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Hemodynamic and Analgesic Actions of Epidurally Administered Clonidine

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Background: **α_2-Adrenergic agonists such as clonidine produce behavioral analgesia and cardiovascular depression in animals, but clonidine's site of action in clinical analgesia and cerebrospinal fluid (CSF) pharmacokinetics have not been defined.**

Methods: **Clonidine was administered in the lumbar epidural space to nine volunteers while monitoring blood pressure, heart rate, finger and toe blood flow, and response to cold pain testing, and while sampling CSF and arterial plasma for clonidine analysis. Effects were correlated to plasma and CSF clonidine concentrations. Ten other volunteers received stepped intravenous infusions of the opioid alfentanil with similar testing.**

Results: **Clonidine decreased pain report in the foot but not the hand, and this effect correlated stronger with CSF than with plasma clonidine, suggesting a spinal site for analgesia. Extrapolation of CSF clonidine pharmacokinetics suggests the minimum effective CSF clonidine concentration for postoperative pain relief is 76 ± 15 ng/ml. Clonidine increased finger and toe blood flow, decreased blood pressure and heart rate, produced sedation, and mildly increased arterial P_{CO_2}, in most cases correlating better with plasma than CSF clonidine concentrations, suggesting actions at central sites. In 10 other volunteers, intravenous infusion of the opioid alfentanil produced analgesia of similar intensity to clonidine but was accompanied by significant respiratory depression.**

Conclusions: **These data support previous studies in animals and provide the scientific rationale for this novel analgesic therapy. In comparison to the potent opioid alfentanil, epidural clonidine produces a similar degree of analgesia but less respiratory depression. (Key words: Pain. Pharmacodynamics. Spinal cord. Sympathetic nervous system, α_2-adrenergic agonists: clonidine.)**

THE last decade has witnessed an explosion in knowledge of spinal pharmacology of noxious sensory information transmission. Of systems examined, opioids and α_2-adrenergic agonists have been most studied in the laboratory and most exploited in the clinic. Compared to systemic administration, intraspinal morphine administration improves the quality of pain relief, reduces morphine dose following surgery, and may decrease morbidity and mortality.[1,2] However, risk of delayed respiratory depression, ascribed to circulation of opioid in cerebrospinal fluid (CSF) to brainstem sites,[3] has limited more widespread use of this therapy.

Spinally administered α_2-adrenergic agonists produce analgesia by mimicking activation of descending noradrenergic pathways. Noradrenergic nuclei in the pons and medulla can be activated by opioids or noxious stimuli, resulting in release of norepinephrine in the dorsal horn of the spinal cord.[4,5] Locally applied norepinephrine in this region of the spinal cord hyperpolarizes dorsal horn neurons,[4] inhibits small-diameter afferent-induced substance P release,[6] and produces behavioral analgesia in several animal models.[7] These effects are mediated through α_2-adrenoceptors, located postjunctionally in the noradrenergic synapse.

Clinical application of spinal α_2-adrenergic agonist analgesia has been prompted by its lack of opioid-type side effects, especially respiratory depression; its efficacy in animal models of opioid-resistance pain, especially neuropathic and sympathetically maintained pain[8]; and its efficacy in the face of tolerance to opioids.[9] Initial experience with epidural administration of the α_2-adrenergic agonist clonidine has consisted primarily of case reports and uncontrolled trials, with dosage guided by oral regimens or pharmacokinetics in animals. This has yielded widely conflicting reports of epidural clonidine efficacy, duration, and potency compared to systemic administration.[10–18] Similarly, cardiovascular and respiratory actions of epidural clo-

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nidine have not been critically evaluated, despite potential risks or potential benefits of such side effects.

The purpose of this study was to define the pharmacokinetics and pharmacodynamics of epidurally administered clonidine on experimental pain, sympathetic reflexes, respiration, and cardiovascular control in healthy volunteers. These data provide evidence for a regional spinal cord mediation of clonidine analgesia, explain discrepancies in initial clinical reports, and guide future application of this novel analgesic therapy.

Methods

Following Institutional Review Board approval and written informed consent, nine healthy volunteers were studied after an overnight fast. A peripheral intravenous catheter was inserted, and 1.5–2 L lactated Ringer's solution infused over the subsequent 8 h. A radial arterial catheter was inserted and connected to a Micronics™ monitor interfaced with a computer data acquisition system for continuous measurement of blood pressure and heart rate. The epidural space was identified *via* loss of resistance at the L2–L3 or L3–L4 interspace using an 18-G Tuohy needle and a single distal port 21-G catheter threaded 2 cm with the needle bevel oriented cephalad. Injection of 5 ml 1.5% lidocaine with 5 μg/ml epinephrine resulted in all cases in bilateral sensory blockade consistent with an epidural injection. The intrathecal space was entered two interspaces caudad to the epidural needle insertion site, using a ramped 19.5-G Sprotte needle, and a single distal port 22-G catheter advanced 3–5 cm with the ramp oriented cephalad. Intrathecal catheter location was confirmed by free aspiration of clear CSF. The catheters were secured with tape and volunteers rested in a semirecumbent position until all signs of epidural lidocaine anesthesia were absent (minimum of 90 min) before study began. All volunteers then received 700 μg clonidine, a dose that produces complete analgesia after surgery,[15] in 7 ml isotonic saline, through the epidural catheter, injected over 5 min.

