{\kappa} = -\nabla \phi + \mu \nabla |\nabla V + \nabla V^T| + \rho f$$

where $\rho$ and $\mu$ are the density (g/cm$^3$) and viscosity (centipoise) of the fluid, respectively; $\mu$ is an “effective” viscosity (centipoise) (including the effect of the medium); and $\Phi$ and $\kappa$ are the porosity and permeability (cm$^2$) of the medium, respectively. $\kappa/\mu$ is usually assumed to be the hydraulic conductivity of the tissue, and its values are very poorly known. $\phi$ is the interstitial pressure (dyn/cm$^2$), and $f$ is the body force (dyn/g), which is considered to be negligible. The time partial derivative term is important at early time points during large velocity changes in the system, whereas the divergence term is the least important of the terms in the equation. Implicit in the above equation is the assumption that the concentration of the transported species is too low to influence the velocity profile of the interstitial fluid.

Under certain conditions, low to moderate concentrations of the distributing drug can influence the velocity profile of the interstitial fluid. The parenchyma of the brain contains a network of blood capillaries, and drug molecules that do not transport across the blood-brain barrier exert an osmotic force, causing an additional amount of fluid to filter from the blood into the brain parenchyma. This results in an increase in the velocity of the interstitial fluid and consequently an increase in the convective transport of the drug.

To incorporate the effect of vasogenic edema caused by surgical trauma, the continuity equation given below is combined with Eq. 2

$$\nabla \cdot V = \rho_l (Q + \dot{q})$$

where $\rho_l$ is density of brain tissue (g/cm$^3$), $Q$ is the rate of water entering the interstitium from the capillaries (cm$^3$/g·s) and $\dot{q}$ is the rate of water generated by metabolism (cm$^3$/g·s). In Eq. 3, $Q$ is given by Starling’s equation

$$Q = I_{\text{cap}} A [(P - \phi) - \sigma (I_{\text{plasma}} - I_{\text{tissue}})]$$

where $I_{\text{cap}}$ is the permeability of the capillaries (cm$^3$/ dyn·s), which increases at the onset of edema in the tissue region right around the injured site; $A$ is the surface area of the capillary bed (cm$^2$/g); $P$ is capillary pressure (dyn/cm$^2$); $\sigma$ is the reflection coefficient; and $I_{\text{tissue}}$ is osmotic pressure (dyn/cm$^2$). The increase in $I_{\text{cap}}$ is known to be as much as two orders of magnitude following cold lesioning. The increase following surgical trauma is not well characterized, and the value from cold lesioning has been used in this study. The terms under the summation account for the net osmotic pressure gradient. Differentiating Eq. 4 and combining with Eq. 3 yield an expression for $-\nabla \phi$. Substituting the value into Eq. 2, we get the momentum balance in the form used in the model

$$\frac{\rho}{\Phi} \frac{\partial V}{\partial t} + \frac{\mu V}{\kappa} = \left[ \mu + \frac{1}{\rho (I_{\text{cap}} A)} \right] \nabla (\nabla \cdot V) + \mu \nabla^2 V$$

At the boundary between the drug carrier and the brain tissue on the implant surface $\Omega_c$, the release kinetics of the implant may be specified as

$$D \nabla C \cdot n + \alpha_1 C = \beta_1$$

where $n$ is the unit normal to the carrier surface and $\alpha_1$ and $\beta_1$ may be functions of both position along the interface and time. For diffusion-limited release from a polymeric carrier, the drug flux from the polymer surface ($\Omega_c$) is given by

$$-D \nabla C \cdot n = \frac{\gamma_1}{\sqrt{t}}$$

where $\gamma_1$ is a constant that depends on the properties of the drug and polymeric matrix. When the polymeric
carrier is biodegradable we can specify \( \Omega_c = \Omega_c(t) \). When a drug is injected as a bolus, we can assume that at time \( t = 0 \), the drug fills a tissue volume \( \zeta_c \) with an amount \( M_c(g) \).

