Cerebrospinal Fluid and Spinal Cord Distribution of Baclofen and Bupivacaine during Slow Intrathecal Infusion in Pigs

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Background: Increasing numbers of patients are receiving chronic intrathecal infusions of local anesthetics, baclofen, opioids, and other analgesics via implanted pumps. These infusions typically deliver drugs at rates measured in microliters per hour. However, to date, there have been no studies aimed at characterizing drug distribution within cerebrospinal fluid (CSF) and spinal cord during these slow infusion rates. Therefore, this study was designed to address this knowledge gap.

Methods: Anesthetized pigs were instrumented with eight intrathecal microdialysis probes placed at multiple points along the neuroaxis in both the anterior and posterior intrathecal space to permit continuous CSF sampling for measurement of bupivacaine and baclofen concentrations. Animals were divided into three groups and received bupivacaine and baclofen concentrations. Animals were divided into three groups and received bupivacaine and baclofen infusions at 20 or 1,000 µl/h or as a 1,000-µl bolus over 5 min every hour. Drug administration continued for 8 h, at which time the animals were killed, and the spinal cord was removed and divided into 1-cm-long sections that were further divided into anterior and posterior portions for measurement of bupivacaine and baclofen concentrations.

Results: In all groups, drug concentration in CSF and spinal cord decreased rapidly as a function of distance from the site of administration, with most drug found within a few centimeters. In addition, there were significant anterior–posterior differences in both CSF and spinal cord drug concentrations.

Conclusions: During slow intrathecal infusion, drug distribution in CSF and spinal cord is severely limited in all groups, although significantly more so in the 20-µl/h infusion group.

BOTH human and animal studies of drug distribution within the intrathecal space have historically been conducted as single bolus injections made at relatively rapid injection rates of tens of milliliters per minute. Studies using this approach are clearly applicable to the typical clinical situation in which a local anesthetic, opioid, α2-adrenergic agonist, or other spinal active drug is administered as a “single-shot” injection of a few milliliters over a few seconds.

However, in recent years, implantable pumps have been developed that permit continuous drug infusion into the intrathecal space at rates as low as a few microliters per day. Given the vastly slower infusion rates used for chronic intrathecal drug administration, it is unclear whether drug distribution data derived from bolus drug studies are applicable to chronic intrathecal infusions.

Therefore, the purpose of this study was to characterize the distribution of baclofen and bupivacaine within cerebrospinal fluid (CSF) and spinal cord when infused at very slow rates. These drugs were chosen because they are commonly administered by continuous intrathecal infusion to treat spasticity or pain, respectively. To characterize the distribution of these drugs in CSF, we used a previously described pig model in which microdialysis techniques are used to continuously sample CSF at multiple sites along the neuroaxis. Microdialysis techniques are ideal for this type of study because they permit CSF sampling without “disturbing” CSF.

Materials and Methods

Studies were approved by the University of Washington Animal Care and Use Committee (Seattle, Washington). American Association for Laboratory Animal Care guidelines were followed throughout.

Preparation of Microdialysis Probes

Microdialysis probes were prepared from cellulose microdialysis fibers (Spectrum Medical Industries, Houston, TX) with a 215-µm inside diameter, a 235-µm outside diameter, and a molecular weight cutoff of 6,000 Da. Epoxy cement was used to coat all but the center 2 cm of the fiber, thus creating a 2-cm dialysis window. Epoxy was spread evenly over the fiber by running a 2-cm length of polyethylene-10 tubing over the fiber while the epoxy was still wet. Polyethylene-10 tubing has an inside diameter of 280 µm; therefore, the dialysis probe had a final outside diameter of 280 µm. To facilitate placement of the dialysis probes within the CSF, a 90-µm diameter wire was inserted into the lumen of the dialysis probe and bent at the center of the dialysis window, thereby creating a microdialysis loop. A 0.5-mm cone-shaped length of silicone caulk was placed approximately 0.5 mm from the dialysis window. To prevent CSF leak, this elastic cone was wicked into the meningeal hole through which the probes were inserted.
into the CSF. All probes were allowed to “cure” for at least 12 h before implantation and were used within 48 h of preparation.