Measurements

To determine clonidine pharmacokinetics, arterial blood and CSF were obtained at 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, and 360 min and venous blood was obtained at 12 and 24 h after clonidine injection. To determine effects on basal sympathetic tone, blood pressure and heart rate were measured continuously, and arterial was blood sampled before and 30, 60, 90, 120, 180, 240, and 360 min after clonidine injection and assayed for norepinephrine and epinephrine. Also, at these times, finger and toe photoplethysmographic (PPG) recordings were obtained. To determine effects on pain perception, volunteers at these times inserted a hand in stirred ice water for 60 s, and 5 min later a foot in stirred ice water for 60 s, and rated their pain to each stimulus using a standard 10-cm visual analog scale (VAS). To determine sympathetic reflex activation by this cold testing, contralateral limb (finger or toe) PPG recordings were obtained during hand or foot immersion. Sedation was assessed before ice-water testing using a 10-cm VAS, anchored at "no drowsiness" and "as drowsy as possible." Volunteers were questioned regarding feeling of weakness or numbness, and sensory testing to light touch was performed. Catheters were removed 6 h after clonidine injection, and the volunteers allowed to go home and to return 6 and 18 h later for sedation assessment, noninvasive blood pressure and heart rate measurement, and venous blood sampling for clonidine assay.

Alfentanil Protocol

To compare the effects of epidural clonidine to those of a standard opioid analgesic, 10 additional volunteers were studied after Institutional Review Board approval and informed consent were obtained. Two peripheral intravenous catheters were inserted in each volunteer for alfentanil administration and repeated venous blood sampling. Volunteers were studied at baseline and at three increasing concentrations of alfentanil with one randomly inserted sham increase. Bolus doses and infusion rates were calculated for each volunteer using available pharmacokinetic parameters[19] to achieve steady-state concentrations of 20, 40, and 80 ng/ml at 15-min intervals. An alfentanil bolus was administered at the beginning of each 15-min interval. The infusion was controlled by a Bard™ infusion pump with manual adjustments of the infusion rate every 5 min. Ice-water immersion testing was done at baseline and at each steady-state concentration of alfentanil and consisted of placing the subject's left foot in stirred ice water for 40 s with PPG recording of the contralateral toe before and during immersion. Oxyhemoglobin saturation was monitored continuously, and blood pressure, heart rate, and ET_{CO_2} were measured noninvasively with Dinamap™ and Nellcor™ capnometers, respectively, before each cold stress test. Nausea (anchored at "no nausea" and "severe nausea") and sedation were assessed using a VAS, and venous blood was sampled for

alfentanil analysis just prior to each cold stress test. A VAS score for pain was obtained after each cold stress test.

Biochemical Analyses

Plasma and CSF samples were stored at −70° C until analysis. Clonidine was determined by radioimmunoassay[20] by Harris Laboratories (Lincoln, NE) with interassay coefficient of variability of 16% at 0.4 ng/ml and detection limit of 0.04 ng/ml. Norepinephrine and epinephrine were determined by high-pressure liquid chromatography with electrochemical detection after alumina extraction.[21] Extraction yielded a 60% recovery, with detection limit of 0.5 pg norepinephrine and 1.5 pg epinephrine, and interassay variability of 9% at 7.5 pg each. Alfentanil was determined by radioimmunoassay[22] by S. Shafer, M.D., Stanford University, with interassay coefficient of variability of 4% and detection limit of 0.05 ng/ml.

Data Analyses

Data are presented as mean ± SEM. Clonidine concentration data were analyzed using Estrip™ and PCNONLIN™. In all cases, the data sets were well fit to a two-compartment model with first-order absorption. This model fits the form: $Cx(t) = Ae^{-\alpha t} + Be^{-\beta t} + C^{-k01\,t}$, where Cx(t) = the concentration of drug in plasma or CSF at time t; A, B, and C = the relative contributions of each exponential term; and α, β, and k01 are the hybrid rate constants corresponding to the distribution, elimination, and absorption half-lifes, respectively. Elimination half-life in plasma was constrained to values reported in humans after intravenous clonidine administration, and absorption half-life in CSF was constrained to values of 10–45 min. Two approaches were used in pharmacokinetic analysis of CSF concentrations using these data. In the first, each data set was individually fit to this model, yielding a set of individual values for the pharmacokinetic parameters. In the second, a pooled pharmacokinetic analysis was performed in which one set of pharmacokinetic parameters was determined that minimized the prediction error to the entire group.[23]

Photoplethysmographic waveforms were analyzed as previously described, with amplitude measured in millimeters on a 1 kHz = 40 mm scale. For responses to ice-water testing, average amplitude of the first five beats following immersion was used, as previously described, and data presented as percent change from amplitude just prior to testing. Effect of clonidine on PPG waveform amplitude, arterial blood gas tensions and pH, norepinephrine and epinephrine, blood pressure, and heart rate was determined by one-way analysis of variance (ANOVA) for repeated measures followed by Dunnett's test. Visual analog scale scores, although not clearly interval values, also were analyzed by the parametric ANOVA test, as has been recommended.[24] Differences in responses to foot and hand immersion were tested by two-way ANOVA for repeated measures.

