Epidural Clonidine Does Not Decrease Blood Pressure or Spinal Cord Blood Flow in Awake Sheep

James C. Eisenach, M.D.,* Stephen C. Grice, M.D.†

Preliminary data in animals and humans suggest that epidurally administered clonidine produces antinociception and is not neurotoxic. However, clonidine can produce vasoconstriction, and epidurally administered clonidine decreases spinal cord blood flow in anesthetized pigs. To examine the effect of epidurally administered clonidine on spinal cord blood flow in awake animals, the authors inserted lumbar epidural, femoral arterial and venous, pulmonary arterial, and left ventricular catheters in 13 adult sheep. Following a 24-h recovery, the authors injected saline (N = 6) or clonidine, 750 μg (17–25 μg/kg; N = 7) epidurally, and measured arterial blood gas tensions; temperature; heart rate; systemic and pulmonary arterial, right atrial, and pulmonary capillary wedge pressures; and spinal cord and renal blood flows (by radioactive microsphere injection) before and at 45 min and 4 h following injection. Epidural saline injection did not affect measured variables. Heart rate decreased from 112 ± 9 to 86 ± 4 beats/min (mean ± SE; P = .003) and arterial PCO2 decreased from 99 ± 3 to 78 ± 6 mmHg (P = .04) 45 min following clonidine injection. Temperature increased from 39.1 ± 2 to 40.6 ± 1 °C (P = .0001) 4 h following clonidine injection. Epidural clonidine administration did not affect cardiac output, pulmonary and systemic pressures, or renal or spinal cord blood flows, except for an increase in mid-thoracic spinal cord blood flow 45 min following injection. The authors conclude that, in sheep, epidural clonidine does not produce dangerous cardiovascular depression or global spinal cord ischemia. (Key words: Anesthesia: epidural. Receptors: alpha-adrenergic. Spinal cord: blood supply; drug effects. Sympathetic nervous system, alpha receptor agonist: clonidine.)

Epidural and intrathecal administration of clonidine produce profound antinociception in animals and humans by a nonopiate, α2-adrenergic action in the spinal cord dorsal horn. Unlike epidural or intrathecal administration of local anesthetics, clonidine does not produce proprioception or motor blockade. Unlike epidural or intrathecal administration of opioids, clonidine does not produce nausea, pruritus, or respiratory depression. Epidural administration of clonidine is less likely to produce hypotension than intrathecal administration, making epidural the preferred route of administration.

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Initial safety assessment of a drug such as clonidine for epidural or intrathecal use should include studies of neurotoxicity and effects on spinal cord blood flow. Epidural and intrathecal administration of clonidine do not produce changes in behavior or spinal cord histology in rats, dogs, sheep, or monkeys. However, clonidine constricts central nervous system arteries in vitro, and epidurally administered clonidine decreases spinal cord blood flow in pigs, accompanied by bradycardia and decreased cardiac output. These data suggest that, although epidurally administered clonidine is not directly neurotoxic, it may, in situations where spinal cord blood flow is compromised (hypotension, compression of spinal cord by epidural hematoma, loss of autoregulation following spinal anesthesia), further decrease blood flow and produce spinal cord ischemia. The effect of epidurally administered clonidine on spinal cord blood flow has been measured only in anesthetized animals, and anesthesia can alter the regional blood flow and hemodynamic effects of drugs. To more closely approximate the eventual clinical use of clonidine, we studied the hemodynamic and spinal cord blood flow effects of epidurally administered clonidine in awake sheep.

Methods and Materials

The Animal Care Committee approved the protocol. We studied 13 adult nonpregnant ewes of mixed Western breeds (30–45 kg). Following a 24-h fast, atropine 0.03 mg/kg, iv, was injected, and anesthesia was induced with 12–16 mg/kg ketamine HCl, iv. Following endotracheal intubation, anesthesia was maintained with halothane 0.5–1.5% in oxygen. After subcutaneous infiltration with 1% lidocaine, a #16 Hythe needle was inserted into the epidural space at the interspace between the last lumbar and first sacral vertebrae using the loss-of-resistance technique. A single port Portex™ catheter was threaded no more than 5 cm in the epidural space, the needle withdrawn, and the catheter sutured to the skin. Polyvinyl catheters were inserted into both femoral arteries for measurement of arterial pressure, arterial blood gas analysis, and reference sampling during microsphere injection, and into a femoral vein for drug administration. Finally, catheters were inserted into a pulmonary artery via an internal jugular vein and into an internal carotid artery (7 Fr. pigtail) under direct vision, and advanced until pulmonary cap-
illary wedge or left ventricular pressure tracings, respectively, were obtained. Epidural catheter location was confirmed following surgery by injecting 6 ml 1% lidocaine and demonstrating segmental analgesia to at least T12 bilaterally. All animals were allowed a 24-h recovery period before the experimental procedure.

