Epidural Clonidine Used as the Sole Analgesic Agent during and after Abdominal Surgery

A Dose-Response Study

M. De Kock, M.D.,* P. Wiederkher, M.D.,† A. Laghmiche, M.D.,† J.-L. Scholtes, M.D.‡

Background: Many studies have shown the beneficial effect of epidural clonidine in postoperative pain management. In these studies, the patients received local anesthetics, opioids, or both in combination with clonidine. Due to the interactive potentiation of those drugs, the importance of the intrinsic analgesic properties of the α₂-adrenoceptor agonist is difficult to establish. The authors investigated the analgesic potency of epidural clonidine when used as the sole analgesic agent during and after major abdominal surgery.

Methods: Fifty young adult patients undergoing intestinal surgery under general anesthesia with propofol were studied. At induction, the patients received epidurally either an initial dose of 2 μg/kg clonidine followed by an infusion of 0.5 μg·kg⁻¹·h⁻¹ (group 1, n = 10) or 4 μg/kg followed by 1 μg·kg⁻¹·h⁻¹ (group 2, n = 20) or 8 μg·kg⁻¹·h⁻¹ followed by an infusion of 2 μg·kg⁻¹·h⁻¹ (group 3, n = 20). During the operation, increases in arterial blood pressure or heart rate that did not respond to a propofol bolus (0.5 mg/kg) were treated with a bolus of intravenous lidocaine (1 mg/kg). Three successive injections were allowed. When baseline values were not restored, opioids were added and the patient was removed from the study. After operation, the clonidine infusions were maintained for 12 h. During this period and at every 30 min, sedation scores and visual analog scale values at rest and at cough were noted. In case of subjective scores up to 5 cm at rest or up to 8 cm at cough, the patients were given access to a patient-controlled analgesia device that delivered epidural bupivacaine. The end point of the study was reached once the patient activated the analgesic delivery button.

Results: During surgery, 60% of patients in group 1 compared with 35% of patients in group 2 and only 5% of patients in group 3 were removed from the study protocol because of inadequate anesthesia (P < 0.05). After operation, epidural clonidine provided complete analgesia lasting 30 ± 21 min in group 1 compared with 251 ± 237 min in group 2 or 369 ± 256 min in group 3 (P < 0.05 for group 1 vs. groups 2 and 3 and group 2 vs. group 3).

Conclusions: Epidural clonidine used as the sole analgesic agent provided dose-dependent control of the hemodynamic changes associated with surgical stimulation. It also produced dose-dependent postoperative analgesia without major side effects. (Key words: Anesthetic technique: epidural clonidine. Pharmacology: clonidine. Pain: postoperative.)

MANY data obtained from animal studies or human volunteers have shown that epidural clonidine produces some analgesia. Many clinical studies also indicate that this α₂-adrenoceptor agonist helps to alleviate postoperative pain. However, in this particular situation, the exact importance of the specific analgesic effect remains unclear. Most of the investigations studying the analgesic effects of α₂-adrenoceptor agonists after operation included previous or concomitant administration of other analgesic drugs such as local anesthetics or opioids. Because clonidine was shown to potentiate the analgesic effects of these drugs, the importance of its own intrinsic analgesic effect is difficult to establish. Only two studies by Filos et al. report the efficacy of spinal clonidine as the sole analgesic agent. These authors found complete and long-lasting analgesia after one intrathecal injection of clonidine given to relieve pain in women recovering from cesarean section deliveries performed without perioperative administration of additional analgesics.

The rationale of our study was to evaluate the dose-response analgesic potency of epidurally administered clonidine during and after abdominal surgery without concomitant administration of opioids or epidural local anesthetics. Our goal was to show that epidural clonidine has analgesic effects on its own against acute surgical pain. Because surgical anesthesia given without opioids or local anesthetics is unusual, only a few patients were included and strict criteria for patient dropout were applied.
Methods

Our double-blinded study was approved by the institutional ethics committee and all participants gave informed consent. We enrolled 50 adults between the ages of 18 and 40 y who were scheduled for extensive intestinal resection for inflammatory bowel disease or second-stage reanastomosis. Exclusion criteria were chronic use of any anti-inflammatory, cardiovascular, or psychotropic medication, including benzodiazepines; any renal or hepatic dysfunction; acute inflammatory bowel process at the time of surgery; inability to understand the study protocol; or a history of allergic reaction to any of the study drugs.

