Anesthesiology
83:33–47, 1995
© 1995 American Society of Anesthesiologists, Inc.
Lippincott–Raven Publishers

Computer-controlled Epidural Infusion to Targeted Cerebrospinal Fluid Concentrations in Humans

Clonidine

James C. Eisenach, M.D., David D. Hood, M.D.,* Robin Tuttle, R.N.,† Steven Shafer, M.D.,‡ Thomas Smith, Ph.D.,§ Chuanyao Tong, M.D.‖*

Background: **Pharmacokinetically designed infusions have been demonstrated to achieve rapidly and maintain desired concentrations of drug in plasma after intravenous administration. In this study we tested whether a similar approach, targeting concentrations in cerebrospinal fluid (CSF), could be used with epidural administration of the α_2-adrenergic analgesic clonidine.**

Methods: **After institutional review board approval and informed consent had been obtained, seven healthy volunteers received a clonidine infusion through a lower lumbar epidural catheter. Infusion of clonidine (10 μg/ml) was controlled by the STANPUMP program for sequential 75-min periods to targeted CSF clonidine concentrations of 25, 50, 75, and 150 ng/ml. Before reprogramming to the next higher targeted concentration, mean arterial blood pressure and heart rate were measured; blood was obtained for clonidine and catecholamine assays; and visual analog score for sedation and pain to immersion of foot and hand in ice water were obtained. CSF was collected during infusion with an indwelling lumbar intrathecal catheter and was analyzed for clonidine, catecholamines, and acetylcholine.**

Results: **CSF clonidine concentrations rapidly increased and were maintained at steady values with the stepped infusion, although observed concentrations were consistently greater than targeted. The relation between CSF clonidine concentration and analgesia in the foot was similar to that previously observed after epidural bolus administration. Clonidine also was associated with concentration-dependent sedation; decreased mean arterial blood pressure, heart rate, and CSF norepinephrine concentration; and increased CSF acetylcholine concentration.**

Conclusions: **This study suggests that pharmacokinetically designed infusions of drugs in the epidural space in humans can maintain steady concentrations of drug in CSF. In addition to providing a useful tool for investigation of mechanisms of action and drug interactions, this technique may improve analgesia and diminish side effects from epidurally administered analgesics. (Key words: Analgesia: epidural. Anesthesia: epidural. Anesthetic techniques: computer-controlled infusion. Pain. Sympathetic nervous system, α_2-adrenergic agonists: clonidine.)**

PHARMACOKINETIC-PHARMACODYNAMIC analysis may improve our understanding of analgesic drug action, explain variability among persons in response to a drug, and improve our ability to titrate drug precisely to the desired effect. Ideally, drug concentration would be measured at its site of action, although in practice drug concentration in blood rather than at its sites of action is measured. If a precise measure of drug effect is available, however, an "effect-site" compartment can be mathematically modeled and the time course of drug concentration at this site relative to blood can be calculated.[1,2] Computer-controlled intravenous infusions of analgesics and anesthetics have been demonstrated to produce precise targeted blood concentrations of drug.[3–7]

* Associate Professor of Anesthesia, Wake Forest University Medical Center.

† Research Nurse, Department of Anesthesia, Wake Forest University Medical Center.

‡ Staff Anesthesiologist, Palo Alto Department of Veterans Affairs Medical Center, Palo Alto, California; Associate Professor of Anesthesia, Stanford University.

§ Research Assistant Professor, Department of Physiology/Pharmacology, Department of Orthopedic Surgery, Wake Forest University Medical Center.

‖ Research Assistant Professor, Department of Anesthesia, Wake Forest University Medical Center.

Received From the Departments of Anesthesia and Orthopedic Surgery, Wake Forest University Medical Center, Winston-Salem, North Carolina, and the Department of Anesthesia, Stanford University, Palo Alto, California. Submitted for publication August 5, 1994. Accepted for publication March 21, 1995. Supported in part by National Institutes of Health grants GM48085 and M01-RR07122. Presented in part at the First International Symposium on Spinal Mechanisms of α_2-Adrenergic Analgesia, Lucerne, Switzerland, August 13, 1993. Dr. Eisenach is a consultant to Fujisawa Pharmaceutical for the development of epidural clonidine.

Address reprint requests to Dr. Eisenach: Department of Anesthesia, Wake Forest University Medical Center, Medical Center Boulevard, Winston-Salem, North Carolina 27157-1009. Address electronic mail to: eisenach@isnet.is.wfu.edu.

This study tested whether a similar approach can be used to administer drugs epidurally to targeted concentrations in lumbar cerebrospinal fluid (CSF). It is presumed that analgesia from the spinal action of epidurally administered opioids and α_2-adrenergic agonists results from movement of drug from the epidural space to the spinal cord dorsal horn. This movement does not appear to occur by a vascular mechanism[8] but rather by entrance of drug into CSF and its diffusion from CSF into the superficial dorsal horn of the cord. Assuming this diffusion into the dorsal horn is rapid, measurement of drug concentration in CSF may predict drug effect, and infusion of drug epidurally to targeted concentrations in CSF may allow rapid and precise titration of drug to the desired analgesic effect.

The purpose of this study was to determine the accuracy of computer-controlled epidural infusion of the α_2-adrenergic analgesic clonidine to targeted concentrations in CSF. We chose clonidine because pharmacokinetic analyses of concentrations in CSF after epidural administration of this drug are available.[9,10] In addition to performing a feasibility study, we also examined the effect of epidurally administered clonidine on analgesia, sedation, blood pressure, heart rate, sympathetic nervous system activity, and concentrations of the neurotransmitter acetylcholine (ACh) and catecholamines in blood and CSF. Measurement of these neurotransmitters may indicate clonidine's mechanisms of action in the spinal cord that produce analgesia and its mechanisms in the spinal cord and periphery that affect blood pressure. The sympatholytic activity of epidural clonidine on the cutaneous circulation was evaluated with laser Doppler fluxmetry on the digit during an inspiratory gasp. Laser Doppler fluxmetry allows evaluation of the participation of sympathetic nerve activity on the cutaneous circulation[11] and has been combined with an inspiratory gasp maneuver to characterize transient sympathetic influences on the skin microvasculature.[12]

Materials and Methods

The study was approved by the Clinical Research Practices Committee; written informed consent was obtained; and seven volunteers reported to the General Clinical Research Center, Wake Forest University Medical Center, at 7:00 AM, having had nothing to eat or drink since midnight. A peripheral intravenous catheter was inserted for infusion of lactated Ringer's solution at 50–100 ml/h and a second intravenous catheter inserted and capped for sampling of venous blood. A 20-G single-distal-port epidural catheter was inserted 3–5 cm in the epidural space at the L2–L3 or L3–L4 interspace *via* an 18-G Tuohy needle and tested with injection of 5 ml 1.5% lidocaine. At the first interspace caudad to the epidural catheter, a 23-G single-distal-port catheter was inserted 3–5 cm in the intrathecal space through a ramped 19.5-G Sprotte tipped spinal needle. Volunteers were studied only after demonstration of bilateral sensory neural blockade consistent with an epidural injection of lidocaine and after complete resolution of blockade (minimum of 90 min from injection).

Outcome Parameters

The following parameters were measured: blood pressure; heart rate; oxyhemoglobin saturation by pulse oximetry (SpO_2); sedation and analgesia scored by visual analog scale (VAS); skin blood flow; and CSF sampling for clonidine, catecholamine, and ACh concentrations. After baseline measurements were obtained, epidural clonidine was infused to targeted concentrations in CSF of 25 ng/ml, then 50 ng/ml, then 75 ng/ml, and finally 150 ng/ml. Each infusion lasted 75 min. Immediately after the 60-min CSF sampling for each infusion period, measurements were obtained in the following order: SpO_2; blood pressure; heart rate; VAS scores of sedation and analgesia; and skin blood flow. These measurements usually were completed within 10 min of the 60-min sampling of CSF.

Sampling of Cerebrospinal Fluid and Plasma

CSF was sampled for clonidine and ACh analysis at 5, 15, 30, and 60 min after initiation of the infusion and after each change in the targeted concentration of the infusion. In each case the initial 0.5 ml CSF, representing 1.8 times the catheter dead space, was discarded, and 1.0 ml was obtained for clonidine and ACh analysis. At each 60-min point an additional 0.5 ml CSF was obtained for measurement of catecholamine concentrations. Blood was sampled before infusion and at each 60-min point during infusion for clonidine, catecholamine, and ACh analysis.

Cardiorespiratory Monitoring

Blood pressure and heart rate were measured by a noninvasive oscillometric device at the same times as CSF sampling and immediately before each change in the targeted concentration. SpO_2 was measured before epidural infusion was begun and at the end of each

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/83/1/33/383285/0000542-199507000-00005.pdf by guest on 10 April 2024

targeted concentration infusion period as described above.

Measurement of Sympatholytic Activity

Volunteers were trained to perform an inspiratory gasp by using techniques previously described.[13] After a verbal command, volunteers inspired as quickly and deeply as they could and held the gasp for 4 s. They were instructed not to perform Valsalva's maneuver.

Digital skin perfusion was assessed by attaching a laser Doppler probe to the pulp on the long finger of one hand and the second toe of one foot and monitoring perfusion with a laser Doppler flowmeter (Dual Channel Laser Doppler flowmeter ALF 21D, Advance Electronics, Tokyo, Japan). The probe had a lightweight plastic head (type L probe) that was held on the finger and toe by double-sided adhesive disks. This flowmeter's laser probe transmitted coherent light at 780 nm, and the output of the flowmeter was sampled at a 0.1-s time constraint. The laser Doppler signal from each channel was recorded on a two-channel strip-chart recorder.

