

Epidural Clonidine Produces Antinociception, But Not Hypotension, In Sheep

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Intrathecaly administered clonidine produces analgesia, but also produces hypotension. To assess the effects of epidural administration, the authors inserted lumbar epidural catheters in seven non-pregnant ewes, and injected, on separate days, clonidine (50-750 mcg), morphine (5-10 mg), and a clonidine-morphine combination (clonidine 150 mcg + morphine 5 mg). Clonidine produced dose-dependent antinociception and sedation, with the lowest maximally effective antinociceptive dose being 300 mcg. Morphine produced less intense antinociception than clonidine, and did not potentiate clonidine's effect. Antinociception, but not sedation, following clonidine injection was reversed by epidural injection of the α_2 -adrenergic antagonist, idazoxan. Epidurally administered naloxone and prazosin did not reverse clonidine's antinociceptive effect, nor did intravenously administered idazoxan. Epidurally administered clonidine did not decrease blood pressure or heart rate or affect arterial blood gas tensions or spinal cord histology. These data suggest that epidurally administered clonidine produces analgesia by a local, α_2 -adrenergic mechanism. In sheep, epidurally administered clonidine does not produce hypotension. (Key words: Alpha-adrenergic receptor, agonist. Clonidine. Analgesia. Anesthesia, epidural. Pain. Receptors: alpha-adrenergic.)

DEMONSTRATION OF SPINAL opiate receptors has led clinically to epidural and intrathecal administration of opiates for analgesia.¹ However, pruritus, nausea, vomiting, delayed respiratory depression, development of tolerance, and, at high doses, hyperesthesia may also occur.^{1,2}

Non-opiate spinal pathways mediating analgesia also exist. For example, stimulation of brainstem neurons produces spinal release of norepinephrine accompanied by analgesia.³ Spinally administered clonidine, an α -adrenergic agonist, inhibits spinal substance P release⁴ and nociceptive neuron firing⁵ produced by noxious stimuli, and produces analgesia.⁶ In humans, intrathecaly administered clonidine does not produce pruritus, nausea, vomiting, or respiratory depression, and provides analgesia in

patients tolerant to intrathecaly administered opiates.⁷ However, sedation, hypotension, and bradycardia may occur.⁷ Epidural administration of clonidine has not been extensively examined. In this study, we examine the analgesic, hemodynamic, respiratory, and neurologic effects of epidurally administered clonidine, and define the location and subtype of receptor activated by it which produces analgesia.

Methods and Materials

This protocol was approved by the Animal Practices Committee. We studied seven nonpregnant adult ewes, having a mean weight of 45 kg. After a 24-h fast, animals were sedated with sodium pentobarbital (4 mg/kg, iv) and ketamine (4 mg/kg, iv) and placed in the left lateral position. Following subcutaneous infiltration with 1% lidocaine, we inserted a #16 Hythe needle into the epidural space at the interspace between the last lumbar and first sacral vertebrae using the loss of resistance technique. A single port PortexTM catheter was threaded no more than 5 cm in the epidural space. The needle was then withdrawn, and the catheter was sutured to the skin. We injected 6 ml 2% lidocaine through the epidural catheter, and, after demonstration of segmental analgesia extending to at least T8 bilaterally, cannulated both femoral arteries for measurement of arterial pressure and arterial blood gas tensions and a femoral vein for drug administration. All animals rested at least 24 h following surgery. Epidural catheter location was tested every 5-7 days by injection of 6 ml 1% lidocaine and demonstration of segmental analgesia to at least T8 bilaterally.

DRUGS AND INJECTION PROTOCOL

On the day of the experiment, we placed the ewes in a quiet room and monitored arterial pressure using a Beckman dynograph. Following a 15-30-min period of stable baseline measurement, we injected the test drug. All injections were given in volumes of 10 ml over a period of 2 min, followed by saline flush to clear the catheters (0.5 ml for epidural injection, 2 ml for intravenous injection). Heart rate, arterial blood pressure, arterial blood gas tensions, and antinociception were measured during the control period, and 15, 30, 45, 60, 90, 120, 180, 240, 360, and 480 min following epidural injections. We measured antinociception using a GrassTM SD-9 stimulator connected to two surface ECG electrodes applied to a shaved and cleaned area on the flank. The inter-electrode

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distance was fixed at 8 cm. During testing, we increased the stimulator voltage (0–4 mA, 0–110 V, DC) until a clear avoidance response was obtained.