At the external boundary of the tissue (\( \Omega_b \)), as well as at the ventricle surface (\( \Omega_v \)), we need to specify other boundary conditions for drug transport. For simplicity, we shall assume that the drug is cleared rapidly from the subdural space, so that

\[
C = 0 \quad \text{on} \quad \Omega_b \tag{8}
\]

At the ventricular surface, drug transport is resisted by the cerebrospinal fluid (CSF)-brain barrier. This may be modeled by a mass transfer coefficient \( k_m \) (cm/s), where

\[-D \nabla C \cdot n + \nu C \cdot n = k_m (C - C_v) \quad \text{on} \quad \Omega_v \tag{9a}\]

If the compound is cleared rapidly from the CSF, concentration in the ventricles \( (C_v; \text{g/cm}^3) \) can be considered to be negligible and Eq. 9a can be written as

\[-D \nabla C \cdot n + \nu C \cdot n = k_mC \quad \text{on} \quad \Omega_v \tag{9b}\]

In general, the ventricles are not a perfect sink. The ventricles are filled up with the drug before the drug is cleared to the plasma. Assuming the concentration in the blood to be negligible, one can rewrite Eq. 9 using an overall mass transfer coefficient \( k_m \) (cm/s) that accounts for both the resistance at the CSF-brain interface and the finite volume of the ventricles

\[-D \nabla C \cdot n + \nu C \cdot n = k_mC \quad \text{on} \quad \Omega_v \tag{9c}\]

The expression for \( k_m \) is derived in APPENDIX A. For the limiting case of negligible mass transfer resistance at the interface and rapid clearance from the ventricles, we may write, \( C = 0 \).

The velocity or stress must also be specified on the boundaries. Fluid is produced throughout the brain by a closely knit network of capillaries. This fluid flows through the interstitium toward the ventricles and subdural space surrounding the brain. To model this phenomenon, we assume that fluid is supplied to the boundaries at a constant velocity \( U_0 \) (cm/s), which can be calculated by making use of the fact that 30% of the CSF flow in the ventricles is parenchymal in origin (22). Hence, we assume that the fluid flows toward (and normal to) both the surface of the brain and the ventricles

\[v \cdot n = U_0 \quad \text{on} \quad \Omega_b, \Omega_v \tag{10}\]

We also specify “no slip” of velocity on the surface of the implant (if present)

\[v = 0 \quad \text{on} \quad \Omega_c \tag{11}\]

The drug present initially in the tissue is given by \( f(x) \)

\[C(x, 0) = f(x) \tag{12}\]

although usually \( f(x) = 0 \).

Equations 1-12 describe the transport of a drug through the interstitium of the brain. We have used the finite element method (FEM) to solve these equations numerically. In this method, the domain of interest (the brain parenchyma) has been discretized into “finite elements.” The governing equations are integrated over each element and the solutions matched at the boundaries of adjoining elements. FEM is a powerful numerical tool especially suited to this particular application, because the boundaries of the domain are irregular and the anatomic properties are nonuniform.

We used rabbit brain for our study, because its brain anatomy is well defined (10) and it has been used extensively for neurological studies (4, 11, 24). We defined a domain that was identical to the actual brain in shape and size. The finite element mesh matched the geometry of a transverse slice through the rabbit brain 1 mm anterior to the bregma. This slice was chosen to correspond to the site of polymeric implant in previous studies (24, 26; unpublished observations). The polymeric carrier was placed in the white matter at the same location as used in the experiments.

This mesh is shown in Fig. 1, depicting the geometry of the domain, the presence of the lateral and third ventricles and regions of white matter, and the polymeric carrier. This mesh comprises 800 triangular elements. The governing system of Eqs. 1-12 were solved using PDE2D, a general second-order differential equation solver on a Silicon Graphics INDY workstation. It is important to note that there are no adjustable parameters in this model and all the physical constants are either available in the literature or can be estimated. The physical constants used in the study are shown in Tables 1 and 2.