We made laser Doppler fluxmetric measurements before the epidural clonidine infusion, at the end of the 50-ng/ml infusion, and at the end of the 150-ng/ml infusion. During testing, each volunteer performed at least five inspiratory gasps. The changes in skin perfusion accompanying each inspiratory gasp were averaged.[14] The vascular responsiveness to the inspiratory gasp was calculated as a percentage change in cutaneous perfusion from baseline as previously described.[12] The skin was heated to 37°C with a regulated heating pad before Doppler flow measurements and the temperature confirmed by measurement with thermistors (YSI series 400, Yellow Springs Instruments, Yellow Springs, OH) taped to the finger and toe. Warming of the skin at the measurement site before reflex testing reduces variability in laser Doppler measurements within and between subjects.[15]

Analgesia

To assess analgesia, pain intensity was assessed by having the volunteers mark a 10-cm VAS after immersion of a foot, and 5 min later, a hand, in stirred ice water. A 60-s cutoff time was used, although volunteers were allowed to remove their hand or foot before this time if they experienced unbearable pain. The foot and hand contralateral to those used for skin blood flow measurements were used for analgesia testing. The volunteer's level of sedation was measured with a 10-cm VAS, anchored at "not drowsy at all" and "as drowsy as possible."

Pharmacokinetic Analysis

We modeled previously published data showing the CSF clonidine concentrations after epidural administration of a 700-μg clonidine bolus.[10] The model used was

$$C_{IT}(t) = \text{dose} \times (C_1e^{-\lambda_1 t} + C_2e^{-\lambda_2 t} - (C_1 + C_2)e^{-\lambda_3 t}) \quad (1)$$

where dose = 700 μg; C_1, C_2, and $-(C_1 + C_2)$ = the weighted coefficients; and λ_1, λ_2, and λ_3 = the positive exponents of a triexponential relation relating a unit dose (*i.e.*, a dose = 1 unit) at time 0 to the intrathecal concentration over time. The third exponential term has the coefficient $-(C_1 + C_2)$ instead of C_3 because at time 0 the concentration in the intrathecal space after administration of an epidural bolus is 0. This can happen only if each coefficient equals the negative of the sum of the other two coefficients.

The model was estimated by using the "solver" function in Excel version 4.0 spreadsheet software (Microsoft, Redmond, WA) and a spreadsheet incorporating the iteratively reweighted least-squares objective function:

$$\text{Objective} = \sum_{i=1}^{n}\left(\frac{\text{measured} - \text{predicted}}{\text{predicted}}\right)^2 \quad (2)$$

A pooled data approach was used in which n = the total number of samples in the study.

The observations from this study were used to estimate a second set of pharmacokinetic parameters to relate the dose given in this study to the measured concentrations. This second analysis was performed with the program MKMODEL, modified to incorporate the complex computer-controlled drug input function used, as previously described.[6,16]

Drug Administration

Clonidine was infused epidurally in a concentration of 10 μg/ml with a pump (552275, Harvard, Quincy, MA) connected to a computer running the STANPUMP program on the MS-DOS (Microsoft) platform. STANPUMP incorporates a control strategy to achieve rapidly and then maintain a desired concentration at the site of observation when the site of observations is linked to the site of injection by a first-order transfer function. The control policy incorporated into STANPUMP is that

described by Shafer and Gregg[17] and was implemented as suggested by Jacobs and Williams.[18]

STANPUMP was programmed with the pharmacokinetic constants estimated as reported above, transformed into V_1, k_{10}, k_{12}, k_{21}, and k_{e0} as described in the appendix. The algebraic manipulations described in the appendix were performed with the software program Mathematica version 2.2 enhanced (Wolfram Research, Champaign, IL). The transformation was performed because the STANPUMP program assumes that when a disequilibrium exists between the site of injection and the site of observation, there is a compartmental model for the plasma pharmacokinetics (described by V_1, k_{10}, k_{12}, and k_{21}) and a first-order transfer of drug from the plasma (the site of injection) to the effect site (described by k_{e0}). To take advantage of STANPUMP's ability to administer drug when disequilibrium exists between the site of drug injection and the site of observation, it was necessary to convert the disposition function of the intrathecal space, relative to epidural drug administration, estimated as described above, into a compartmental representation. STANPUMP, in turn, then computed the disposition function of the intrathecal space from the parameters V_1, k_{10}, k_{12}, k_{21}, and k_{e0}.

Analysis of Performance

The measures of performance were based on the performance error (PE), defined for each observation as

$$PE = \frac{\text{measured} - \text{predicted}}{\text{predicted}} \times 100\%. \qquad (3)$$

The performance error was based on the prediction rather than the target because in some settings the target and prediction may differ, as might occur if the pump is briefly interrupted while a target concentration is maintained.

Two summary measures were used to measure the aggregate trend of the weighted residuals: the median weighted performance error (MDPE), calculated as

$$MDPE = \text{median}(PE_1, PE_2, \ldots, PE_n) \qquad (4)$$

which estimated the overall bias in the results, and the median absolute performance error (MDAPE), calculated as

$$MDAPE = \text{median}(|PE_1|, |PE_2|, \ldots, |PE_n|) \qquad (5)$$

which estimated the overall inaccuracy of the performance. These measures of performance are adapted from the recommendations of Varvel *et al.*[19] and have been previously used in prospective studies of computer-controlled drug delivery.[5–7]

The new pharmacokinetic parameter set derived from these data were measured for their ability to predict these observations as well. Because this second pharmacokinetic parameter set was derived from the same observations, errors in prediction are the "residual errors" from the pharmacokinetic analysis. Thus, we calculated the weighted residual precisely as we calculated the performance error, described above, except that the prediction was based on the new pharmacokinetic parameter set. We then calculated the median weighted residual and the median absolute weighted residual based on the weighted residual error, in a way exactly analogous to the calculations of the median weighted performance error and the median absolute performance error described above.

Drug Assay

Clonidine was measured by Harris Laboratories (Lincoln, NE) with a radioimmunoassay with limit of sensitivity of 0.13 ng/ml.[10] Plasma clonidine concentrations below this limit were assigned a value of 0. Concentrations of catecholamines and ACh were measured by high-performance liquid chromatography with electrochemical detection as previously described.[20,21]

Drugs

Clonidine hydrochloride, 100 μg/ml in preservative-free saline, was obtained from Fujisawa Pharmaceutical Co. (Deerfield, IL) under Investigational New Drug approval from the United States Food and Drug Administration and was diluted with preservative-free normal saline before epidural injection.

Statistics

Unless otherwise indicated, data are presented as means ± SEM. The effect of infusion on continuous variables, including VAS measurements, was determined by one-way analysis of variance for repeated measures followed by Dunnett's test. The relation between plasma or CSF clonidine concentrations and VAS pain scores on foot and hand testing was assessed by using Pearson's product-moment correlation.

Results

All volunteers were women, 39 ± 2 yr old, height 167 ± 2 cm, and weight 78 ± 7 kg. In all cases the

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/83/1/33/383283/0000542-199507000-00005.pdf by guest on 10 April 2024

lidocaine test dose resulted in bilateral sensory changes consistent with an epidural injection. All volunteers completed the study, and they received a total of 442 ± 1 μg epidural clonidine. Two volunteers experienced a postdural puncture headache, although no volunteer required an epidural blood patch for treatment of the headache.

Subject 1 had a continuous decrease in concentration after 210 min, despite an increase in target concentration and continuous administration of clonidine from 210 to 300 min. This decrease may have been caused by intravascular migration of the epidural catheter, which would result in no delivery of clonidine to the epidural space after 210 min. We therefore excluded the data from subject 1 from subsequent analysis after 210 min. A single data point in subject 7 also was excluded from the analysis: at 210 min the observed clonidine concentration was a full order of magnitude less than the observed concentration at 180 and 230 min, despite continuous clonidine administration. This situation is biologically impossible. The observation at 210 min was probably an artifact of unclear cause (such as mislabeling of a sample or improper dilution in the assay).

Clonidine Analysis

With one exception, clonidine concentration in the CSF increased approximately 5 min after initiation of or changing of the targeted concentration. The pharmacokinetic analysis predicted a delay of approximately 15 min between a change in the target concentration and attainment of a new plateau in the CSF. Observation of the observed concentrations suggests that there was an initial delay of approximately 5–15 min between a change in target concentration and each plateau in the concentration in CSF (fig. 1). During the first plateau (target = 25 ng/ml), the average concentration was 50 ± 13 ng/ml; during the second plateau (target = 50 ng/ml) the average concentration was 92 ± 15 ng/ml; during the third plateau (target = 75 ng/ml) the average concentration was 140 ± 19 ng/ml; and during the final plateau (target = 150 ng/ml) the average plateau was 215 ± 37 ng/ml. Clonidine concentration in the plasma increased from 0.10 ± 0.04 ng/ml after the first infusion to 0.30 ± 0.10 ng/ml after the second, 0.70 ± 0.08 ng/ml after the third, and to 1.1 ± 0.12 ng/ml after the last infusion. One hour after discontinuation of epidural clonidine infusion, plasma clonidine concentration was 1.2 ± 0.18 ng/ml.