Correlations between plasma or CSF drug concentrations and other variables were by Pearson correlation. Concentration-response curves were fitted to a sigmoid agonist-effect model according to the law of mass action using SigmaPlot™. In addition, data for analgesic response in the foot were related to CSF concentrations of clonidine with the use of an effect site compartment and an inhibitory sigmoid E_{max} pharmacodynamic model[25]: $\text{VAS Pain}(t) = E_0 - E_{max}\,Ce(t)^{\gamma}/[IC_{50} + Ce(t)^{\gamma}]$, where VAS Pain(t) is the VAS pain score in the foot at time t; E_0 is the VAS pain score in the foot prior to drug injection; E_{max} is the maximal decrease in VAS pain score in the foot after drug injection; IC_{50} is the concentration in CSF of clonidine that produces 50% of the maximal decrease in VAS pain score; γ is a number reflecting the sigmoidicity of the curve representing VAS pain score *versus* time; and Ce(t) is the predicted concentration of drug in the effect compartment at time t. To describe the lag time between changes in CSF clonidine concentration and analgesic effect, a hypothetical effect compartment is modeled. Keo is the rate constant describing the transfer of drug from the central compartment to the effect compartment. T½Keo is the half-life of Keo, calculated by 0.693/Keo.

Change in pain, P_{CO_2} or ET_{CO_2}, and sedation were compared between those receiving clonidine and those receiving alfentanil by Student's *t* test. $P < .05$ was considered significant.

Results

Clonidine Pharmacokinetics

Clonidine was rapidly absorbed into the systemic circulation with peak concentrations (C_{max}) of 3.8 ± 0.6 ng/ml and time of peak concentration (T_{max}) of 11.8 ± 1.9 min (fig. 1). Cerebrospinal fluid pharmacokinetics were calculated for only seven of the nine volunteers, due to intermittent inability to aspirate CSF in the others. Clonidine was absorbed rapidly into CSF, with C_{max} of 390 ± 78 ng/ml and T_{max} of 31 ± 4 min (fig. 1). Modeling to a two-compartment, first-order

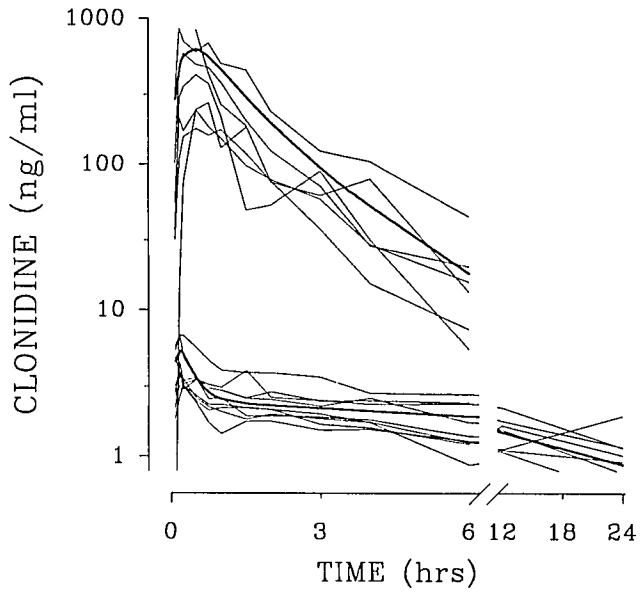

Fig. 1. Cerebrospinal fluid *(top)* and plasma *(bottom)* concentration of clonidine for 24 h following epidural administration of 700 μg at time 0. Individual volunteer data shown in light lines and average fitted curves in dark lines.

absorption model was consistent and with good fit in all cases (table 1).

Pharmacokinetic modeling of CSF clonidine concentrations using a pooled approach yielded the following coefficients: A = −1262, α = 0.0864, B = 975, β = 0.0302, C = 288, and k01 = 0.00646. The initial two-stage analysis was compared to the pooled analysis using the weighted residual error from each approach. The weighted residual error is the square of the difference between the observed and predicted concentration divided by the observed concentration. Pooled analysis reduced the median weighted residual error to 26% from 44% with the two-stage approach.

Clonidine Analgesia

Two individuals reported minimal pain to ice-water immersion (VAS score 1.7 to hand and 1.3 to foot) and stated there was essentially no pain to this test. Since their response differed significantly from the remaining seven volunteers (VAS score 7.7 in the hand and 8.4 in the foot), the pain data from these two were excluded from analysis. However, analysis of data from all nine subjects, resulted in the same statistical conclusions as the subset of seven.

Epidural clonidine significantly reduced pain report to testing in the foot, but not the hand (fig. 2). Visual analog scale pain to testing in the foot has a stronger correlation to CSF clonidine concentration (Pearson coefficient −0.615; P = .0002) than to plasma clonidine concentration (Pearson coefficient −0.476; P = .007). The apparent EC_{50} for CSF clonidine to re-