**Experimental Protocol**

On the day of the experiment, the ewe, standing in a portable metabolic cage, was placed in a quiet room, the femoral arterial catheter connected to a Gould pressure transducer (model P231ID), and arterial blood pressure and heart rate recorded using a Grass™model 7D polygraph recorder. Following 15 min of stable baseline recordings, each ewe received either 10 ml preservative-free saline (N = 6) or 10 ml saline containing 750 μg clonidine (17–25 μg/kg; N = 7) epidurally over a 2-min period. Cardiac output (by thermodilution), systemic and pulmonary arterial, right atrial, and pulmonary capillary wedge pressures, and pulmonary artery temperature were measured, and arterial blood samples were obtained before and 45 min and 4 h following epidural injection. Blood samples were analyzed for arterial PO₂, PCO₂, and PH using a Radiometer BMS blood microanalysis system.

To determine spinal cord blood flow, 2–6 × 10⁶ presonicated microspheres (15 μm in diameter) labeled with ¹⁵³Gd, ⁸⁵Sr, ⁴⁶Sc, or ¹¹¹Sn were injected through the left ventricular catheter and 45 min and 4 h following epidural catheter injection. Prior to microsphere injection reference sampling from the femoral artery was begun at a constant rate of 7 ml·min⁻¹ and collected into four test tubes, each containing 1 min of sampling. In all cases, the fourth minute's sample was free of radioactivity. Two different isotopically labeled microspheres were injected simultaneously in one animal to document similar mixing of microspheres in blood.

Following completion of the study, the animals were killed by heavy sedation with intravenous sodium pentobarbital followed by intravenous KCl. Methylene blue was injected through the epidural catheter, a dorsal lumbar laminectomy was performed, and, following confirmation of epidural catheter placement (by direct vision and diffuse spread of methylene blue in the epidural space), sections of spinal cord were removed. The spinal cord was separated into three 10-cm sections, approximately representing segments T6–T10, T10–L2, and L2–S1, for blood flow determinations. Finally, cortical portions of both kidneys were removed for renal blood flow determination to document adequate mixing of microspheres in blood.

Arterial blood reference and tissue samples were placed in tared counting tubes, weighed, and analyzed for radioactivity in an LKB 1282 CompuGamma® gamma counter, making appropriate corrections for energy overlap between isotopes.

**Calculations**

Spinal cord and renal blood flow were determined by: 
\[ Q_c = \left( \frac{100 \times Q_r \times C_r}{C_c} \right) / G_r \] where \( Q_r \) = reference sample blood flow (ml/min), and \( C_c \) and \( C_r \) = radioactivity in the tissue and reference samples, respectively. Blood flow is represented in ml·min⁻¹·100 g⁻¹ tissue.

**Statistical Analysis**

All data are expressed as the mean ± SEM. Data following epidural injections were compared to baseline using a one-way analysis of variance for repeated measures followed by Newman-Keuls analysis. Data following epidural clonidine were compared to the saline control by a Wilcoxon two-sample test for baseline measures followed by an analysis of covariance, with the baseline measure as the covariate. In each case, there was no significant group·baseline interaction. Statistical difference was considered present at \( P < 0.05 \).

**Drugs**

The following drugs were utilized in this study: atropine (Elkin-Sinn, Inc., Cherry Hill, NJ), ketamine HCl and sodium pentobarbitol (Barber Veterinary Supply Co., Richmond, VA), and lidocaine HCl (1% and 2%, Astra Pharmaceuticals, Westborough, MA). Clonidine HCl was a generous gift from Ms. Heidi Riedes-Esche (Boehringer Ingelheim, Ltd., Ridgefield, CT). Clonidine was prepared in 0.9% preservative-free saline.

**Results**

**Hemodynamic Effects**

Epidural saline injection did not significantly affect any of the parameters measured (table 1). When compared to saline injection or pre-injection values, epidural clonidine injection significantly decreased heart rate and arterial PO₂, and increased temperature (table 2).