**EXPERIMENTAL METHODS**

To track the true evolution of drug concentration distribution over time in the brain, we decided to use magnetic resonance imaging (MRI). A previous study (24) demonstrated the effectiveness of this method in following the time course of drug transport in the brain. Gadolinium(III) diethylenetriaminepentaacetic acid (Gd-DTPA), a common clinical MRI contrast agent, was used in this study. To study the effect of molecular weight on transport, Gd-DTPA was attached to dextrans of different molecular weights by covalent coupling (31). The same dose of Gd-DTPA was delivered either as a bolus injection (injection time of 1 min) or metered into the brain using an implanted osmotic minipump (Alzet model 2002, Alza) at a constant rate of 18.75 μg/h with the use of a stereotaxic guide. The minipump delivered the contrast agent at a volumetric infusion rate of 0.5 μl/h for 14 days. The bolus injection was performed using a 23-gauge needle, and the minipump was connected to a 22-gauge implanted cannula (Plastics One) by Silastic tubing. The sites of delivery were either the parenchyma, 0.5 mm anterior to the bregma, or the lateral ventricles of the rabbit brain. At selected time points after the delivery, the animal was scanned in a 4.7-tesla research MRI scanner (General Electric Medical Systems) to obtain T1-weighted and proton density images using standard spin-echo multislice (2-mm slice thickness) imaging sequences.
In other experiments, a cannula was implanted into the lateral ventricles and a bolus of 250 mg Gd-DTPA was injected. At selected time points after the delivery, 50-µl samples of CSF were collected. Microcapillary tubes were filled with each CSF sample and imaged to acquire T1-weighted and proton density images using spin-echo imaging sequences. All the images were postprocessed as described below to obtain relaxation rate data. The mass transfer coefficient at the CSF-brain interface was then calculated by the analysis described in APPENDIX B.

Postprocessing Magnetic Resonance Images

The relationship between the signal intensity of the image and the concentration of the contrast agent is nonlinear in nature. For a spin-echo imaging sequence, the signal intensity (S) in a voxel is given by Ref. 30

\[ S = \rho_p (1 - 2e^{-(T_e - T_r)T_1} + e^{-T_rT_1})e^{-T_eT_2} \]  

(13)

where \( \rho_p \) is the proton density in the voxel, \( T_r \) is the recycle time (s), \( T_1 \) is the shortened longitudinal relaxation time constant (s), \( T_e \) is the echo time (s), and \( T_2 \) is the relaxation time constant of the transverse magnetization (s). The longitudinal relaxation rate (1/T1) can be related to the concentration of the contrast agent by the relation

\[ \frac{1}{T_1} = \frac{1}{T_{10}} + R \times [\text{Gd}] \]  

(14)

where [Gd] is the concentration of the contrast agent in mmol/L.

Table 1. Drug properties

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IL-2</th>
<th>Gd-DTPA</th>
<th>Gd-DTPA-Dextran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>15,800</td>
<td>550</td>
<td>48,000</td>
</tr>
<tr>
<td>D, (10^{-7}) cm/s</td>
<td>5</td>
<td>10</td>
<td>1.74</td>
</tr>
<tr>
<td>(k, \text{cm}^2)</td>
<td>1.92 \times 10^{-4}</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are estimated. IL-2, interleukin-2; Gd-DTPA, gadolinium (III) diethylenetriaminepentaacetic acid; D, diffusivity; \(k\), consumption constant.

Table 2. Parameters used in the simulations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ref.</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\rho), g/cm³</td>
<td>5</td>
<td>1.0</td>
</tr>
<tr>
<td>(\psi), tissue porosity</td>
<td>20</td>
<td>0.2</td>
</tr>
<tr>
<td>(\mu), g/cm·s</td>
<td>Normal tissue</td>
<td>5</td>
</tr>
<tr>
<td>Edematous tissue</td>
<td>5</td>
<td>1.2 \times 10^{-4}</td>
</tr>
<tr>
<td>(U_o), cm/s</td>
<td>Estimated</td>
<td>4.67 \times 10^{-7}</td>
</tr>
<tr>
<td>(A_1), cm²/g</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>(P), mmHg</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>(\kappa), cm²</td>
<td>White matter</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>Gray matter</td>
<td>10^{-11}</td>
<td></td>
</tr>
<tr>
<td>(\gamma)</td>
<td>Unpublished observations</td>
<td>1</td>
</tr>
<tr>
<td>White matter</td>
<td></td>
<td>2.6</td>
</tr>
<tr>
<td>Gray matter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\Sigma_{O_{f, P}}), mmHg</td>
<td>Estimated</td>
<td>24</td>
</tr>
<tr>
<td>Before edema</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>After edema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\Sigma_{O_{f, A}}), mmHg</td>
<td>Estimated</td>
<td>14</td>
</tr>
<tr>
<td>Before edema</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>After edema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(I_{cap}), cm²/dyn·s</td>
<td>Estimated</td>
<td>3.0615 \times 10^{-13}</td>
</tr>
<tr>
<td>Before edema</td>
<td>3.0615 \times 10^{-11}</td>
<td></td>
</tr>
<tr>
<td>After edema</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(\rho\), Density of interstitial fluid; \(\psi\), tissue porosity; \(\mu\), viscosity; \(\bar{\mu}\), effective viscosity; \(U_o\), specified normal velocity; \(\dot{\omega}\), water generated by metabolism; \(A_1\), surface area of capillary bed; \(P\), capillary pressure; \(k\), permeability of tissue; \(\gamma\), tortuosity of tissue; \(\Pi\), osmotic pressure; \(\sigma\), reflection coefficient; \(I_{cap}\), permeability of capillary bed.
one voxel, 1/T10 is the relaxation rate when no contrast agent is present, and R is a proportionality constant (cm³/g·s). Because the difference in relaxation rate is directly proportional to the concentration of the contrast agent, the relaxation rate map is equivalent to a concentration map. A proton density image is used to get the value of \( \rho_p \). In a T1-weighted sequence, Te is very small compared with T2 and Tr. Hence Eq. 13 reduces to