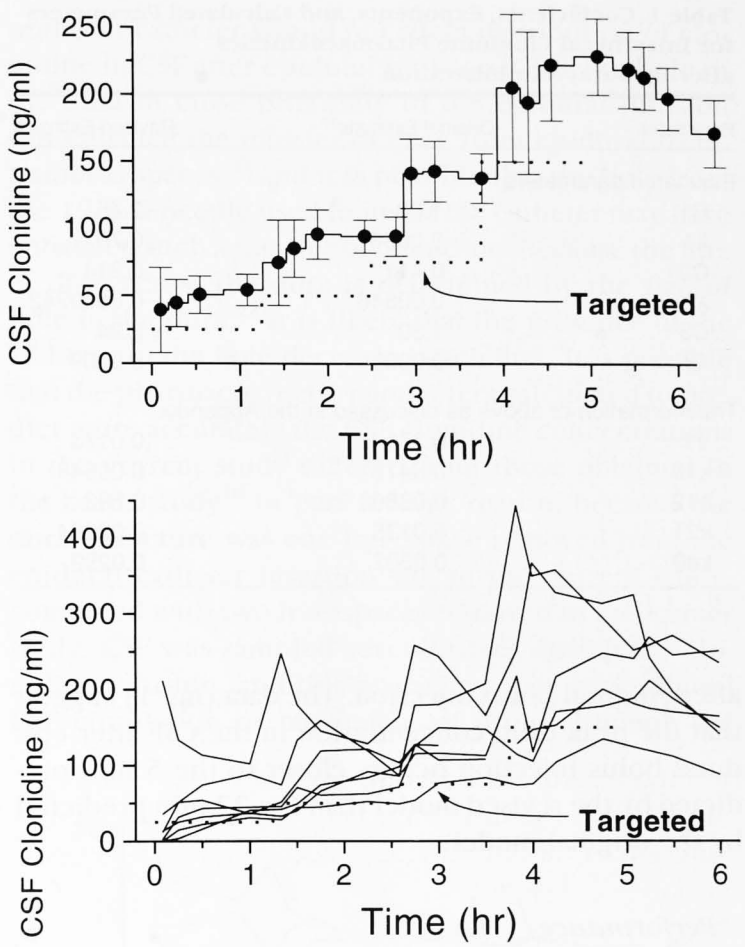


Fig. 1. Average (± SEM) clonidine concentration in cerebrospinal fluid (CSF) *versus* time (*top*) and individual data (*bottom*). Dotted lines = targeted concentrations in CSF.

Pharmacokinetic Results

Table 1 shows the parameters of the triexponential disposition function relating intrathecal concentration to a unit epidural bolus dose and the transformation of those parameters into a compartmental model for use with the STANPUMP program, as described in the appendix. Each of the coefficients is the negative of the sum of the other coefficients, which gives the resulting curve a convex shape after bolus injection, with an intrathecal concentration of 0 at time 0, a subsequent peak, and then a return to an intrathecal concentration of 0 at time ∞. Table 1 also shows the parameters of the new pharmacokinetic model estimated from these data.

The disposition functions of the intrathecal site predicted by these two models is shown in figure 2. The original pharmacokinetic parameter set predicted a peak intrathecal concentration 22 min after epidural bolus administration. The revised pharmacokinetic parameter set predicts a much more rapid peak at 5 min

Table 1. Coefficients, Exponents, and Calculated Parameters for Intrathecal Clonidine Pharmacokinetics after Epidural Administration

Parameter	Original Estimate[10]	Revised Estimate
Estimated parameters		
C1	−1.80	−2.45
λ1	0.0864	0.707
C2	0.411	0.214
λ2	0.00646	0.0000242
C3	1.39	2.24
λ3	0.0302	0.0289
Transformation of above as discussed in the Appendix		
V1	0.271	0.0173
k10	0.0415	0.00648
k12	0.0380	0.698
k21	0.0135	0.00264
ke0	0.0302	0.0289

after epidural bolus injection. The data (fig. 1) suggest that the peak drug concentration in the CSF after epidural bolus injection occurs closer to the 5 min predicted by the revised model than the 22 min predicted by the original model.

Performance

In general, the observed concentrations exceeded the target concentrations during the plateau phase. The overshoot ranged from nearly 100% at the lowest target to about 40% at the highest target. The median weighted performance error was +55%, and the median absolute performance error was 60% with the initial pharmacokinetic parameter set.

The computer-controlled infusion pump did reasonably well at achieving pseudo-steady-state concentrations and providing proportional increases in the pseudo-steady-state concentrations. However, there was considerable variability in the individual responses, as shown in figure 1. The variability is demonstrated in the top graph of figure 3. Each line has a fairly constant offset from the y = 1 line, indicating that the proportional error was fairly steady at each target.

The weighted residuals with the new pharmacokinetics are shown in the bottom graph of figure 3. In this figure, the systematic overshoot is eliminated, in that the errors are now evenly divided into overshoot and undershoot of the predicted concentration. This comes at the expense of slightly more misspecification, in that the observed concentrations at 5 min after each change are, in general, slightly less than the model prediction, resulting in the sawtooth pattern seen in the residuals. The addition of a fourth exponential term to the pharmacokinetic model did not eliminate this pattern, suggesting that additional data about the early increase in concentration would be necessary to model properly the expected concentrations in CSF within the 1st 5 min of epidural bolus administration. The median weighted residual for the revised model is −8%, and the median absolute weighted residual is 37%.

Cardiorespiratory and Sedative Effects

Clonidine decreased mean arterial blood pressure and heart rate, and this decrease was related to the duration of infusion (fig. 4) and CSF clonidine concentration (data not shown). In contrast, clonidine had no effect on SpO_2 (fig. 4). Clonidine also caused dose-related sedation (table 2).

Sympatholytic Activity

The laser Doppler flow in the foot increased from 13.2 ± 5.8 mV (arbitrary values) before epidural clonidine to 27.0 ± 3.4 mV after targeted infusion to CSF clonidine concentration of 150 ng/ml ($P < 0.05$). The percentage change in skin perfusion in the foot at the time of maximum change after a deep gasp with 50 ng/ml clonidine was −63.1 ± 6.4% and with 150 ng/ml clonidine was −54.8 ± 8.7%. These changes did not differ from baseline. The time required to attain the minimum value of laser Doppler flow after initiation of the gasp reflex was approximately 7.5 s and did not vary with clonidine concentration. Similar results were observed in the hand tests.

Analgesia

Clonidine caused similar dose-related analgesia in both the foot and the hand (fig. 5). Because this finding was in contrast to the result of a previous study[10] that was of similar design but that used a single bolus of epidural clonidine rather than prolonged infusion, we examined the relation between lumbar CSF clonidine concentration and analgesia in the hand and the foot in both studies. This analysis revealed no difference between bolus and infusion administration in the linear regression of CSF clonidine and VAS pain score in the foot but a significant difference in this relation in the hand (fig. 6). The VAS pain score in the foot to ice-water immersion was more tightly correlated to lumbar CSF clonidine concentration ($r = -0.70$; $P = 0.0000064$) than to plasma clonidine concentration

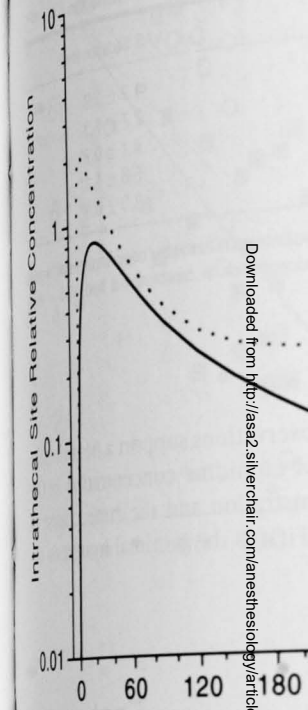


Fig. 2. Disposition functions describing of clonidine in the intrathecal site u macokinetic parameters (solid line)[10] ters (dotted line).

($r = -0.53$; $P = 0.0014$) in the the study of bolus administration

Neurotransmitter Analysis

Clonidine decreased the norep centration but did not affect the pamine concentration in plasma concentration increased in CSF a nidine infusion and was maintai clonidine infusion (fig. 7).

Discussion

These data provide information bility of infusing drugs into the geted concentrations in CSF and anism of action of epidural cloni

Feasibility of Epidural Compu Infusion

Several assumptions implicit in explanation. We assumed that the

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/83/1/38/483/0000542-199507000-00005.pdf by guest on 10 April 2024

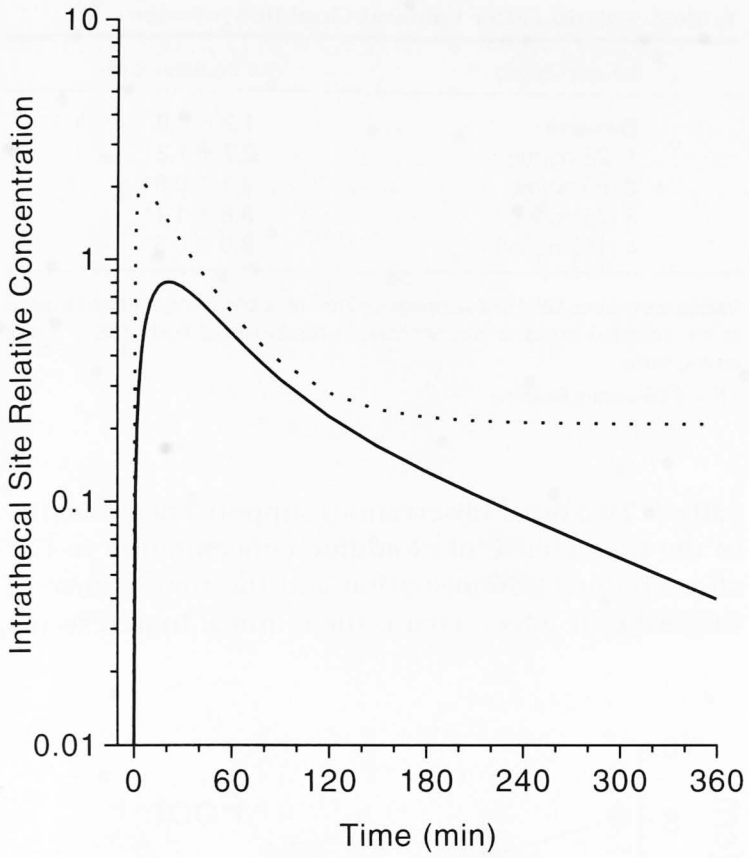


Fig. 2. Disposition functions describing relative concentration of clonidine in the intrathecal site using the original pharmacokinetic parameters (solid line)[10] or the revised parameters (dotted line).

