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

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ABSTRACT

Background: Despite the widespread use of implanted pumps for continuous intrathecal drug delivery, there have been no studies aimed at defining the effect of baricity and posture on drug distribution in the cerebrospinal fluid and spinal cord during the very slow infusion rates typically used for chronic intrathecal drug administration.

Methods: Intrathecal microdialysis probes were placed at six points along the neuraxis in both the anterior and posterior intrathecal space of anesthetized pigs to permit cerebrospinal fluid sampling. Animals were then positioned either vertically or horizontally (prone), and a hyperbaric solution containing bupivacaine (7.5 mg/ml) and baclofen (2 mg/ml) was infused at 20 μl/h for 6 h, while the cerebrospinal fluid was collected for measurement of drug concentration. At the end of the experiment, the animals were killed, and the spinal cord was removed and divided into 1-cm sections that were further divided into anterior and posterior portions for measurement of drug concentration.

Results: Bupivacaine and baclofen distribution was biased caudally in the vertical group and cephalad in the horizontal group. Drug concentration decreased rapidly in the cerebrospinal fluid and spinal cord as a function of distance from the site of administration in both groups, resulting in most drugs being located in very close proximity to the site of infusion.

Conclusion: Even at very slow infusion rates, drug distribution within the cerebral spinal fluid and spinal cord are affected by baricity/posture. These findings suggest that patient position and solution baricity may be important clinical factors determining the distribution and ultimate efficacy of chronic intrathecal drug infusions.

What We Already Know about This Topic

❖ Drug spread in spinal cord and fluid during very slow infusion rates, such as used in chronic pain treatment, has been minimally studied

What This Article Tells Us That Is New

❖ In normal pigs, very slow infusion of a hyperbaric solution resulted in restricted spread, which was affected by body position

❖ Drug distribution during chronic spinal infusion might differ between ambulation and sleep

THE development of implantable pumps has resulted in a marked increase in chronic intrathecal drug administration as a means to treat both pain and spasticity. Despite the increasing frequency with which this therapeutic modality is used, there are few data describing drug distribution within the cerebrospinal fluid (CSF) and spinal cord during the very slow infusion rates used for chronic intrathecal drug delivery (generally $\leq$ 20 μl/h). What data do exist indicate that CSF and spinal cord drug distribution data derived from bolus drug studies are not applicable to these very slow intrathecal infusions. For example, by using an anesthetized pig model, we previously demonstrated that bupivacaine and baclofen distribution during chronic intrathecal infusion is very limited compared with that which occurs with bolus administration, with most of the infused drug recovered in the CSF and spinal cord found within 1 cm of the administration site.[1]

In our earlier study, we infused an effectively isobaric saline solution. However, in an attempt to limit the frequency of pump refills, clinicians frequently use highly concentrated drug solutions for chronic intrathecal infusions. Hejtmanek *et al.*[2] recently demonstrated that many of these solutions are hyperbaric. Consequently, our earlier study is not applicable to many highly concentrated drug solutions that may be used for chronic intrathecal infusion.

We designed this study to test the hypothesis that infusing hyperbaric drug solutions would result in gravity-driven, largely unidirectional drug distribution in CSF and spinal cord. To test this hypothesis, we used a robust pig model[1,3–5] in which microdialysis techniques were used to continuously

sample CSF at multiple sites along the neuraxis while a hyperbaric solution of bupivacaine and baclofen was infused. Bupivacaine and baclofen were chosen as the study drugs, because they are commonly infused intrathecally to treat pain and spasticity, respectively, and they represent significant differences in hydrophobicity.

Materials and Methods

This study was approved by the University of Washington Animal Care and Use Committee (Seattle, WA). The American Association for Laboratory Animal Care Guidelines were followed throughout.

Preparation of Microdialysis Probes

As for all of our previous studies in both animals and humans,[1,3,4,6–9] microdialysis probes were made from cellulose dialysis fibers (Spectrum Medical Industries, Inc., Houston, TX) with a 235-μm outside diameter and a molecular weight cutoff of 6000 Da. Epoxy cement (System Three Resins, Inc., Quick Cure 5, Auburn, WA) is used to coat all but the center 10 mm of the dialysis fiber, thus creating a 10-mm "dialysis window." After the epoxy cures, a 90-μm diameter tungsten wire (Hamilton Company; Reno, NV) is placed in the lumen of the dialysis probe and the probe is bent in half, so that the terminal 5 mm of the loop encompasses the 10-mm dialysis window. A silicone elastomer is spread in the shape of a cone at the base of the probe; this serves to plug the hole in the meninges through which the probe is inserted. The probes are allowed to cure for at least 24 h before use, and all the probes are used within 72 h of manufacture.

Surgical Preparation

Farm-bred, Yorkshire cross pigs (n = 18) weighing 20 ± 4.5 kg were anesthetized (isoflurane 1.5–2.5%), intubated, and mechanically ventilated throughout the study. Femoral intravenous and arterial lines were placed for maintenance fluid administration and cardiovascular monitoring, respectively. Ventilation (100% O_2) was adjusted to maintain end-tidal CO_2 = 35–40 mmHg (Criticare Systems Inc. POET IQ, model 602-6B; Waukesha, WI). Mean arterial pressure and heart rate were continuously monitored (Datex model AS/3 Anesthesia monitor; Helsinki, Finland). Animals were paralyzed by continuous pancuronium infusion to prevent sudden movement caused by electrocautery-mediated depolarization of the spinal nerves during surgery. Phenylephrine was infused as needed to maintain normotension (mean arterial pressure = 60–90 mmHg) relative to the skull base, particularly for animals in the vertical position. Temperature was maintained at 37.0 ± 0.5°C by servo-controlled heat lamps and a nasopharyngeal thermister. Depth of anesthesia was ensured during surgery and before the administration of phenylephrine or pancuronium by maintaining end-tidal isoflurane no less than 1.5% and noting appropriate mean arterial pressure and heart rate.

