

Epidural Clonidine Analgesia following Surgery: Phase I

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Epidurally administered clonidine has been reported to produce postoperative analgesia. To assess the efficacy, safety, and appropriate dose of epidural clonidine for postoperative analgesia, clonidine (range, 100–900 μg in 100- μg increments) was injected in 22 patients following abdominal surgery or total knee arthroplasty (TKA). Clonidine produced analgesia, as measured by change in verbal pain scores and supplemental iv morphine usage. The largest doses examined (700–900 μg) produced complete pain relief for 5.0 ± 0.8 h (mean \pm SEM; range 2–11 h), without other sensory or motor blockade. Clonidine also produced dose dependent decreases in blood pressure, being less following small (100–300 μg) and large (700–900 μg) doses than following intermediate (400–600 μg) doses. Six patients required iv ephedrine for treatment of blood pressure decrease of $>30\%$. Clonidine decreased heart rate 10–30% and produced transient sedation. Oxyhemoglobin saturation, serum glucose, and arterial blood gas tensions were not altered by clonidine, whereas there was a small (28%) dose-independent decrease in serum cortisol following clonidine injection. Clonidine was absorbed in a dose-dependent manner into the systemic circulation, with plasma concentrations 0.1–3.3 ng/ml 1 h following injection. These results suggest that hemodynamic depression and short-lasting analgesia may limit the usefulness of bolus epidural clonidine analgesia in the postoperative setting. (Key words: Anesthetic techniques: epidural Pain, postoperative, Sympathetic nervous system, alpha-adrenergic receptor: clonidine.)

DESCRIPTION of spinal opiate mechanisms of analgesia has led rapidly to the widespread use of epidural and intrathecal opioid administration in the treatment of acute and chronic pain syndromes.¹ Unfortunately, intraspinally administered opioids produce side effects (urinary retention, pruritus, nausea, and life-threatening respiratory depression) and patients may develop tolerance to their analgesic effects.^{1,2}

In addition to opiate mechanisms, other spinal mechanisms producing analgesia exist, and other receptor-specific agents produce analgesia in animals and humans when injected in the epidural or intrathecal space.³ Clonidine, an α_2 -adrenergic agonist used in oral form primarily for the treatment of hypertension, produces analgesia when applied near the spinal cord.^{4,5} Clonidine

blocks transmission of pain information by activating pre-synaptic and postsynaptic α_2 -adrenoceptors in the spinal cord, which inhibit substance P release⁶ and dorsal horn neuron firing,⁷ respectively.

Preclinical toxicity testing of clonidine is reasonably complete.⁸ Animal data suggest that clonidine is safe,^{5,9,10} but that it may, depending on route of administration, produce side effects. These include hypotension and bradycardia (intrathecal $>$ epidural $>$ iv), hyperglycemia (epidural, iv), decreased serum cortisol (epidural), sedation (all routes), and hypoxemia (iv).^{11–13}

Epidural clonidine analgesia following surgery has been the subject of several recent reports.^{14–19} Unfortunately, studies to date consist of examination of a single dose, isolated case reports, or are of extremely limited scope, and their results conflict. For example, epidurally administered clonidine has been reported to produce complete¹⁴ or no¹⁹ pain relief, and wide ranges have been reported for effective dose (75–1,000 μg) and duration of action (2–24 h). In addition, these studies have not investigated possible toxicities suggested by animal research. In this study using an open-label, dose-ranging design, we examine the analgesic, neurologic, hemodynamic, respiratory, and hormonal effects of epidural clonidine (100–900 μg) for postoperative analgesia.

Materials and Methods

The Clinical Research Practices Committee approved the protocol, all patients gave written informed consent, and clonidine was supplied under an Investigational New Drug from the FDA. Twenty-two ASA physical status 1, 2, or 3 patients undergoing abdominal surgery or total knee arthroplasty (TKA) were studied. Patients with diabetes mellitus, neurologic disease, angina, congestive heart failure not stable on current medications, pulmonary disease requiring therapy, or poorly controlled hypertension were excluded. In addition, patients weighing over 250 pounds, older than 70 yr, or taking tricyclic antidepressants, α_2 -adrenergic agonists, or opioids other than codeine were excluded.