**Regional Blood Flow**

All tissue samples contained >400 microspheres. Blood flows to both right and left kidneys were similar (table 3), and blood flows obtained by separate analysis of the two different isotopically labeled microspheres injected simultaneously differed by <4%.
**EPIDURAL CLONIDINE**

### TABLE 1. Hemodynamic and Respiratory Variables Following Epidural Saline Injection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>45 Min</th>
<th>4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>108 ± 8</td>
<td>133 ± 13</td>
<td>110 ± 6</td>
</tr>
<tr>
<td>Cardiac output (/min)</td>
<td>5.6 ± 0.5</td>
<td>5.0 ± 0.4</td>
<td>5.8 ± 0.4</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>101 ± 4.4</td>
<td>96 ± 4.6</td>
<td>96 ± 4.0</td>
</tr>
<tr>
<td>Right atrial pressure (mmHg)</td>
<td>2 ± 1.3</td>
<td>6.2 ± 2.0</td>
<td>4 ± 1.9</td>
</tr>
<tr>
<td>Systemic vascular resistance (mmHg · min · 1⁻¹)</td>
<td>19 ± 2.4</td>
<td>17 ± 1.7</td>
<td>16 ± 1.7</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mmHg)</td>
<td>22 ± 2.7</td>
<td>20 ± 1.7</td>
<td>20 ± 5.2</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mmHg)</td>
<td>8 ± 1.9</td>
<td>11 ± 1.5</td>
<td>6 ± 1.9</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (mmHg · min · 1⁻¹)</td>
<td>2.5 ± 0.6</td>
<td>2.0 ± 0.5</td>
<td>2.6 ± 0.7</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>38.8 ± 0.1</td>
<td>39.5 ± 0.2</td>
<td>38.7 ± 0.1</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.54 ± 0.02</td>
<td>7.54 ± 0.02</td>
<td>7.56 ± 0.02</td>
</tr>
<tr>
<td>$P_{CO_2}$ (mmHg)</td>
<td>31 ± 2.4</td>
<td>31 ± 1.4</td>
<td>31 ± 1.5</td>
</tr>
<tr>
<td>$P_{O_2}$ (mmHg)</td>
<td>95 ± 4.7</td>
<td>92 ± 3.5</td>
<td>95 ± 2.8</td>
</tr>
</tbody>
</table>

No significant difference from baseline by analysis of variance.

Blood flow prior to epidural injection was higher in the lumbar spinal cord than in the thoracic cord ($P = .002$; table 3). The tip of the epidural catheter was located overlying the lumbar segment. Neither epidural saline nor epidural clonidine injection decreased spinal cord blood flow at any segment (table 3). Mid-thoracic spinal cord blood flow increased 45 min following epidural injection in both groups, although the increase was significant only in the clonidine group ($P = .04$; table 3). Neither epidural saline nor clonidine injection increased spinal cord or renal vascular resistance (data not shown).

**Discussion**

Drug toxicity may be examined by injecting clinically used doses in a large number of animals, or, more commonly, by injecting larger doses in a small number of animals. We chose the latter method, using a dose (750 μg) which is 2.5 times the maximal antinociceptive dose in sheep, and is over two times the effective analgesic dose (150–300 μg) in humans. We did not measure antinociception in this study, as such testing produces excitement and movement, which could affect hemodynamic parameters and regional spinal cord metabolism and flow.

**Experimental Design**

Data following epidural clonidine in this study were compared to two sets of controls. First, each animal served as its own control, thereby enhancing statistical sensitivity. Second, animals receiving epidural clonidine were compared to those receiving epidural saline, to control for possible effects of microsphere injection itself on hemodynamics and regional blood flow. In this study, injection of a total of 6–15 × 10⁶ 15-μm microspheres did not alter measured parameters in the saline control sheep.

The microsphere method of measuring regional blood flow used was validated by demonstrating adequate numbers of microspheres/sample, similar mixing of microspheres (by simultaneous injection of two sets of microspheres), and adequate mixing of microspheres and blood (by similar right and left renal blood flows). Our results agree with previous work in awake sheep.

