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Epidural Clonidine after Cesarean Section

Appropriate Dose and Effect of Prior Local Anesthetic

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Epidurally administered clonidine represents a new approach to postcesarean section pain therapy, yet the appropriate bolus dose and infusion to provide effective pain relief have not been defined. In addition, whether 2-chloroprocaine, a commonly used local anesthetic for intraoperative anesthesia, interferes with clonidine's analgesia, as it does with that of opioids, has not been examined. In this study, using a randomized, blinded design, 63 women received either bupivacaine or 2-chloroprocaine for epidural anesthesia for cesarean section and then received, upon request for analgesia in the recovery room, epidural clonidine 400 μg or 800 μg bolus, each followed by a 24-h infusion of 40 μg/h, or an equivalent volume bolus and infusion of saline. In the bupivacaine group, both clonidine doses produced equivalent analgesia, as determined by pain scores and time to first supplemental intravenous morphine request, and sustained analgesia was produced by clonidine infusion, as measured by need for supplemental morphine. In contrast, 2-chloroprocaine diminished analgesia from 800 μg by 21% and abolished analgesia from 400 μg clonidine. After 2-chloroprocaine, sustained analgesia from continuous clonidine infusion was present only in the group who had received 800 μg clonidine. Clonidine did not alter resolution of residual local anesthetic sensory blockade, as measured by 2- or 4-segment regression following either local anesthetic, but did prolong duration of motor blockade in women receiving bupivacaine. Clonidine produced small decreases in heart rate and blood pressure. One patient received iv fluids for hypotension; one had asymptomatic bradycardia resolving without therapy; and one had mild hypoxemia with snoring during clonidine-induced sedation, responding to supplemental oxygen. These results demonstrate a profound inhibition of clonidine-induced analgesia by 2-chloroprocaine solutions and suggest that a 400-μg bolus plus 40 μg/h is an appropriate initial regimen for epidural clonidine analgesia after bupivacaine anesthesia in this patient population. (Key words: Anesthetics, local: 2-chloroprocaine; bupivacaine. Anesthetic techniques: epidural. Pain: postoperative cesarean section. Sympathetic nervous system, α-adrenergic agonist: clonidine.)

EPIDURALLY ADMINISTERED CLONIDINE produces analgesia by an α_2-adrenergic mechanism and may provide postoperative analgesia without the nausea, pruritus, and respiratory depression associated with systemic or intraspinal opioid administration.[1] Although epidural clonidine has been the subject of several investigations, the appropriate dose remains controversial. Some report sustained analgesia from 150 μg,[2] whereas others report no effect from the same dose.[3] We observed in an open-label, dose-ranging study that >600 μg clonidine was necessary to provide complete analgesia reliably[4] but found in a double-blind study that 400 μg was effective following cesarean section.[5] Whether this latter difference is due to removal of investigator bias or prolongation of epidural local anesthetic blockade by clonidine in that study is not clear.

Clonidine produces only brief analgesia following epidural bolus administration and should logically be administered by continuous infusion for sustained analgesia. Although preliminary studies suggest at least 20 μg/h is necessary to provide pain relief, either alone or in combination with morphine,[5,6] supplemental opioids still are required, and analgesia and side effects from higher infusion rates have not been examined.

2-Chloroprocaine, administered even in small doses remote from the time of epidural opioid injection, dramatically interferes with opioid-induced analgesia.[7–9] Although this has been suggested to be specific to the μ-opioid receptor subtype,[10] lack of saline controls in that study leave this question in doubt. Since epidural anesthesia resolves more quickly after 2-chloroprocaine than after other local anesthetics, and since prolongation of bupivacaine-induced sensory and motor blockade for several hours is a bothersome side effect of epidural clonidine therapy,[5] use of clonidine after 2-chloroprocaine is of clinical interest; however, it has not been examined.

To address the issues of appropriate bolus dose, use of a larger infusion rate than previously reported, and alteration by 2-chloroprocaine of epidural clonidine-induced analgesia following cesarean section, we performed the following study. Patients were randomly assigned to receive bupivacaine or 2-chloroprocaine for intraoperative epidural anesthesia; they then received, at the time of a request for analgesia when local anesthetic block was resolving, saline control or one of two clonidine bolus doses, followed by saline or a higher clonidine infusion rate, 40 μg/h, than previously examined. Analgesic efficacy and side effects were examined to provide the rationale for future use of this therapy in this patient population.