An epidural catheter was inserted (lumbar in 21 cases and thoracic in one case) and tested preoperatively by injection of 2% lidocaine to produce bilateral, segmental anesthesia, following which the patient received either general or epidural anesthesia for the surgical procedure. Epidural anesthesia was provided with 2% lidocaine with 1:200,000 epinephrine or 0.5% bupivacaine. General anesthesia was provided with enflurane or isoflurane. In the recovery room 3 ml of 1.5% lidocaine with 15 μg

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epinephrine were injected epidurally to exclude intrathecal or iv migration of the epidural catheter. Five minutes later clonidine diluted in 10 ml saline was injected at a rate of 30 µg/min. In this dose escalation study, three patients were studied at each clonidine dose (100–900 µg in 100-µg increments), except 200 µg, which was received by only two patients. Four patients following TKA received two clonidine doses each, with injections separated by 24 h. Preliminary studies at our institution have shown that pain stimulus, as measured by iv opioid usage, remains constant for 48 h following this surgery.

Supplemental analgesia was provided by patient-controlled analgesia (PCA) with iv morphine. Patient demographic data were recorded and blood obtained for arterial blood gas tension, clonidine, cortisol, and glucose analysis before and 1 h after injection. Arterial blood gas tensions were analyzed using a Radiometer BMD microanalysis system. Clonidine concentrations were determined by radioimmunoassay with minimal detectable concentration of 0.05 ng/ml and intraassay and interassay variation of 7% and 11%, respectively.²⁰ Cortisol concentrations were determined using a specific radioimmunoassay²¹ and serum glucose was determined using a BeckmanTM glucose analysis system. Patients rated their level of pain using a 5-point verbal scale (1 = comfortable, 2 = mildly uncomfortable, 3 = very uncomfortable, 4 = in pain, 5 = in bad pain),²² and investigators assessed sedation using a 5-point scale (1 = wide awake, 2 = drowsy, 3 = dozing intermittently, 4 = mostly sleeping, 5 = only awakens when aroused)²² at specified times for

TABLE 1. Intraoperative Characteristics

Clonidine Dose (µg)	Procedure	Epidural Anesthesia (% of patients)	Time from Last Opioid to Clonidine (min)
100–300	TKA (4 patients) Colectomy Radical prostatectomy	67	231 ± 41
400–600	TKA (3 patients) Radical prostatectomy Gastrectomy Radical hysterectomy Colectomy	43	260 ± 52
700–900	Cesarean section (6 patients) Cholecystectomy Gastrectomy Radical hysterectomy	67	199 ± 41

6 h following injection. Morphine use, neurologic function (mental status, sensation, deep tendon reflexes), blood pressure, and heart rate were monitored at specified intervals for 6 h following injection. Time of first morphine use, if longer than 6 h, was also recorded. A decrease in mean arterial blood pressure >30% not responsive to 500 ml iv crystalloid fluid administration was treated with ephedrine, 5 mg iv. Oxyhemoglobin saturation was continuously monitored by pulse oximetry.

Because the purpose of this study was to provide initial data addressing several safety and efficacy issues, statistical methods used were primarily descriptive. For clarity, data following injection of small (100–300 µg), intermediate (400–600 µg), and large (700–900 µg) doses of clonidine were combined, and group comparisons were performed. Morphine use in the four patients following the second dose of clonidine was less than other patients receiving the same clonidine dose. For this reason, morphine use and pain scores following these four injections were not included in data analysis. Data are presented as mean ± SEM. Hemodynamic and morphine use data were compared among groups using analysis of variance (ANOVA) either for single or repeated measures. Noncontinuous variables were compared using either Fisher's exact test or chi-square test. For clarity, pain scores are depicted in figure 1 as mean ± SEM. Separate analysis of distribution of pain scores yielded similar results. *P* < 0.05 was considered significant.

Results

Six of the patients were male and 16 were female. The three dosage groups did not differ in age, height, or weight. Overall their age was 51 ± 3 yr, height was 166 ± 6 cm, and weight was 67 ± 0.9 kg. Seven patients had