### TABLE 2. Hemodynamic and Respiratory Variables Following Epidural Clonidine Injection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>45 Min</th>
<th>4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>112 ± 9</td>
<td>86 ± 4*†</td>
<td>89 ± 9</td>
</tr>
<tr>
<td>Cardiac output (/min)</td>
<td>6.2 ± 0.4</td>
<td>5.3 ± 0.5</td>
<td>5.4 ± 0.6</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>98 ± 4.0</td>
<td>90 ± 6.6</td>
<td>90 ± 3.9</td>
</tr>
<tr>
<td>Right atrial pressure (mmHg)</td>
<td>2 ± 2.6</td>
<td>8 ± 2.6</td>
<td>3 ± 1.2</td>
</tr>
<tr>
<td>Systemic vascular resistance (mmHg · min · 1⁻¹)</td>
<td>15 ± 1.2</td>
<td>16 ± 1.7</td>
<td>18 ± 8.1</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mmHg)</td>
<td>18 ± 3.1</td>
<td>22 ± 2.0</td>
<td>14 ± 1.6</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mmHg)</td>
<td>8.2 ± 1.8</td>
<td>11 ± 1.9</td>
<td>7 ± 1.4</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (mmHg · min · 1⁻¹)</td>
<td>1.6 ± 0.5</td>
<td>1.9 ± 0.3</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>39.1 ± 0.2</td>
<td>40.1 ± 0.2</td>
<td>40.6 ± 0.1</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.49 ± 0.03</td>
<td>7.50 ± 0.01</td>
<td>7.59 ± 0.01</td>
</tr>
<tr>
<td>$P_{CO_2}$ (mmHg)</td>
<td>35 ± 1.6</td>
<td>34 ± 1.8</td>
<td>34 ± 0.0</td>
</tr>
<tr>
<td>$P_{O_2}$ (mmHg)</td>
<td>99 ± 3.0</td>
<td>78 ± 6.1*</td>
<td>85 ± 3.1</td>
</tr>
</tbody>
</table>

* $p < .05$ vs. baseline by analysis of variance.  † $P < .05$ vs. saline control by analysis of covariance.
showing adequate mixing of microspheres and blood following left ventricular injection, and similar baseline spinal cord blood flows.\textsuperscript{15}

**Hemodynamic and Systemic Effects**

In this study, epidurally administered clonidine did not affect blood pressure or cardiac output, although it did decrease heart rate. Clonidine's effect on blood pressure depends on the dose and route of administration. Clonidine decreases blood pressure, primarily by actions at brainstem\textsuperscript{16} and spinal cord\textsuperscript{17} sites, and increases blood pressure by peripheral vasconstriction.\textsuperscript{18} Intrathecal injection of clonidine decreases blood pressure more than epidural injection,\textsuperscript{13,15} perhaps due to higher spinal and lower peripheral clonidine concentrations following intrathecal injection.

Clonidine's effect on cardiac output is altered by the baseline hemodynamic state. Intravenous injection of clonidine decreases cardiac output 30–40\% in patients with initially high cardiac outputs (>6 l/min),\textsuperscript{19} but improves cardiac performance in patients with severe hypotension, possibly by decreasing afterload.\textsuperscript{20} In normal individuals, clonidine decreases cardiac output by a small and variable amount (10–20\%).\textsuperscript{19,21} The effect of \( \alpha \)-adrenergic agonists on cardiac output can also be altered by anesthesia: cardiac output decreases more in anesthetized\textsuperscript{22} than awake\textsuperscript{23} animals. Effects of anesthesia may explain why epidurally administered clonidine decreases cardiac output by 27\% in anesthetized pigs\textsuperscript{12} and by 21\% in anesthetized dogs,\textsuperscript{24} but does not decrease cardiac output in awake sheep.

Intravenous administration of clonidine (15 µg/kg) decreases arterial \( P_{O_2} \) from a resting value of 91 ± 4 mmHg to 50 ± 3 mmHg in awake sheep, without affecting arterial \( P_{CO_2} \) or blood pressure.\textsuperscript{25} Although the etiology of this effect is not known, platelet activation and pulmonary microembolism have been suggested.\textsuperscript{25} Arterial \( P_{O_2} \) decreased significantly following epidural clonidine injection in this study, suggesting that, until more is known, arterial oxygenation should be monitored in patients receiving epidural clonidine.

Increases in temperature in our unshorn sheep in a 25°C environment following epidural clonidine may be explained by clonidine's effect on central \( \alpha_2 \)-adrenergceptors. Such receptors are important in thermoregulatory control and temperature homeostasis in sheep, goats, and humans.\textsuperscript{26,27} Alteration of thermoregulation by epidurally administered clonidine is not observed in reports in anesthetized animals, because temperature is controlled externally.\textsuperscript{12,24}

**Effect on Spinal Cord Blood Flow**

Clonidine's effect on vascular tone depends on the species and vascular bed studied. *In vitro* studies reveal that the ratio of postsynaptic \( \alpha_1/\alpha_2 \)-adrenergceptors varies widely between veins and arteries,\textsuperscript{29} among arterioles from different vascular beds in the same species,\textsuperscript{11} and among arteries from the same vascular beds in different species.\textsuperscript{29} For example, \( \alpha_2 \)-adrenoceptor stimulation constricts cerebral arteries of dogs,\textsuperscript{11} cats,\textsuperscript{30} and pigs,\textsuperscript{31} but not monkeys\textsuperscript{29} or baboons.\textsuperscript{32} The importance of \( \alpha_2 \)-adrenergceptors in regulating sheep or human central nervous system arterial tone is not known. Intravenous clonidine injection decreases cerebral blood flow by 30\% in awake humans\textsuperscript{35} and 36\% in anesthetized cats\textsuperscript{34} by a central mechanism.\textsuperscript{34} However, whether this decrease is due to direct vasoconstriction or is in response to decreased cerebral metabolism from clonidine's depressant action on the central nervous system is not known.