($r = -0.53$; $P = 0.0014$) in the current study and in the study of bolus administration.[10]

Neurotransmitter Analyses

Clonidine decreased the norepinephrine (NE) concentration but did not affect the epinephrine or dopamine concentration in plasma or CSF (table 3). ACh concentration increased in CSF after initiation of clonidine infusion and was maintained throughout the clonidine infusion (fig. 7).

Discussion

These data provide information regarding the feasibility of infusing drugs into the epidural space to targeted concentrations in CSF and regarding the mechanism of action of epidural clonidine analgesia.

Feasibility of Epidural Computer-controlled Infusion

Several assumptions implicit in this paradigm require explanation. We assumed that the presence of the intrathecal catheter would not affect distribution of clonidine in CSF after epidural infusion. Clearly a hole in the dura in close proximity to the epidural infusion can enhance the transfer of drug from epidural to intrathecal spaces,[22] and it is possible that the hole from the 19.5-G needle used to insert the catheter may have enhanced such a transfer of clonidine. Because the flux of drug across the dura is determined by the size of hole in the dura,[22] it is likely that the presence of the catheter in the hole decreased such flux. It is possible that the pharmacokinetic parameters calculated to predict more accurately the CSF clonidine concentrations in the current study differed from those obtained in the bolus study[10] in part for this reason, because the dural puncture was one interspace removed from the epidural catheter insertion site in the current study, compared with two interspaces removed in the former study. CSF was sampled several times during the clonidine infusion, and this procedure may have altered CSF circulation or movement of drug, although the

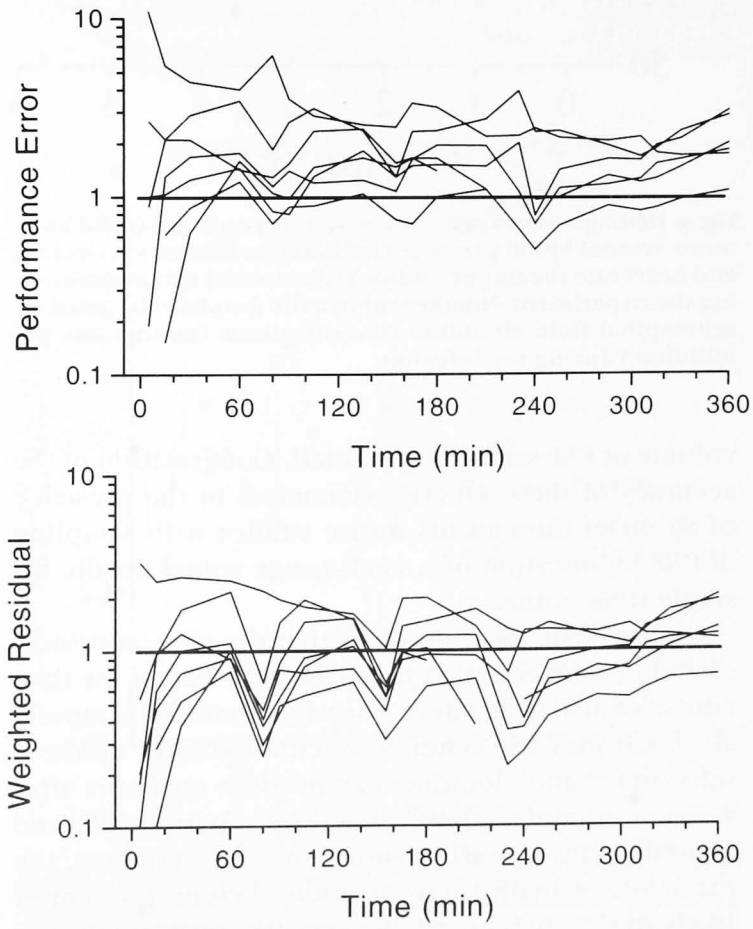


Fig. 3. Relative residual errors for each volunteer *versus* time using the original pharmacokinetic parameters (*top*)[10] or the revised parameters (*bottom*).

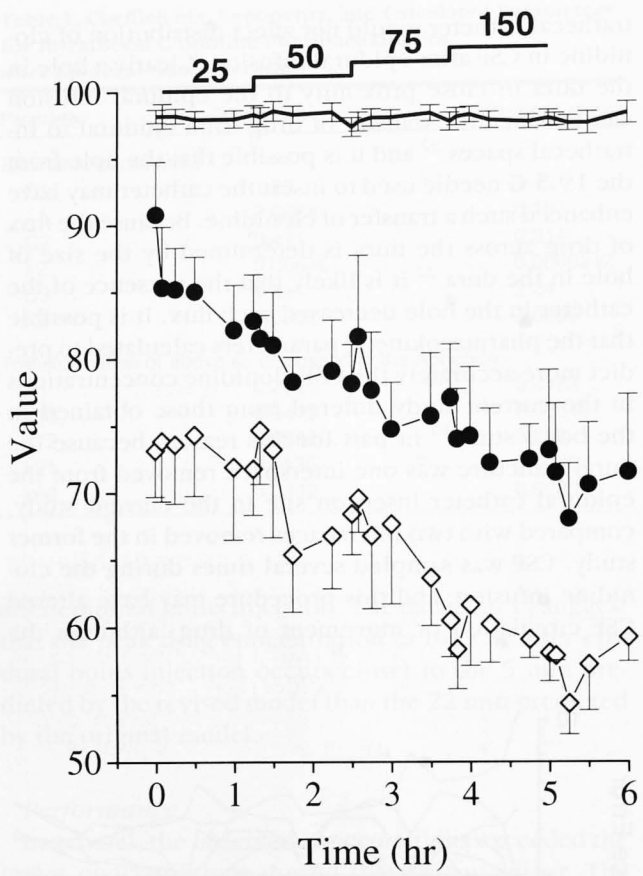


Fig. 4. Hemoglobin oxygen saturation (percentage) (solid line), mean arterial blood pressure (millimeters mercury) (circles), and heart rate (beats per minute) (diamonds) *versus* time during the experiment. Numbers above the graphs = targeted cerebrospinal fluid clonidine concentrations (nanograms per milliliter) during the infusion.

volume of CSF sampled was small. Confirmation of the accuracy of these kinetic parameters in the presence of an intact dura awaits future studies with sampling of CSF by insertion of a small-gauge spinal needle for single time points.

A more basic assumption is that the time course of clonidine concentration in CSF closely reflects the time course of analgesic effect. Clearly, clonidine is rapidly absorbed into the systemic circulation after epidural injection,[10] and clonidine can produce analgesia after systemic administration[23] by actions at peripheral[24] and central[25] sites as well as spinal sites. Nonetheless, the major site of analgesia from epidural clonidine is most likely in the spinal cord, because it is reversed by epidural injection of a specific α_2-adrenergic antagonist in a dose that has no effect when administered systemically.[26] Two other observations support a near identity of the time course of clonidine concentration in CSF after epidural administration and the time course of the analgesic effect. First is the minimal hysteresis ob-

Table 2. Sedation after Epidural Clonidine Infusion

Infusion Period	VAS Sedation (cm)
Baseline	1.2 ± 0.9
1 (25 ng/ml)	2.7 ± 1.3
2 (50 ng/ml)	4.1 ± 0.9*
3 (75 ng/ml)	5.8 ± 1.1*
4 (150 ng/ml)	8.0 ± 0.8*

Values are mean ± SEM of 7 volunteers 60 min after beginning infusion targeted at the indicated clonidine concentration in cerebrospinal fluid. VAS = visual analog scale.

* $P < 0.05$ *versus* Baseline.

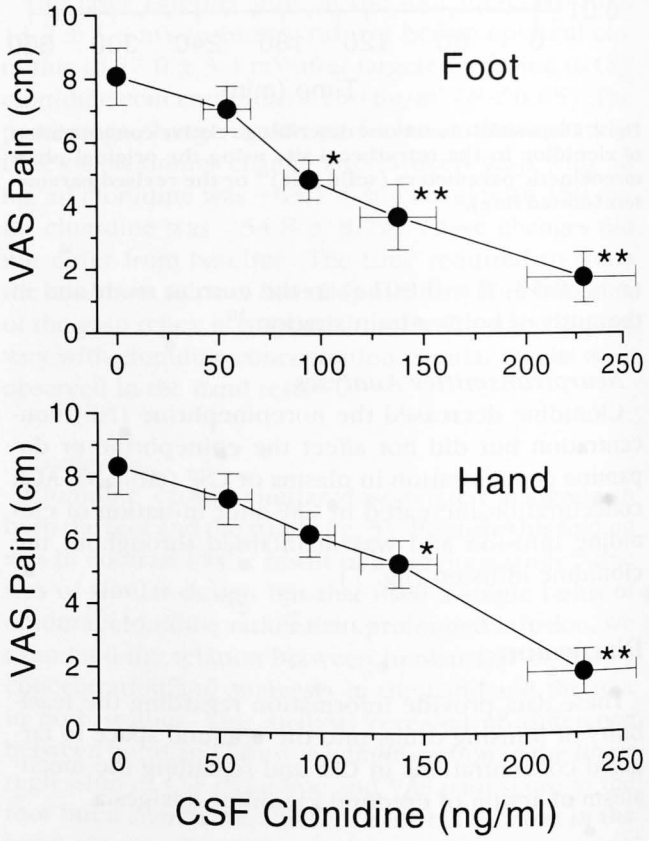


Fig. 5. Visual analog scale (VAS) pain scores (centimeters) in the foot (*top*) or the hand (*bottom*) *versus* clonidine concentration at the end of each 60-min infusion period. CSF = cerebrospinal fluid. *$P < 0.05$ *versus* baseline. **$P < 0.01$ *versus* baseline.