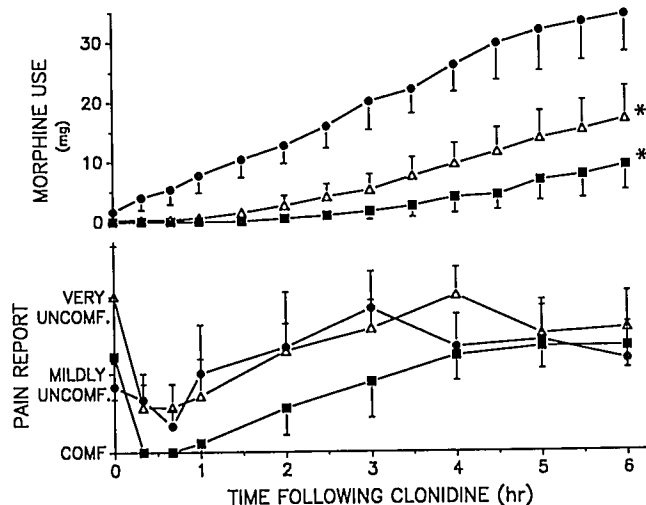


FIG. 1. Cumulative supplemental iv morphine use (upper panel) and pain scores (lower panel; corresponding to scores 1, 2, or 3) following epidural injection of clonidine, 100–300 µg (●), 400–600 µg (Δ), and 700–900 µg (■). Each point represents the mean ± SEM of 8–9 determinations. For pain scores, a time-dependent effect is present only in the 400–600 µg and 700–900 µg groups (*P* < 0.05, one-way ANOVA). **P* < 0.05 versus 100–300 µg group (two-way ANOVA).

a history of hypertension, and five of these were receiving antihypertensive therapy. Intraoperative characteristics are shown in table 1. The groups did not differ in amount of intraoperative opioid received. Overall, 19 of 22 patients received opioids intraoperatively, either fentanyl ($n = 12$; $154 \pm 92 \mu\text{g}$; range = 50–150 μg) or morphine ($n = 7$; $14 \pm 3 \text{ mg}$; range = 5–25 mg).

Epidurally administered clonidine produced a dose-dependent decrease in supplemental morphine usage, whereas pain scores were minimally affected (fig. 1). Intraoperative anesthetic type did not influence postoperative morphine use. Onset of analgesia was within 20 min of injection, and duration of complete analgesia (defined as time to first PCA morphine) was $0.8 \pm 0.4 \text{ h}$ following small doses, $4.0 \pm 0.7 \text{ h}$ following intermediate doses, and $5.0 \pm 0.8 \text{ h}$ following large doses of clonidine (all groups differ; $P < 0.05$). No other alterations in sensory, motor, or reflex function were observed. Sedation following clonidine was variable, not clearly dose-dependent, and lasted 1–3 h (fig. 2).

Mean arterial pressure prior to clonidine injection in the groups was $86 \pm 4 \text{ mmHg}$ (100–300 μg), $90 \pm 5 \text{ mmHg}$ (400–600 μg), and $83 \pm 4 \text{ mmHg}$ (700–900 μg). All doses of clonidine decreased mean arterial pressure (fig. 3), with maximal change occurring in most cases within 1 h of injection (table 2). The degree of hypotension was greatest following intermediate doses (400–600 μg) and least following large doses (700–900 μg) (fig. 3; table 2). Six patients required ephedrine for a $>30\%$ decrease in blood pressure. These patients had received 300–700 μg clonidine. One of them was anemic following surgery (hemoglobin 7.1 g/dl) and her blood pressure increased following transfusion. Another had received clonidine in the thoracic epidural space. Hypotension requiring ephedrine was more likely in patients with a his-

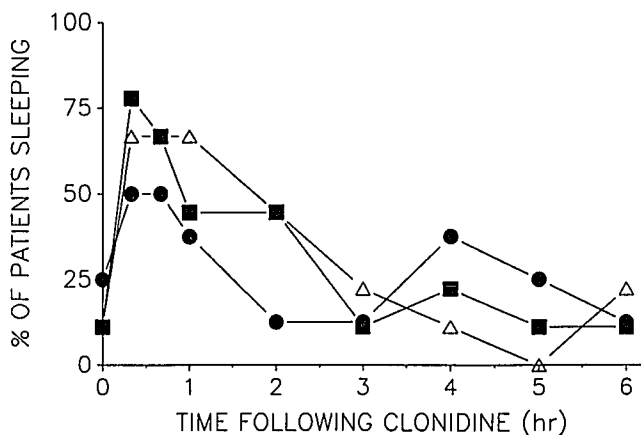


FIG. 2. Percentage of patients scoring 3 (dozing intermittently) or 4 (most sleeping) on sedation scale following epidural injection of clonidine, 100–300 μg (●), 400–600 μg (Δ), and 700–900 μg (■). A time-dependent effect is present in all groups ($P < 0.05$, one-way ANOVA).