\[
S = \rho_p (1 - e^{-T_1/T})
\]  

which can be rewritten to yield the relaxation rate map

\[
\frac{1}{T_1} = \frac{1}{T_1} \ln \frac{\rho_p}{\rho_p - S}
\]  

Because all the contrast agent lies in the extracellular region, the concentration in the extracellular space can be calculated from Eqs. 14 and 16, making use of the fact that this region accounts for 20% of the volume of the normal tissue. In the presence of edema, this region may account for as much as 35–40% of the tissue.

Velocity Profiles From the Images

The postprocessing yields relaxation rate maps (concentration profiles) of the contrast agent in the brain. Direct injection of contrast agents into the parenchyma yields time-varying concentration profiles, whereas experiments that involved implantation of a cannula connected to an osmotic minipump yield steady-state concentration profiles of contrast agents in the brain. The two sets of data are analyzed in the manner described below.

Time-varying data sets. Equation 1 is discretized using a second-order centered finite difference (FD) scheme. The boundary of the domain over which the discretization was performed was the CSF-parenchymal boundary. The time-varying concentration profiles are fed into the discretized equations, yielding algebraic equations of the form \( Ax = b \). In the equations, the unknowns \( x \) are the components of the interstitial velocity profiles, which are assumed to be constant over that particular time period. A linear least-squares regressive method is used to obtain a “best fit” to the velocity profile over that time period.

![Fig. 2. A: interstitial velocities in the brain parenchyma (smallest arrow is $5 \times 10^{-6}$ cm/s; largest arrow is $7 \times 10^{-4}$ cm/s). B: interstitial velocities in the parenchyma next to the lateral ventricles (smallest arrow is $1.0 \times 10^{-6}$ cm/s; largest arrow is $2.0 \times 10^{-5}$ cm/s).](image)
Steady-state data sets. The steady-state concentration profiles are fed into Eq. 1, which along with Eq. 5 is discretized using a FD scheme as described above. The two discretized sets of equations are then rewritten to yield a set of algebraic equations of the form \( Fx = g \), where the unknowns \( x \) are the components of interstitial velocity in the brain. The solution to this equation set is simply obtained as \( x = F^{-1}g \). These velocity profiles are compared with the model predictions.

With the use of the above methods, the interstitial velocity in the brain was estimated for 12 animals. The primary source of error in this analysis is that all the transport is assumed to be constrained in a plane and the effect of transport across different MRI slices is not considered.

RESULTS AND DISCUSSION

The experiments described above were used to calculate the values of interstitial velocity profiles and mass transfer coefficients at the boundaries. These mass transfer coefficients and the velocity at the CSF-parenchymal boundary were input into Eqs. 7-10, and the model was solved to gain insight into the transport in the brain. The results of the experiments and the model predictions are described below.

Experimental Observations

Estimation of transport parameters. We have previously reported (13) the use of magnetic resonance imaging to calculate the diffusivity of Gd-DTPA in water and in a freshly killed rabbit brain. These values enabled us to calculate the spatially dependent tortuosity of the extracellular space in the brain. These values were used in calculating the interstitial velocity profiles as described in Velocity Profiles From the Images.