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Materials and Methods

The Clinical Research Practices Committee approved the protocol; all patients gave written informed consent; and clonidine was supplied under Investigational New Drug approval from the Food and Drug Administration. Sixty-three women, ASA physical status 1 or 2, scheduled for elective cesarean section during epidural anesthesia were studied. Women with preeclampsia and women taking opioids, tricyclic antidepressants, or clonidine were excluded. Patients were randomly assigned to receive 3% 2-chloroprocaine or 0.5% bupivacaine epidurally for intraoperative anesthesia. An epidural catheter was inserted at the third or fourth lumbar interspace, and its tip location confirmed with injection of 2% lidocaine, 2 + 5 ml, in the bupivacaine group, or 3% 2-chloroprocaine, 2 + 3 ml, in the 2-chloroprocaine group. Anesthesia was then established and maintained with 5-ml increments of either bupivacaine or 2-chloroprocaine, according to study group assignment. Patients receiving more than 50 ml local anesthetic or supplemental intravenous (iv) analgesia intraoperatively were excluded.

Upon first request for analgesia in the recovery room, patients were given, in a randomized, balanced, blinded manner, epidural infusions of low-dose clonidine (400-μg bolus + 40 μg/h), high-dose clonidine (800-μg bolus + 40 μg/h); or an equivalent volume of saline (10-ml bolus over 5 min; 2 ml/h) with infusions lasting 24 h. Supplemental analgesia was provided beginning 15 min after epidural bolus injection by iv morphine *via* patient-controlled analgesia (PCA; dose 2 mg, lockout 5 min, hourly limit 20 mg). Blood pressure and heart rate were measured noninvasively every 5 min for 90 min after the end of study solution injection and then at 2, 2.5, 3, 4, 6, 8, 12, 16, 20, and 24 h postoperatively. Oxyhemoglobin saturation (Sp_{O_2}) was continuously monitored by pulse oximetry for 2 h following study solution injection.

One of the investigators assessed sensory level to pin prick and degree of motor blockade by the method of Bromage *et al.*,[11] every 0.5 h for 4 h following study solution injection. At these same time intervals, patients rated their level of pain on a five-point verbal scale (1 = comfortable; 2 = mild discomfort, 3 = pain; 4 = bad pain; 5 = very bad pain) and investigators assessed sedation on a five-point scale (1 = wide awake; 2 = drowsy; 3 = dozing; 4 = mostly sleeping; 5 = awakening only when aroused) and measured blood pressure and heart rate with the patient in the sitting and supine positions. From 4 to 24 h following study solution injection, pain and sedation data were recorded every 2 h by nurses on the postpartum ward. Respiratory rate was monitored and recorded every 2 h for 24 h and the presence of pruritus or nausea noted. Any medications administered during the 24-h study period were recorded, as was time of each PCA morphine use.

Side effects and their treatment were defined as follows: 1) symptomatic hypotension or a decrease in blood pressure by >30%: discontinuation of clonidine infusion, iv fluid administration, and if necessary, iv ephedrine 15 mg; 2) symptomatic bradycardia or heart rate <50 beats/min: iv atropine 0.4 mg; 3) bothersome pruritus: iv diphenhydramine 25 mg; 4) nausea: iv droperidol 0.5 mg; and 5) marked sedation: discontinuation of clonidine infusion.

Drugs

The following drugs were used in the study: clonidine (Fujisawa Pharmaceutical Co., Deerfield, IL), bupivacaine, 2-chloroprocaine, and lidocaine (Astra Pharmaceuticals, Westborough, MA), and morphine sulfate (Wyeth Laboratories, Inc., Philadelphia, PA).

Statistical Analysis

Groups were compared for continuous demographic data by one-way analysis of variance (ANOVA) followed by Scheffé tests, and for noncontinuous data by chi-square analysis. Time to first morphine use was compared by Kaplan-Meier survival analysis followed by the Wilcoxon test. Time to two- and four-segment sensory block regression after epidural study solution injection, motor block regression sedation, and pain scores over the first 4 h were compared by Friedman's ANOVA for nonparametric data. Hemodynamic and cumulative morphine use data were compared by two-way ANOVA for repeated measures. $P < 0.05$ was considered significant.

Results

The groups did not differ in demographic or intraoperative characteristics (table 1). Three patients withdrew from the study within 6 h of study solution injection (one bupivacaine + high-dose clonidine, one 2-chloroprocaine + high-dose clonidine, and one bupivacaine + saline) at patient request because of desire to have the epidural catheter removed. Following each of these patient dropouts, their study group assignment was reinserted in the randomization schedule. As a result, 60 patients completed the study.