On the day before surgery, a visual analog scale of pain was clearly explained to the patients. Arterial blood pressure and heart rate were recorded at rest. On the night before surgery, all patients received 2 mg lorazepam. Another 2 mg was given sublingually 1 h before the procedure.

In the operating theater, an epidural catheter was inserted in all patients at the T8–T9 vertebral interspace using the loss-of-resistance technique (no local anesthetic test dose was used). Four centimeters (average) of the epidural catheter was threaded into the epidural space. At that time, patients were randomly assigned to receive, in a double-blinded manner, one of the three dose regimens of epidural clonidine.

Patients in group 1 (n = 10) received an initial dose of clonidine of 2 µg/kg in 10 ml saline given in 20 min followed immediately by an infusion of 0.5 µg·kg⁻¹·h⁻¹ (5 ml/h).

Patients in group 2 (n = 20) received an initial dose of clonidine of 4 µg/kg in 10 ml saline given in 20 min followed immediately by an infusion of 1 µg·kg⁻¹·h⁻¹ (5 ml/h).

Patients in group 3 (n = 20) received an initial dose of clonidine of 8 µg/kg in 10 ml saline given in 20 min followed immediately by an infusion of 2 µg·kg⁻¹·h⁻¹ (5 ml/h).

The maintenance infusion was kept flowing in all three groups during the first 12 h after operation.

Only 10 patients were included in group 1, in which a low dose of epidural clonidine was administered because, based on our unpublished and published data, we expected poor intraoperative results. We enrolled 20 patients in groups 2 and 3 because of the results obtained in two previous studies. In these studies, analysis of the intraoperative opioid requirements of patients who received a bolus dose of 4 µg/kg epidural clonidine followed by 2 µg·kg⁻¹·h⁻¹ revealed that most of the patients did not require additional opioids to maintain stable hemodynamic parameters.

In addition to routine monitoring (electrocardiographs, body temperature, oxygen saturation, and twitch depression), intraoperative monitoring included an intra-arterial catheter for systemic blood pressure monitoring and a central venous catheter for venous pressure monitoring.

General anesthesia was induced concomitantly with the epidural infusion. Anesthesia was induced using propofol titrated until loss of consciousness (approximately 2 mg/kg) and atracurium (0.5 mg/kg). An intravenous bolus of lidocaine (1 mg/kg) was given before tracheal intubation. Anesthesia was maintained with a propofol infusion of 5 mg·kg⁻¹·h⁻¹. Mechanical ventilation was adjusted to maintain a carbon dioxide end-expiratory concentration of approximately 36 mmHg. Boluses of atracurium were administered only according to clinical need.

Additional doses of propofol (0.5 mg/kg in bolus) were given when the mean arterial pressure, heart rate, or both increased 20% compared with the baseline values recorded after the initial dose of the epidural drugs and before skin incision (epidural baseline). If the heart rate, mean arterial blood pressure, or both did not return to this epidural baseline 3 min after an additional dose of propofol, an intravenous bolus of 1 mg/kg lidocaine was injected. Additional doses of propofol were also given in response to signs (sweating, tears, or movements) of inadequate anesthesia depth. Three successive propofol injections followed by one lidocaine injection were allowed to control the same hemodynamic episode. If baseline values were not restored, opioids were added to the anesthesia and the patient was excluded from the study protocol. No opioids or epidural local anesthetics were used during the study protocol. The propofol infusion was discontinued at the final skin suture.

After recovery, the clonidine infusion was continued during the first 12 h after operation, at which time the following observations were made every 30 min.