To determine the importance of bulk flow of interstitial fluid in affecting transport in the brain, we calculated the Pedlet number (Pe) in the interstitium. Pe is the ratio of resistance to transport by diffusion and resistance to transport by convection and is given by \( Pe = \frac{v}{D} \), where \( l \) is the characteristic length (cm). In the rabbit brain, \( l \) is \( \sim 0.1 \) cm, and for most drugs \( D \) is \( \sim 10^{-6} \) cm²/s. For \( Pe \sim 1 \), \( v \) must be \( \sim 10^{-5} \) cm/s. Higher values of \( Pe \) will be obtained for higher molecular weight drugs or when interstitial velocities are higher. Figure 2 shows the interstitial velocity profile at various points in the brain parenchyma for a representative animal. The velocity varies from \( 10^{-5} \) cm/s nearer the ventricles (Fig. 2B) to \( 10^{-4} \) cm/s at the site of delivery (Fig. 2A). This corresponds to Pedlet numbers ranging from 1 to 10, indicating the importance of convection as a mode of transport in the brain parenchyma. The higher velocities closer to the site of delivery are seen in the white matter, which has a higher permeability than gray matter, allowing for a higher velocity at the same pressure difference. Besides, surgical trauma at the site of delivery causes edema, which also leads to higher velocities, as discussed below.

Figures 3 and 4 show the distribution of Gd-DTPA delivered by two methods. In Fig. 3, an osmotic minipump was implanted in the brain, and the contrast agent was delivered at a constant rate and imaged at the end of 8 days. In Fig. 4, a bolus of Gd-DTPA was delivered to the brain and imaged after 2.5, 5.5, and 9.5 h. The bolus dose spreads rapidly at early time points, with contrast agent filling up the whole hemisphere at the end of 9.5 h (Fig. 4C). At much later times, the steady-state spread of Gd-DTPA from a constant source is limited to only part of the ipsilateral hemisphere (Fig. 3). This indicates the presence of a strong convective component to the transport at early time points, consistent with the presence of edema, which is discussed below.

Edema at early time points. Equation 4 describes the balance of forces that govern capillary filtration. Surgical trauma damages the endothelial blood barrier, increasing the permeability of the blood capillaries to both water and dissolved plasma substances such as salts and proteins. The former results in a direct increase in hydrostatic pressure at the site of the surgery, whereas the latter causes an increase in the osmotic pressure in the interstitium, reducing the osmotic driving force for fluid from the tissue to the capillary. Hence, both these phenomena cause a net increase in the filtration of water across the capillary endothelium, resulting in increased interstitial hydrostatic pressure and consequently edema in the tissue (22).

The presence of edema is marked by an increase in interstitial fluid velocities, which can modify the transport of any drug delivered to the brain. This effect is seen in the magnetic resonance images of Gd-DTPA and Gd-DTPA-dextran delivered to the rabbit brain (Fig. 4). The spread of the contrast agent is rapid, filling the whole ipsilateral hemisphere with Gd-DTPA at 9.5 h postimplantation (Fig. 4, a-c). In the other hemisphere, the contrast agent used is Gd-DTPA linked to dextran (48 kDa). The higher molecular mass contrast...
Fig. 4. Spread of contrast agent in the rabbit brain. a: 2.5 h. b: 5.5 h. c: 9.5 h. Gd-DTPA is in right hemisphere and Gd-DTPA-dextran is in left hemisphere (as seen). Dark regions in the parenchyma are susceptibility artifacts of MRI. Highest value is 0.15 g/cm³.

Fig. 5. Predicted distribution of Gd-DTPA and Gd-DTPA-dextran (bolus dose), taking into account the presence of edema. A: 2.5 h. B: 5.5 h. C: 9.5 h. Values are in g/cm³.
agent fills up most of the hemisphere (Fig. 4c). As demonstrated below, when transport is mediated only by diffusion or bulk flow without the presence of edema, the predicted spread of contrast agent is much lower than what is observed in Fig. 4.

Figure 5 shows the predicted distribution of the contrast agent at the same time points as in Fig. 4, when the effect of edema is taken into account. It is apparent that the increased bulk flow due to the presence of edema strongly affects the spread of either contrast agent (Fig. 5, A-C). At the end of 9 h, the whole ipsilateral hemisphere is full of contrast agent. The spread is greater along the white matter tracts. Edema presents an increase in bulk flow in both the gray and the white matter, with the largest increases in the white matter. The higher permeability (hydraulic conductivity) of white matter presents a lower resistive path for convective bulk flow. The increase in hydrostatic pressure at the site of edema provides the driving force for the transport, causing preferential flow through the white matter tracts toward the boundaries. Because the greatest interstitial fluid flows are observed in the white matter, the nature of the spread suggests the presence of a convective component to the transport.