The posterior epidural space was 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, 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 at the T12 vertebral level. This 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 at the same level, and a second microdialysis probe was inserted through this hole to lie along the anterior surface of the spinal cord immediately opposite the posterior microdialysis probe, which was affixed to the epidural infusion catheter. The probes were secured with cyanoacrylate glue at the point they pierced the dura mater, and the integrity of the epidural space was restored by sealing the hole through the ligamentum flavum with cyanoacrylate glue. Dialysis probes were likewise placed in the CSF along the posterior surface of the spinal cord at points 5 and 10 cm caudad of T12 and 5 cm cephalad of T12. An additional anterior dialysis probe was placed along the anterior surface of the spinal cord at the point 5 cm caudad to the T12 drug infusion site. Figure 1 depicts the relative locations of all microdialysis probes and the drug infusion catheter. To help put the distances between microdialysis probes into clinical perspective, 5 cm is approximately the height of one adult human vertebral body.

Intrathecal Drug Administration

Baclofen hydrochloride (Sigma-Aldrich; St Louis, MO) and bupivacaine hydrochloride (Sigma-Aldrich) were mixed in
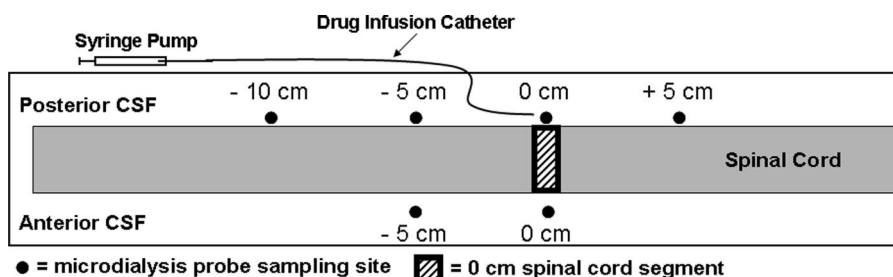

Fig. 1. Diagram of the relative positions of the drug administration site, cerebrospinal fluid (CSF) sampling sites (*black circles*), and 0-cm spinal cord segment (*hatched box*). The CSF and spinal cord samples collected cephalad of the 0-cm site are identified by positive numbers, and those collected caudad of the 0-cm site are identified by negative numbers.

normal saline containing 7.5% dextrose to produce final concentrations of 2 and 7.5 mg/ml, respectively. Radiotracer amounts of ^{14}C-baclofen (American Radiolabeled Chemicals, St. Louis, MO; specific activity 56 mCi/mmol, radiochemical purity > 98%) and ^{3}H-bupivacaine (Moravek Biochemicals, Inc., Brea, CA; specific activity 12.1 Ci/mmol, radiochemical purity > 97%) were added to each drug solution, so that drug concentration could be determined by liquid scintillation counting.

Animals were assigned to a vertical or horizontal group (n = 9 per group). The vertical animals were strapped to a specially designed board, and the board was secured in a vertical position so as to approximate the posture of an upright human. The horizontal animals were placed sternally recumbent and positioned such that a line between the shoulders and hips was parallel to the floor to ensure that the spinal cord was as close to horizontal as physically possible.

After positioning, the intrathecal drug infusion was administered by a syringe pump (Harvard Apparatus, model 22; Holliston, MA) at 20 μl/h for 6 h.

Dialysis Protocol

Mock CSF (140 mEq NaCl, 25 mEq NaHCO$_3$, 2.9 mEq KCl, 0.4 mEq MgCl$_2$, 3.5 mEq urea, 4.0 mEq glucose, and 2.0 mEq CaCl$_2$; pH 7.38–7.42; 295 mOsm) was used to perfuse the dialysis probes. The dialysate was pumped through the probes at 10 μl/min. Although this may seem like an unusually fast infusion rate, it was necessary to obtain adequate temporal resolution of drug concentration in CSF, especially early in the study when the concentration had not reached steady state. Dialysis samples were collected at 10-min intervals (100 μl volumes) for the first 2 h, at 15-min intervals (150 μl volumes) for the next 2 h, and at 20-min intervals (200 μl volumes) for the remaining 2 h.

At the end of each study, the dialysis probes were removed and calibrated, so that the samples from each individual probe could be corrected for recovery efficiency as follows: the probes were placed in a vial containing mock CSF with a known concentration of the study drugs, and this solution was dialyzed at 10 μl/min for 10 min. Three 100-μl samples were obtained, and the average concentration of the study drugs in the dialysate samples was divided by the known drug concentration in the mock CSF to produce the unique "fractional recovery quotient" for each individual probe. Recovery for bupivacaine averaged 10.4 ± 10.7% and for baclofen averaged 15.8 ± 14.8%. Drug concentration measured in each dialysis sample obtained during the experiment was then divided by the recovery quotient for the probe from which it was obtained so as to correct for differences in the dialysis efficiency of each individual probe.