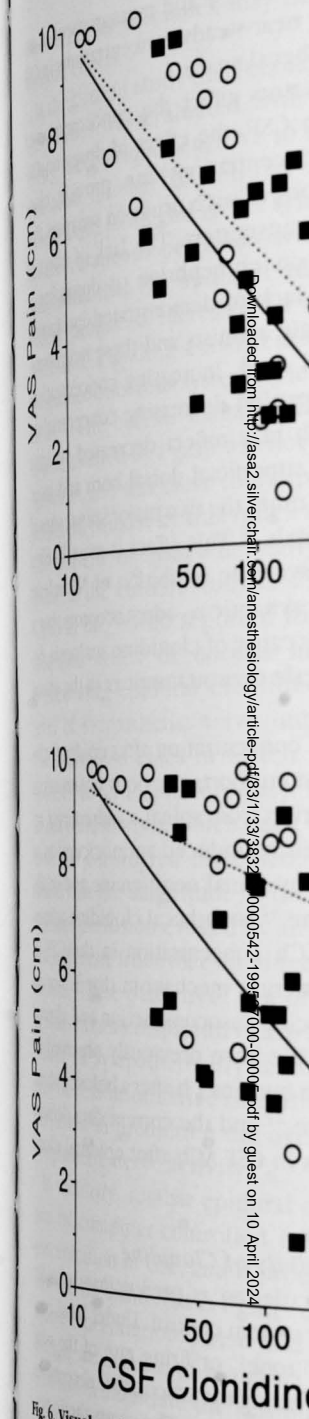
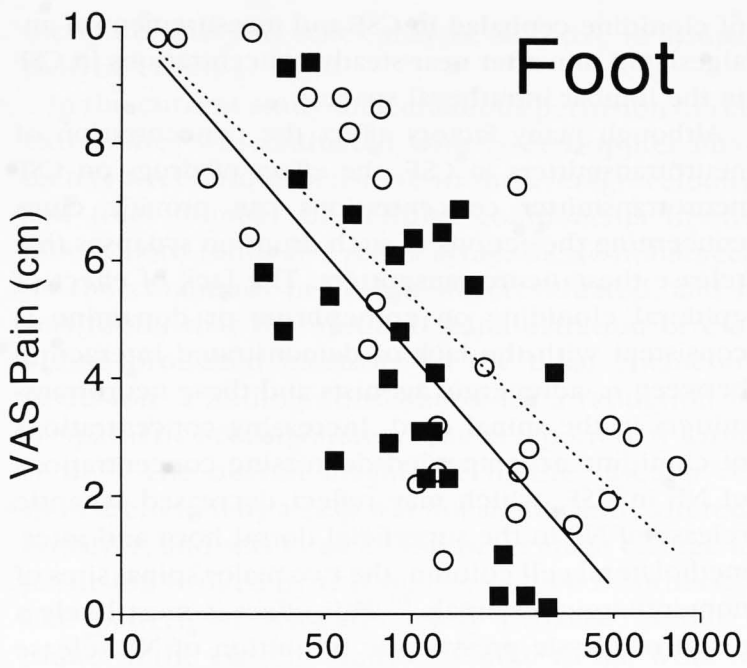


Fig. 6. Visual analog scale (VAS) pain
the foot (*top*) or the hand (*bottom*) ve
tration in the current study (squares) a
after bolus epidural clonidine injectio
lines for the current infusion study (s
vious bolus study (dotted line) reveal
these methods of administration for ar
more analgesia in the hand at the end
of infusion than after a single bolus in
spinal fluid.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/83/1/33/383200/0000542-199507000-00005.pdf by guest on 10 April 2024



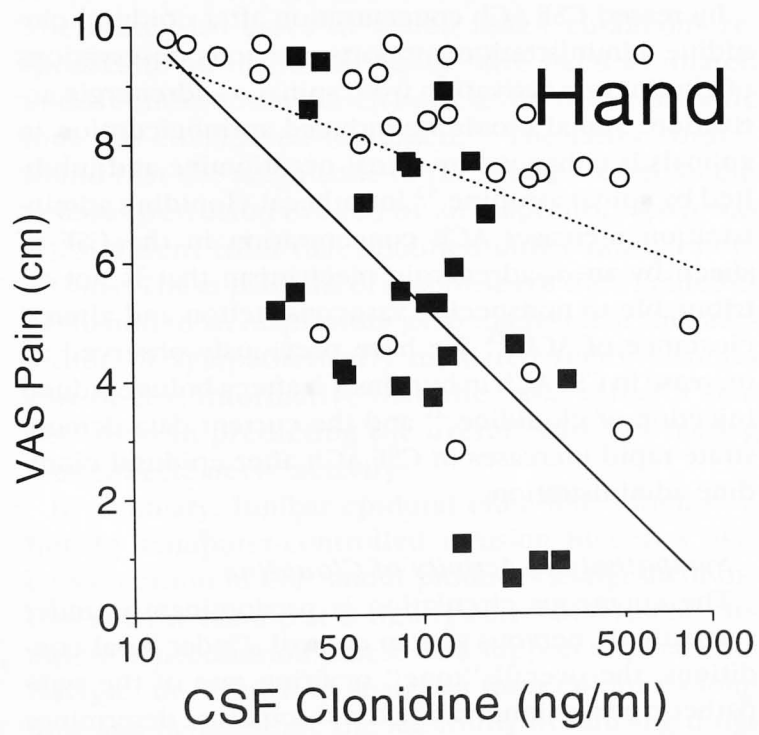


Fig. 6. Visual analog scale (VAS) pain scores (centimeters) in the foot (*top*) or the hand (*bottom*) *versus* clonidine concentration in the current study (squares) and in a previous study[10] after bolus epidural clonidine injection (circles). Regression lines for the current infusion study (solid line) and the previous bolus study (dotted line) reveal no difference between these methods of administration for analgesia in the foot, but more analgesia in the hand at the end of the end of each hour of infusion than after a single bolus injection. CSF = cerebrospinal fluid.

Table 3. CSF Epinephrine and Dopamine and Plasma Catecholamines during Clonidine Infusion

		Targeted Clonidine Infusion			
	Baseline	25 ng/ml	50 ng/ml	75 ng/ml	150 ng/ml
Plasma					
NE	310 ± 89	200 ± 57	150 ± 48*	240 ± 120	130 ± 37*
EPI	240 ± 44	190 ± 53	240 ± 44	211 ± 43	190 ± 60
Dopamine	28 ± 11	16 ± 5	36 ± 8	28 ± 12	21 ± 10
CSF					
NE	201 ± 25	109 ± 20*	60 ± 18*	60 ± 10*	58 ± 24*
EPI	170 ± 31	180 ± 37	160 ± 31	210 ± 52	204 ± 34
Dopamine	58 ± 27	30 ± 5	26 ± 8	53 ± 25	51 ± 9

NE = norepinephrine; EPI = epinephrine; CSF = cerebrospinal fluid.

Values are mean ± SEM (pg/ml) of 7 volunteers 60 min after beginning infusion targeted at the indicated clonidine concentration in CSF.

* $P < 0.05$ *versus* Baseline.

served in CSF clonidine *versus* analgesia over time in volunteers who received epidural clonidine by a single bolus.[10] This characteristic suggests rapid equilibration between clonidine in CSF and at its active site for analgesia. Second is the nearly identical relation between CSF clonidine and analgesia in the foot observed in that study,[10] with constantly changing CSF clonidine con-

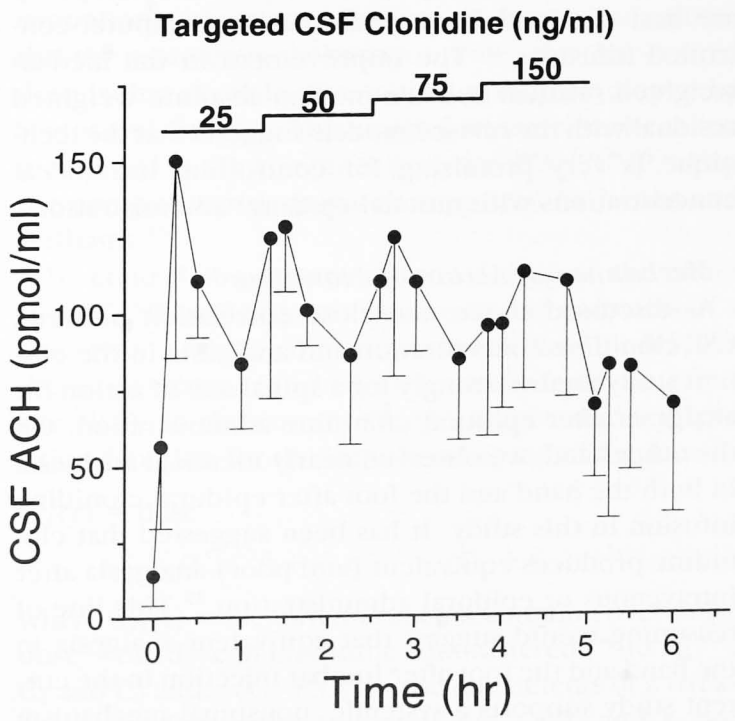


Fig. 7. Cerebrospinal fluid (CSF) acetylcholine (ACh) concentration *versus* time of epidural clonidine infusion, beginning at time 0. Each point represents the mean − SEM of six or seven volunteers. All time points except the second differ from baseline.

centrations after a bolus, and that observed in the current study after 60 min of nearly steady CSF clonidine concentrations (fig. 6).