Transport into the ventricles. Any time a drug is delivered to the brain, it can be cleared from the brain through the CSF into the blood. The transport of the drug molecule is first resisted at the CSF-brain interface and then in the ventricles before it reaches the blood. Hence, its clearance depends mainly on the relative speed of two parameters: 1) diffusion and bulk flow into the ventricles from the parenchyma, which may be represented by a mass transfer coefficient, and 2) transfer from the ventricles into the blood, due to bulk flow of CSF into the blood.

A bolus of Gd-DTPA was delivered to the ventricles, and the time-varying concentration of Gd-DTPA was plotted. Figure 6 is the solution to Eq. A2, and the slope of the line is used to determine $k_m$, the mass transfer resistance at the CSF-brain interface. We represent the overall resistance to transport by the boundary resistance, ventricular filling, and clearance from the ventricles by $k_m$. Once $k_m$ is known, $k_m$ can be estimated as shown in APPENDIX B.

Model Predictions

The parameters estimated by the experiments above and values obtained from literature were fed into the FEM, which was then used to predict the time-varying...
transport and distribution of interleukin (IL)-2, a cytokine that has been shown to be a potent activator of the immune system and is currently under investigation in the immunotherapy of different types of cancers, including gliomas. Release kinetics of IL-2 from a biodegradable polymeric carrier were estimated by a compartmental analysis of in vivo data (14). The results of the simulation have been compared with the predicted distribution of a bolus administration of the drug to the same site.

Bolus administration. Figures 7–9 show the distribution of IL-2 in the rabbit brain when delivered by a bolus administration of 7 µg. The total volume infused was 10 µl into normal extracellular space. The bolus dose was modeled to fill a region of tissue of the volume of administration. If the transport of IL-2 was affected only by diffusion, the spread of IL-2 would be as shown in Fig. 7. The spread is not radially symmetrical, because of the differences in the tortuosity of the white and gray matter. But the spread is rather slow, and at the end of 12 h, 1% of the original dose still remains in the brain. When the bulk flow of the interstitial fluid is also considered (Fig. 8), IL-2 is cleared from the brain more rapidly, with transport directed preferentially along white matter tracts. Yet, one sees IL-2 at the end of 12 h. When edema is present (Fig. 9), the concentrations seen in the brain are an order of magnitude lower than what is seen in Figs. 7 and 8 by the end of 12 h. IL-2 also spreads farther in the parenchyma, filling up the whole ipsilateral hemisphere at the end of 12 h.

Microsphere administration. The release kinetics of the microspheres are shown in Fig. 10. Although the
total dose of the drug is the same as in the bolus dose, IL-2 concentrations in the parenchyma at early time points are lower. Due to the sustained release of the drug, at times greater than a day, a much higher percentage of the drug remains in the brain. The initial spread of the drug is influenced by the presence of edema (Fig. 12A). The presence of edema causes high interstitial velocities around the implant, with the fluid flow directed away from the implant toward the boundaries and with the largest velocities occurring in the white matter tracts (Fig. 11B). This causes the drug to spread out from the implant into the tissue in a rapid manner (Fig. 12A). The spread of IL-2 increases for up to 2 days as more of the drug is released and eventually some of the drug enters the contralateral hemisphere (Fig. 12B). One can also see the effect of the finite volume of the ventricles. As the ventricles are filled up with the drug, the drug concentrations are not negligible at the CSF-brain interface. The clearance of the drug from the ventricles is much lower than if the ventricles were considered to be a perfect sink.

Once edema is resolved, the interstitial velocities decrease to their steady-state (lower) values (Fig. 11A) and convection is no longer the major determinant of transport, although the direction of spread is still influenced by it. The clearance of the drug due to factors such as metabolism, enzymatic degradation, and uptake becomes important. Hence, IL-2 remains confined to a smaller region around the implant (Fig. 12, C and D). A significant amount of drug remains in the brain for more than 14 days (Fig. 12D).