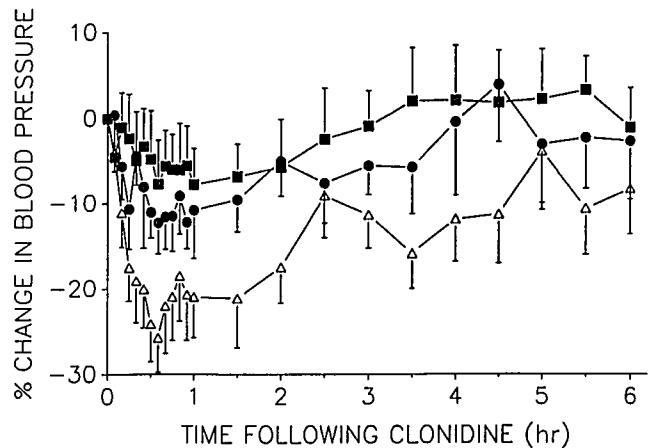


FIG. 3. Change in mean arterial pressure following epidural injection of clonidine, 100–300 μg (●), 400–600 μg (Δ), and 700–900 μg (■). Each point represents the mean \pm SEM of 8–9 determinations. A time-dependent effect is present in all groups ($P < 0.05$, ANOVA). Groups 400–600 μg and 700–900 μg differ by two-way ANOVA ($P < 0.05$).

tory of hypertension (3 of 7) than in those without hypertension (2 of 15), although this trend was not significant ($P = 0.16$).

All doses of clonidine decreased heart rate (fig. 4). Maximal change in heart rate occurred later than maximal change in blood pressure, and was more variable in timing (table 2). This effect did not require treatment. The first patient studied developed atrial fibrillation without hypotension 4 h following epidural injection of 100 μg clonidine. In retrospect, she recalled a history of palpitations and a cardiologist telling her she had a dysrhythmia.

Clonidine did not alter arterial blood gas tensions or serum glucose but produced a minor decrease in serum cortisol (table 3). The effect of clonidine on serum cortisol was of similar magnitude in all groups but only reached statistical significance in the 400–600 μg group. Serum clonidine concentrations 1 h following injection ranged from 0.13 to 3.3 ng/ml (table 3).

TABLE 2. Maximal Hemodynamic Changes Following Epidural Clonidine

Parameter	Dose (μg)	Maximal Change (%)	Time of Maximal Change (min)
Blood pressure	100–300	-21 ± 4.0	47 ± 4 (range 15–90)
	400–600	-28 ± 4.2	
	700–900	-12 ± 4.4	
Heart rate	100–300	-19 ± 2.1	113 ± 18 (range 20–300)
	400–600	-21 ± 1.8	
	700–900	-24 ± 2.5	

All groups differ from baseline.

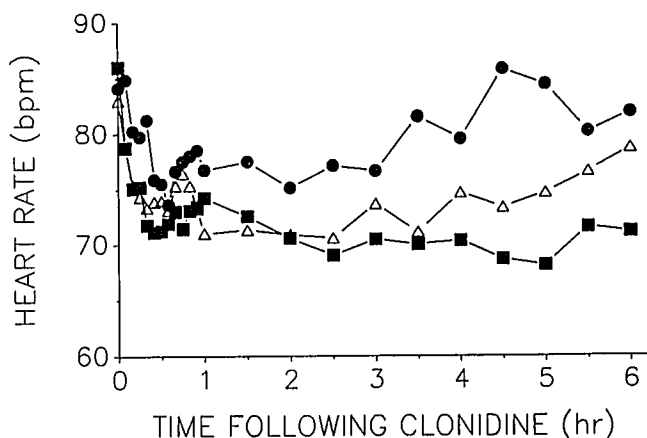


FIG. 4. Heart rate following epidural injection of clonidine, 100–300 µg (●), 400–600 µg (Δ), and 700–900 µg (■). Each point represents the mean ± SEM of 8–9 determinations. A time-dependent effect is present in all groups ($P < 0.05$, ANOVA). Groups do not differ by two-way ANOVA.

Discussion

Open-label, dose-ranging studies, although descriptive in nature, are essential first steps in application of new drugs for human use. Phase I trials in the FDA process of drug development are generally open-label, dose-ranging in nature, with emphasis on defining safety of the new agent or route of administration.²³ This is the first systematic study of safety, efficacy, and dose–response characteristics of epidurally administered clonidine in humans, and addresses questions raised in preclinical toxicity test-

ing of this agent. These data provide the basis for subsequent placebo-controlled, double-blind studies.