Clonidine administration by continuous lumbar epidural infusion resulted in analgesia in the upper extremities of volunteers in the current study, whereas analgesia in the upper extremities was not observed after a single lumbar epidural bolus in our previous study.[10] This result may reflect continuous addition of clonidine to lumbar CSF, allowing cephalad spread of drug in CSF as has been observed previously in humans receiving opioids of lipophilicity similar to that of clonidine.[27,28]

Pharmacokinetic Considerations

Although the computer-controlled infusion pump was fairly successful at providing pseudo-steady-state concentrations and making proportional changes in those concentrations, its absolute accuracy was poor because of a large and consistent overshoot. The large and fairly consistent bias in the results suggests that the intrathecal pharmacokinetics of epidurally administered clonidine could be further refined from our initial estimates after bolus drug administration.[10] Reports suggest that refining pharmacokinetic parameters intended for use in a computer-controlled infusion pump are best obtained from studies using computer-controlled infusions.[16] The improvement in the median weighted residual and the median absolute weighted residual with the revised models suggests that the technique is very promising for controlling intrathecal concentrations with rational epidural administration.

Mechanism of Action of Clonidine

As discussed above, the close correlation between CSF clonidine concentration and analgesia in the current study argues strongly for a spinal site of action for analgesia after epidural clonidine administration. On the other hand, we observed nearly identical analgesia in both the hand and the foot after epidural clonidine infusion in this study. It has been suggested that clonidine produces equivalent (and poor) analgesia after intravenous or epidural administration.[29] This line of reasoning would suggest that equivalent analgesia in the hand and the foot after lumbar injection in the current study supports a systemic, nonspinal mechanism of action. However, we did observe analgesia restricted to the foot after epidural bolus administration of clonidine,[10] and "spread" of analgesia to the hand in the current study. This spread may reflect rapid movement of clonidine cephalad in CSF and measurement of analgesia 60 min after near-steady concentrations in CSF in the lumbar intrathecal space.

Although many factors affect the concentration of neurotransmitters in CSF, the effect of drugs on CSF neurotransmitter concentrations can provide clues concerning the actions of such drugs on synapses that release these neurotransmitters. The lack of effect of epidural clonidine on epinephrine or dopamine is consistent with the lack of demonstrated interaction between α_2-adrenergic agonists and these neurotransmitters in the spinal cord. Increasing concentrations of clonidine accompanied decreasing concentrations of NE in CSF, which may reflect decreased synaptic release of NE in the superficial dorsal horn and intermediolateral cell column, the two major spinal sites of noradrenergic terminals.[30] This effect is most likely a result of classic presynaptic inhibition of NE release by stimulation of presynaptic α_2-adrenoceptors, but it would not be a likely cause of clonidine analgesia, because NE is an analgesic neurotransmitter in the spinal cord.[31]

Increased CSF ACh concentration after epidural clonidine administration supports previous observations of cholinergic activation from spinal α_2-adrenergic activation. Spinal clonidine-induced antinociception in animals is enhanced by spinal neostigmine and inhibited by spinal atropine.[32] Intrathecal clonidine administration increases ACh concentration in the CSF of sheep by an α_2-adrenergic mechanism that is not attributable to nonspecific vasoconstriction and altered clearance of ACh.[21] We have previously observed an increase in CSF ACh in humans 1 h after a bolus epidural injection of clonidine,[21] and the current data demonstrate rapid increases in CSF ACh after epidural clonidine administration.

Sympatholytic Activity of Clonidine

The cutaneous circulation is predominantly under sympathetic nervous system control. Under basal conditions, the overall "tone" or firing rate of the sympathetic nerves innervating the vasculature determines the overall cutaneous perfusion. The sympathetic nervous system also controls reflex responses of the cutaneous circulation. Reflex changes in cutaneous perfusion may be invoked by an inspiratory gasp. Cutaneous perfusion transiently decreases with this maneuver, and the magnitude of the decrease in perfusion accompanying the reflex reflects the degree of sympathetic activity evoked. It has been suggested,

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/83/1/38/383283/0000542-199507000-00005.pdf by guest on 10 April 2024

therefore, that this reflex may be sensitive to sympatholytic effects.

In the current study the cutaneous perfusion of the extremities was evaluated with laser Doppler fluxmetry, a technique sensitive to the average velocity and total number of cellular components in the blood. Both tonic and reflex sympathetic influences on the cutaneous perfusion were evaluated, and it was found that the epidural administration of clonidine produced increases in the basal cutaneous perfusion, a finding consistent with a reduction in sympathetic nervous system tone as reported by Kirnö *et al.*[11] The overall magnitude of the vascular response elicited by a gasp was not significantly altered, however, and was close to the percentage change in perfusion evoked by this reflex as noted by others.[33] The pattern of sympathetically evoked responses found in the current study is similar to the work of Kirnö *et al.*,[11] who reported that a sympathetically mediated reflex of normal magnitude could be evoked after epidural clonidine but that the basal level of sympathetic nerve impulses was reduced. There are also cases in which reflex cutaneous responses to an inspiratory gasp have been evaluated under conditions in which basal levels of sympathetic tone are considered increased.[33] The latter study[33] found that the magnitude of the reflex change in cutaneous perfusion evoked by an inspiratory gasp was not different from that obtained under normal conditions. These patterns of responses of the cutaneous perfusion to an inspiratory gasp suggest that the magnitude of sympathetically mediated reflex changes may be less informative than the basal value of skin perfusion in predicting the overall status of resting sympathetic nerve activity.

In summary, lumbar epidural clonidine administration by computer-controlled infusion increases ACh concentration in CSF, and it produces analgesia in the foot and the hand that is tightly correlated to CSF clonidine concentration. These data support a spinal cholinergic mechanism of analgesia from epidural clonidine and demonstrate the feasibility of infusing drugs epidurally to targeted concentrations in CSF for research and clinical applications. The errors are only moderately larger than those observed with intravenous drug administration by computer-controlled infusion, and this approach may be particularly important as a research tool, just as intravenous computer-controlled administration has become a recognized tool for investigation of intravenous drugs.

Appendix

In this study clonidine was administered into the epidural space to achieve a given intrathecal concentration profile. There was a disequilibrium between clonidine administration into the epidural space and the appearance of clonidine in the intrathecal space. There is an obvious parallel between this model and the conventional "effect-site" model that relates the time course of drug concentration in the plasma with the time course of concentration at the hypothetical site of drug effect.

The question of how to calculate the time course of epidural dosing to achieve a desired intrathecal concentration is similar to the question of how to calculate the time course of plasma dosing to achieve a target concentration at the effect site. Because we cannot inject drug directly into the effect site, it is impossible to obtain instantly a target effect-site concentration. There are many ways to give drug to achieve a specific target in the effect site, depending on how the advantages of a slow increase to the desired target are balanced with the advantages of a rapid increase to the target but with some overshoot. If we restrict ourselves to solutions in which the effect-site concentration increases as rapidly as possible to the desired target concentration without overshooting the target, and assume that the parameters are known a priori, then the desired dose is that given by the control policy developed by Shafer and Gregg.[17] This control strategy has been implemented in the computer program STANPUMP, using the computational approach suggested by Jacobs and Williams.[18]

To control the concentration of drug at the effect site, STANPUMP requires the micro-rate constants of a one-, two-, or three-compartment mamillary model plus the rate constant for drug elimination from the effect site (k_{e0}). In the current study we estimated a disposition function for the intrathecal space of the form;

$$C_{IT}(t) = \text{dose} \times (C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} - (C_1 + C_2) e^{-\lambda_3 t}) \quad \text{(A1)}$$

where $C_{IT}(t)$ = the intrathecal concentration over time; dose = the dose of clonidine administered (700 μg)[10]; C_1 and C_2 and $-(C_1 + C_2)$ = the coefficients of a triexponential disposition function; and λ_1, λ_2 and λ_3 are the exponents of the disposition function. Each coefficient is the negative of the sum of the other coefficients, which gives the disposition function the necessary shape, which is 0 at time 0, increases to a peak,

and then decreases to 0 again at $t = \infty$. To administer clonidine by using this disposition function it is necessary to convert equation A1 to a series of rate constants representing a two-compartment mamillary model with an effect site, which is the model used internally by STANPUMP. This transformation is performed as follows.

The standard two-compartment pharmacokinetic model,[17] is represented by the following differential equations:

$$\frac{dx_1(t)}{dt} = k_{21}x_2(t) - (k_{10} + k_{12})x_1(t)$$

$$\frac{dx_2(t)}{dt} = k_{12}x_1(t) - k_{21}x_2(t). \quad \text{(A2)}$$

We will transform this set of differential equations into an equation that describes the concentration over time after injection of a single unit of drug into the central compartment (V_1). Such an equation is called a "unit disposition function" and has the biexponential form (for this exercise);

$$C_P(t) = Ae^{-\alpha t} + Be^{-\beta t} \quad \text{(A3)}$$

where $C_p(t)$ = the plasma concentration at time t that would be expected after an injection of 1 unit of drug, and A, B, α, and β = pharmacokinetic parameters directly estimated or mathematically derived from the parameters estimated (*e.g.*, the volumes and clearances of a two-compartment model or the rate constants shown in eq. A1).