**Surgical Preparation**

Farm-bred pigs (n = 19) weighing 20 ± 1.4 kg were used. Each animal was anesthetized by mask inhalation of sevoflurane (2–3%) and nitrous oxide (70%) in oxygen, paralyzed with intramuscular succinylcholine, orotracheally intubated, and mechanically ventilated. Nitrous oxide was discontinued and anesthesia was maintained with 1.5% sevoflurane in balance oxygen. Pancuronium bromide (5 mg) was given as an intravenous bolus and was added to the maintenance fluid (0.05 mg/ml) to maintain muscle relaxation. End-tidal carbon dioxide was continuously monitored (Datex model AS/3 airway gas analyzer; Helsinki, Finland), and ventilation was adjusted to maintain end-tidal carbon dioxide at 38–42 mmHg. Body temperature was maintained at 37°–38°C using a servo-controlled heat lamp and a rectal thermistor.

The left femoral artery was cannulated for blood pressure measurement and blood sampling. The left femoral vein was cannulated for infusion of lactated Ringer’s solution (4 ml/kg/h) as a maintenance fluid. The posterior epidural space was then exposed in the midline through an approximately 0.5-cm hole at T12. An iris scissor was used to cut a small (approximately 1-mm) hole through the meninges at T12, and a microdialysis probe affixed to an epidural catheter (B. Braun Medical, Bethlehem, PA) was inserted through the hole in a cephalad direction to lie in the midline along the posterior surface of the spinal cord. This epidural catheter was used for drug infusion. The dura mater was gently retracted to permit a second 1-mm incision through the anterior–lateral spinal meninges. A second microdialysis probe was inserted through this hole to lie along the anterior surface of the spinal cord immediately opposite the posterior probe. The probes were secured with cyanoacrylate glue, and the integrity of the epidural space was restored by sealing the entry hole with cyanoacrylate glue.

Dialysis probes were likewise placed in the CSF along the anterior and posterior surfaces of the spinal cord at points 5 cm caudad of T12 and 5 cm cephalad of T12. A single posterior probe was placed 10 cm cephalad of T12, and a final microdialysis probe was placed via a burr hole into the CSF overlying the right parietal lobe. This cerebral dialysis probe served as a control for drug re-entering the CSF from the plasma. In the remainder of the article, probes are named by their location (anterior or posterior subarachnoid space) and distance from the site of drug administration in centimeters with the probes adjacent to the infusion site designated as 0 cm. Probes caudal to the administration site are designated as “−,” and those cephalad are designated as “+.”

After completing the insertion of dialysis probes, the epidural catheter was tunneled through approximately 8–10 cm of paraspinal muscle so that the infused solution would be warmed to body temperature. The animal was then strapped to a specially designed board, and the board was secured in a vertical position so that the animal’s posture approximated that of an upright human.

**Dialysis Protocol**

Mock CSF (140 mEq NaCl, 25 mEq NaHCO₃, 2.9 mEq KCl, 0.4 mEq MgCl₂, 3.5 mEq urea, 4.0 mEq glucose, and 2.0 mEq CaCl₂; pH 7.38–7.42; 295 mOsm) was oxygenated and pH-adjusted by bubbling with 95% O₂–5% CO₂. It was then pumped through the eight dialysis probes at 10 µl/min. Dialysate samples were collected from each of the eight dialysis probes at 10-min intervals (100-µl samples) for the first 120 min, at 15-min intervals for the next 120 min (150-µl samples), and at 20-min intervals for the final 240 min (200-µl samples).

**Correction for Recovery.** At the end of the experiment, the dialysis probes were placed in a solution of known concentration of bupivacaine and baclofen, and three 10-min dialysis samples (100 µl) were collected from each probe. The recovery fraction was calculated for each probe by dividing the average bupivacaine and baclofen concentrations in the three dialysis samples by the known concentration of the drugs in the dialyzed solution. The bupivacaine and baclofen concentrations from all of the experimental samples were corrected for differences in recovery by dividing the measured drug concentration by the individual probe’s recovery fraction. Recovery fraction for bupivacaine averaged 0.11 ± 0.04, and that for baclofen averaged 0.14 ± 0.06.