ANALGESIA

A clear definition of analgesic efficacy and duration in an open-label trial without a placebo control is difficult. Use of PCA for supplemental analgesia in this setting has certain advantages: all patients can achieve adequate pain relief, an objective measure of analgesic efficacy (dosage of PCA morphine administered) and duration (time to first use of PCA) for the test agent is obtained, and placebo controls could ethically be included. However, access to PCA renders subjective pain assessment suspect because all patients titrate supplemental PCA morphine to a similar level of analgesia. This study uses both pain scores and PCA usage to define the appropriate dose of epidurally administered clonidine for subsequent placebo-controlled, blinded studies.

Based on its molecular weight (230 daltons), lipid solubility (octanol:water partition coefficient = 114), and cerebral spinal fluid (CSF) pharmacokinetics,^{12,19} clonidine should have an onset of action and duration of analgesia resembling epidurally administered fentanyl. Our data in acute postoperative patients support this hypothesis and do not substantiate previous reports of prolonged analgesia (18–24 h) following bolus epidural clonidine injection.¹⁴ However, duration of analgesia may be prolonged by injecting large doses, and patients receiving >700 µg clonidine in this study had complete analgesia for up to 11 h following injection.

TABLE 3. Serum Analyses Following Epidural Clonidine

	Dose (µg)								
	100	200	300	400	500	600	700	800	900
Clonidine (pg/ml) (mean)	132	579	882	1,190	2,039	1,907	1,625	2,968	3,056
SEM	10	65	176	143	181	189	410	325	284
Glucose (mg/dl)									
Before		111 ± 13			117 ± 15			87 ± 6	
After		137 ± 24			129 ± 13			104 ± 6	
Cortisol (µg/dl)									
Before		15.5 ± 1.6			9.9 ± 1.3			27 ± 7.7	
After		12.0 ± 1.9			7.0 ± 0.9*			19 ± 5.8	
Arterial pH									
Before		7.39 ± 0.01			7.38 ± 0.02			7.39 ± 0.01	
After		7.39 ± 0.02			7.38 ± 0.01			7.41 ± 0.01	
Arterial P _{CO₂} (mmHg)									
Before		36 ± 3			40 ± 3			37 ± 2	
After		38 ± 2			37 ± 2			35 ± 2	
Arterial P _{O₂} (mmHg)									
Before		89 ± 9			105 ± 10			113 ± 8	
After		81 ± 5			91 ± 9			107 ± 2	

* $P < 0.05$ versus before value.

Our data suggest that, in contrast to initial reports,¹⁴ but in agreement with more recent data,^{15-17,19} epidural clonidine injection of doses <400 μg is relatively ineffective against acute postoperative pain. However, in agreement with a recent report,¹⁸ doses >600 μg are effective. Interestingly, these larger doses are less likely than the smaller, ineffective doses to produce significant hypotension.

HEMODYNAMICS

In humans the main side effect following intraspinal clonidine injection is hypotension.^{4,15,17,18,24,25} Intraspinally administered clonidine decreases blood pressure in part by inhibiting preganglionic sympathetic nerve activity in the spinal cord.²⁶ Two observations support the relevance of this effect. First, hypotension following this "partial sympathectomy" should be exacerbated by decreased intravascular volume, as exemplified by the patient with inadequately replaced blood loss in our series. Second, the degree of decreased sympathetic activity should be greater following intrathecal than epidural clonidine administration, and blood pressure decreases more in animals¹² and humans following intrathecal⁴ than epidural¹⁴ administration.

Clonidine affects blood pressure regulation at two other sites. In the brain stem, clonidine decreases blood pressure by inhibiting sympathetic and enhancing parasympathetic nervous system activity.²⁷ It is conceivable that rostral spread of clonidine in CSF following epidural injection could produce delayed hypotension, analogous to delayed respiratory depression following epidural morphine injection. Larger amounts of clonidine reaching brain stem centers in the one patient receiving clonidine in the thoracic epidural space may have contributed to her more marked hypotension. However, delayed decreases in blood pressure or heart rate following epidural clonidine injection have not been observed in animals or humans, and clonidine's high lipid solubility²⁸ and rapid absorption and elimination in CSF^{12,19} argue against a residence time long enough for extensive rostral distribution. In the periphery, clonidine increases blood pressure by α_2 -adrenoceptor-mediated vasoconstriction.²⁹ This may partially explain the lesser degree of hypotension following epidural than intrathecal injection, and following injection of larger doses of drug, which were accompanied by plasma concentrations believed to produce peripheral vasoconstriction.