Table 1. Pharmacokinetic Parameters

	A	B	k01	α	β	α_{HL} (min)	β_{HL} (min)	$k01_{HL}$ (min)
Volunteer								
1	5.8	2.1	0.20	0.082	0.00098	8.4	708	3.4
2	84.0	2.2	0.14	0.13	0.00059	5.2	1175	4.8
3	7.3	3.8	0.19	0.048	0.00085	14.0	812	3.6
4	64.0	2.9	0.18	0.15	0.00067	4.7	1039	3.9
5	2.1	2.7	0.11	0.030	0.00059	23.0	1174	6.2
6	1.5	2.1	0.30	0.030	0.0010	23.0	694	2.3
7	2.4	1.8	0.20	0.030	0.00059	23.0	1173	3.4
8	3.4	1.7	0.26	0.067	0.00072	10.0	969	2.6
9	83.0	3.0	0.35	0.32	0.0011	2.2	623	2.0
Mean ± SEM	28 ± 12	2.5 ± 0.2	0.21 ± 0.02	0.098 ± 0.03	0.00079 ± 0.00007	12 ± 2.8	930 ± 75	3.6 ± 0.4
CSF								
1	−2995	599	0.069	0.058	0.0133	12	52	10
2	−1003	720	0.0176	0.142	0.0091	5	76	39
3	−2999	210	0.0362	0.05	0.0077	14	90	19
4	−2995	10	0.0304	0.43	0.0131	16	53	23
6	−1452	131	0.0373	0.05	0.0057	14	121	19
8	−458	373	0.023	0.0462	0.0131	15	53	27
9	−2520	185	0.0335	0.0532	0.0065	12	106	21
Mean ± SEM	−2060 ± 405	318 ± 98	0.0352 ± 0.0062	0.0631 ± 0.0132	0.0098 ± 0.0012	13 ± 1	79 ± 11	23 ± 3

HL = half-life; CSF = cerebrospinal fluid.

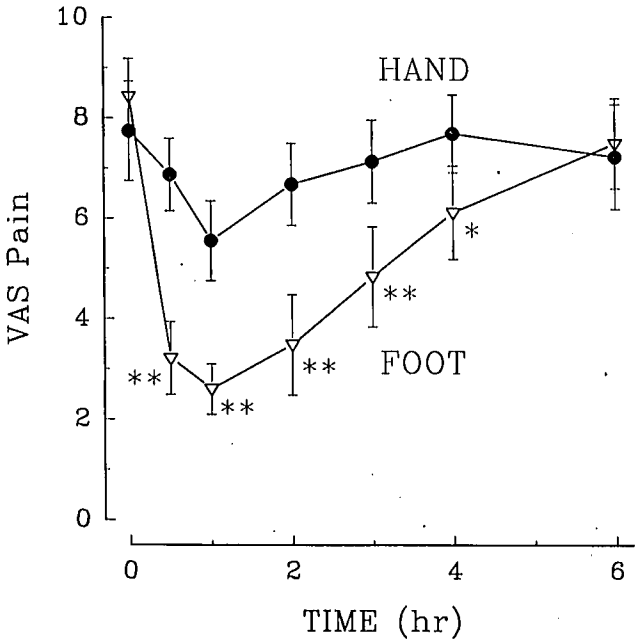

Fig. 2. Visual analog scale pain in hand (●) and foot (▽) to noxious cold stimulation before and up to 6 h after lumbar epidural injection of 700 μg clonidine. Each symbol represents the mean ± SEM of seven subjects. *$P < .05$ *versus* baseline. **$P < .01$ *versus* baseline.

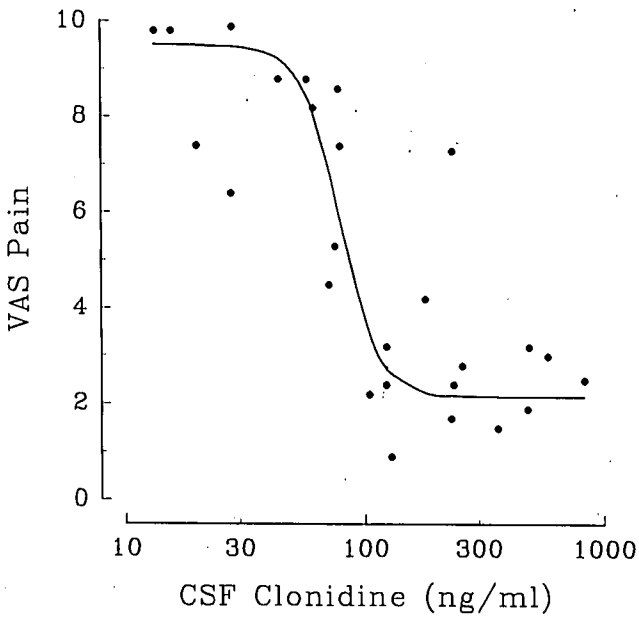

Fig. 3. Simultaneous measurement of visual analog scale pain to foot testing and lumbar cerebrospinal fluid clonidine concentration demonstrating a significant ($P < .0001$) sigmoid correlation.

duction in foot VAS pain was 80 ± 6 ng/ml (fig. 3). A small degree of hysteresis was noted in the CSF clonidine concentration–VAS pain relationship (fig. 4). Effect site compartment modeling resulted in a T½Keo of 21 ± 6 min (range 10–34 min).

Clonidine Sympathetic Responses

Epidural clonidine decreased plasma norepinephrine, but not epinephrine throughout the initial 6-h period (fig. 5). Epidural clonidine increased the amplitude of PPG waveforms and reduced the decrease in PPG waveform amplitude to ice-water immersion in both foot and hand (table 2). Correlations were observed with either CSF or plasma clonidine concentration and these PPG effects (table 2).

