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Pharmacokinetics and Dynamics of Intravenous, Intrathecal, and Epidural Clonidine in Sheep

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Epidural clonidine administration produces analgesia by a spinal action but may produce hemodynamic depression by activating other central or peripheral α_2-adrenoceptors. To determine clonidine's distribution and cardiorespiratory effects 300 μg clonidine was injected epidurally, intrathecally, and intravenously in six chronically prepared sheep, and cerebrospinal fluid (CSF) and arterial plasma clonidine were measured. Dural transfer of epidurally administered clonidine was rapid and extensive: time to maximal concentration (T_{max}) in CSF was 32 ± 8 min, bioavailability in CSF was 14 ± 4% of the administered dose, and maximal CSF concentrations following epidural administration (820 ± 30 ng/ml) were three orders of magnitude greater than those following iv injection (0.71 ± 0.06 ng/ml). Systemic absorption of epidurally administered clonidine occurred rapidly: T_{max} in plasma was 34 ± 6 min and plasma concentrations were similar to those following iv injection at all time points beyond 20 min. Elimination half-lives from plasma were similar for all three routes of administration (81–95 min). Clonidine's effect on blood pressure differed with route of administration. Blood pressure increased and heart rate decreased following iv injection when plasma clonidine concentrations were high (>2 ng/ml). Clonidine, following all routes of administration, numerically decreased blood pressure, but this decrease was significant only following epidural (mean arterial pressure = 97 ± 6 mmHg before, 86 ± 6 mmHg after; $P < 0.05$) and intrathecal (93 ± 9 mmHg before, 79 ± 10 mmHg after; $P < 0.05$) injection. Blood pressure decreased earlier following intrathecal than following epidural injection, corresponding with higher CSF clonidine concentrations. Arterial P_{O_2} decreased only following iv injection (from 97 ± 6 mmHg to 74 ± 7 mmHg; $P < 0.05$). These results support initial clinical experience with intraspinal clonidine administration, and provide a rationale for choice of route and method of administration. (Key words: Analgesia. Anesthetic techniques: epidural, intrathecal. Pharmacodynamics, clonidine.)

INTRATHECAL or epidural administration of the α_2-adrenergic agonist, clonidine, produces analgesia in animals,[1,2] and initial clinical trials suggest a powerful analgesic effect of clonidine in humans.[3–6] However, onset and duration of analgesia following intrathecal or epidural clonidine injection have not been well defined, and reports of the incidence and extent of hypotension following intraspinal clonidine injection vary widely.[3–7]

Recently, onset and duration of analgesia and side effects following intraspinal opiate administration have been correlated and predicted by determination of cerebrospinal fluid (CSF) and plasma opiate pharmacokinetics.[8–10] For example, morphine, a relatively lipid-insoluble opioid, does not distribute readily into spinal cord tissue and ascends the neuraxis *via* bulk CSF flow, producing prolonged and extensive analgesia and delayed brain stem mediated respiratory depression.[11] Distribution and elimination of clonidine in CSF and plasma following intraspinal injection have not been examined, and could prove of value in predicting time course and extent of analgesia and side effects. This study describes the CSF and plasma pharmacokinetics and the hemodynamic pharmacodynamics of epidurally administered clonidine. To more fully characterize both kinetics and dynamics, these effects were compared with those following intrathecal and iv injection.

Materials and Methods

ANIMALS

Following approval by the Animal Practices Committee, six nonpregnant ewes of mixed Western breeds were studied. Animals were fasted and deprived of water 24 h prior to surgery. Anesthesia was induced with sodium pentobarbital (4 mg/kg iv) and ketamine (4 mg/kg iv) and was maintained with halothane, 1–2% in oxygen. Polyvinyl catheters were inserted into the descending aorta and inferior vena cava *via* a femoral artery and vein, respectively, tunneled subcutaneously to the flank, and maintained in a canvas pouch. The animal was then placed in the prone position and a bilateral laminectomy was performed at L4–5 or L3–4 as described by Payne *et al.*[12] Approximately 2–3 cm of spinal dura mater was exposed by gentle retraction of epidural fat. A single port 20-G Portex™ catheter was inserted through a small nick in the dura, advanced 3 cm into the subarachnoid space, and the dural hole sealed with two 8-0 silk sutures. The epidural fat was replaced around the catheter, and a second single port Portex™ catheter was advanced 3 cm in the epidural space. Catheters were secured, the incision closed, and animals returned to metabolic carts for the remaining period of study. A three-day recovery period elapsed before study, during which the animals were