• Patient sedation scores were assigned using a four-point sedation scale: 0 = alert or drowsy but easily aroused to an alert state by verbal commands alone; 1 = sleeping and arousable by verbal command; 2 = sleeping and not aroused by verbal stimuli, but aroused to a drowsy state by tactile stimulation; 3 =
Epidural Clonidine During and After Surgery

Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 10)</th>
<th>Group 2 (n = 20)</th>
<th>Group 3 (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>35.5 ± 6</td>
<td>35.5 ± 7</td>
<td>37.7 ± 6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.6 ± 9</td>
<td>66.3 ± 11</td>
<td>62.8 ± 10</td>
</tr>
<tr>
<td>Male/female</td>
<td>4/6</td>
<td>10/10</td>
<td>11/9</td>
</tr>
<tr>
<td>Procedure (n)</td>
<td>1.5 ± 0.4</td>
<td>1.6 ± 0.5</td>
<td>1.5 ± 0.8</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>296 ± 43</td>
<td>279 ± 48</td>
<td>251 ± 72</td>
</tr>
</tbody>
</table>

Values are mean ± SD. No statistically significant differences were noted between the three groups.

The correct placement of the epidural catheter in the 50 initial patients was confirmed a posteriori after operation by the effective analgesia afforded by bupivacaine when patients required it.

Intraoperative hemodynamics were monitored continuously during the study and for the first 48 h afterward. During the first 2 h after the start of the epidural infusions, and during the first hour after the propofol infusions were discontinued, the hemodynamic values (systolic and diastolic arterial blood pressure and heart rate) were recorded at 2-min intervals.

Perioperative complications (e.g., heart block, intraoperative hypotension defined as a 30% decrease in systolic arterial blood pressure, orthostatic hypotension, rebound hypertension, nausea and vomiting) were recorded during the first 48 h. Episodes of awareness were detected using a personal stereo playing either classical, jazz, or rock music. Music was introduced at the end of the induction and discontinued at the end of surgery just before the propofol infusion was discontinued.

Comparisons of independent variables were based on analysis of variance. Comparisons of the duration of adequate anesthesia, postoperative analgesia, and sedation among the three groups were analyzed by survival analysis using Gehan’s generalized Wilcoxon test. Intergroup comparison for these parameters was done using the Cox F test. Variables over time were evaluated statistically using two-way univariate analysis of variance with repeated measures. Post hoc comparisons were made using Tukey’s test (CSS Statistica; Statsoft, Tulsa, OK). Observed proportions were compared using chi-squared and the Fisher exact test with Yates correction when appropriate. Correlations between duration of analgesia and sedation were made using the Pearson correlation coefficient.

A probability value less than 0.05 was considered significant.

Results

The demographic data of the patients enrolled in the study are summarized in table 1. There was no significant difference in the demographic data between the three groups. The efficacy of the anesthesia provided by the different epidural clonidine solutions assessed by the intravenous bolus of sufentanil required to blunt the episodes of tachycardia and hypertension occurring with surgical stimulation. Patients in group 1 (n = 10) received an initial dose of clonidine of 2 µg/kg in 10 ml saline given in 20 min and followed immediately by an infusion of 0.5 µg·kg⁻¹·h⁻¹ (5 ml/h); patients in group 2 (n = 20) received an initial dose of clonidine of 4 µg/kg in 10 ml saline given in 20 min followed by an infusion of 1 µg·kg⁻¹·h⁻¹ (5 ml/h); and patients in group 3 (n = 20) received an initial dose of clonidine of 8 µg/kg in 10 ml saline given in 20 min followed by an infusion of 2 µg·kg⁻¹·h⁻¹ (5 ml/h). The data are presented as survival proportions. Time 0 represent the induction of anesthesia. The three groups are significantly different (P = 0.003 by Gehan’s generalized Wilcoxon test). The duration of analgesia observed in Group 3 is significantly different from groups 1 and 2 (P < 0.05).