Other Effects

Epidural clonidine decreased both blood pressure and heart rate (table 3) and produced intense sedation, lasting 6 h (fig. 6). During the 2 h of peak sedation, volunteers were easily aroused, but asleep when not disturbed. Change in blood pressure or heart rate did not correlate with either plasma or CSF clonidine concentration. Visual analog pain sedation correlated with CSF clonidine concentration (Pearson coefficient

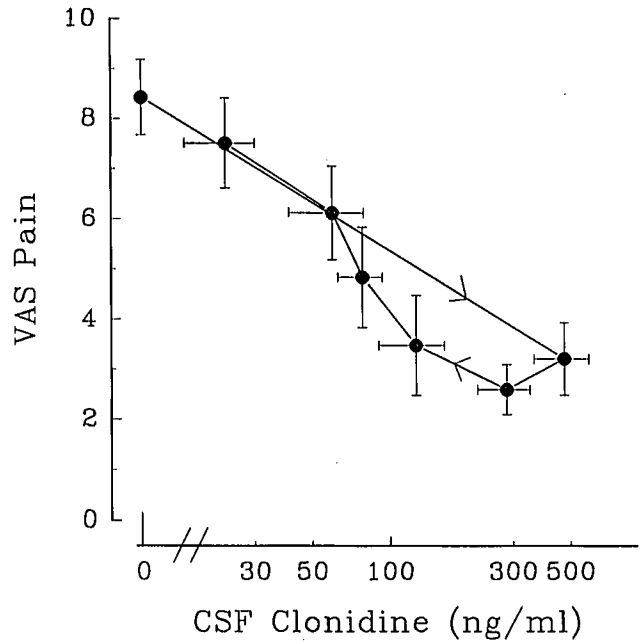

Fig. 4. Hysteresis curve of visual analog scale pain to foot testing *versus* simultaneous measurement of lumbar cerebrospinal fluid clonidine concentration. Each symbol represents the mean ± SEM of six or seven subjects. Arrows designate time course of observations.

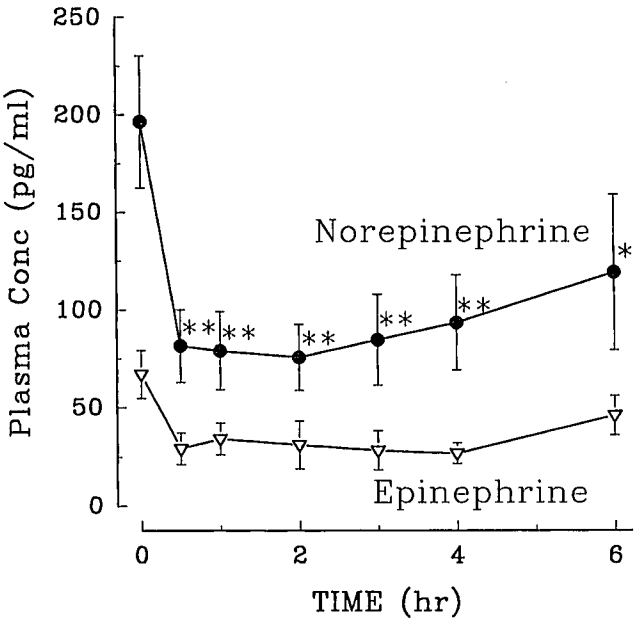

Fig. 5. Plasma norepinephrine (●) and epinephrine (○) concentrations before and after epidural injection of 700 μg clonidine. **$P < .01$ *versus* baseline.

0.439; $P < .0001$) and with plasma concentration (Pearson coefficient 0.304; $P = .009$). Clonidine produced minor but statistically significant changes in arterial pH and P_{CO_2} (table 4). Arterial pH correlated with plasma clonidine concentration (Pearson coefficient −0.454; $P = .004$), but not CSF concentration. No volunteer noted subjective change in motor or sensory function after epidural clonidine injection, and there was no evidence of change to testing to light touch.

Alfentanil Infusion

Two of the 10 volunteers reported minimal pain to ice-water testing, and their VAS pain scores were excluded from analysis. Alfentanil decreased pain report to ice-water immersion in a concentration-dependent fashion (fig. 7), decreased oxyhemoglobin saturation and heart rate, and produced nausea (table 5). The highest infusion rate of alfentanil (plasma concentration = 92 ± 6 ng/ml), compared to the time of peak analgesia after epidural clonidine, produced similar analgesia, accompanied by less sedation, but more respiratory depression (fig. 8).

Discussion

These data suggest that epidural clonidine produces *regional* analgesia in humans by a local, spinal action, and *generalized* inhibition of sympathetic nervous sys-

Table 2. Plethysmographic Responses

	Time after Clonidine (min)							Correlation to Plasma Clon	Correlation to CSF Clon
	0	30	60	120	180	240	360		
Foot									
Baseline	13 ± 3.2	39 ± 8.7*	41 ± 10*	38 ± 5.5†	28 ± 5.6	26 ± 6.1	12 ± 2.2	0.406 ($P = .004$)	0.572 ($P = .0008$)
% change with ice testing	−38 ± 5.1	−12 ± 5.0*	−10 ± 4.6*	−11 ± 5.6*	−17 ± 4.2†	−13 ± 3.9*	−12 ± 4.6	0.415 ($P = .003$)	NS
Hand									
Baseline	19 ± 4.7	61 ± 12†	53 ± 6.3*	65 ± 16†	50 ± 11	49 ± 12	41 ± 14	0.429 ($P = .002$)	NS
% change with ice testing	−45 ± 7.4	−25 ± 7.8	−24 ± 5.9†	−20 ± 5.7	−20 ± 5.8*	−25 ± 5.1	−22 ± 6.4†	NS	0.486 ($P = .006$)

CSF = cerebrospinal fluid.

* $P < .01$ *versus* baseline.