**Drug Administration.** Baclofen hydrochloride (Sigma-Aldrich, St. Louis, MO) and bupivacaine hydrochloride (Sigma-Aldrich) were mixed together in normal saline at concentrations of 2 and 7.5 mg/ml, respectively. ³H-bupivacaine (Moravek Biochemicals, Inc., Brea, CA; specific activity 12.1 Ci/mmol, radiochemical purity > 97%) and ¹⁴C-baclofen (American Radiolabeled Chemicals, St. Louis, MO; specific activity 56 mCi/mmol, radiochemical purity > 98%) were added to serve as radiotracers.

The animals were divided into three groups. At time zero, continuous drug infusion was begun at 20 µl/h in group 1 (n = 7) or at 1,000 µl/h in group 1,000 (n = 7). These infusion rates were chosen as representative of a clinically relevant infusion rate (“group 20”) and of the maximum infusion rate achievable with commercially available infusion pumps (“group 1,000”). “Group bolus” (n = 4) received a 1,000-µl bolus over 5 min at time zero and then again every hour. Drug administration continued for 8 h in all three groups. Importantly, the bolus group did not receive a bolus at the end of the eighth hour.
Spinal Cord Samples. At the end of each experiment, the spinal cord was removed and cut into 1-cm-long sections. Each section was further divided into anterior and posterior halves. Tissue specimens were briefly rinsed in ice water, patted dry, weighed, and solubilized (Solvable Tissue and Gel Solubilizer; Packard Instruments, Downer’s Grove, IL) at 50°C.

In the remainder of the article, spinal cord specimens are named by their position (either anterior or posterior side of the spinal cord) and by their distance in centimeters from the site of drug administration with the spinal cord segment adjacent to the tip of the infusion catheter designated as 0 cm. Specimens obtained from points caudal to the 0 cm spinal segment are designated as “−,” and those cephalad are designated as “+.”

Drug Assay

Drug concentrations in dialysate and spinal cord samples were determined by counting the amount of radio-labeled bupivacaine and baclofen in each sample using liquid scintillation. Hydrofluor (National Diagnostics, Mannville, NJ) scintillation fluid (5 ml) was added to dialysate samples, and Formula 989 (Packard Instruments) scintillation fluid (10–20 ml) was added to tissue samples. All samples were counted in a liquid scintillation counter (Tri-Carb 2000; Packard Instruments) for 15 min or until the SD of disintegrations per minute (DPM) was 2% or less. Background DPM from mock CSF pumped through the probes before injection of any radioactivity were subtracted from total DPM of samples collected during the postinjection period. Samples with a total DPM less than the average plus 2 SDs of the background DPM were considered to contain no drug.

Statistical Analysis

Differences within and among groups were assessed for statistical significance by analysis of variance, and the Fisher protected least squares difference was used for post hoc testing. All data are reported as average ± SD. Differences were considered statistically significant for \( P < 0.05 \).

Results

Bupivacaine and baclofen were not detected in any samples from cerebral CSF microdialysis probes from any experiment in any group. This fact indicates that all drug concentrations measured in samples from other probes reached the sampling site by movement through CSF and not by uptake into plasma and redistribution back into CSF.

Figure 1 shows the posterior, lateral, and anterior surface of the spinal cord from a single pilot animal in which methylene blue was added to the drug infusion (20 \( \mu \)l/h for 8 h). The photos show heavy staining of the posterior surface of the spinal cord adjacent to the tip of the infusion catheter (A), minimal staining of the lateral surface of the spinal cord (B), and no visible staining of the anterior surface of the spinal cord (C).

Fig. 1. Photographs of an approximately 3-cm-long section of spinal cord from a single pilot animal in which methylene blue was added to the drug infusion (20 \( \mu \)l/h for 8 h). The photos show heavy staining of the posterior surface of the spinal cord (A), minimal staining of the lateral surface of the spinal cord (B), and no visible staining of the anterior surface of the spinal cord (C).
concentration in this segment (51 ± 33 ng/mg) was more than 14 times greater than the concentration in the segment with the next highest concentration (i.e., the anterior half of the same 0 cm spinal segment).