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closely monitored and received daily penicillin (900,000 units, im). All animals were standing on all four limbs and eating and drinking adequately within 4–8 h following surgery. Femoral catheters were flushed daily with sterile heparinized saline and filled with sterile heparin solution.

Experimental Protocol

On the day of the study, the femoral arterial catheter was connected to a Gould™ transducer for the continuous measurement of arterial pressure and heart rate using a Grass™ 7D polygraph. Following 15 min of stable baseline measurements, clonidine, 300 μg in 0.9% saline, was injected epidurally (10 ml volume), intravenously (10 ml volume), or intrathecally (1.5 ml volume) over 2 min. Catheters were then flushed with one void volume (3 ml for the iv catheter, 0.3 ml for the epidural and intrathecal catheters). Prior to injection, 0.1% of the administered dose was separated for clonidine analysis. The order of injections was randomly assigned to each animal. Injections were separated by a minimum of 48 h following epidural or intrathecal injections, or 24 hours following iv injection. Pilot data suggested that these intervals allowed complete clearance of clonidine from CSF and plasma.

Arterial blood (1 ml) and CSF (0.3–0.5 ml) were obtained for clonidine analysis and arterial blood pressure and heart rate recorded before and at 1, 10, 20, 60, 120, and 240 min following iv injection at 1, 10, 40, 60, 120, 240, and 360 min following intrathecal injection, and at 1, 10, 20, 40, 60, 90, 120, 240, and 360 min following epidural injection. These time points were determined from pilot data to provide minimum sampling points needed to define clonidine pharmacokinetics without causing significant depletion of CSF volume. One void volume was withdrawn from both the CSF and arterial catheters prior to sampling; each catheter void volume was replaced with saline for the intrathecal catheter or heparinized saline for the intraarterial catheter. In addition, arterial blood was obtained for blood gas tension determination before and at 10, 60, and 240 min following iv injection and at 40, 60, and 240 min following epidural and intrathecal injection. These time points were determined from pilot data to correspond with times of maximal plasma clonidine concentrations. Arterial blood gas tensions were determined using a Radiometer BMD blood microanalysis system. CSF and plasma samples were frozen at −20° C until time of assay. Clonidine concentrations were determined by EG & G Mason Research (Worcester, Massachusetts) using a specific radioimmunoassay with no specific cross-reactivity with three major clonidine metabolites (2,6-dichlorophenyl-guanidine, 1-[2,6-dichloro-4-hydroxyphenyl]-guanidine, and 2-[2,6-dichlorophenyl] imino-imidazoline-4-one).[13] The minimal detectable concentration is 0.05 ng/ml and intraassay and interassay variation is 7 and 11%, respectively, at concentrations ranging from 0.01 to 0.64 ng/ml. Plasma and CSF samples were appropriately diluted to be within a range of 0.01–10 ng/ml.[13]

Pharmacokinetics

Pharmacokinetic analysis was performed using PCNONLIN™ software (Statistical Consultants, Inc., Lexington, Kentucky). Time *versus* clonidine concentration points for each animal were fit to either a two-compartment, first-order elimination model with bolus injection or to a one-compartment model with first-order absorption and elimination. These models were chosen as the most appropriate models from visual inspection of log concentration *versus* time plots and form *a priori* correlation coefficients obtained when estimating coefficients and exponential constants from the data sets (ESTRIP™, Statistical Consultants, Inc., Lexington, Kentucky). Initial estimates of kinetic parameters were chosen from a curve-stripping technique using ESTRIP™ and, in some instances, using hand calculated methods. Pharmacokinetic parameters of elimination ($t_{1/2}el$) and absorption half-times ($t_{1/2}ab$), maximal concentrations (C_{max}), time to maximal concentration (T_{max}), and initial volume of distribution (Vd_i) were determined according to standard equations. Volume of distribution for the elimination phase (Vd_β) in plasma following iv injection or in CSF following intrathecal injection were calculated from the equation:

$$Vd_\beta = \frac{DOSE}{(AUC)ke}$$

where AUC is the area under the time concentration points as obtained from integration of the data set with a spline function, and ke is the elimination rate constant. Bioavailability in plasma following intrathecal or epidural injection was calculated by dividing the AUC following these injections by the AUC following iv injection. Similarly, bioavailability in CSF following iv or epidural injection was calculated by dividing the AUC following these injections by the AUC following intrathecal injection.

Statistical Analysis

Data are presented as mean ± SEM. Changes in mean blood gas tensions, mean arterial pressures, or heart rate following epidural, intrathecal, or iv clonidine injection were determined by one-way analysis of variance followed by Dunnett's test. Pharmacodynamic correlations were tested by linear regression.

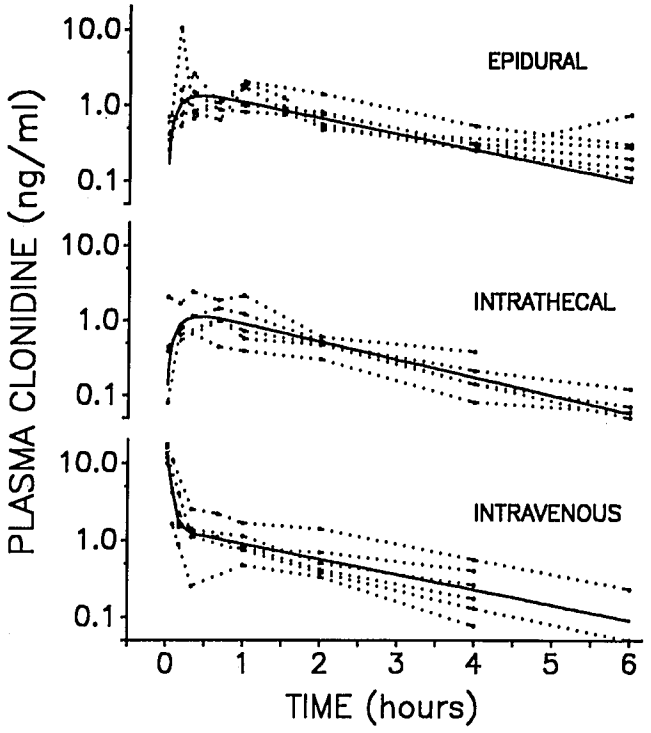

FIG. 1. Plasma clonidine concentrations following epidural, intrathecal, and iv clonidine administration. The dotted lines represent individual animal data. The solid lines depict the predicted time–concentration curves obtained from mean solutions of each original data set for iv, intrathecal, and epidural routes of administration.

DRUGS

The following drugs were used in this study: ketamine HCl and sodium pentobarbital (Barber Veterinary Supply Co., Richmond, Virginia), halothane (Halocarbon Laboratories, Inc., Hackensack, New Jersey), heparin (Lypho-Med, Inc., Rosemont, Illinois), and procaine penicillin G (Pfizer, New York, New York). Clonidine HCl was a generous gift from Boehringer-Ingelheim, Ltd. (Ridgefield, Connecticut).

Results

PHARMACOKINETIC ANALYSIS

Plasma. Plasma clonidine concentrations differed among the three routes of administration only during the first 20 min following injection (fig. 1). Following iv injection, clonidine rapidly distributed ($t_{1/2}\alpha$ = 2.9 ± 0.8 min) into a second compartment with a large apparent volume of distribution (250 ± 79 l) and slower elimination half-life (table 1). Plasma clonidine concentrations following iv injection best fit a two-compartment model, whereas those following epidural or intrathecal injection were best described by a single-compartment model due to the relatively slow first-order absorption (table 1). The predicted curve obtained from nonlinear regression solution of each data set correlated highly with the actual data points ($R > 0.90$). Absorption into plasma did not differ between intrathecal and epidural administration, and was complete: bioavailability of clonidine in plasma following intrathecal and epidural injection was 85 ± 20% and 105 ± 15%, respectively, of that following iv injection.