† $P < .05$ *versus* baseline.

Table 3. Hemodynamic Effects of Clonidine

	0 min	5 min	10 min	15 min	30 min	60 min	1.5 h	2 h	3 h	4 h	6 h	12 h	24 h
MAP (mmHg)	91 ± 3	88 ± 5	87 ± 6*	78 ± 3†	78 ± 3†	72 ± 3†	72 ± 3†	72 ± 3†	71 ± 4†	73 ± 3†	72 ± 3†	76 ± 1†	73 ± 2
HR (beats/min)	68 ± 4	67 ± 7	65 ± 6.1	68 ± 5	60 ± 7	64 ± 5*	53 ± 3	57 ± 5	60 ± 6*	52 ± 4	58 ± 4	56 ± 4	64 ± 7

Values are mean ± SEM.

MAP = mean arterial pressure; HR = heart rate.

* $P < .05$ *versus* baseline.

† $P < .01$ *versus* baseline.

tem activity and reflexes. Comparison of type and intensity of side effects to a standard opioid analgesic yields significant differences as would be expected from the different receptor types being activated. These data help to clarify the mechanism of action of α_2-adrenergic agonists in analgesia and other effects in humans, correlate these responses in humans to other animal species, and guide future clinical application of such therapy.

Analgesia

A variety of experimental data support a primary spinal action of α_2-adrenergic agonists in producing analgesia. Autoradiography utilizing selective α_2-adrenergic ligands demonstrates dense binding in the superficial layers of the dorsal horn,[26] an important site of transmission and modulation of noxious sensory information. α_2-Adrenoceptor density is not affected by spinal cord transection or by treatment with noradrenergic neurotoxins,[27] suggesting a postsynaptic location to the descending noradrenergic fibers originating in the brainstem. These α_2-adrenoceptors are important inhibitors of spinal transmission of noxious sensory information. Reduction in α_2-adrenergic density following dorsal rhizotomy suggests some of these receptors are located on sensory afferents,[28] and spinally applied α_2-adrenergic agonists reduce substance P release from high-intensity neural stimulation.[6] Finally, intrathecal administration of α_2-adrenergic agonists produces analgesia in a variety of species and behavioral tests.[7]

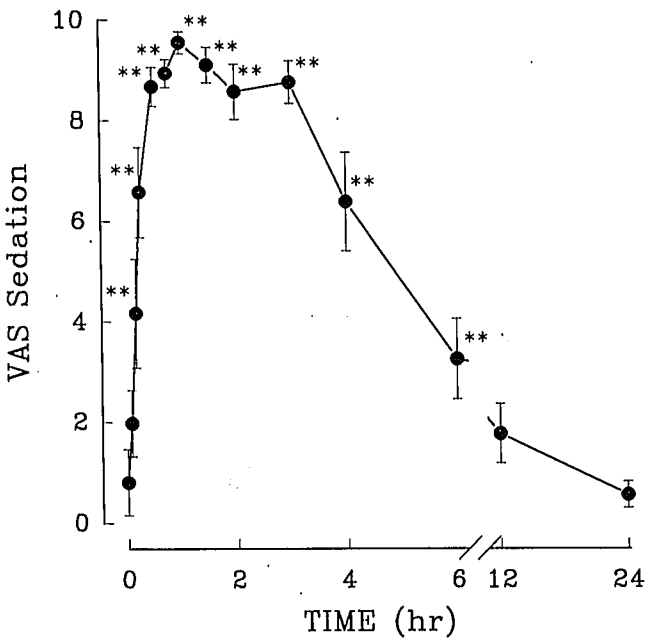

Fig. 6. Sedation before and after epidural injection of 700 μg clonidine. Each symbol represents the mean ± SEM of nine subjects. **$P < .01$ *versus* baseline.

Analgesia in foot but not hand following lumbar epidural injection in this study supports a spinal mechanism of clonidine-induced analgesia in humans. Cerebrospinal fluid is clearly not the site of action of clonidine analgesia. Nonetheless, there was excellent correlation between pain report reduction and clonidine concentration in CSF and minimal hysteresis of these variables. Such tight correlation logically follows from the two observations that analgesic action of spinally administered drugs results from diffusion from CSF to superficial dorsal horn[29,30] and that a highly lipid-soluble drug such as clonidine will rapidly traverse this small distance.[29] For comparison, the lag time between CSF concentration and effect in this study, estimated to be 21 min, is similar to that obtained by analysis of plasma concentrations of morphine after intravenous administration[31] but greater than that of fentanyl.[25] Part of this lag time may be an artifact of the experimental design, in that CSF was sampled at a site separate from that overlying the spinal cord and clonidine's site of action.

Pharmacokinetic analysis of CSF clonidine concentrations in this study is inadequate to describe pharmacokinetic parameters precisely. One can infer that absorption from epidural to the intravascular and spinal

Table 4. Effect of Clonidine on Arterial Blood Gas Tensions and *p*H

	0 h	0.5 h	1 h	2 h	3 h	4 h	6 h
*p*H	7.41 ± 0.01	7.38 ± 0.01*	7.37 ± 0.01*	7.37 ± 0.01*	7.37 ± 0.01*	7.38 ± 0.01*	7.40 ± 0.01
P_{CO_2} (mmHg)	38 ± 1.2	41 ± 1.4†	41 ± 1.5†	42 ± 0.9*	42 ± 0.9*	41 ± 1.0†	38 ± 1.4
P_{O_2} (mmHg)	117 ± 8.3	107 ± 4.5	106 ± 3.7	111 ± 5.0	110 ± 4.5	114 ± 2.8	112 ± 6.4

Values are mean ± SEM.