Spinal Cord Samples

At the end of each study, while the animal was still fully anesthetized, it was killed by an intravenous injection of 10 ml saturated KCl. The spinal cord was removed and sectioned into 1-cm pieces, and each of these pieces was further divided into an anterior and a posterior half for measurement of bupivacaine and baclofen concentrations as described in the next paragraph. These pieces were weighed "wet" on an analytical balance with an accuracy to 4 decimal places. (Mettler, model AE-100S; Columbus, OH).

Drug Assay

Drug concentrations in the dialysate and spinal cord samples were determined by counting the amount of radiolabeled baclofen and bupivacaine in each sample using liquid scintillation counting. Hydrofluor (National Diagnostics, Mannville, NJ) scintillation fluid (5–10 ml) was added to dialysate samples for scintillation counting. The spinal cord samples were first digested with Solusol tissue solubilizer (National Diagnostics), and then Soluscint (National Diagnostics) scintillation fluid (10–20 ml) was added to the tissue digest. All samples were counted in a liquid scintillation counter (Packard Instruments, model Tri-Carb 2500; Downer's Grove, IL) for 15 min or until the SD of disintegrations/min was less than or equal to 2%. Background disintegrations/min were measured from mock CSF pumped through the probes before injection of any radioactivity, and the values were averaged. CSF samples with a total of disintegrations/min less than the average plus 3 standard deviations of the background disintegrations/min were considered to contain no drug.

Background disintegrations/min was also calculated for the spinal cord segments as follows. Twenty brain samples (0.22 g ± 0.15 g) were taken from a pig that did not receive any radioactive drug. The disintegrations/min for each sample was calculated three times for a total of 60 measurements using the same method described in the preceding paragraph. The spinal cord samples with a total of disintegrations/min less than the average plus 3 standard deviations of the brain sample disintegrations/min were considered to contain no drug.

Statistics

Both groups (vertical vs. horizontal) consisted of nine animals each. Prospective power analysis was not performed. All comparisons were planned prospectively. The exact statistical test to be used for each comparison was not chosen prospectively, because it was impossible to know the nature of the data in advance (e.g., normally vs. nonnormally distributed). No attempt was made to correct for multiple comparisons. All statistical tests were performed using Instat software (GraphPad Software, Inc., LaJolla, CA). Exponential curve fitting was performed using Kaleidagraph software (Synergy Software, Inc., Reading, PA).

Statistical analysis was designed to determine whether animal position (vertical vs. horizontal) had an effect on the distribution and/or amount of drug recovered in the CSF and spinal cord. The rationale for this approach was the assumption that animal position would affect drug distribution only if the infused solution behaved hyperbarically.

Table 1. Steady-state Bupivacaine and Baclofen CSF Concentrations

	Vertical		Horizontal	
	ng/ml	95% CI	ng/ml	95% CI
Bupivacaine				
CSF sampling Site				
Posterior +5 cm	0 (0–0)*	0–0	0 (0–20)*	−2.4–24.7
Posterior 0 cm	1250 (600–3800)	600–2600	200 (65–2150)	−1477–5982
Anterior 0 cm	10.9 (0.3–308)*	−967–2728	230 (0–3055)	−320–3352
Posterior −5 cm	5.4 (0.17–37.7)*#	−6.7–50.4	0 (0–0)*	0–0
Anterior −5 cm	31.8 (0.3–93.1)*	−5.5–42.4	0 (0–0)*	0–0
Posterior −10 cm	0.62 (0–18.5)*#	−0.7–11.4	0 (0–0)*	0–0
Baclofen				
CSF sampling Site				
Posterior +5 cm	0 (0–0)*#	0–0	60 (15–160)	−0.7–214
Posterior 0 cm	478 (319–1063)	149–1602	110 (10–1070)	−200–1623
Anterior 0 cm	57.7 (4.5–317)*	−223–902	600 (0–1815)	83.7–1676
Posterior −5 cm	55.3 (2.3–118)*#	12.8–123	0 (0–0)*	0–0
Anterior −5 cm	17.8 (3.7–103)*#	2.7–127	0 (0–0)*	0–0
Posterior −10 cm	6.9 (0–100)*#	−1.0–78.7	0 (0–0)*	0–0

Data are median plus (interquartile range).

* Indicates concentrations that are significantly different from the steady-state concentration at the Posterior 0 cm site, *i.e.*, the site of drug administration for that drug (bupivacaine or baclofen) in that group (vertical *vs.* horizontal). # Indicates a significant between-group (vertical *vs.* horizontal) difference in steady-state concentration for that drug at that sampling site.

CSF = cerebrospinal fluid.

The Friedman test was used to determine whether steady-state CSF drug concentrations differed significantly between sampling sites within group and within drug. Steady-state drug concentration was defined as the average of the final five CSF samples (80-min sampling period). The Mann–Whitney U test was used *post hoc* to determine which sampling sites had steady-state CSF drug concentrations that differed significantly from the concentration at the posterior 0-cm sampling site. Steady-state concentrations at some CSF sampling sites (table 1) were zero in all animals. Consequently, the data from these sampling sites had an SD of zero, which precludes use of the Mann–Whitney U test. To obviate this limitation and permit application of the Mann–Whitney U test in this situation, a single value was given a steady-state CSF concentration of 1×10^{-12} ng/ml (*i.e.*, mathematically nonzero but clinically equivalent to zero).