Fig. 1. Efficacy of the anesthesia provided by the different epidural clonidine solutions assessed by the intravenous bolus of sufentanil required to blunt the episodes of tachycardia and hypertension occurring with surgical stimulation. Patients in group 1 (n = 10) received an initial dose of clonidine of 2 µg/kg in 10 ml saline given in 20 min and followed immediately by an infusion of 0.5 µg·kg⁻¹·h⁻¹ (5 ml/h); patients in group 2 (n = 20) received an initial dose of clonidine of 4 µg/kg in 10 ml saline given in 20 min followed by an infusion of 1 µg·kg⁻¹·h⁻¹ (5 ml/h); and patients in group 3 (n = 20) received an initial dose of clonidine of 8 µg/kg in 10 ml saline given in 20 min followed by an infusion of 2 µg·kg⁻¹·h⁻¹ (5 ml/h). The data are presented as survival proportions. Time 0 represent the induction of anesthesia. The three groups are significantly different (P = 0.003 by Gehan’s generalized Wilcoxon test). The duration of analgesia observed in Group 3 is significantly different from groups 1 and 2 (P < 0.05).
Fig. 2. The proportion of the patients who required sufentanil, propofol, or lidocaine injection to control the hypertension and tachycardia subsequent to surgical noxious stimulations in the different epidural clonidine groups. Patients in group 1 (n = 10) received an initial dose of clonidine of 2 μg/kg in 10 ml saline given in 20 min followed immediately by an infusion of 0.5 μg·kg⁻¹·h⁻¹ (5 ml/h); patients in group 2 (n = 20) received an initial dose of clonidine of 4 μg/kg in 10 ml saline given in 20 min followed by an infusion of 1 μg·kg⁻¹·h⁻¹ (5 ml/h); and patients in group 3 (n = 20) received an initial dose of clonidine of 8 μg/kg in 10 ml saline given in 20 min followed by an infusion of 2 μg·kg⁻¹·h⁻¹ (5 ml/h). *P < 0.05 for comparisons between groups 3 or 2 and group 1. ††P < 0.05 for comparisons between groups 3 and 2.

cant difference between the groups with respect to age, weight, sex, and duration of surgery. All the patients enrolled in the study had already undergone at least one previous abdominal procedure for bowel disease. Epidural catheters were placed easily and successfully at the first attempt in all patients.

The dose of propofol required to induce anesthesia was similar in the three groups (171 ± 27 mg in group 1 vs. 185 ± 36 mg in group 2 and 179 ± 28 mg in group 3).

According to the importance of the surgically induced episodes of tachycardia and hypertension and the clinical signs of anesthesia depth, inadequate anesthesia and consequent sufentanil administration occurred in 6 of 10 patients in group 1 (60%), in 6 of 20 patients in group 2 (33%), and in only 1 of 20 patients in group 3 (5%) (P = 0.003; fig. 1). In accordance with the study protocol, those patients were withdrawn.

In the remaining participants, significantly fewer patients in group 3 than in groups 2 and 1 required supplemental propofol or lidocaine injections (P < 0.05; fig. 2). Table 2 shows the number of propofol or lidocaine injections per patients.

At the end of the procedure, there was no difference in latency to spontaneous breathing among the three groups (4.6 ± 4.2 min). At the time of tracheal extubation, no patient complained of major abdominal pain.

Patients in groups 1, 2, and 3 were aroused by verbal comments (score 2 to 1) after 37.7 ± 7.5 min, 20.7 ± 31.43 min, and 39.5 ± 37.1 min, respectively. No significant differences were found among the groups.

Meanwhile, because some patients were removed from the study protocol during anesthesia and some other patients never reached a score 2 (score 1 immediately after extubation (5 of 4 patients in group 1, 7 of 14 in group 2, and 5 of 19 in group 3), the small number of patients considered in each group reduced the power of comparative testing (fig. 3). No patient, at any time considered, reached a sedation score of 3.