* $P < .01$ *versus* baseline.

† $P < .05$ *versus* baseline.

spaces is rapid and extensive by the observed T_{max} and C_{max}. However, without description of pharmacokinetics of clonidine following intravenous and intrathecal injection in these same individuals, one cannot deconvolute the data obtained after epidural injection to define the *true* absorption rates. As such, the parameters in table 1 are one set of many that could describe the data equally well. Nonetheless, these parameters, especially those obtained by analysis using the pooled approach, fulfill our primary intention to define pharmacokinetic parameters predicting plasma and CSF concentrations with this and other dosing regimens.

These pharmacokinetic-dynamic observations clarify the confusing array of reports of epidural clonidine analgesia. Calculation of anticipated CSF clonidine concentrations over a bolus dose range of 100–900 μg and correlation with the period of complete analgesia in each patient receiving these doses[15] demonstrate that calculated CSF clonidine concentration at the time of first request for additional analgesia is consistent (76 ± 15 ng/ml) over this large dose range. Using this value and the pharmacokinetic constants from the current study predicts no period of *complete* analgesia from an epidural clonidine bolus of 150 μg, but >100 min of >50% reduction in VAS pain from the same bolus, both aspects having been observed clinically.[13,14]

In contrast to the consistent observations of analgesia from intraspinal administration, the degree of pain relief obtained after systemic administration of α_2-adrenergic agonists is much less clear. For example, clonidine administration to certain brainstem sites yields an anti-analgesic effect[32,33] and clinical studies demonstrate weak analgesia[34] or hyperalgesia[§] following systemic clonidine. Analgesic actions are confounded by the drug's anesthetic action at high doses[35] in addition to its inhibition of opioid metabolism.[34] The current study supports a primary spinal, rather than peripheral or supraspinal, mechanism of clonidine analgesia in humans, in accordance with data in animals.

Sympathetic Outflow

Although extremity plethysmography and circulating catecholamine concentrations are inexact measures of sympathetic outflow, both have been well validated in humans to measure effects of drug therapy and drug action on reflex responses.[36,37] Increased blood flow in the extremities, suggested by PPG recordings in the current study by clonidine, also has been observed using laser Doppler flow methods.[38,39] Studies of clonidine's actions in individuals with pre- and postganglionic sympathetic lesions[38,39] and decreased plasma catecholamines after clonidine in the current study

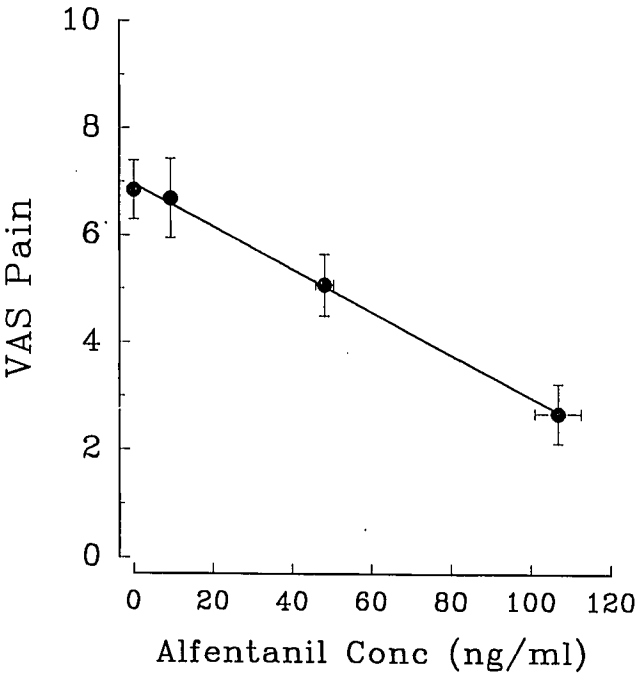

Fig. 7. Plasma alfentanil concentration *versus* visual analog scale pain to foot testing. Each symbol represents the mean ± SEM of eight subjects. *$P < .05$ *versus* baseline.

§ Gordh TE, Tamsen A: A study of the analgesic effect of clonidine in man. Acta Anaesthesiological Scandinavica 78(suppl):72, 1983.

Table 5. Side Effects of Intravenous Alfentanil

Alfentanil Concentration (ng/ml)	ET_{CO_2} (mmHg)	Oxyhemoglobin Saturation (%)	Heart Rate (beats/min)	Nausea VAS (cm)
0	41 ± 0.7	99 ± 0.3	70 ± 3	0.07 ± 0.03
12 ± 2	43 ± 0.7*	97 ± 0.3†	70 ± 2	0.20 ± 0.08
50 ± 2	45 ± 0.8†	96 ± 0.6†	67 ± 3	0.78 ± 0.64
106 ± 1	48 ± 1.0†	94 ± 1.0†	60 ± 1†	2.1 ± 1.0*

VAS = visual analog scale.

* $P < .05$ *versus* alfentanil concentration.