To determine dose response curves, we injected saline, clonidine (50, 150, 300, 750 mcg), morphine (5, 10 mg), and a clonidine-morphine combination (clonidine 150 mcg + morphine 5 mg) epidurally into the seven ewes. Injections were given in a random, blinded manner, with a minimum of 24 h between injections.

To assess the receptor subtype involved in the antinociceptive effect of clonidine, 300 mcg of clonidine was injected epidurally into four ewes, followed in 30 min by epidural injection of an antagonist. We used the α_2 -adrenergic antagonist idazoxan (30 mcg), the α_1 -adrenergic antagonist prazosin (1 mg), and the opiate antagonist naloxone (1 mg). The dose of idazoxan was the smallest effective reversal dose determined in pilot experiments. The doses of prazosin and naloxone were 50 and 10 times, respectively, the intrathecal doses required to reverse analgesia produced by intrathecally injected α_1 -adrenergic and opiate agonists.^{6,8} In control studies, we examined the effects of the antagonists administered epidurally alone and the effects of epidural injection of an equal volume of saline or 20% dimethylsulfoxide (DMSO)-saline.

To assess the site of action of epidurally administered clonidine, we injected clonidine, followed in 30 min by intravenous injection of idazoxan. The dose of idazoxan used was the effective reversal dose when administered epidurally. We also assessed the site of antinociception by injecting saline and clonidine (300, 750 mcg) intravenously in four ewes, and measuring antinociception for 4 h following injection.

All drugs are expressed as salts. The following drugs were generous gifts: clonidine HCL (Ms. Heidi Reidies-Esche, Boehringer-Ingelheim, Ridgefield, CT), idazoxan HCL (John C. Doxey, Ph.D., Reckitt-Colman, Kingston-Upon-Hull, England), morphine HCL (Duramorph[®], Ann Board, M.D., AH Robins, Richmond, VA), and prazosin HCL (Mr. Nathan Belcher, Pfizer, Groton, CT). We also used lidocaine HCL (1% and 2%, Astra, Westborough, MA) and naloxone HCL and yohimbine (Sigma, St. Louis, MO). Prazosin was dissolved in DMSO (20% v/v) in saline. Other drugs were dissolved in saline.

PATHOLOGY

Following completion of the study, we examined spinal cord histology in four of the ewes. Following sacrifice, we injected the epidural catheter with methylene blue, performed a dorsal lumbar laminectomy and removed portions of the lumbosacral cord with dura and epidural catheter intact. Specimens were fixed in formalin and catheters removed. Transverse sections were cut, stained with hematoxylin and eosin, and examined by a neuropathologist.

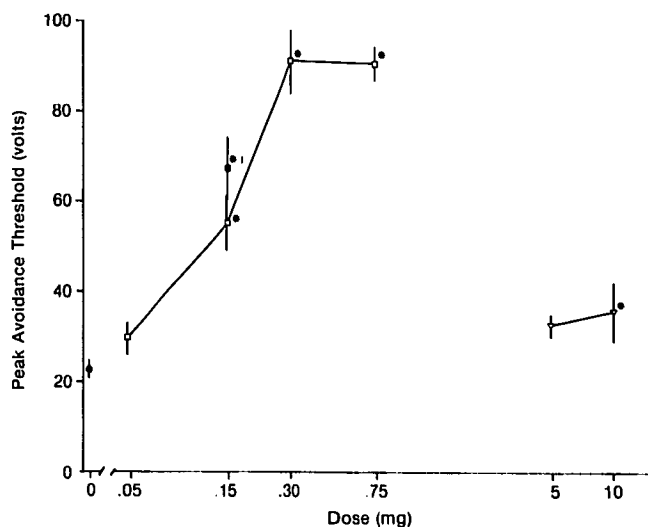


FIG. 1. Log dose-response curves of the nociceptive responses on electrical stimulus test after epidural administration of saline (●), clonidine (□), and morphine (▽). The ■ (■) indicates the effect produced by epidural administration of 5 mg morphine + 150 mcg clonidine. Each point represents the mean \pm SEM of 7 animals. * $P < 0.05$ compared to saline control; †Not significantly different from 150 mcg clonidine alone.