Conclusion

The blood-brain barrier poses the major obstacle to drug therapy of the central nervous system. As new drugs for neurological disorders are discovered, ingenious new delivery techniques will have to be developed in concert to overcome this transport barrier. Optimization of these delivery methods will be aided by an understanding of the transport processes in the brain. The distribution of any drug in the brain, such as IL-2, is strongly dependent both on the transport pathways present in the brain and on the drug properties, such as diffusivity, hydrophilicity/lipophilicity, and its interaction with brain tissue. Our study of IL-2 demonstrates the complex nature of its transport in the brain, being affected by transport modalities that may vary temporally and spatially. Bulk flow of interstitial fluid augmented by edema plays a critical role in the spread at early time points. To maintain high local concentrations in the brain over long periods of time, a sustained release of the drug is necessary, since a bolus dose is cleared rapidly from the brain within 36 h.

Without a sophisticated theoretical framework of transport in the brain and consideration of factors such as edema, one could make serious errors in the estimation of transport parameters. This model is a preliminary approach at incorporating the effects of edema and time-varying convective forces on transport in the brain. It, however, does not take into account the effect of edema on the properties of tissue. In particular, the poroelastic deformation of tissue, which could both vary the extracellular fraction and have an effect on the transport, is not considered. A rigorous analysis will help define the potential and limitations of any mode of delivery to the brain and particularly aid the development and rational design of polymeric drug carriers for intracranial implantation.
APPENDIX A

A one-compartment model of the ventricular system is shown in Fig. 13. A bolus dose, $M_o$, of contrast agent is injected into the ventricles. $C(t)$ is the concentration of the contrast agent in the ventricles at any time $t$. $V$ is the volume of the ventricles ($cm^3$), and $A_s$ is the surface area of the CSF-brain interface ($cm^2$). $Q_c$ is the volumetric flow rate of CSF produced in the choroid plexus ($cm^3/s$), and $Q_p$ is the flow rate of interstitial fluid entering the ventricles from the parenchyma ($cm^3/s$). The net transport of the drug from the ventricles into the parenchyma depends on $k_m$, the mass transfer coefficient at the interface, and $C_s$, the concentration in the parenchyma at the CSF-brain interface ($g/cm^3$). The clearance into the blood depends on the flow of the CSF into the jugular vein given by $Q_b$ ($cm^3/s$).

A fluid mass balance gives

$$Q_b = Q_p + Q_c \quad (A1)$$

A mass balance on the contrast agent yields

$$V \frac{dC_v}{dt} = -(Q_v + Q_p + k_m A_s C_v + k_m A_s C_s) \quad (A2)$$

at time $t = 0$

$$C = M_o/V \quad (A3)$$

A plot of $dC_v/dt$ vs. $C_v$ can be used to determine $k_m$, since the values of $Q_v$, $Q_p$, and $A_s$ can be estimated from the literature (15, 22).

APPENDIX B

A mass balance over the drug in the ventricles yields

$$A_s k_m (C_s - C_v) = V \frac{dC_v}{dt} + Q_b C_v \quad (B1a)$$

(input) (accumulation) (output)

Assuming that drug concentration in ventricles varies slowly, we may put $dC_v/dt = 0$ and write

$$A_s k_m (C_s - C_v) = Q_b C_v$$

Rewriting the above expression, we get

$$C_v = \frac{A_s k_m}{A_s k_m + Q_b} C_s$$

and

$$\frac{C_s - C_v}{C_s} = \frac{Q_b}{A_s k_m + Q_b} \quad (B1b)$$

If we define an overall mass transfer coefficient such that $k_m (C_s - C_v) = k_m' C_s$, then

$$k_m = \frac{k_m' (C_s - C_v)}{C_s} = \frac{Q_b}{A_s k_m + Q_b} k_m$$

$$k_m' = \frac{Q_b}{A_s k_m/Q_b + 1} \quad (B2)$$

For very large values of $Q_b$, the drug entering the ventricles is cleared rapidly, such that $C_v$ approaches zero, $A_s k_m/Q_b \ll 1$, and $k_m'$ reduces to $k_m$. For very small values of $Q_b$, the resistance to transport is much higher in the clearance pathway compared with the CSF-brain boundary. Therefore, we can assume the concentration of the drug at the CSF-brain interface to be the same as in the ventricles, so that $C_s = C_v$, $A_s k_m/Q_b \gg 1$, and $k_m'$ reduces to $Q_b/A_s$.

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