CSF. Initial CSF clonidine concentrations differed significantly among all groups (fig. 2). Following intrathecal injection, clonidine was distributed in a small initial volume (6.9 ± 2.4 ml), and rapidly redistributed ($t_{1/2}\alpha$ = 7.3 ± 2.2 min) into a second compartment with an elimination half-life similar to that of plasma (table 2). Following iv and epidural injection, however, CSF clonidine concentrations were best described by a single-compartment model, due to a relatively slow first-order absorption (table 2). The predicted curve obtained from nonlinear regression solution of each data set correlated highly with the actual data points ($R > 0.92$). Clonidine concentrations in CSF following redistribution were similar following epidural and intrathecal injection, and were more than 1,000 times those observed following iv injection. Bioavailability of clonidine in CSF following epidural and iv injection was 14 ± 2% and 0.022 ± 0.007%, respectively, of that following intrathecal injection.

TABLE 1. Pharmacokinetics of Clonidine in Plasma Following Intravenous (IV), Intrathecal (IT), or Epidural (EP) Injection

		Individual Animal Values						
		1	2	3	4	5	6	Mean + SE
$t_{1/2}$ ab (min)	IT	16.4	3.1	9.1	—	8.1	0.6	7.5 ± 2.7
	EP	5.0	14	22	10	8.7	2.3	10.3 ± 2.8
T_{max} (min)	IT	37	17	34	—	29	5	24 ± 6
	EP	19	46	53	36	38	14	34 ± 6
C_{max} (ng/ml)	IT	1.37	2.32	0.89	—	0.92	0.65	1.23 ± 0.30
	EP	2.15	2.02	1.35	1.09	0.89	0.91	1.40 ± 0.23
$t_{1/2}$ el (min)	IV	42	167	84	111	72	—	95 ± 21
	IT	42	119	90	—	70	85	81 ± 12
	EP	50	97	69	96	141	130	98 ± 15

PHARMACODYNAMICS

Clonidine did not influence arterial P_{CO_2} or *p*H. Arterial P_{O_2} significantly decreased only following iv injection (table 3) at times after plasma clonidine concentrations had exceeded 10 ng/ml. Baseline mean arterial pressure did not differ among groups (97 ± 5, 93 ± 9, and 97 ± 6 mmHg prior to iv, intrathecal, and epidural injection, respectively). Intravenous clonidine increased blood pressure immediately following injection (fig. 3). Intrathecal injection decreased blood pressure significantly within 10 min, whereas epidural injection decreased blood pressure significantly only 2 h following injection. A clear correlation between plasma clonidine concentration and blood pressure was present only following the iv injection ($R = 0.79$), with decreased pressure at concentrations > 2 ng/ml and increased pressure at concentrations > 2 ng/ml. Baseline heart rate did not differ among groups (79 ± 4, 80 ± 8, and 87 ± 8 beats/min prior to iv, intrathecal, and epidural injection, respectively). Heart rate decreased similarly following clonidine injection in all groups (fig. 4), although this effect was not significant following epidural injection.