As determined by the spontaneous complaint of unbearable abdominal pain or the visual analog scale scores at rest and when coughing, the infusions of clonidine provided complete postoperative analgesia lasting 30 ± 21 min in patients in group 1 compared with 251 ± 237 min in group 2 and 369 ± 256 min in group 3.

Table 2. Intraoperative Anesthetic and Analgesic Requirements

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 10)</th>
<th>Group 2 (n = 20)</th>
<th>Group 3 (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol (injections/patients)</td>
<td>5 (70%)</td>
<td>3* (50%)</td>
<td>1 (15%)</td>
</tr>
<tr>
<td>Lidocaine (injections/patients)</td>
<td>4 (60%)</td>
<td>3 (20%)</td>
<td>2.5 (32%)</td>
</tr>
</tbody>
</table>

Values are number of reinjections per patients in different groups (results are median).

*P < 0.05 for comparisons between group 3 or 2 and group 1.
Epidural clonidine during and after surgery

Fig. 3. Time spent before patients could be aroused by verbal (sedation score 2 compared with sedation score 1) in patients having received different clonidine solutions. Patients in group 1 (n = 1) received an initial dose of clonidine of 2 μg/kg in 10 ml saline given in 20 min and followed immediately by an infusion of 0.5 μg·kg⁻¹·h⁻¹ (5 ml/h); patients in group 2 (n = 7) received an initial dose of clonidine of 4 μg/kg in 10 ml saline given in 20 min followed by an infusion of 1 μg·kg⁻¹·h⁻¹ (5 ml/h); and patients in group 3 (n = 1) received an initial dose of clonidine of 8 μg/kg in 10 ml saline given in 20 min followed by an infusion of 2 μg·kg⁻¹·h⁻¹ (5 ml/h). The data are presented as survival proportions. Time 0 represent the extubation time. The three groups are not significantly different (by Gehan’s generalized Wilcoxon test).

Fig. 4. Duration of postoperative analgesia provided by epidural clonidine as the sole analgesic agent in the different groups expressed as a survival curve. Patients in group 1 (n = 4) received an initial dose of clonidine of 2 μg/kg in 10 ml saline given in 20 min and followed immediately by an infusion of 0.5 μg·kg⁻¹·h⁻¹ (5 ml/h); patients in group 2 (n = 14) received an initial dose of clonidine of 4 μg/kg in 10 ml saline given in 20 min and followed by an infusion of 1 μg·kg⁻¹·h⁻¹ (5 ml/h); and patients in group 3 (n = 19) received an initial dose of clonidine of 8 μg/kg in 10 ml saline given in 20 min and followed by an infusion of 2 μg·kg⁻¹·h⁻¹ (5 ml/h). The data are presented as survival proportions. Time 0 represent the extubation time. The durations of analgesia among the three groups are significantly different (P = 0.025 by Gehan’s generalized Wilcoxon test). The duration of analgesia observed in group 1 is significantly different from group 1 (P = 0.025) and group 2 (P = 0.04, by Cox’s F test).

The duration of complete analgesia in group 3 differed significantly from that observed in group 1 and in group 2 (P < 0.05).

During the first 12 h after operation, epidural clonidine was the only analgesic agent required in four patients in group 3. Two patients in group 1 and three patients in groups 2 and 3 reported severe abdominal pain before a visual analog scale evaluation could be performed. The imposed stress of coughing was the primary reason that supplemental analgesia was required by all the study patients. This occurred in 80% of the patients (2 of 4 in group 1, 10 of 12 in group 2, and 15 of 15 in group 3) who required supplemental analgesia during the first 12-h period.

Epidural clonidine produced detectable sensory block at the mid or low thoracic segment in 11 patients in group 3, in five patients in group 2 (NS), and in no patients in group 1.

We found no correlation between the duration of analgesia produced by epidural clonidine and the duration of sedation (score 2).