Baclofen behaved similarly in the 20-µl/h infusion group (additional information regarding this is available on the ANESTHESIOLOGY Web site). As with bupivacaine, baclofen was also highly concentrated around the drug infusion site, as indicated by the number of samples from each probe that contained measurable baclofen concentrations (table 1). There was no difference between bupivacaine and baclofen in terms of the number of samples containing measurable drug quantities.

As with bupivacaine, baclofen was also highly concentrated in the posterior 0 cm spinal cord segment in the 20-µl/h group (additional information regarding this is available on the ANESTHESIOLOGY Web site). Baclofen content in the posterior 0 cm spinal cord segment accounted for 56 ± 17% of the baclofen recovered in the spinal cord and the concentration in this segment (39 ± 27 ng/mg) was 8 times greater than the concentration in the corresponding anterior half of the same spinal cord segment.

Figure 3A shows bupivacaine concentrations over time in CSF dialysate samples in the 1,000-µl/h group. Baclofen distribution was similar (additional information regarding this is available on the ANESTHESIOLOGY Web site). As with the 20-µl/h group, the average peak concentration and AUC of bupivacaine and baclofen were highest at the posterior 0 cm sampling site (table 1). However, in contrast with the 20-µl/h group, there were measurable concentrations of bupivacaine and baclofen at many more sampling sites (table 1). Also noticeably different from the 20-µl/h group is the fact that CSF concentrations of bupivacaine and baclofen reached steady state earlier, and the second highest average peak drug concentrations occurred at the posterior −5 cm sampling site and not the anterior 0 cm sampling site.

Figure 3B shows the average bupivacaine concentrations in spinal cord tissue in the 1,000-µl/h group. Baclofen distribution was similar (additional information regarding this is available on the ANESTHESIOLOGY Web site). Consistent with the CSF concentration data, the highest average tissue concentration for both drugs occurred in the posterior 0 cm spinal cord specimen. For bupivacaine, drug concentration was significantly different between the anterior and posterior halves of the spinal cord and as a function of distance from the site of administration. Bupivacaine concentration in the 0 cm posterior specimen was greater than that in all other specimens which did not differ significantly from one another.

For baclofen, drug concentration differed significantly as a function of distance from the site of administration but did not differ significantly between anterior and posterior spinal cord (additional information regarding this is available on the ANESTHESIOLOGY Web site).

Figure 4 show the bupivacaine CSF concentration data from the bolus drug administration group. Baclofen distribution was similar (additional information regarding this is available on the ANESTHESIOLOGY Web site). Not surprisingly, the data demonstrate the intermittent increase and subsequent decrease in concentration coinciding with the hourly bolus. As with the 20-µl/h and peak baclofen concentration and the highest AUC were obtained from the posterior 0 cm probe (table 1). Baclofen was also highly concentrated around the drug infusion site, as indicated by the number of samples from each probe that contained measurable baclofen concentrations (table 1). There was no difference between bupivacaine and baclofen in terms of the number of samples containing measurable drug quantities.

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Figure 3B shows the average bupivacaine concentrations in spinal cord tissue in the 1,000-µl/h group. Baclofen distribution was similar (additional information regarding this is available on the ANESTHESIOLOGY Web site). Consistent with the CSF concentration data, the highest average tissue concentration for both drugs occurred in the posterior 0 cm spinal cord specimen. For bupivacaine, drug concentration was significantly different between the anterior and posterior halves of the spinal cord and as a function of distance from the site of administration. Bupivacaine concentration in the 0 cm posterior specimen was greater than that in all other specimens which did not differ significantly from one another.