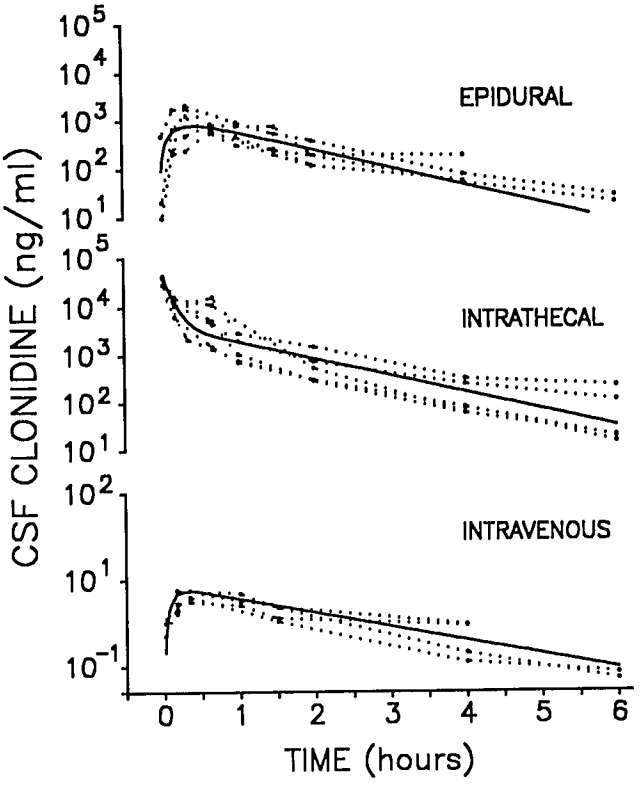

FIG. 2. CSF clonidine concentrations following epidural, intrathecal, and iv clonidine administration. The dotted lines represent individual animal data. The solid lines depict the predicted time–concentration curves obtained from the mean solutions of each original data set for intrathecal, epidural, and iv routes of administration. Note differences in scale.

Discussion

Clinical experience with intraspinal clonidine is minimal and the preferred route (epidural or intrathecal) and method (bolus or infusion) of administration is unclear. Although it can be argued that clonidine pharmacokinetics could differ between sheep and humans, CSF pharmacokinetics of opioids of differing lipid solubility in sheep correlate with extent of dural transfer and residence time in CSF in humans,[12,14–16] and preliminary results of CSF pharmacokinetics following epidurally administered clonidine in humans are similar to values obtained in this study in sheep.[7] Therefore, by defining plasma and CSF pharmacokinetics and hemodynamic effects following iv, epidural, and intrathecal injection in sheep, one may predict time course and extent of analgesia and side effects in humans, and provide a rationale for guiding clinical choices of route and method of administration. Initial clinical experience with intraspinally administered clonidine is in agreement with these predictions.[6]

ANALGESIA

Like intraspinally applied opioids, intraspinal clonidine administration produces analgesia by an action in the spinal cord.[17–19] CSF is clearly not the site of action of these

TABLE 2. Pharmacokinetics of Clonidine in CSF Following Intravenous (IV), Intrathecal (IT), or Epidural (EP) Injection

		Individual Animal Values						
		1	2	3	4	5	6	Mean + SE
$t_{1/2}$ ab (min)	IV	3.9	—	—	10.4	1.6	7.0	5.8 ± 1.9
	EP	3.6	—	35.1	5.4	21.3	13.9	15.9 ± 5.8
T_{max} (min)	IV	21.8	—	—	38.7	10.1	27.9	24.6 ± 6.0
	EP	11.4	—	59.0	17.8	38.8	31.9	31.8 ± 8.4
C_{max} (ng/ml)	IV	0.59	—	—	0.78	0.83	0.62	0.71 ± 0.06
	EP	1,970	—	817	752	338	1,327	1042 ± 280
$t_{1/2}$ el (min)	IV	177	—	—	106	109	89	120 ± 20
	IT	30	30.8	106	62	106	44	64 ± 14
	EP	22	—	48	38	35	39	36.4 ± 4.2

TABLE 3. Arterial Blood Gas Tensions prior to and Following Intravenous (IV), Intrathecal (IT), and Epidural (EP) Clonidine

		Time Following Injection (min)				
		0	10	40	60	240
P_{O_2} (mmHg)	IV	97 ± 6	74 ± 7	—	74 ± 6*	84 ± 10
	IT	87 ± 11	—	82 ± 9	80 ± 7	85 ± 7
	EP	76 ± 5	—	69 ± 3	81 ± 6	76 ± 5
P_{CO_2} (mmHg)	IV	33 ± 2	34 ± 3	—	33 ± 2	33 ± 3
	IT	32 ± 3	—	38 ± 3	36 ± 2	38 ± 2
	EP	33 ± 2	—	34 ± 3	33 ± 2	33 ± 3
*p*H	IV	7.48 ± 0.02	—	7.52 ± 0.03	7.50 ± 0.01	7.52 ± 0.01
	IT	7.49 ± 0.01	—	7.53 ± 0.01	7.53 ± 0.02	7.54 ± 0.01
	EP	7.48 ± 0.02	—	7.52 ± 0.03	7.50 ± 0.01	7.52 ± 0.02

Values are expressed as SEM.