The Mann–Whitney U test was used to determine whether steady-state CSF drug concentrations differed between groups and within sampling sites (*e.g.*, steady state baclofen concentration at the posterior 0-cm sampling site in the horizontal group was compared only with steady-state baclofen concentration at the posterior 0-cm sampling site in the vertical group). No between-sampling site or between-drug comparisons were made as part of the between-group analysis.

As a further measure of drug distribution in CSF, the number of CSF samples from each CSF sampling site that had detectable concentrations of bupivacaine and baclofen were compared between groups using the Mann–Whitney U test. This between-groups analysis was performed only between the probes at the same sampling site and only for the posterior probes. The pairwise comparisons were limited to the four posterior probes because the question being ad-

dressed was the effect of the position of longitudinal spread from the site of administration, and there were too few anterior probes (two) to address this question.

Differences between the groups with respect to the spinal cord content of bupivacaine and baclofen were assessed by comparing both the amount of each drug in the spinal cord and the distribution of drugs within the cord. Drug content differences between the groups were quantified as the total amount of bupivacaine and baclofen recovered in the spinal cord and as the maximum amount of bupivacaine and baclofen in a single spinal cord sample. Mann–Whitney U test was used to determine whether the differences were statistically significant.

The affect of animal position on longitudinal drug distribution within the spinal cord was assessed by between-group comparison of total drug content (anterior plus posterior spinal cord segments) at the point of drug administration (0 cm segment), at the most caudal point (−10 cm segment), and at the most cephalad point (+5 cm segment). Statistical significance was determined by Mann–Whitney U test (nonparametric data) or Student *t* test (parametric data; Welch correction applied to data with unequal standard deviations). Between-group differences in drug distribution were also assessed by comparing the location of the spinal cord segment containing the highest concentration of baclofen and bupivacaine. The Mann–Whitney U test was used to determine whether these differences were significantly different.

Results

Steady-state CSF concentrations of bupivacaine and baclofen differed significantly as a function of sampling site in both the vertical and horizontal groups (fig. 2; table 1).
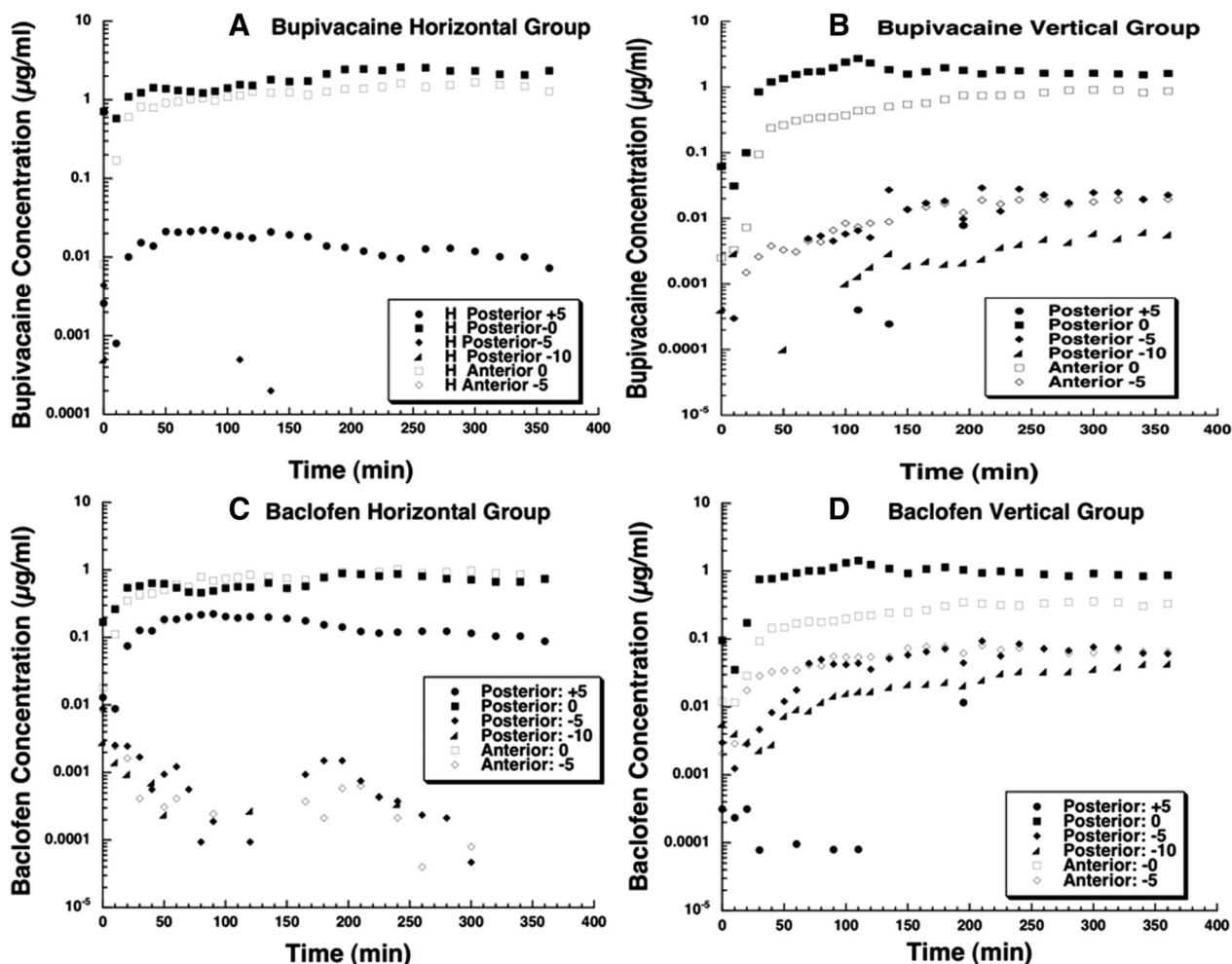
Fig. 2. Cerebrospinal fluid concentrations in the horizontal and vertical groups for bupivacaine (*A, B*) and baclofen (*C, D*). Data points are averages, and *error bars* are omitted for clarity. The average of the last five data points (280–360 min) from each probe site was used to calculate the steady-state concentration of each drug in both groups. Values equal to zero are omitted to permit use of log-scale.