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Table 1. CSF Bupivacaine and Baclofen Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>20 µl/h</th>
<th>1,000 µl/h</th>
<th>Bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bupivacaine</td>
<td>Baclofen</td>
<td>Bupivacaine</td>
</tr>
<tr>
<td>Peak concentration, µg/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a 0 cm posterior</td>
<td>37.3 ± 30.5</td>
<td>18.1 ± 20.9</td>
<td>304 ± 142</td>
</tr>
<tr>
<td>b 0 cm anterior</td>
<td>4.1 ± 7.0</td>
<td>3.7 ± 6.3</td>
<td>109 ± 186</td>
</tr>
<tr>
<td>c −5 cm posterior</td>
<td>0.03 ± 0.08</td>
<td>0.24 ± 0.57</td>
<td>111 ± 135</td>
</tr>
<tr>
<td>d −5 cm anterior</td>
<td>0.02 ± 0.04</td>
<td>0.12 ± 0.28</td>
<td>47 ± 51</td>
</tr>
<tr>
<td>e +5 cm posterior</td>
<td>0.0 ± 0.0</td>
<td>0.03 ± 0.07</td>
<td>65 ± 146</td>
</tr>
<tr>
<td>f +5 cm anterior</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>16 ± 29</td>
</tr>
<tr>
<td>g +10 cm posterior</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.1 ± 0.3</td>
</tr>
<tr>
<td>h Cerebral</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>AUC, µg · min/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample site</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>a 0 cm posterior</td>
<td>12,373 ± 11,160</td>
<td>5,294 ± 6,200</td>
<td>103,399 ± 39,100</td>
</tr>
<tr>
<td>b 0 cm anterior</td>
<td>954 ± 1,744</td>
<td>839 ± 1,392</td>
<td>36,596 ± 76,700</td>
</tr>
<tr>
<td>c −5 cm posterior</td>
<td>0.3 ± 0.8</td>
<td>29.8 ± 71.8</td>
<td>13,744 ± 14,458</td>
</tr>
<tr>
<td>d −5 cm anterior</td>
<td>0.17 ± 0.4</td>
<td>4.7 ± 8.5</td>
<td>9,512 ± 12,725</td>
</tr>
<tr>
<td>e +5 cm posterior</td>
<td>0.03</td>
<td>0.3</td>
<td>9,333 ± 20,641</td>
</tr>
<tr>
<td>f +5 cm anterior</td>
<td>0.0</td>
<td>0.0</td>
<td>2,182 ± 4,564</td>
</tr>
<tr>
<td>g +10 cm posterior</td>
<td>0.0</td>
<td>0.0</td>
<td>5.3 ± 14.6</td>
</tr>
<tr>
<td>h Cerebral</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Percentage of samples with measurable drug concentrations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a 0 cm posterior</td>
<td>96 ± 53</td>
<td>97 ± 53</td>
<td>100 ± 0</td>
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<tr>
<td>b 0 cm anterior</td>
<td>35 ± 23</td>
<td>26 ± 38</td>
<td>96 ± 6</td>
</tr>
<tr>
<td>c −5 cm posterior</td>
<td>0.5 ± 1.3</td>
<td>21 ± 38</td>
<td>85 ± 22</td>
</tr>
<tr>
<td>d −5 cm anterior</td>
<td>0.5 ± 1.3</td>
<td>13 ± 25</td>
<td>83 ± 22</td>
</tr>
<tr>
<td>e +5 cm posterior</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>47 ± 4</td>
</tr>
<tr>
<td>f +5 cm anterior</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>49 ± 3</td>
</tr>
<tr>
<td>g +10 cm posterior</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>h Cerebral</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
</tr>
</tbody>
</table>

Superscript letters indicate which values are different from one another. AUC = area under the curve; CSF = cerebrospinal fluid.

1,000-µl/h groups, there were significant differences in bupivacaine and baclofen concentration over time among the different sampling sites. Unlike the other two groups, there are few differences in average peak concentration among the different sampling sites (table 1). Specifically, for both drugs the only significant difference was between the site with the highest concentration (0 cm posterior) and the cerebral sampling site (which had no measurable drug concentrations).

Also, unlike the other two groups, there were no differences in AUC (table 1) among the sampling sites for either bupivacaine or baclofen (power = 0.5 for each), nor were there differences in the number of samples with measurable concentrations of bupivacaine (power = 0.35) or baclofen (power = 0.5). Figure 5 shows the average bupivacaine (A) and baclofen (B) concentrations in spinal cord tissue in the bolus group. Consistent with the CSF concentration data, the highest average tissue concentration for both drugs occurs in the posterior 0 cm spinal cord sample. As with the 1,000-µl/h group, bupivacaine concentration was significantly different between the anterior and posterior spinal cord samples and was also significantly different as a function of distance from the site of drug administration. Also like the 1,000-µl/h group, baclofen concentration differed as a function of distance from the site of drug administration but did not differ significantly between anterior and posterior spinal cord.