STATISTICS

Data are presented as means \pm SEM. We tested the dose-response curves for statistical significance using a repeated measures one way analysis of variance followed by the Newman-Keuls test. For drug effect versus time curves, we used a repeated measures two-way analysis of variance to test for a dose-related effect and one-way analysis of variance followed by Dunnett's multiple range test to demonstrate the effective duration for each dose. We used Student's *t* test for independent samples to compare the effect of epidural clonidine alone with clonidine plus morphine. We considered $P < 0.05$ significant.

Results

ANTINOCICEPTION

The avoidance threshold prior to drug injection remained constant from day to day, and was unaffected by saline injection. Epidural catheters were inserted percutaneously without difficulty and remained patent throughout the 3–5-week study period, with no loss of effectiveness of injected drug (analgesics or local anesthetic) over time.

Epidurally administered clonidine was more potent than morphine in producing antinociception, and was not potentiated by the addition of 5 mg of morphine (fig. 1). Figure 2 shows the time course of antinociception produced by epidural and intravenous clonidine injection.

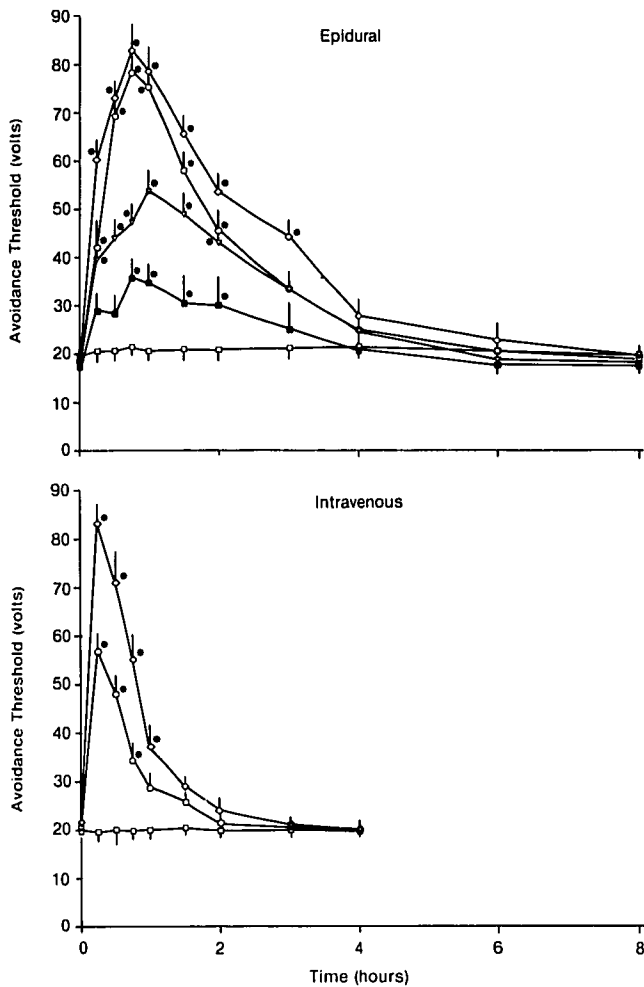


FIG. 2. Time course of the nociceptive responses on electrical stimulus test after epidural (*top*) or intravenous (*bottom*) injection of saline (\square) or clonidine, 50 mcg (\blacksquare), 150 mcg (∇), 300 mcg (\circ), or 750 mcg (\diamond). Each point represents the mean \pm SEM of four to seven animals. * $P < 0.05$ compared to control.

Epidurally administered clonidine produced a dose-dependent increase in intensity of antinociception, up to 300 mcg. Increasing the dose further to 750 mcg increased the duration, but not the intensity of antinociception. Intravenous injection of clonidine produced antinociception of similar intensity, but shorter duration, than that following epidural injection. Clonidine, in doses greater than 150 mcg by either route, produced behavioral sedation, whereas morphine did not.

Only the α_2 -adrenergic antagonist idazoxan, given epidurally, reversed antinociception produced by epidural clonidine injection (fig. 3). Despite the rapid reversal of antinociception, ewes remained sedated following idazoxan injection. Intravenous injection of idazoxan did not reverse antinociception or sedation produced by epidurally administered clonidine. In control experiments, avoidance threshold was unaffected by epidurally admin-

istered antagonists or equal volumes of saline or 20% DMSO-saline.