To assess the effect of animal position, and thus baricity, on the longitudinal spread of bupivacaine and baclofen in CSF, we examined the caudad and cephalad distribution of both drugs in the posterior CSF. In the vertical group, median bupivacaine and baclofen steady-state concentrations at the posterior CSF sampling sites decreased with increasing caudad distance from the drug administration site (fig. 2; table 1). For both drugs, the relationship between decreasing median concentrations and increasing caudad distance could be fitted very well ($r^2 > 0.999$) by exponential equations (fig. 3). In contrast, for the horizontal group, the median steady-state concentrations of bupivacaine and baclofen were zero at all sampling points caudad to the site of drug administration (fig. 2; table 1).

Median steady-state bupivacaine and baclofen concentrations cephalad of the drug administration site were zero in the vertical group (fig. 2; table 1). In the horizontal group, the median concentration of bupivacaine was also zero, whereas the median concentration of baclofen was greater than zero (fig. 2; table 1).

Drug movement from the posterior to the anterior CSF was assessed by comparing drug concentration in the posterior and anterior 0-cm sampling sites. In the vertical group, concentrations of bupivacaine and baclofen at the anterior 0-cm sampling site were statistically significantly less (by 1 to 2 orders of magnitude) than at the posterior 0-cm site of drug administration (table 1). In contrast, the median concentrations of bupivacaine and baclofen in the horizontal group were not statistically significantly different between the posterior and anterior 0-cm sampling sites, although they were numerically greater at the anterior sampling site for both drugs (table 1).

As another measure of the effect of animal position on the magnitude of drug distribution from the site of drug administration, we assessed whether there were differences between the two groups in the number of CSF samples that had measurable concentrations of bupivacaine and baclofen. For both drugs, the horizontal group had significantly more samples with measurable drug concentration cephalad of the drug administration site, and the vertical group had significantly more positive samples caudad of the drug administration site (figs. 4 and 5). There were no differences between the two groups in the number of samples containing either drug at the 0-cm site of drug administration.
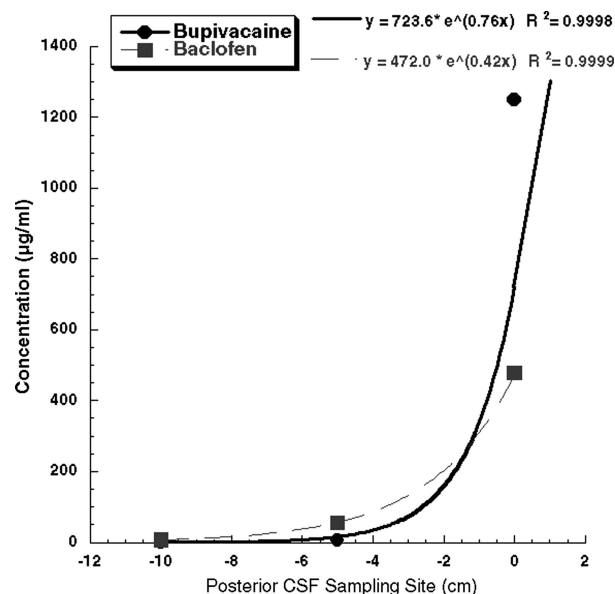
Fig. 3. Plot of median steady-state concentrations of bupivacaine and baclofen as a function of caudad distance from the site of drug administration (0 cm). Both data sets were well described by exponential functions ($r^2 > 0.999$). CSF = cerebrospinal fluid.
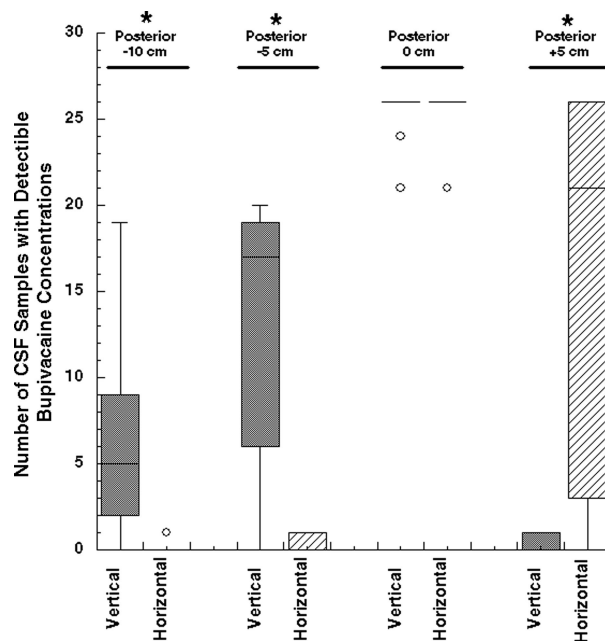