Based on the preceding discussion, hypotension following intraspinally administered clonidine should be more likely in hypovolemic patients, following thoracic injection, following intrathecal rather than epidural injection, and following injection of small doses. In addition, our data suggest that the degree of hypotension following

epidural clonidine injection, similar to systemic clonidine administration,³⁰ may be greater in patients with hypertension than in those without.

Clonidine decreases heart rate by direct cardiac as well as central mechanisms. As observed following systemic administration, this effect is minor following epidural injection and does not require treatment. However, patients with resting bradycardia, sinoatrial or atrioventricular nodal dysfunction, or taking agents slowing heart rate or cardiac conduction may have severe bradycardia following clonidine administration.³¹ The effect of clonidine on cardiac electrophysiology is controversial: clonidine has been reported to have no effect³² or to decrease³³ conduction velocity. It is unlikely that clonidine caused atrial fibrillation in the first patient in this study: the dose was small (100 μg) and the onset of dysrhythmia was delayed (4 h following injection) and did not resolve over the subsequent days. Although the history of previous dysrhythmia suggests a chronic condition, it is conceivable that clonidine may have contributed to the onset of fibrillation postoperatively. Until a larger experience with epidurally administered clonidine is obtained, it would seem prudent to avoid this therapy in patients with cardiac conduction system disturbances.

HORMONAL AND RESPIRATORY EFFECTS

Clonidine increases serum glucose by inhibiting insulin release,³⁴ and epidurally administered clonidine increases serum glucose by 200% in sheep.¹³ However, systemically administered clonidine alters fasting glucose little or none, and decreases exercise-induced hyperglycemia in volunteers.³⁵ The reason for this species difference is unknown. Our results suggest that epidural administration similarly does not affect serum glucose in humans.

Clonidine decreases stress-induced adrenocorticotrophic hormone (ACTH) release,³⁶ and hence cortisol release, including the stress of surgery in humans.³⁷ Serum cortisol decreased in a majority of patients receiving epidural clonidine following surgery in this study. However, the consequences of this effect are probably trivial because the decrease is small and may be due to effective analgesia³⁸ or the normal rapid decline in serum cortisol following surgery.³⁹ Activation of central α_2 -adrenoceptors by clonidine diminishes a variety of responses to stress,⁴⁰ an action that may be beneficial in many patients following surgery. Unlike agents that interfere with cortisol synthesis,⁴¹ clonidine would not be expected to decrease cortisol below the normal range, and chronic clonidine administration has no effect on serum cortisol.⁴²

In sheep systemic (but not epidural) clonidine administration produces dose-dependent hypoxemia, mediated by a peripheral α_2 -adrenoceptor, and not due to respiratory or cardiovascular depression.¹¹ Although the

mechanism of this effect in sheep is unknown, it is suggested to be due to platelet aggregation and pulmonary microembolism.¹¹ Preliminary studies suggest that clonidine produces an unusual form of activation of sheep but not human platelets. In humans iv⁴³ or epidural injection of clonidine does not alter arterial P_{O₂} or oxyhemoglobin saturation.

In agreement with others,¹⁹ epidural clonidine injection produced no evidence of respiratory depression in this study, as measured by arterial P_{CO₂} 1 h following injection. Although it could be argued that a more sensitive test (ventilatory response to inhaled CO₂) may have demonstrated mild respiratory depression, or that we could not exclude rare respiratory depression with a small sample size, there is no physiologic basis for anticipating respiratory depression following epidural clonidine injection. This distinction represents a clear advantage over morphine, which commonly produces mild respiratory depression and rarely produces life-threatening respiratory depression.¹

In summary, epidural clonidine administration represents a new approach to postoperative pain therapy. In contrast to epidurally administered opioids, clonidine does not affect respiration, and produces side effects within 1 h following injection, when the patient is likely to be under close supervision. Hemodynamic depression and short-lasting analgesia, however, may limit the usefulness of bolus epidural clonidine analgesia in the postoperative setting. This study identifies factors (dose, epidural catheter location, intravascular volume status, preexisting hypertension) that may be important in improving efficacy and enhancing safety of this agent. Widespread clinical use of this investigational therapy should await further studies to define incidence and risk factors of epidural clonidine-induced hypotension and bradycardias.

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