To determine whether there were significant differences among the groups in the pattern of drug distribution within CSF, the AUC for each sampling site was normalized by dividing each value by the dose of drug administered (additional information regarding this is available on the ANESTHESIOLOGY Web site). For both baclofen and bupivacaine, the dose-normalized AUCs for group 20 differed significantly from group 1,000 and group bolus, which did not differ significantly from one another.

To determine whether there were differences between groups in terms of drug distribution within the spinal cord, drug concentration in each cord sample was also dose-normalized for samples between −3 cm and +3 cm. This range was chosen to achieve adequate power (0.5) to detect significant differences among the three groups. As with the dose-normalized CSF AUC data, the dose-normalized spinal cord concentration for group 20 differed significantly from the other two groups for bupivacaine (fig. 6) and baclofen (additional information regarding this is available on the ANESTHESIOLOGY Web site). Group bolus and group 1,000 did not differ significantly from one another for either drug.
Discussion

This is the first study to provide a detailed examination of drug distribution within CSF and spinal cord tissue during relatively slow drug infusion. The most prominent finding is the limited distribution of bupivacaine and baclofen from the site of administration, especially in the 20-μl/h group. For both bupivacaine and baclofen, most of the drug recovered in the CSF and spinal cord in this group was found within 1 cm of the site of administration.

The fact that drug concentrations in CSF reached steady state in the two continuous infusion groups before the midpoint of the 8-h study would suggest that a longer period of drug administration would be unlikely to significantly alter the limited distribution of either bupivacaine or baclofen. This hypothesis is supported by the fact that normal constituents of CSF exhibit marked rostrocaudal concentration gradients throughout an individual’s lifetime. For example, Degrell and Nagy measured concentrations of multiple CSF components in adult lumbar and cisternal CSF. They found that homovanillic acid concentrations were 6 times higher and 5-hydroxyindole acetic acid concentrations were nearly 3 times higher in cisternal CSF than in lumbar CSF. In contrast, the rostrocaudal uric acid concentration gradient was reversed with lumbar CSF concentrations that were twice as high as cisternal CSF than in lumbar CSF. CSF proteins are also nonuniformly distributed in CSF. Weisner and Bernhardt measured albumin, immunoglobulin, and prealbumin concentrations in lumbar, cisternal, and ventricular CSF of nondiseased adults. They found that albumin concentration increased 2.2 times and immunoglobulin G concentration increased 2.6 times from ventricular to lumbar CSF, whereas prealbumin concentration decreased by a factor of 0.7. The origin of these gradients is not fully understood, but the fact that they can persist throughout a human lifetime attests to the poor “mixing” of CSF and supports the idea that a longer period of drug infusion would not necessarily have resulted in more distant or more uniform drug distribution.

In considering why the distribution of these drugs is so limited, it is perhaps useful to consider the mechanisms...
all molecules move in space by Brownian motion at a rate that is proportional to temperature and inversely proportional to the square root of the molecule’s molecular weight. However, Brownian motion is too slow to account for drug movement over distances greater than a few hundred microns. For example, small solutes are estimated to require 14 h to diffuse a distance of only 1 cm, and drug molecules, which are much larger, will require a proportionally longer period of time. Therefore, diffusion driven by Brownian motion cannot explain drug distribution within the CSF.

A second source of energy to facilitate drug distribution within the CSF is the kinetic energy imparted to the drug by the act of injection. As anybody who has ever used a syringe to inject fluid through a needle can attest, “drug” can be rapidly “distributed” many yards by this mechanism if the syringe plunger is pushed rapidly enough. However, in the current study, drug infusion at 20 μL/h is almost imperceptible and in a standing fluid column does not propel the solution forward at all (unpublished observations by the author). The faster infusion rates in the 1,000-μL/h group and especially in the bolus group do impart slight, but observable, forward motion to the injectate, and differences among the groups in drug distribution may be in part the result of differences in kinetic energy associated with the different infusion rates.