Fig. 4. Box plot of the median number of the cerebrospinal fluid (CSF) samples that had measurable concentrations of bupivacaine at each sampling site. The total number of samples collected at each sampling site was 26 per animal. *Box* indicates interquartile range, *line across box* indicates median, *whiskers* indicate range excluding outliers, and *open circles* indicate outliers. * Indicates a statistically significant difference ($P < 0.05$, Mann–Whitney U test) between the horizontal and vertical groups within sampling sites. No between-sampling site comparisons were made.

When plotted, the distribution of baclofen and bupivacaine within the spinal cord seemed to be shifted caudad in the vertical group compared with the horizontal group (figs. 6 and 7). To quantify this apparent difference, we examined several measures of drug content and drug distribution within the spinal cord. Maximum baclofen content in any one spinal cord segment was significantly greater in the horizontal group (9,914 ng [5,759–20,480 ng]) than in the vertical group (1,307 ng [841–4,425 ng]). Maximum bupivacaine content in any one spinal cord segment was also significantly greater in the horizontal group (19,030 ng [3,959–37,620 ng]) than in the vertical group (8,085 ng [1,918–10,390 ng]). As an additional measure of differences between the groups in drug distribution within the spinal cord, we compared drug content at the level of drug infusion (0 cm) at the most caudad site (−10 cm) and at the most cephalad site (6 cm). For both drugs, the amount in the spinal cord at the 0-cm and +6-cm spinal cord segments was significantly greater for the horizontal group than for the vertical group (fig. 6). In contrast, the content of both drugs was greater for the vertical group compared with the horizontal group within the −10-cm spinal cord segment (fig. 7). Finally, the total amount of drug recovered in all the spinal cord segments was significantly greater in the horizontal group compared with the vertical group for both bupivacaine (horizontal: 37,640 ± 37,590 ng; vertical: 14,000 ± 7,215 ng) and baclofen (horizontal: 34,450 ± 24,680 ng; vertical 10,390 ± 9,380 ng).

To quantify the location of the spinal cord segments with the maximum drug content, the median location of the segment with the highest drug content was located for each group. For baclofen, the location of the spinal cord segment containing the maximum amount of drug was significantly more caudad in the vertical group (−2 cm [−5.5 to 0 cm]) compared with the horizontal group (0 cm [0–0 cm]). In contrast, the distribution of bupivacaine segments containing the maximum drug content did not differ significantly between the vertical (0 cm [−1 to 0 cm]) and horizontal (0 cm [0–0 cm]) groups.

Discussion

By using this same animal model, we have previously shown that drug distribution in the CSF and spinal cord is extremely limited during slow intrathecal infusions.[1] Our earlier study, however, was performed with an essentially isobaric saline solution. Because we have subsequently shown that high concentrations of drugs that are custom compounded for intrathecal infusion are frequently hyperbaric,[2] we conducted this study to test the hypothesis that drug distribution during slow intrathecal infusion would be affected by solution baricity. Our finding of significant differences in drug distribution in the CSF and spinal cord in both the rostro-caudal and anterior–posterior axes as a function of animal position confirms this hypothesis.

Our study was not specifically designed to examine the differences between the study drugs; however, the fact that both drugs were administered simultaneously as a part of the same drug solution makes it possible to draw some conclusions. For example, the fact that the median steady state CSF concentration of bupivacaine was zero, whereas that of ba-
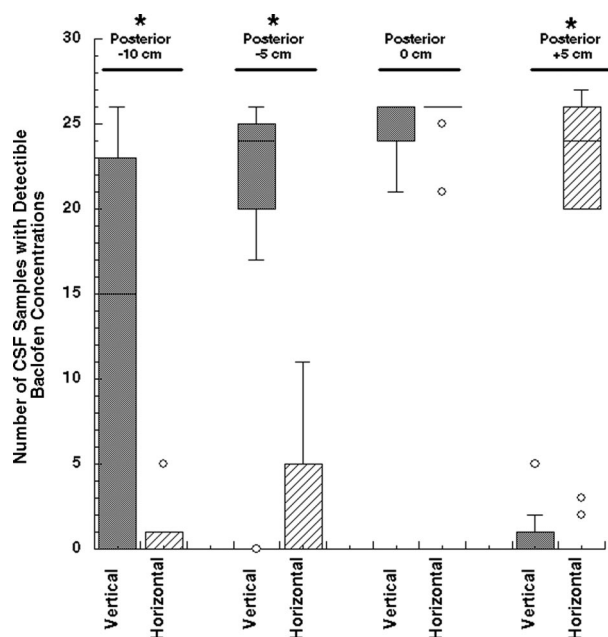
Fig. 5. Box plots of the median number of the cerebrospinal fluid (CSF) samples that had measurable concentrations of baclofen at each sampling site. The total number of samples collected at each sampling site was 26 per animal. *Box* indicates interquartile range, *line across box* indicates median, *whiskers* indicate range excluding outliers, and *open circles* indicate outliers. * Indicates a statistically significant difference ($P < 0.05$, Mann–Whitney U test) between the horizontal and vertical groups within sampling sites. No between-sampling site comparisons were made.