The first dose of bupivacaine, self-administered as a supplemental analgesic, was sufficient to alleviate pain in all the remaining patients and those removed from the study. In the patients that remained in the study, the intervals between the first and the second demand were 120 ± 85 min in group 1, 256 ± 109 min in group 2, and 298 ± 172 min in group 3). In the patients removed, this interval was 152 ± 56 min.

Table 3 summarizes the intra- and postoperative analgesic requirements of the patients removed from the study.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 6)</th>
<th>Group 2 (n = 6)</th>
<th>Group 3 (n = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of sufentanil (2.5 μg) injections per patients</td>
<td>2.8 ± 1</td>
<td>2.2 ± 1</td>
<td>1</td>
</tr>
<tr>
<td>Lapse of time (min) before the first postoperative analgesic request</td>
<td>59 ± 43</td>
<td>94 ± 58</td>
<td>360</td>
</tr>
<tr>
<td>Lapse of time (min) before the first and second postoperative analgesic request</td>
<td>152 ± 54</td>
<td>138 ± 54</td>
<td>240</td>
</tr>
</tbody>
</table>

Values are mean ± SD. No statistically significant differences were noted between the three groups.
The three groups. Epidural clonidine given during anesthesia induction significantly \((P < 0.001)\) reduced the preinduction values of heart rate and arterial blood pressure to the same extent in the three groups (fig. 5). Significant differences compared with preinduction systolic arterial blood pressure occurred after 22 min in all the groups. Significant reduction in heart rate was observed after 40, 28, and 30 min in groups 1, 2, and 3, respectively. Minimum values for systolic arterial blood pressure were obtained after 56, 46, and 40 min in groups 1, 2, and 3, respectively. The lowest heart rate was observed after 48, 40, and 40 min after the start of the epidural infusions in groups 1, 2, and 3, respectively. We found no significant intergroup difference in the evolution of the hemodynamic variables. In none of the patients considered was bradycardia (heart rate \(< 40\) bpm) or hypotension sufficient to require a specific intervention during the operation. After operation, two patients, one in group 2 and one in group 3, experienced orthostatic hypotension when they tried to stand for the first time. This occurred 10 and 1 1/2 h, respectively, after the clonidine infusions were discontinued (after the 12th postoperative h).

None of the 50 study patients could remember specifically having heard music during anesthesia. Only one patient, in group 2, experienced mild nausea.

The postoperative course was uncomplicated for all the patients, and we observed no rebound hypertension during the first postoperative week. The most frequent discomforts reported were dry mouth and throat irritation caused by the gastric tube.

**Discussion**

This study considering patients undergoing extensive abdominal surgery confirms the observations made in volunteers and in patients recovering from cesarean section\(^5\). Epidural clonidine, used as the sole analgesic agent, provides dose-dependent analgesia for surgical pain. However, our results appear somewhat less impressive than those reported by Filos et al.\(^4\) The largest bolus dose of spinal clonidine \((450 \mu g = \text{approximately} 6 \mu g/kg)\) used by those authors produced complete postoperative analgesia lasting 86±80 min. Several factors can explain this difference.

First, the studies considered different patient populations and pain stimuli. In Filos and colleagues' study, healthy women with Pfannenstiel incisions were considered in the early postpartum period. In our study, young adults with chronic inflammatory bowel disease with a skin incision beginning at the xiphoid and ending at the pubis were enrolled. Along with the evident psychological benefits related to the delivery, the end of pregnancy is associated with high levels of endorphins in humans.\(^17\) Furthermore, naloxone-sensitive au-
toanalgesia has been shown in pregnant animals.\textsuperscript{18,19} A potentiation by clonidine of endorphin-mediated autoanalgesia similar to that reported in animals may account for the longer-lasting analgesia reported by these authors.