† $P < .01$ *versus* alfentanil concentration.

suggest that this effect is due to diminished sympathetic outflow. The generalized nature of this response is in agreement with its primary site of action in the brainstem, which clonidine reaches either through systemic absorption or rapid distribution in CSF (see below). Whereas α_2-adrenergic agonists can inhibit preganglionic sympathetic neuronal activity in the spinal cord directly,[40] and some evidence suggests regional sympatholysis following intraspinal clonidine in animals and humans,[41,42] we observed no such regional effects on sympathetic reflexes in this study.

Intraspinal analgesics may inhibit autonomic reflexes to certain stimuli while leaving others intact. For example, spinal opioids diminish sympathetic activation produced by noxious stimuli in animals and humans,[43]

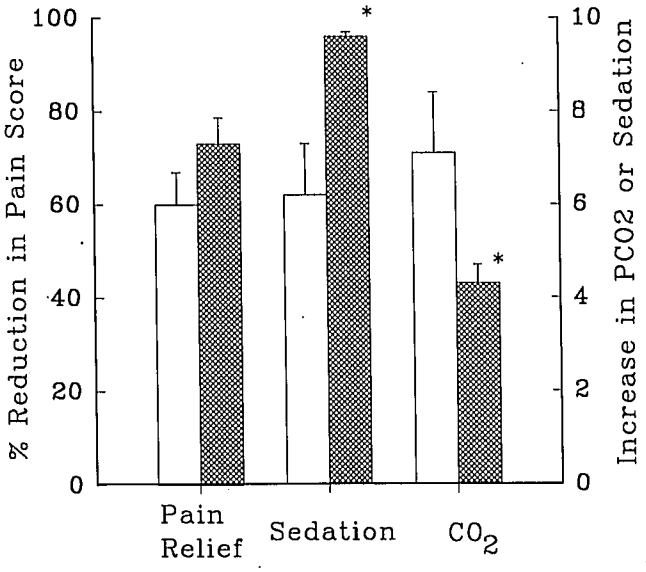

Fig. 8. Pain relief (percent reduction in visual analog scale pain to foot testing compared to baseline), sedation (visual analog scale score in cm), and change in arterial (clonidine) or end-tidal (alfentanil) CO_2 after clonidine (hatched bars) or alfentanil (open bars). *$P < .05$ groups differ.

but do not alter sympathetic responses to hemorrhage in animals or PPG evidence of sympathetic activation to breath-holding in humans (C. Chaball, M.D., personal observations; presented at the annual meeting of the Association of University Anesthesiologists, May 1990). In contrast to this selective inhibition by opioids, α_2-adrenergic agonists inhibit sympathetic responses to both noxious stimuli and other stimuli (*e.g.*, hemorrhage) in animals.[43,44]

Whether reduction in sympathetic tone and reflexes induced by epidural clonidine is a risk or benefit in postoperative patients is unclear. On the one hand, postoperative hemorrhage may occur, and animal studies suggest that clonidine therapy may diminish the amount of blood loss that is tolerated before hypotension ensues.[44] On the other hand, recent work suggests that inhibition of sympathetic hyperactivity following surgery may diminish both major morbidity (hypercoaguable state and venous thrombosis) and mortality.[1,2] Whether α_2-adrenergic agonists would perform this function better than opioids has not been addressed.

Comparison to Alfentanil

These data agree closely with a study of similar design in volunteers[45,46] and demonstrate alfentanil-induced analgesia to experimental pain that is highly correlated to plasma alfentanil concentrations, despite weaknesses in study design in the current study (venous rather than arterial blood sampling; no direct proof that a steady state had been reached). As with clonidine, the experimental pain dose response accurately predicts the drug concentrations required clinically for postoperative analgesia (EC_{50} = 50 ng/ml, EC_{95} = 120 ng/ml, for alfentanil in plasma).[47]

Despite similar degrees of analgesia, side-effect profiles for the opioid alfentanil and the α_2-adrenergic agonist clonidine were distinct. For example, at equally

analgesic times, clonidine produced greater sedation than did alfentanil. The rapid onset of sedation following clonidine administration could be due to rapid systemic absorption and central redistribution and could limit the usefulness of this therapy. On the other hand, epidural administration of the lipid-soluble opioid fentanyl results in rapid appearance of high drug concentrations in cervical CSF unexplained by time for CSF circulation.[48] Clonidine's rapid and more profound effect on electroencephalogram following epidural rather than intravenous administration[49] suggests that an analogous rapid central redistribution may occur.

The major difference between alfentanil and clonidine in this study was the degree of respiratory depression at rest. We chose to use ET_{CO_2} as a measure of respiratory depression in the alfentanil group, based on a previous report demonstrating this to be a sensitive measure of respiratory depression in volunteers from this agent.[46] The minor change in arterial P_{CO_2} following clonidine in this study is consistent with minor or no effects of α_2-adrenergic agonists on resting respiratory control.[50]

In conclusion, these data demonstrate profound analgesia from epidural clonidine in humans. Regional pain relief, good correlation of pain relief with CSF clonidine concentration, and minimal hysteresis of pain *versus* simultaneous CSF clonidine concentration all argue for a local spinal action of clonidine and clarify conflicting initial clinical reports. Generalized decrease in sympathetic tone and reflex activity probably represents a central redistribution effect of clonidine. In comparison to the potent opioid alfentanil, epidural clonidine produces a similar degree of analgesia with minimal respiratory depression. In a recent review on the use of α_2-adrenergic drugs for anesthesia and analgesia, Maze and Tranquilli[45] conclude that we yet do not know "whether we are riding a horse or an ass." These data suggest we are riding a horse.

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