Fig. 6. Baclofen content of the spinal cord segments between −10 cm and +6 cm in the vertical (*open circle*) and horizontal groups (*closed circle*). Differences between groups were assessed for statistical significance only at the 0-cm segment (the point of drug administration) and at the caudad (−10 cm) and cephalad (+6 cm) extremes. * Indicates significant difference between the vertical and horizontal groups.

clofen was not zero, cephalad of the drug administration site in the horizontal animals suggests pharmacokinetic differences between the drugs. This is even more notable because the dose of bupivacaine was 3.75 times greater than that of baclofen. Moreover, the location of the spinal cord segment containing the highest concentration of baclofen was significantly more caudad in the vertical group than in the horizontal group, but there was no difference between the horizontal and vertical groups in the location of the spinal cord segment with the highest bupivacaine concentration. We attribute these differences to more rapid clearance of bupivacaine from the CSF, resulting in more limited spread. Because Ummenhofer *et al.*[5] has previously shown that hydrophobic drugs are cleared more rapidly from the CSF than are more hydrophilic drugs, we think that greater hydrophobicity of bupivacaine is responsible for these observations.

We began this series of studies in an effort to understand what seems to be a relatively high pharmacokinetically mediated failure rate for chronic intrathecal infusions in patients. For example, Walker *et al.*[10] implanted chronic intrathecal pumps for baclofen administration in 14 patients with dystonia who had shown significant improvement after an intrathecal, single-shot, trial bolus of 25–75 μg baclofen. They found that 40% of these patients, all of whom had responded favorably to the baclofen trial bolus, failed to improve with chronic intrathecal baclofen infusion despite
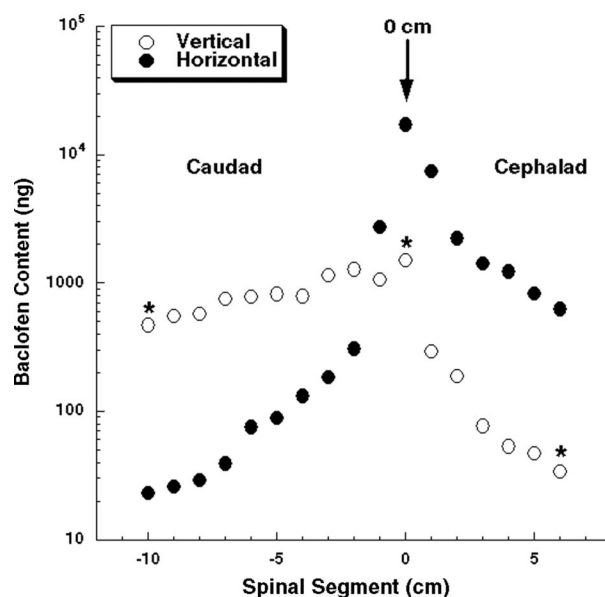
doses as high as 1,000 μg/d. Given that baclofen was an effective drug in these patients when administered as an intrathecal bolus, the failure to improve despite much larger doses of the same drug administered by slow continuous infusion cannot reasonably be explained as a pharmacodynamic failure. Rather, this observation is most readily ex-
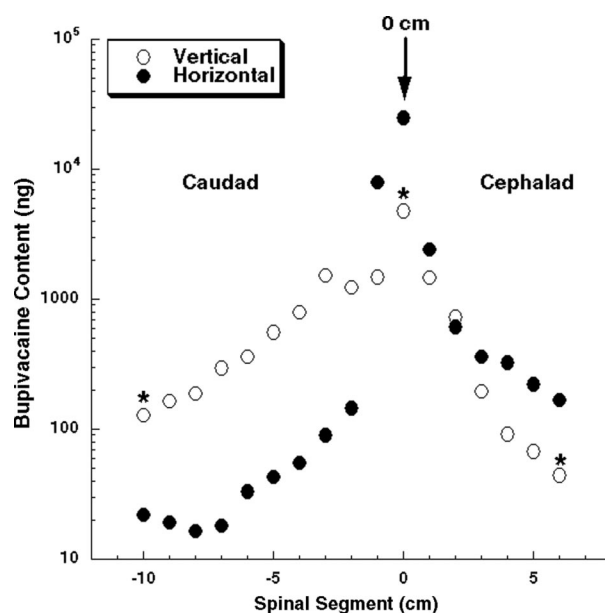

Fig. 7. Bupivacaine content of the spinal cord segments between −10 cm and +6 cm in the vertical (*open circle*) and horizontal groups (*closed circle*). Differences between groups were assessed for statistical significance only at the 0-cm segment (the point of drug administration) and at the caudad (−10 cm) and cephalad (+6 cm) extremes. * Indicates significant difference between the vertical and horizontal groups.

plained as a pharmacokinetic failure, that is, a failure of baclofen to distribute from the administration site to the effect site in sufficient quantity to reproduce the previously demonstrated pharmacodynamic effect.