HEMODYNAMIC AND RESPIRATORY EFFECTS

Epidurally administered clonidine did not decrease blood pressure at any dose, and increased blood pressure following the 750 mcg dose (fig. 4). It did not affect heart rate or arterial blood gas tensions. In the four animals receiving intravenous clonidine, we noted mild hypoxemia. Epidurally administered morphine did not affect blood pressure, heart rate, or arterial blood gas tensions.

PATHOLOGY

We examined spinal cord histology in four ewes who received a total dose of 2.0–2.8 mg clonidine epidurally and had epidural catheters in place for 20–32 days. Although we observed a sheath surrounding the epidural catheter at laminectomy, in no instance was the catheter obstructed, and methylene blue spread freely in the epidural space. In all sections examined by light microscopy, we observed a fibrotic sheath surrounding the catheter tract and a diffuse granulomatous reaction in the dorsal epidural space (fig. 5). Other than one instance of mild deformation of the cord with local demyelination at the point of contact of the catheter and dura with the cord, we observed no leptomeningeal or cord inflammation or histological damage.

Discussion

In this study, we describe epidural catheterization and nociceptive testing in sheep, and use these methods to

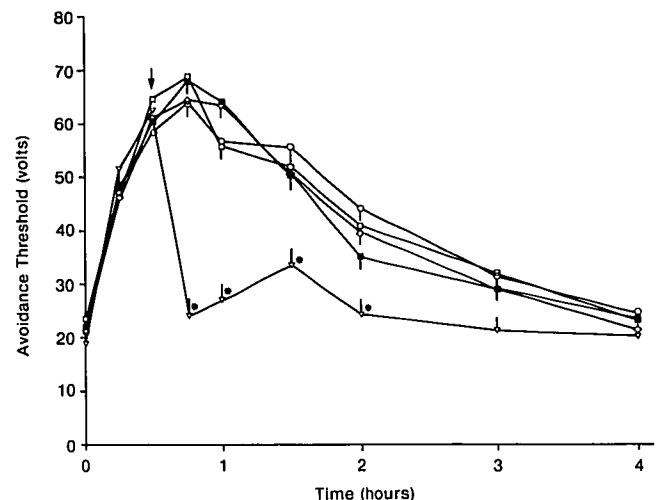


FIG. 3. Time course of the nociceptive responses on electrical stimulus test after epidurally administered clonidine (300 mcg) at time 0 followed by the epidural injection at the arrow of saline (\square), DMSO (20%)-saline (\blacksquare), idazoxan (∇), prazosin (\diamond), or naloxone (\circ). Each point represents the mean \pm SEM of four animals. * $P < 0.05$ compared to saline control.

characterize analgesic and other effects produced by epidurally administered clonidine.

EPIDURAL CATHETERIZATION AND NOCICEPTIVE TESTING

In certain animal species, epidural drug studies are difficult to perform for two reasons: difficulty in epidural catheter insertion, and obstruction of inserted catheters. Epidural catheterization in dogs,⁹ cats,¹⁰ and rats¹¹ requires surgical exposure. In contrast, epidural catheters were easily inserted percutaneously in all sheep in this study. In rats, epidural catheterization for 10 days results in intense fibrosis surrounding the catheter, limited access of injected solution to the epidural space, and diminution in injected drug effect.¹¹ Although an inflammatory reaction to the epidural catheter occurred in the sheep in this study, all catheters remained effective throughout the 3–5-week duration of the study.

The method of nociceptive testing we devised fulfills the general criteria of an effective pain model as described by Kamerling *et al.*¹² Specifically, the end point to the test was clear, stable over time, and reproducible within subjects; the pain stimulus was administered repeatedly without producing significant tissue damage; and the pain model was sufficiently sensitive to detect a dose-related effect independent of the sedation caused by the medication.

EPIDURAL CLONIDINE ANALGESIA

Both α_1 - and α_2 -adrenergic receptors are present in the spinal cord dorsal horn,^{13,14} and both α_1 - and α_2 -adrenergic agonists produce analgesia when given intrathecally.¹⁵ Since clonidine is a nonspecific α -adrenergic agonist at high doses,¹⁶ it could produce analgesia by an α_1 - or α_2 -adrenergic mechanism. Since α_2 -, but not α_1 -adrenergic antagonists are preferentially effective in reversing antinociception produced by intrathecal clonidine injection in rats,⁸ and epidural clonidine injection in sheep, clonidine probably produces analgesia by an α_2 -adrenergic mechanism.