The transformation between equation set A2 and equation A3 is outlined in many pharmacokinetic textbooks but is reviewed here because several solutions developed from the transformation are required to convert the intrathecal disposition function (eq. A1) into a compartmental representation used by STANPUMP. Although symbolic manipulation programs such as Mathematica can directly perform the transformation between equation set A2 and equation A3 in the time domain, the process generates huge intermediate equations. Therefore, to simplify the algebra, it is common first to transform equation set A2 into the Laplace domain. Applying the Laplace transformation to equation set A2 yields;

$$sX_1(s) - x_1(0) = k_{21}X_2(s) - (k_{10} + k_{12})X_1(s)$$

$$sX_2(s) - x_2(0) = k_{12}X_1(s) - k_{21}X_2(s) \quad \text{(A4)}$$

where s = the independent variable in the Laplace domain; $X_1(s)$ and $X_2(s)$ = the Laplace transform $x_1(t)$ and $x_2(t)$; and $x_1(0)$ and $x_2(0)$ = the initial conditions of compartments 1 and 2, respectively. Because we are interested in the response of this system to the instantaneous injection of 1 unit of drug at time 0, the initial condition of $x_1(0)$ is 1 (*i.e.*, the initial amount in the central compartment is 1 unit). We assume, of course, that initially there is no drug anywhere else in the body, and so $x_2(0)$ is 0. Substituting 1 and 0 for $x_1(0)$ and $x_2(0)$, respectively, into equation set A4 and rearranging generates the following simultaneous equations:

$$sX_1(s) = k_{21}X_2(s) - (k_{10} + k_{12})X_1(s) + 1$$

$$sX_2(s) = k_{12}X_1(s) - k_{21}X_2(s). \quad \text{(A5)}$$

If we solve equation set A5 for $X_1(s)$, the Laplace transform of the amount of drug in the central compartment as a function of s, we obtain;

$$X_1(s) = \frac{k_{21} + s}{k_{10}k_{21} + k_{10}s + k_{12}s + k_{21}s + s^2}. \quad \text{(A6)}$$

Returning to equation A3, and recognizing that the concentration in the plasma (C_p) is the amount of drug in the central compartment (x_1) divided by the volume of the central compartment (V_1), we can rewrite equation A3 in terms of $x_1(t)$:

$$x_1(t) = V_1(Ae^{-\alpha t} + Be^{-\beta t}). \quad \text{(A7)}$$

The Laplace transformation of equation A7 is

$$X_1(s) = V_1\left(\frac{A}{\alpha + s} + \frac{B}{\beta + s}\right). \quad \text{(A8)}$$

If we are to transform equation set A2, the differential equations, into equation A3, the unit disposition function, we must find definitions of A, B, α, and β such that equation A8 can be transformed into equation A6. Therefore our puzzle is to define A, B, α, and β so that they satisfy the following identity, derived from equations A6 and A8:

$$\frac{k_{21} + s}{k_{10}k_{21} + k_{10}s + k_{12}s + k_{21}s + s^2} \equiv V_1\left(\frac{A}{\alpha + s} + \frac{B}{\beta + s}\right). \quad \text{(A9)}$$

To do si, we first recognize that the denominator of the left hand expression of identity 9 is a quadratic expression,

$$k_{10}k_{21} + (k_{10} + k_{12} + k_{21})s + s^2 \quad \text{(A10)}$$

which can be factored by using the
Two solutions are generated:

$$s = \frac{-(k_{10} + k_{12} + k_{21}) + \sqrt{(-k_{10} - k_{12} - k_{21})}}{2}$$

and

$$s = \frac{-(k_{10} + k_{12} + k_{21}) - \sqrt{(-k_{10} - k_{12} - k_{21})}}{2}$$

If we define α and β as the negat
shown in equation A11, that is,

$$\alpha = -\frac{-(k_{10} + k_{12} + k_{21}) + \sqrt{(-k_{10} - k_{12} - k_{21})}}{2}$$

and

$$\beta = -\frac{-(k_{10} + k_{12} + k_{21}) - \sqrt{(-k_{10} - k_{12} - k_{21})}}{2}$$

we can simplify identity 9 to the

$$\frac{k_{21} + s}{(\alpha + s)(\beta + s)} \equiv \left(\frac{A}{\alpha +$$

With some algebraic manipulatio
identity 13, we can rearrange it t

$$V_1\left(\frac{\left(\frac{\alpha - k_{21}}{V_1(\alpha - \beta)}\right)}{\alpha + s} + \frac{\left(\frac{\beta - k_{21}}{V_1(\beta - \alpha)}\right)}{\beta + s}\right)$$

$$\equiv V_1\left(\frac{A}{\alpha$$

It follows directly from identity 1
solutions exist for A and B:

$$A = \frac{\alpha - k_{21}}{V_1(\alpha - \beta)}$$

and

$$B = \frac{\beta - k_{21}}{V_1(\beta - \alpha)}$$

Thus, when we define A and B as
and α and β as in equation set A1

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/83/1/33/383283/0000542-199507000-00005.pdf by guest on 10 April 2024

which can be factored by using the quadratic equation. Two solutions are generated:

$$s = \frac{-(k_{10} + k_{12} + k_{21}) + \sqrt{(-k_{10} - k_{12} - k_{21})^2 - 4k_{10}k_{21}}}{2}$$

and

$$s = \frac{-(k_{10} + k_{12} + k_{21}) - \sqrt{(-k_{10} - k_{12} - k_{21})^2 - 4k_{10}k_{21}}}{2} \quad (A11)$$

If we define α and β as the negative of the roots of s shown in equation A11, that is,

$$\alpha = -\frac{-(k_{10} + k_{12} + k_{21}) + \sqrt{(-k_{10} - k_{12} - k_{21})^2 - 4k_{10}k_{21}}}{2}$$

and

$$\beta = -\frac{-(k_{10} + k_{12} + k_{21}) - \sqrt{(-k_{10} - k_{12} - k_{21})^2 - 4k_{10}k_{21}}}{2} \quad (A12)$$

we can simplify identity 9 to the following identity:

$$\frac{k_{21} + s}{(\alpha + s)(\beta + s)} \equiv V_1\left(\frac{A}{\alpha + s} + \frac{B}{\beta + s}\right) \quad (A13)$$

With some algebraic manipulation of the left side of identity 13, we can rearrange it to

$$V_1\left(\frac{\left(\frac{\alpha - k_{21}}{V_1(\alpha - \beta)}\right)}{\alpha + s} + \frac{\left(\frac{\beta - k_{21}}{V_1(\beta - \alpha)}\right)}{\beta + s}\right) \equiv V_1\left(\frac{A}{\alpha + s} + \frac{B}{\beta + s}\right) \quad (A14)$$

It follows directly from identity 14 that the following solutions exist for A and B:

$$A = \frac{\alpha - k_{21}}{V_1(\alpha - \beta)}$$

and (A15)

$$B = \frac{\beta - k_{21}}{V_1(\beta - \alpha)}$$

Thus, when we define A and B as in equation set A15 and α and β as in equation set A12, then equation set A2 (the differential equations for a two-compartment model) and equation A3 (a biexponential decay) become identical representations of the same system after a unit dose at time 0. Similar derivations to that above can be found in many pharmacokinetic texts.

To calculate the intravenous dose of drug required to produce a given effect-site concentration, STANPUMP must calculate the response of the effect site to an intravenous bolus of 1 unit. The response of the effect site to a bolus of 1 unit, the unit disposition function of the effect site relative to an intravenous bolus, can be computed as the convolution of the plasma concentrations over time after a bolus of 1 unit (*e.g.*, eq. A3 above) with the disposition function of the effect site itself,

$$C_E(t) = k_{e0}e^{-k_{e0}t} \quad (A16)$$

where $C_E(t)$ = the effect-site concentration over time. Convolution of two functions is easily performed as multiplication of the functions in the Laplace domain. The Laplace transformation of the right side of equation A3 is

$$\frac{A}{\alpha + s} + \frac{B}{\beta + s} \quad (A17)$$

and the Laplace transformation of the right side of equation A16 is

$$\frac{k_{e0}}{k_{e0} + s} \quad (A18)$$

and the product of these is

$$\left(\frac{k_{e0}}{k_{e0} + s}\right)\left(\frac{A}{\alpha + s} + \frac{B}{\beta + s}\right). \quad (A19)$$

If we take the inverse Laplace transformation of equation A19, we obtain the disposition function of the effect site for a unit intravenous bolus:

$$C_E(t) = \left(\frac{A\,k_{e0}}{k_{e0} - \alpha}\right)e^{-\alpha t} + \left(\frac{B\,k_{e0}}{k_{e0} - \beta}\right)e^{-\beta t} - \left(\frac{A\,k_{e0}}{k_{e0} - \alpha} + \frac{B\,k_{e0}}{k_{e0} - \beta}\right)e^{-k_{e0}t}. \quad (A20)$$

Equation A1 can be rewritten to express the response of the intrathecal space to an epidurally administered unit dose as

$$C_{IT}(t) = C_1e^{-\lambda_1 t} + C_2e^{-\lambda_2 t} - (C_1 + C_2)e^{-\lambda_3 t}. \quad (A21)$$