Importantly, even those studies of chronic intrathecal infusions with a higher success rate than demonstrated by Walker *et al.* report dramatically wide-ranging doses in their patients receiving chronic intrathecal infusions despite the fact that all patients showed similar improvement after an intrathecal trial bolus. In fact, in their recent review, Brennan and Whittle[11] noted that explaining the wide range in dosing observed is one of the major questions yet to be answered regarding chronic intrathecal infusions.

We hypothesize that these "failures of pharmacokinetics" result from the very limited spread of drugs within the subarachnoid space that we observed in our earlier study using this model and an isobaric drug solution. This study suggests that drug distribution may be either increased or decreased by the use of a hyperbaric solution, depending on the position of the subject. For example, in the vertical position, the hyperbaric solution used in this study produced bupivacaine and baclofen concentrations in the spinal cord segments caudad to the site of administration that were an order of magnitude greater than that achieved in the horizontal position. In contrast, drug concentration in the spinal cord cephalad of the drug administration site was significantly greater when the animals were horizontal (of note, even though we positioned the animals horizontally, the anatomy of the pig is such that there is a gentle downward slope from the thoracic cord to the cervical cord when the animal is sternally recumbent). This finding contrasts with our earlier study using an isobaric solution of these study drugs in which cephalad distribution was somewhat less than caudad distribution in the horizontal position.[1] Thus, when using a hyperbaric solution, our results suggest that caudad drug distribution may be increased and cephalad distribution decreased while patients are upright.

Anterior-posterior distribution was also altered by position, with the vertical position producing a marked bias toward posterior location of the study drugs compared with the horizontal position. This posterior bias quite likely results from the posterior location of the infusion catheter combined with anatomic barriers to circumferential drug movement (*e.g.*, dentate ligaments). To the extent that a given drug targets the posterior spinal cord, some advantage may be derived from this distribution pattern. This contrasts with our earlier study using an isobaric solution of these same drugs in which there was a marked bias for the drug to remain on the posterior side of the spinal cord in horizontal animals.[1]

Importantly, one can also envision situations in which the distribution pattern that results from the use of a hyperbaric drug solution may act to diminish drug bioavailability at the spinal target site. For example, if the intrathecal catheter tip is located caudad to the targeted spinal cord segments, then drug will flow away from the target site anytime the patient is in a position that puts the catheter tip lower than the spinal target. Similarly, if the catheter is located in the posterior subarachnoid space, then any time the patient is supine (*e.g.*, sleeping) the drug will "fall" away from the surface of the cord to lie on the meninges through which it can be cleared into the epidural space[5] and effectively lost from the CSF-spinal cord system. The opposite effect will occur if the patient is prone or the catheter tip is in the anterior subarachnoid space.

Thus, we submit that this study provides experimental evidence to support multiple hypotheses that help to explain both the high failure rate seen in some studies of chronic intrathecal drug delivery and the very wide range of effective doses seen in others. That is, this study supports the hypotheses that (1) drug distribution in CSF and spinal cord during slow intrathecal infusions is much more limited than that which occurs after an intrathecal bolus; (2) drug baricity and patient position may be important factors in determining the drug spread; and (3) the location of the intrathecal catheter tip relative to the targeted spinal cord segment(s) is a potentially important determinant of efficacy. Moreover, this study suggests that the measurements of the density of custom-compounded drug solutions reported by Hejtmanek *et al.*[2] may be important in determining the distribution of chronic intrathecal infusions in some patients. Whether these observations are born out in patients await appropriate clinical studies, which, unfortunately, have been lacking to date.

There are several potential limitations to our study that warrant consideration. First, these are acute studies conducted more than 6 h in nonambulatory animals. Whether distribution is different over time in ambulating humans is unknown. However, the authors have performed preliminary chronic studies (14 d intrathecal infusion) in freely ambulatory pigs that demonstrate a restricted drug distribution pattern that is qualitatively identical to our earlier acute (8 h) studies. In addition, CSF concentrations reached steady state in less than 2 h in this study. Thus, we think that the results of this study are qualitatively similar to what would occur with chronic administration. It is also possible that some of the difference in drug distribution between the vertical and horizontal positions is the result of changes in spinal curvature and not baricity. Although subtle differences in spinal curvature are likely between the horizontal and vertical animals, we do not think this explains our observations any more than changes in human spinal curvature explains differences in hyperbaric local anesthetic distribution during spinal anesthesia administered in the sitting (*i.e.*, saddle block) and the horizontally recumbent positions. Finally, we administered drug at 20 μl/h, which is probably faster than the average rate for chronic intrathecal infusions. Whether slower infusion rates would alter the effect of baricity (either accentuate or diminish) is unknown.

Finally, these data should not be construed as an indication that baricity-driven distribution is a major determinant of drug spread in the intrathecal space of all patients. Rather, we think these data should be viewed as supportive of an

emerging picture in which the CSF is no longer viewed as a "circulatory system" that assures uniform drug distribution during chronic intrathecal infusion. In this context, we think baricity should be viewed as one of the multiple factors that determine drug distribution within the intrathecal space. However, it differs from other factors (*e.g.*, individual anatomy, drug physicochemical properties, and drug clearance rate) in that it is under the control of the clinician and as such should be given some consideration as a potential influence on drug distribution when clinicians are designing drug regimens for individual patients.

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