The above conclusion assumes that prazosin achieved adequate concentrations spinally to block α_1 -adrenergic receptors. The dose of prazosin used was 33 times the effective idazoxan dose, although idazoxan and prazosin are equipotent at their respective receptors.¹⁷ A nonspecific effect of DMSO obscuring prazosin's effect is unlikely, since the DMSO solution alone did not affect avoidance threshold. Likewise, altered distribution of prazosin due to DMSO is unlikely, since the potency of centrally administered α -adrenergic antagonists is unaltered by their administration in DMSO solutions.¹⁸

α_2 -adrenergic agonists exert opposing actions on pain threshold depending on their site of injection: in the spinal

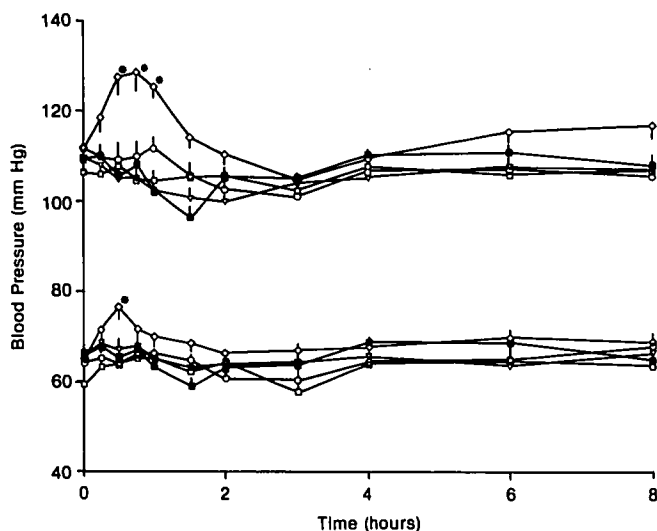


FIG. 4. Systolic and diastolic arterial pressure following the epidural injection of saline (\square), or clonidine, 50 mcg (\blacksquare), 150 mcg (∇), 300 mcg (\circ), or 750 mcg (\diamond). Each point represents the mean \pm SEM of six to seven animals. * $P < 0.05$ compared to control.

cord¹⁵ and in the peritoneal cavity,¹⁹ they raise pain threshold; whereas, in the brainstem, they lower it.²⁰ In humans, intravenous injection of 100 mcg of clonidine produces analgesia, whereas a larger dose (200 mcg) produces analgesia.²¹ In sheep, intravenous injection in the dose range studied (300–750 mcg) also produces analgesia. In humans, intrathecal⁷ and epidural²² injection produce analgesia. In sheep, epidural injection of clonidine produces analgesia by a local (spinal) action. Sedation, on the other hand, is produced by an action of clonidine at central sites,²³ and is not reversed in sheep by the small dose of α_2 -adrenergic antagonist administered epidurally.

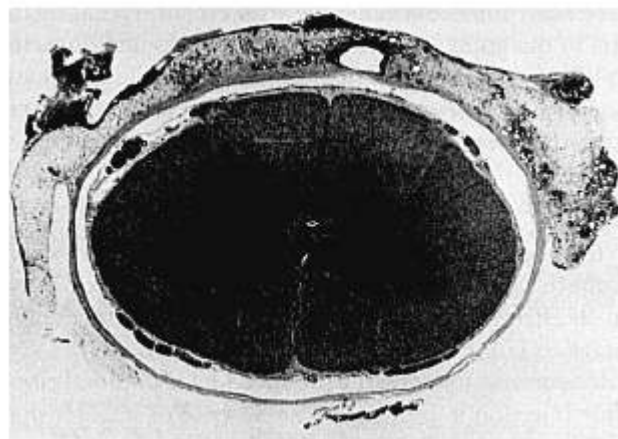


FIG. 5. Histologic section of the lumbar spinal column in a ewe that had received 2.8 mg of clonidine epidurally. There is a proliferation of dural connective tissue surrounding the catheter tract and a diffuse inflammatory response in the dorsal epidural space.

Following intravenous injection, lipid soluble drugs are initially concentrated in, then redistributed away from neural tissue, producing a brief but intense effect. This may explain the equivalent analgesic potency following intravenous compared to epidural or intrathecal injection of sufentanil in rats,²⁴ alfentanil in cats,²⁵ and clonidine in sheep. However, epidural or intrathecal injection provide a local depot of drug and produce analgesia of longer duration than intravenous injection of alfentanil in cats²⁵ and clonidine in sheep.