* $P < .05$ vs 0′ time point.

compounds. Nonetheless, in clinical studies, CSF pharmacokinetics of intraspinally injected opiates are powerful predictors of onset and duration of analgesia, therapeutic drug concentrations, and relative potency.[8–10] For a novel drug, these parameters may be estimated by the drug's physicochemical properties. Clonidine's molecular weight (230 Daltons) is similar to clinically used opioids, and its lipid solubility (octanol:water partition coefficient = 114) is similar to methadone,[11] suggesting a similar clinical action.

Onset of action. Onset of action can often be predicted by absorption half-life and time to maximal concentration. Epidurally administered clonidine is rapidly absorbed into CSF, reaching peak concentrations within 32 min. These absorption times are similar to those reported in pigs,[20] and suggest an onset of action more similar to meperidine (T_{max} = 17 min in humans) than morphine (T_{max} = 75 min in humans).[9] Assuming clonidine reaches its site of action for analgesia by diffusion from CSF, one would expect a slight delay between peak CSF concentrations and peak analgesic effect. Indeed, in sheep 300 μg clonidine epidurally produces antinociception within 15 min, with peak analgesia at 45–60 min following injection.[2] Preliminary data in humans suggest that epidural clonidine injection produces analgesia within 30 min.[4–6]

Duration of action. Elimination half-life often correlates with duration of pharmacologic effect.[21] Clonidine elimination from CSF in sheep following epidural or intrathecal injection follows a similar time course to clonidine elimination from spinal cord tissue following intrathecal clonidine injection in rats[22] and clonidine elimination from CSF following epidural injection in humans.[7] These three species also exhibit similar durations of analgesia following intraspinal clonidine injection (4 h).[2,23] Comparison between clonidine elimination in sheep CSF and opiate elimination in human CSF is difficult due to variable results in the literature. For example, the elimination half-life in sheep CSF (49–64 min) is more similar to that in human CSF of meperidine than to that of morphine in one study,[10] and intermediate to those of diamorphine

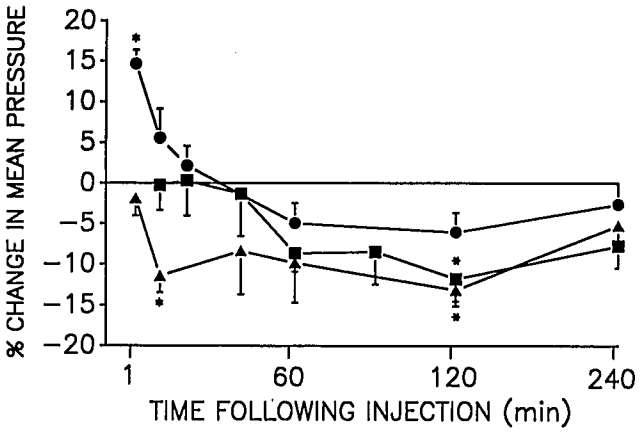

FIG. 3. Percent change in mean arterial pressure from baseline measurement following iv (●), epidural (■), or intrathecal (▲) clonidine administration at time zero. Each point represents mean ± SEM of six animals. *$P < 0.05$ *versus* baseline by Dunnett's test.