The third, and likely the primary, mechanism responsible for drug distribution within CSF in this study is CSF motion itself. Any drug suspended in CSF will be carried along by the motion of the CSF in which it is dissolved. The drug will move in this way for as long as it is suspended in CSF, and its distribution will be limited only by the rate and extent of CSF motion. For decades, textbooks have portrayed CSF as “flowing” caudad by bulk flow along the posterior surface of the spinal cord and returning cephalad along the anterior surface as if it were a river. Such CSF motion would be expected to move drugs considerable distances. However, although oft repeated, this portrayal of CSF “flow” is incorrect. Numerous human studies using magnetic resonance imaging techniques have shown that CSF oscillates to-and-from the site of administration.
fro along the rostrocaudal axis. This motion is driven by cyclic expansion and contraction of the cerebrospinal vasculature during cardiac systole and diastole. The magnitude of the motion is greatest in the upper cervical regions and decreases with distance from the cranial vault, becoming negligible at the level of the cauda equina. In addition, Henry-Feugeas et al. have shown that spinal CSF motion can be divided into three distinct channels— medioventral, dorsomedial, lateral—that can be distinguished from one another by the timing and magnitude of CSF oscillation. Even within a given channel, the timing and magnitude of CSF motion was highly variable, with some areas along the cord devoid of either rostral or caudal motion in some subjects even though there was no evident anatomical basis for the lack of CSF motion. For example, only 23% of subjects had detectable motion in the low thoracic ventral subarachnoid space, only 50% had motion in the dorsomedial channel between the midthoracic and thoracolumbar levels, and only 65% of subjects had motion in the lateral channel at the level of the thoracolumbar junction. Whether motion is continually absent or only transiently absent was not examined. Completely undetected was circumferential motion of CSF between the anterior and posterior sides of the spinal cord. Lack of circumferential motion likely reflects the fact that denatured ligaments and spinal nerve roots traversing the lateral subarachnoid space act as an effective baffle. Therefore, net CSF motion is limited for multiple reasons: (1) CSF is propelled in opposite directions during each cardiac cycle; (2) the more caudal from the foramen magnum, the smaller is the CSF pulse wave; (3) some regions are devoid of motion at least at some times in some subjects; and (4) most CSF motion occurs only in the rostrocaudal axis and not circumferentially. This more accurate view of CSF motion helps to explain why humans can have marked, permanent rostrocaudal CSF concentration gradients for multiple endogenous molecules.

Therefore, both the direct measurements of CSF motion as well as the permanent concentration gradients that exist for endogenous constituents of CSF strongly support the idea that CSF is poorly mixed. In turn, this limited movement of CSF is the most likely explanation for the findings of this study, i.e., that baclofen and bupivacaine undergo restricted distribution from their site of administration when infused at the relatively slow infusion rates studied.

The 20-μl/h infusion rate was chosen because it probably represents the upper end of the range of infusion rates typically used for chronic intrathecal drug delivery. The other two groups were included to determine whether a faster continuous infusion rate or an intermittent bolus regimen would significantly alter drug distribution. Not surprisingly, the data demonstrate that the distribution of bupivacaine and baclofen within CSF and/or spinal cord parenchyma is increased in the 1,000-μl/h and bolus groups compared with the 20-μl/h group. Evidence of greater distribution comes from the dose-normalized CSF AUC and spinal cord concentration data presented above. Evidence that the bolus group achieved better drug distribution than did the 1,000-μl/h group is more subtle but still present. For example, the bolus group had fewer differences in average peak concentration among the CSF probes than did the 1,000-μl/h group. Too, there were no differences in AUC or the number of samples with measurable drug concentrations among the different CSF sampling sites in the bolus group, although there were such differences among CSF probes in the 1,000-μl/h group. These data are consistent with greater, i.e., more uniform, drug distribution in the bolus group compared with the 1,000-μl/h group. As noted above, the relatively greater distribution of the study drugs in the 1,000-μl/h and bolus groups compared with the 20-μl/h group may be explained by the greater kinetic energy imparted to the infusate by the faster infusion rates.