The relative potencies of α_2 -adrenergic and opiate agonists depend on the route of administration. In humans, clonidine is 10–20 times more potent than morphine in relieving pain following intrathecal injection.⁷ Since clonidine is more lipophilic than morphine,²⁶ and presumably more efficiently transferred across the dura, this potency ratio increases to 33 following epidural administration.²² Species differences are also important; the clonidine:morphine potency ratio following intrathecal administration varies from 0.5 in monkeys⁶ to 10–20 in humans,⁷ and following epidural administration from 33 in humans²² to 200 sheep. Although morphine was relatively ineffective in producing antinociception in sheep, the magnitude of the response we observed is similar to that reported by DiFazio using the same preparation and similar testing procedures.¹

Other studies have shown that clonidine and morphine act synergistically to produce analgesia after intrathecal injection in monkeys,⁶ but not intraperitoneal injection in rats.¹⁹ Peripherally, opiate and α_2 -adrenergic receptors are located postsynaptically on the same neurons, and do not have additive effects.²⁷ In contrast, spinal opiate receptors are primarily pre-synaptic,¹ and may, therefore, be synergistic with the post-synaptic α_2 -adrenergic receptors⁸ in inhibiting transmission from sensory afferents. Possible explanations for the absence of synergism between morphine and clonidine after epidural administration in this study include inadequate morphine dose, inability of morphine to cross the sheep dura in adequate amounts, or species differences in spinal adrenergic and opiate pain modulating systems.

HEMODYNAMIC, RESPIRATORY, AND OTHER EFFECTS

In sheep, epidural clonidine administration does not produce hypotension. At a dose $2\frac{1}{2}$ times the lowest maximally effective analgesic epidural dose, clonidine actually increases blood pressure. This is in contrast to the hypotension and bradycardia produced by intrathecal clonidine injection in humans.⁷ The absence of hypotension in this study may in part be due to the decreased hypo-

tensive effect of clonidine in non-hypertensive subjects.²⁸ Alternatively, we may have had an inadequate sample size to detect significant changes in blood pressure. However, power analysis showed an 80% probability of detecting a sustained reduction in blood pressure of at least 15%.

The effect of α_2 -adrenergic agonists on blood pressure depends on their lipophilicity and plasma concentration. Intrathecally administered clonidine produces hypotension by two mechanisms: redistribution to brainstem sites of action,²⁹ and direct spinal inhibition of preganglionic sympathetic outflow.³⁰ Systematically administered lipid soluble drugs, such as clonidine and guanfacine, produce hypotension by actions in the brainstem.³¹ This action is antagonized, at plasma concentrations above 1.5 and 15 ng/ml respectively,^{28,32,33} by peripheral vasoconstriction.³⁴ For this reason, no change or an increase in blood pressure may occur following intravenous³⁵ or, in high doses, intrathecal⁷ administration of clonidine. We postulate that plasma clonidine concentrations were sufficiently high and sustained following epidural administration to trigger peripheral vasoconstriction, thus preventing any hypotensive effect at central sites.

In sheep, epidurally administered clonidine does not produce side effects which occur with other spinally administered analgesics. Unlike intrathecally administered α_1 -adrenergic agonists,¹⁵ clonidine does not produce gross weakness or excitatory motor effects. Unlike epidurally administered opiates,¹ clonidine does not produce delayed respiratory depression.

PATHOLOGY

Neurotoxicity following spinally administered clonidine has not been observed. Intrathecally administered clonidine does not affect spinal cord histology in dogs,³⁶ motor tone, reflex function, or proprioception in monkeys,⁶ or neurological status or somatosensory evoked potentials in humans. ** Epidurally administered clonidine does not affect spinal cord histology in dogs³⁶ or sheep.^{††} In this study, epidurally administered clonidine produced no evidence of spinal cord damage in sheep, as assessed by light microscopy.

In conclusion, chronic epidural catheterization and analgesia studies are feasible in sheep. Epidurally administered clonidine produces antinociception in sheep by a local, α_2 -adrenergic mechanism. In doses up to the lowest maximally effective analgesic dose, epidural clonidine does not decrease blood pressure or heart rate, and has no

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effect on arterial blood gas tensions or spinal cord histology. Controlled clinical trials of epidural clonidine for analgesia are warranted.

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