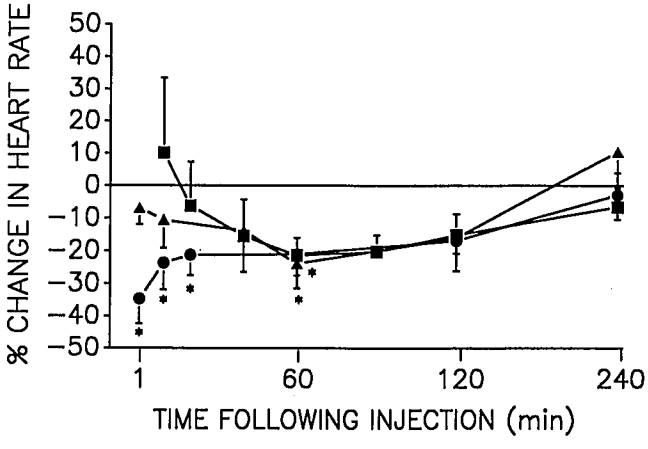

FIG. 4. Percent change in heart rate from baseline measurement following iv (●), epidural (■), or intrathecal (▲) clonidine administration at time zero. Each point represents the mean ± SEM of six animals. *$P < 0.05$ *versus* baseline by Dunnett's test.

and morphine in another.[24] The large variability reported in the clinical literature likely reflects study design limitations due to ethical and safety considerations. Although preliminary clinical studies of epidurally administered clonidine indicate a prolonged plasma half-life similar to that following oral administration (18 h),[25] other studies[5,6] suggest a duration of action for analgesia (3–6 h), which is similar to that of epidurally administered fentanyl and meperidine but briefer than that following morphine.[26] In this respect, clonidine is similar to methadone: brief analgesia following epidural administration despite a long plasma half-life.

Therapeutic concentrations. Clinically, CSF opioid concentrations more effectively predict degree of analgesia than do plasma concentrations following intraspinal opiate administration.[9–11] These CSF pharmacokinetic data in sheep, coupled with analgesia studies,[2] suggest that lumbar CSF clonidine concentrations need to exceed 200 ng/ml to produce analgesia in this species. Preliminary data suggest a similar CSF clonidine threshold for analgesia in humans.[6,7]

The dose of epidural clonidine required to produce analgesia in humans is unclear. Although preliminary experience in humans suggests 2–4 μg/kg is effective,[4,27] our experience in a dose-ranging study[6] and those of others[5,7] suggest that results in sheep more accurately predict the effective dose in humans (6–15 μg/kg). Because effective dose, and onset and duration of analgesia following epidurally administered clonidine are similar between sheep and humans, the CSF distribution and elimination profiles obtained in this study may be useful in predicting appropriate loading dose and infusion regimens for prolonged epidural clonidine analgesia.

Apparent drug potency *in vivo* is determined in part by physicochemical characteristics and the ability to reach its site of action. CSF bioavailability of epidurally administered clonidine in sheep (14 ± 2%) is considerably greater than that of other opioids in humans,[9] suggesting efficient dural transfer. Although it could be argued that direct transfer could occur along the intrathecal catheter path through the dura, we consider this unlikely. The dura was sutured around the catheter with no apparent CSF leak at the time of surgery, at no time was it possible to aspirate CSF from the epidural catheter, dural proliferation and fibrosis surrounding such catheters occurs in sheep, and the tips of both catheters were 3 cm from the site of dural penetration by the intrathecal catheter. That dural transfer of clonidine is also extensive in humans is supported by measurements of CSF clonidine[7] and by observations that effective analgesic doses of intrathecally and epidurally injected clonidine differ by less than a factor of three.[3,5,6]

Rostral redistribution. Clinically, the ability of intraspinally applied opioids to exert analgesic effects at dermatomal levels distant from the site of injection depends on lipid solubility. These data in sheep suggest that clonidine is quickly removed from CSF, making extensive dermatomal spread of analgesia unlikely.

Hemodynamics

Clonidine's effect on the circulation is complicated due to its action at several sites: brain stem, peripheral sympathetic nerves, spinal cord, myocardial conduction system, and peripheral vasculature. These data in sheep provide a pharmacokinetic explanation for clonidine's hemodynamic effects and a rationale for diminishing the likelihood of hypotension following clonidine injection.