Interestingly, there were few differences in distribution between the two study drugs. These drugs were chosen because they are both used clinically for chronic intrathecal infusions and because they have different physicochemical properties, particularly lipid solubility. It was hypothesized that baclofen, the more hydrophilic drug, would demonstrate significantly greater distribution because of longer residence time in CSF; i.e., by remaining in CSF longer before being cleared, baclofen was hypothesized to have a greater “opportunity” to be distributed away from the site of administration. The only finding consistent with this hypothesis was the fact that baclofen concentration in spinal cord in the bolus and 1,000-μl/h groups did not differ significantly between the anterior and posterior sides of the spinal cord, whereas bupivacaine concentrations did differ significantly between the anterior and posterior spinal cord in these two groups. This finding would suggest that baclofen had better circumferential distribution than did bupivacaine. Whether this was the result of longer CSF residence time cannot be determined from the data.

This study’s findings have several important clinical implications for chronic intrathecal drug administration. First, they suggest that the location of the tip of the infusion catheter relative to the targeted spinal cord segment(s) may be critical given the limited capacity for CSF to distribute drugs away from the catheter tip. Anecdotal experience suggests that this is the case. For example, the author is aware of numerous cases in which patients had marked improvement of spasticity or pain after a trial intrathecal bolus of baclofen or morphine but then obtained only limited or no relief after they received an implanted intrathecal pump to deliver the same drug. In many of these cases, repositioning the catheter tip resulted in improved symptom control. The
likely explanation for these findings is that better drug distribution associated with the bolus injection resulted in much better drug delivery to the relevant spinal target site than was achieved with the very slow drug infusion. This is true with respect to both cephalocaudal drug distribution as well as anterior-posterior distribution. For cases where the dorsal horn is the target, a posteriorly positioned catheter tip may well be important, whereas for targeting the anterior horn, an anteriorly positioned catheter tip may well provide better drug coverage for the targeted segments.

A second clinical implication pertains to the development of the spinal granulomas that are associated with chronic intrathecal morphine infusion. These granulomas invariably form at the tip of the intrathecal catheter, and animal studies demonstrate that they are related to the concentration of morphine infused. Therefore, it seems that limited distribution of morphine away from the catheter tip predisposes to formation of these inflammatory masses and that development of methods to improve drug distribution may decrease the risk of granuloma formation and the spinal cord injuries that often accompany them.

There are several potential limitations of this study that merit mention. First, relevance of the pig model to human anatomy and physiology is an important issue. However, there are numerous relevant similarities between pig and human spinal physiology. For example, the pig spinal cord averages 45–55 cm in adult humans; spinal cord diameter in these pigs averages 0.6–1.1 cm, compared with 0.7–1.4 cm in adult humans; and CSF formation rate, as a percentage of total CSF volume, is 0.4%/min, compared with 0.58%/min in humans. Too, the fact that the findings of this study are consistent with what is known about human CSF motion and the “permanent” concentration gradients that exist for endogenous CSF components in humans suggests that the model is relevant and does represent, at least qualitatively, drug distribution in humans.

A second important issue is that our pigs were upright and motionless as opposed to freely moving and in multiple positions, as is the case with humans. Again, however, the lifelong persistence of concentration gradients in human CSF suggests that movement and position changes do not result in overwhelming increases in CSF mixing. Too, changes in posture and ambulation have been shown not to affect CSF motion in humans. Therefore, the vertical position of the animals and their lack of motion are probably not important shortcomings of the model.

Finally, normal saline was used as the solution for the infusions; therefore, we do not know how solutions that are significantly hypobaric or hyperbaric would behave in this model. Nor do we know how differences in drug concentration would affect drug distribution. Studies designed to address both of these issues are currently under way.

In conclusion, this is the first study to undertake a detailed examination of baclofen and bupivacaine distribution when infused at rates that are relevant to those that might be used for chronic intrathecal therapy. The principal finding is that drug distribution is quite limited, and significant drug concentration gradients exist within CSF and spinal cord tissue. The limited drug distribution is consistent with what is known about CSF motion and the existence of large permanent concentration gradients for endogenous CSF components. The clinical implications of the study are that catheter position in relation to the targeted spinal cord segment may be critical to efficacy, especially with very slow infusion rates. In addition, the data may help to explain the pharmacokinetics underlying concentration related toxicities that occur at the catheter tip. Additional studies are under way to more fully explore drug distribution in this increasingly important area of spinal drug delivery.

References

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