The effect of clonidine infusion on pain scores and supplemental morphine use depended on the local anesthetic previously administered. Compared to saline, both low- and high-dose clonidine decreased pain scores during the first 4 h following injection in the bupivacaine group, whereas only high-dose clonidine decreased pain scores

TABLE 1. Group Demographic and Labor Characteristics

Local Anesthetics	Treatment	Age (yr)	Height (cm)	Weight (kg)	Nulliparity	Local Anesthetic Dose (mg)
Bupivacaine	Saline	31 ± 1	162 ± 1	83 ± 7	3	132 ± 15
Bupivacaine	Clonidine-400	31 ± 1	163 ± 2	77 ± 4	1	164 ± 17
Bupivacaine	Clonidine-800	31 ± 2	166 ± 3	83 ± 6	0	158 ± 7
2-Chloroprocaine	Saline	30 ± 2	160 ± 2	71 ± 4	2	1143 ± 76
2-Chloroprocaine	Clonidine-400	30 ± 1	159 ± 2	78 ± 5	0	1122 ± 63
2-Chloroprocaine	Clonidine-800	29 ± 1	163 ± 2	78 ± 3	1	1257 ± 53

Data expressed as mean ± SEM of ten patients in each group. No significant differences.

in the 2-chloroprocaine group (fig. 1). Clonidine produced a longer period before first use of supplemental morphine in patients who had received bupivacaine (median times: saline 0.8 h, low-dose clonidine 3.5 h, high-dose clonidine 5.5 h; $P < 0.05$) than those who had received 2-chloroprocaine (median times: saline 0.5 h, low-dose clonidine 0.5 h, high-dose clonidine 0.8 h; P = not significant). Compared to saline, both low- and high-dose clonidine decreased morphine usage throughout the 24-h study in the bupivacaine group, whereas only high-dose clonidine decreased morphine usage in the 2-chloroprocaine group (figs. 2 and 3). Within the bupivacaine groups there was no difference between low- and high-dose clonidine in pain scores, time to first morphine use, or morphine use throughout the 24-h period (figs. 1 and 3).

Clonidine did not alter resolution of motor or sensory blockade in the 2-chloroprocaine group but prolonged resolution of motor blockade in the bupivacaine group (fig. 4). Although patients in the bupivacaine group who received clonidine had a more cephalad level of sensory blockade at time of study solution injection than did those who received saline, clonidine did not alter time to two- or four-segment regression (table 2).

Mean arterial pressure prior to study solution injection was similar in all groups. Blood pressure was lower in the low-dose clonidine group than in the saline or high-dose clonidine groups in patients who received bupivacaine (average mean arterial pressure in millimeters mercury over entire study period: 83 ± 0.5 for saline, 78 ± 0.5 for low-dose clonidine, 86 ± 0.5 for high-dose clonidine; $P < 0.05$ only for low-dose clonidine *vs.* saline by two-

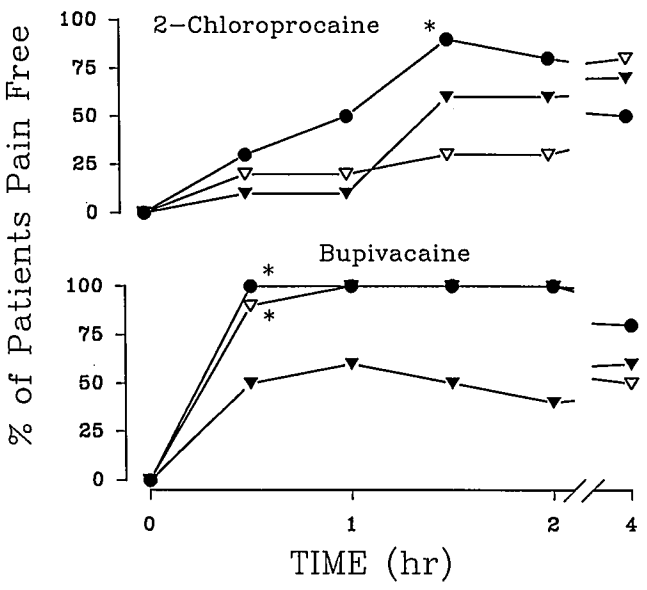

FIG. 1. Percentage of patients reporting no pain after epidural injection of saline (▼), low-dose clonidine (▽), or high-dose clonidine (●) in women receiving intraoperative anesthesia from 2-chloroprocaine (*top*) or bupivacaine (*bottom*). *$P < 0.05$. High-dose clonidine (*top*) and both clonidine doses (*bottom*) differ from their respective saline controls by Friedman's ANOVA on the entire data set.