Blood pressure. Following systemic administration, clonidine's net effect on blood pressure is a balance between a direct vasoconstrictor action on peripheral blood vessels[28] and a brain stem-mediated inhibition of sympathetic and enhancement of parasympathetic nervous system activity.[29] At plasma clonidine concentrations greater than approximately 2 ng/ml, as seen following clonidine overdose,[30] or initially following iv bolus,[31] the peripheral action predominates and a pressor response is observed.[32] Although not obtained at steady state, the data following iv clonidine suggest that the plasma clonidine threshold for a pressor response is similar in sheep and humans.

Epidural and intrathecal clonidine administration produce plasma concentrations similar to those following iv injection beyond the first 10–20 min, yet produce significantly different hemodynamic effects. This likely reflects a direct action of clonidine on the spinal cord, where it inhibits preganglionic sympathetic nerve activity,[33] decreasing sympathetic outflow and blood pressure. The observation that intrathecally injected clonidine decreases blood pressure quicker and longer than that following epidural injection, in addition to reinforcing this concept, suggests hemodynamic depression is less likely following epidural than intrathecal clonidine administration. Anecdotal reports suggest that this is true in humans.[3,6]

Because clonidine decreases blood pressure primarily by an action in the brain stem, one could argue that rostral spread of clonidine in CSF following intraspinal injection could produce delayed hypotension, analogous to delayed respiratory depression following intraspinally administered morphine. Although the time of maximal depression in blood pressure following intraspinal clonidine injection (2 h) is consistent with rostral CSF transport to brain stem levels in sheep,[12] there are several arguments against this hypothesis. First, this was the same time as maximal depression in blood pressure (although not statistically significant) following iv injection, which produced negligible CSF clonidine concentrations. Second, no delayed bradycardia occurred, as would be expected from high cisternal concentrations of clonidine. Third, the lipid sol-

ubility and rapid absorption and elimination of clonidine in CSF[7] argue against a residence time long enough for extensive rostral distribution. Fourth, blood pressure decrease at 2 h was not significantly greater following intrathecal than epidural injection, despite a greater CSF clonidine exposure following intrathecal injection. We[6] and others[4,5] have found no evidence of delayed hypotension following epidurally administered clonidine in humans.

Systemic absorption of clonidine is equally rapid and extensive following intrathecal and epidural injection, consistent with rapid and extensive dural transfer. Elimination of clonidine in sheep plasma ($t_{1/2}$el = 1.5–2 h) is not, however, a good predictor of elimination in human plasma following iv[34] (8 h) or epidural[25] (19 h) administration. Sheep may not be predictive of hemodynamic effects of prolonged epidural infusion because plasma accumulation would occur to a lesser extent than in the human.

Heart rate. Clonidine decreases heart rate by enhancing baseline vagal activity and baroreceptor reflexes, and by a direct action on the heart.[35] As such, clonidine decreases heart rate to the greatest extent following iv injection, likely due to the baroreflex response to its transient pressor effect and to a direct action on the heart as a result of high circulating clonidine concentrations. Clinically, epidural and iv clonidine administration produce mild, non–dose-dependent reductions in heart rate.[5,6,36]

Arterial blood gas tensions. Epidural or intrathecal clonidine injection does not produce respiratory depression, as measured by resting arterial P_{O_2}, consistent with previous reports.[3,5,6] Clonidine-induced hypoxemia in sheep is produced following activation of peripheral α_2-adrenoceptors, postulated to be located on platelets, by high circulating plasma clonidine concentrations.[37] There is no evidence that iv or epidural clonidine administration decreases arterial P_{O_2} in humans.

In summary, pharmacokinetic analysis of clonidine in sheep suggests that intraspinal injection will likely produce analgesia of rapid onset, brief duration, and limited dermatomal spread. Dural transfer of epidurally administered clonidine is more efficient than that of clinically used opioids. Epidural injection may decrease blood pressure less than that caused by intrathecal clonidine injection. These results agree with initial clinical experience with epidurally administered clonidine and provide a rationale for investigating the effects of epidural clonidine infusion.

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