Despite *in vitro* evidence of vasoconstriction, intrathecal administration of drugs such as norepinephrine and epinephrine, which activate \( \alpha_2 \)-adrenergceptors, does not decrease spinal cord blood flow.\textsuperscript{13,35,36} Likewise, epidurally administered clonidine (17–25 µg/kg) does not decrease lumbar spinal cord blood flow in awake sheep. In contrast to these results, Gordh *et al.*\textsuperscript{12} reported a 25–35\% reduction in spinal cord blood flow following

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**Table 3. Regional Blood Flows Following Epidural Injections***

<table>
<thead>
<tr>
<th>Organ</th>
<th>Baseline</th>
<th>45 Min</th>
<th>4 h</th>
<th>Baseline</th>
<th>45 min</th>
<th>4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right kidney</td>
<td>487 ± 73</td>
<td>550 ± 88</td>
<td>538 ± 78</td>
<td>514 ± 43</td>
<td>491 ± 64</td>
<td>528 ± 64</td>
</tr>
<tr>
<td>Left kidney</td>
<td>468 ± 62</td>
<td>544 ± 63</td>
<td>552 ± 72</td>
<td>516 ± 51</td>
<td>514 ± 67</td>
<td>533 ± 72</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>42 ± 1.9</td>
<td>21 ± 5.7</td>
<td>10 ± 0.8</td>
<td>11 ± 1.5</td>
<td>19 ± 2.6</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>T6–T10</td>
<td>13 ± 1.9</td>
<td>18 ± 2.7</td>
<td>12 ± 1.4</td>
<td>13 ± 1.0</td>
<td>18 ± 3.8</td>
<td>16 ± 1</td>
</tr>
<tr>
<td>T10–L2</td>
<td>20 ± 3.5</td>
<td>27 ± 5.8</td>
<td>19 ± 2.0</td>
<td>22 ± 2.3</td>
<td>25 ± 2.7</td>
<td>22 ± 2</td>
</tr>
</tbody>
</table>

No significant differences between groups by analysis of covariance. * ml·min\textsuperscript{-1}·100 gm\textsuperscript{-1}.

† P = .04 vs. baseline by analysis of variance.
epidural clonidine administration (10–30 μg/kg) in pigs. Possible explanations for this discrepancy include the species studied, the effects of anesthesia, and a larger total dose in the study by Gordh et al. Both studies are limited by small sample sizes. However, power analysis revealed that a decrease in lumbar spinal cord blood flow of >20% would have been detected in our study. Both studies are also limited by the ability to measure only an average flow from a large section of spinal cord. Like fentanyl, clonidine inhibits neuronal transmission in the spinal cord dorsal horn and may, like fentanyl, reduce metabolism in the dorsal horn. However, the initial toxicity question is not whether clonidine alters regional blood flow within the spinal cord, but whether this vasoactive substance, when introduced into the CSF, constricts arterial flow to the entire cord.

This study agrees with the conclusion of Gordh et al. that epidurally administered clonidine, in clinically relevant doses (1–5 μg/kg), is unlikely to produce a dangerous reduction in global spinal cord blood flow. These results support the lack of direct neurotoxicity of intrathecal and epidural administration of clonidine in rats, dogs, monkeys, sheep, and humans. Likewise, this study confirms the lack of marked hemodynamic depression following epidural administration of clonidine in sheep, pigs, dogs, and humans.

In conclusion, epidurally administered clonidine (750 μg) does not decrease blood pressure or global spinal cord blood flow in awake sheep. Although clonidine could produce local spinal cord ischaemia not measurable in this study, these animal data, along with previous studies in animals and preliminary results in humans, suggest that epidural injection of clonidine is safe and that controlled clinical trials of epidurally administered clonidine are warranted.

The authors wish to thank Ms. Barbara Tucker for technical assistance, Dr. Jakob Vinter-Johansen for help in experimental design and utilizing the radioactive microsphere technique, and Ms. Patricia Hogan for help in statistical analysis of data.

References
J. C. EISENACH AND S. C. GRICE

340

Aesthesiology
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