Second, the severity of the criteria chosen to affirm the efficacy of clonidine analgesia during and after surgery may explain the apparent difference. Because of the unusual requirement that surgical anesthesia be provided without any opioids or local anesthetics, strict hemodynamic criteria for adequate anesthesia were assigned. Consequently, 26\% of the initial population did not complete the study protocol. After operation, the primary determinant for patients to require supplemental analgesic and therefore to leave the study was pain after imposed deep coughing and not spontaneous pain perception. The number of patients removed from the study, particularly in the low and medium clonidine dose groups, probably limits the value of the statistical analysis of some data. However, the results obtained clearly show a dose-dependent efficacy of epidural clonidine to blunt the episodes of hypertension or tachycardia related to the surgery. More than a pure hemodynamic effect, it probably represents an important reduction of the noxious afferent inputs to the central sites from a dose-dependent regional spinal effect.\textsuperscript{20} This reduction of the noxious afferent inputs may account for the reduced anesthetic requirements in patients receiving epidural clonidine compared with patients receiving the same dose intravenously.\textsuperscript{18} It is unlikely that the intravenous bolus of lidocaine significantly influenced this observation. Only two patients in group 3 required intravenous lidocaine injection. Furthermore, intravenous lidocaine has a potent but short-lasting antinociceptive action that is less likely to interfere with clonidine-induced antinociception.\textsuperscript{21} Because of the potent synergistic interactions reported between benzodiazepines and $\alpha_2$-adrenoceptor agonists for their anesthetic-sparing effects,\textsuperscript{22} we cannot preclude a positive influence of the lorazepam given as premedication. After operation, a dose-dependent analgesic effect was also demonstrated. These results confirm the observations made by Eisenach \textit{et al.}\textsuperscript{5} in humans showing that large doses are required to unmask the antinociceptive properties of epidural clonidine. This is in contrast to the smaller doses reported to potentiate opioid analgesia. This observation may also explain the lack of major clinical differences observed in a previous study comparing the analgesic effects of epidural and intravenous clonidine,\textsuperscript{16} a finding that contrasts, in part, with the experimental data establishing the dorsal horn of the spinal cord as the major site of the analgesic action of the $\alpha_2$-adrenoceptor agonists. In this study, a dose of epidural clonidine intermediate to that administered in groups 2 and 3 was used and opioids were given as rescue medication during and after anesthesia. The results obtained (reduction of rescue analgesic requirements) may stem not solely from the intrinsic analgesic properties of the $\alpha_2$-adrenoceptor agonists but may also account for their potentiating effects of opiate analgesia. Because potentiation of opioid analgesia is independent of the route of clonidine administration,\textsuperscript{17} it may explain the relatively modest advantage of epidural clonidine in that investigation.

Finally, does the intrathecal route of administration used by Filos \textit{et al.}\textsuperscript{11} account for the longer-lasting effect obtained with a lower dose compared with the epidural route? A pharmacokinetic study in sheep did not provide arguments for considering the intrathecal route as a major determinant of the observed difference.\textsuperscript{23} When clonidine is given intrathecally, more drug is immediately available at its site of analgesic action (the spinal dorsal horn) than by the epidural route. After an early redistribution phase, however, the concentrations of clonidine in cerebrospinal fluid are similar with the two routes.

The epidural clonidine-induced adverse effects at all of the doses considered were tolerable. In particular, we found no major hypotension or bradycardia requiring specific management. These results are consistent with our previous observations.\textsuperscript{3,15,24,25} No patients suffered postoperative oversedation. The lack of significant difference between the three groups for sedation scores must be interpreted cautiously because of the probability of a type II error. Nevertheless, we found no correlation between the duration of analgesia and sedation, indicating that, in our study, as in those by others,\textsuperscript{5,14} the sedative effect of clonidine can be dissociated from its analgesic effect.

Our results show that the large dose of epidural clonidine used in this study can provide substantial intrapartum and postoperative analgesia without any other analgesic. This study extends the observations made in human volunteers and women recovering from cesarean section delivery to patients undergoing major abdominal surgery.

\textbf{References}

5. Eisenach J, Detweiler D, Hood D: Hemodynamic and analgesic actions of epidurally administered clonidine. Anesthesiology 1993; 78:777-87

Anesthesiology. V 86, No 2, Feb 1997