These are obviously parallel equations. Comparison of equations A20 and A21 shows that STANPUMP can administer drug to a targeted intrathecal concentration provided the following solutions that make equations A20 and A21 identical are observed:

$$\left(\frac{A\,k_{e0}}{k_{e0}-\alpha}\right) = C_1$$

$$\left(\frac{B\,k_{e0}}{k_{e0}-\beta}\right) = C_2$$

$$\alpha = \lambda_1$$

$$\beta = \lambda_2$$

$$k_{e0} = \lambda_3. \qquad \text{(A22)}$$

If we combine equation set A22 above with equation set A12 for the exponents α and β and equation set A15 for the coefficients A and B, we have a series of equations that can be solved simultaneously for the parameters required by STANPUMP to administer drug to the effect site, V_1, k_{10}, k_{12}, k_{21}, and k_{e0} in terms of the parameters estimated for the disposition function of the intrathecal space, C_1, C_2, λ_1, λ_2, and λ_3. The resulting definitions of V_1, k_{10}, k_{12}, k_{21}, and k_{e0} are as follows:

$$V_1 = \frac{\lambda_3}{C_1\lambda_3 + C_2\lambda_3 - C_1\lambda_1 - C_2\lambda_2}$$

$$k_{10} = \frac{\lambda_1\lambda_2(C_1\lambda_1 + C_2\lambda_2 - C_1\lambda_3 - C_2\lambda_3)}{C_1'\lambda_1'\lambda_2 + C_2\lambda_1\lambda_2 - C_2\lambda_1\lambda_3 - C_1\lambda_2\lambda_3}$$

$$k_{12} = \frac{C_1C_2(\lambda_2 - \lambda_1)^2\,(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)}{(C_1\lambda_3 + C_2\lambda_3 - C_1\lambda_1 - C_2\lambda_2) \times (C_2\lambda_1\lambda_3 + C_1\lambda_2\lambda_3 - C_1\lambda_1\lambda_2 - C_2\lambda_1\lambda_2)}$$

$$k_{21} = \frac{C_2\lambda_1\lambda_3 + C_1\lambda_2\lambda_3 - C_1\lambda_1\lambda_2 - C_2\lambda_1\lambda_2}{C_1\lambda_3 + C_2\lambda_3 - C_1\lambda_1 - C_2\lambda_2}$$

$$k_{e0} = \lambda_3. \qquad \text{(A23)}$$

Using the above definitions, we entered into STANPUMP the micro-rate constants and k_{e0} for epidurally administered clonidine, enabling the program to target the intrathecal space as the effect site based on the control policy proposed by Shafer and Gregg.[17]

The mathematically inclined reader may attempt this derivation. If so, it should be noted that there are numerous approaches, only one of which is described here, and that solutions superficially different than those shown in equation set A23 may be derived. Close inspection should reveal that the alternative solutions are mathematically equivalent to those shown above. The above derivation is available as a Mathematica notebook by FTP to pkpd.icon@palo_alto.med.va.gov in file \clonidine.dir\clonccip.ma.

References

1. Shafer SL, Varvel JR: Pharmacokinetics, pharmacodynamics, and rational opioid selection. ANESTHESIOLOGY 74:53–63, 1991

2. Shafer SL, Stanski DR: Improving the clinical utility of anesthetic drug pharmacokinetics. ANESTHESIOLOGY 76:327–330, 1992

3. Ausems ME, Stanski DR, Hug CC: An evaluation of the accuracy of pharmacokinetic data for the computer assisted infusion of alfentanil. Br J Anaesth 57:1217–1225, 1985

4. Alvis JM, Reves JG, Spain JA, Sheppard LC: Computer-assisted continuous infusion of the intravenous analgesic fentanyl during general anesthesia: An interactive system. IEEE Trans Biomed Eng 32: 323–329, 1985

5. Glass PSA, Jacobs JR, Smith LR, Ginsberg B, Quill TJ, Bai SA, Reves JG: Pharmacokinetic model-driven infusion of fentanyl: Assessment of accuracy. ANESTHESIOLOGY 73:1082–1090, 1990

6. Shafer SL, Varvel JR, Aziz N, Scott JC: Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. ANESTHESIOLOGY 73:1091–1102, 1990

7. Dyck JB, Maze M, Haack C, Azarnoff DL, Vuorilehto L, Shafer SL: Computer-controlled infusion of intravenous dexmedetomidine hydrochloride in adult human volunteers. ANESTHESIOLOGY 78:821–828, 1993

8. Bernards CM, Sorkin LS: Radicular artery blood flow does not redistribute fentanyl from the epidural space to the spinal cord. ANESTHESIOLOGY 80:872–878, 1994

9. Glynn CJ, Jamous MA, Teddy PJ: Cerebrospinal fluid kinetics of epidural clonidine in man. Pain 49:361–367, 1992

10. Eisenach J, Detweiler D, Hood D: Hemodynamic and analgesic actions of epidurally administered clonidine. ANESTHESIOLOGY 78:277–287, 1993

11. Kirnö K, Lundin S, Elam M: Epidural clonidine depresses sympathetic nerve activity in humans by a supraspinal mechanism. ANESTHESIOLOGY 78:1021–1027, 1993

12. Khan F, Spence VA, Wilson SB, Abbot NC: Quantification of sympathetic vascular responses in skin by laser Doppler flowmetry. Int J Microcirc Clin Exp 10:145–153, 1991

13. Valley MA, Bourke DL, Hamill MP, Raja SN: Time course of sympathetic blockade during epidural anesthesia: Laser Doppler flowmetry studies of regional skin perfusion. Anesth Analg 76:289–293, 1993

14. Line PD, Moninckel P, Lien B, Kvenebo K: Repeated measurement variation and precision of laser Doppler flowmetry measurements. Microvasc Res 43:285–293, 1992

15. Netten PM, Keeris LM, DeBoo TH, Wollersheim H, Thein T: A clinical comparison of two laser Doppler instruments. Int J Microcirc Clin Exp 12:185–192, 1993

16. Gustafsson LL, Ebling WF, Osaki E, Harapat S, Stanski DR, Shafer SL: Plasma concentration clamping in the rat using a computer-controlled infusion pump. Pharmacol Res 9:800–807, 1992

17. Shafer SL, Gregg KM: Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer-controlled infusion pump. J Pharmacokinet Biopharm 20:147–169, 1992

Downloaded from http://esa2.silverchair.com/anesthesiology/article-pdf/83/1/33/383283/0000542-199507000-00005.pdf by guest on 10 April 2024

18. Jacobs JR, Williams EA: Algorithm to control 'effect compartment' drug concentrations in pharmacokinetic model-driven drug delivery. IEEE Trans Biomed Eng 40:993–999, 1993

19. Varvel JR, Donoho DL, Shafer SL: Measuring the predictive performance of computer-controlled infusion pumps. J Pharmacokinet Biopharm 20:63–94, 1992

20. Eisenach JC, Tong C, Limauro D: Intrathecal clonidine and the response to hemorrhage. ANESTHESIOLOGY 77:522–528, 1992

21. Detweiler DJ, Eisenach JC, Tong C, Jackson C: A cholinergic interaction in *alpha*$_2$ adrenoceptor-mediated antinociception in sheep. J Pharmacol Exp Ther 265:536–542, 1993

22. Bernards CM, Kopacz DJ, Michel MZ: Effect of needle puncture on morphine and lidocaine flux through the spinal meninges of the monkey *in vitro*: Implications for combined spinal–epidural anesthesia. ANESTHESIOLOGY 80:853–858, 1994

23. Bernard J-M, Hommeril J-L, Passuti N, Pinaud M: Postoperative analgesia by intravenous clonidine. ANESTHESIOLOGY 75:577–582, 1991

24. Bentley GA, Newton SH, Starr J: Studies on the antinociceptive action of α-agonist drugs and their interactions with opioid mechanisms. Br J Clin Pharmacol 79:125–134, 1983

25. Sagen J, Proudfit HK: Evidence for pain modulation by pre- and postsynaptic noradrenergic receptors in the medulla oblongata. Brain Res 331:285–293, 1985

26. Eisenach JC, Dewan DM, Rose JC, Angelo JM: Epidural clonidine produces antinociception, but not hypotension, in sheep. ANESTHESIOLOGY 66:496–501, 1987

27. Gourlay GK, Murphy TM, Plummer JL, Kowalski SR, Cherry DA, Cousins MJ: Pharmacokinetics of fentanyl in lumbar and cervical CSF following lumbar epidural and intravenous administration. Pain 38:253–259, 1989

28. Stevens RA, Petty RH, Hill HF, Kao T-C, Schaffer R, Hahn MB, Harris P: Redistribution of sufentanil to cerebrospinal fluid and systemic circulation after epidural administration in dogs. Anesth Analg 76:323–327, 1993

29. Carroll D, Jadad A, King V, Wiffen P, Glynn C, McQuay H: Single-dose, randomized, double-blind, double-dummy cross-over comparison of extradural and i.v. clonidine in chronic pain. Br J Anaesth 71:665–669, 1993

30. Roy G, Philippe E, Gaulin F, Guay G: Catecholaminergic innervation of the spinal dorsal horn: A correlated light and electron microscopic analysis of tyrosine hydroxylase-immunoreactive fibres in the cat. Neuroscience 45:177–183, 1991

31. Yaksh TL: Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing. Pharmacol Biochem Behav 22:845–858, 1985

32. Gordh T Jr, Jansson I, Hartvig P, Gillberg PG, Post C: Interactions between noradrenergic and cholinergic mechanisms involved in spinal nociceptive processing. Acta Anaesthesiol Scand 33:39–47, 1989

33. Wollersheim H, Droste H, Regenga J, Thien TH: Laser Doppler evaluation of skin vasomotor reflexes during sympathetic stimulation in normals and in patients with primary Raynaud's phenomenon. Int J Microcirc Clin Exp 10:33–42, 1991