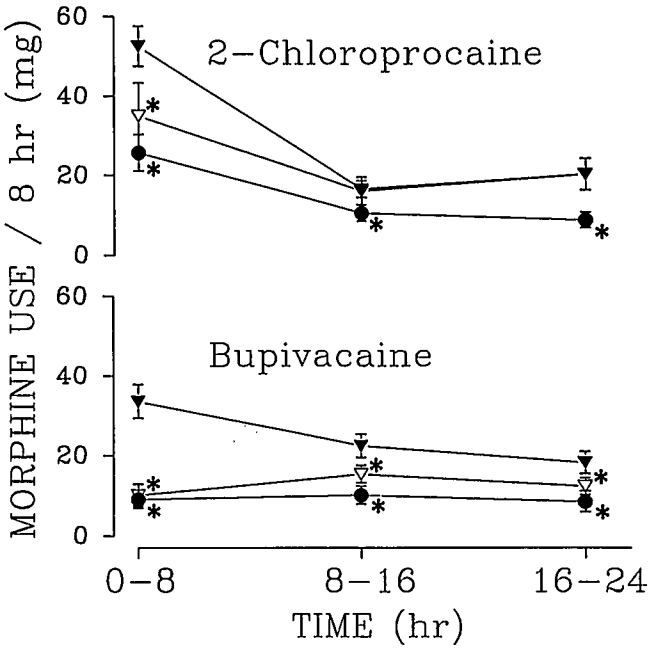

FIG. 2. Morphine use following epidural injection of saline (▼), low-dose clonidine (▽), or high-dose clonidine (●) in women receiving intraoperative anesthesia from 2-chloroprocaine (*top*) or bupivacaine (*bottom*). Data expressed as mean ± SEM. *$P < 0.05$ *versus* saline control.

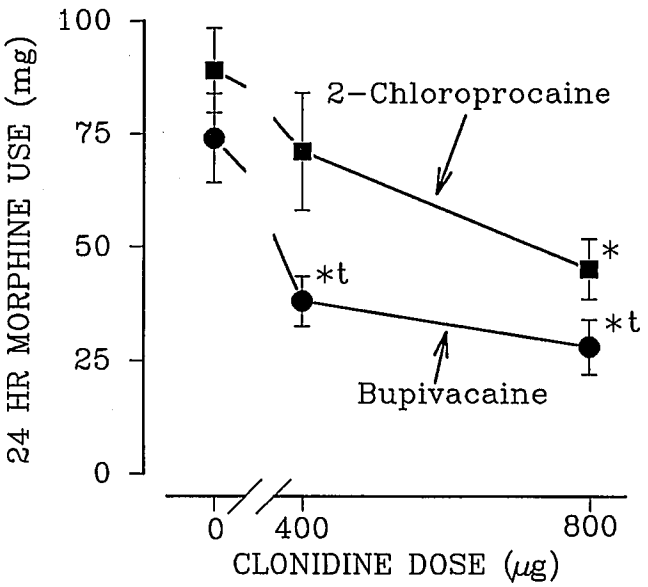

FIG. 3. Twenty-four-hour morphine use after epidural injection of clonidine in women receiving intraoperative anesthesia from 2-chloroprocaine (■) or bupivacaine (●). *$P < 0.05$ *versus* saline control. †$P < 0.05$ *versus* 2-chloroprocaine group.

way ANOVA of full blood pressure *vs.* time data set), whereas blood pressure did not differ in study groups in patients who received 2-chloroprocaine. One woman in the bupivacaine + low-dose clonidine group received iv fluids as treatment for a transient, asymptomatic 32% decrease in mean arterial pressure, occurring 30 min after clonidine injection. Orthostatic changes in blood pressure did not differ among study groups. In no case were there orthostatic symptoms upon sitting, and maximal decrease in blood pressure upon sitting exceeded 15% in only 5 of 300 observations, of which only 2 were in clonidine-treated patients.

Heart rate prior to study-solution injection was lower in the bupivacaine + high-dose clonidine group than in any other group. Compared to saline, low- and high-dose clonidine decreased heart rate by a similar degree ($P < 0.01$ by two-way ANOVA), and this response was not affected by choice of local anesthetic (average percent decrease in heart rate: in bupivacaine groups, 12% in low-dose and 4% in high-dose clonidine; in 2-chloroprocaine groups, 15% in low-dose and 12% in high-dose clonidine). One patient, in the 2-chloroprocaine + high-dose clonidine group, had asymptomatic bradycardia with a rate of 48 beats/min, occurring 90 min after clonidine injection. She refused atropine treatment, and her heart rate did not decrease further. Orthostatic changes in heart rate upon sitting did not differ among study groups, and maximal increase in heart rate upon sitting exceeded 15% in only 12 of 300 observations, of which 6 were in clonidine-treated patients.

Clonidine produced dose-dependent sedation lasting 3–4 h in the bupivacaine groups, whereas only the high-dose clonidine treatment produced sedation in the 2-chloroprocaine group (fig. 5). One patient in the bupivacaine + saline group was observed for 2 h with a respiratory rate of 8 breaths/min. Only one patient (in the 2-chloroprocaine + high-dose clonidine group) had an oxyhemoglobin saturation <90%. Despite a respiratory rate of 16 breaths/min, her Sp_{O_2} decreased to 84% during periods of snoring, and she was treated for 2 h with supplemental oxygen by nasal cannula. Thereafter, Sp_{O_2} was >94% without oxygen supplementation. The groups did not differ in the incidence of nausea or pruritus, except the bupivacaine + saline group, which had a higher incidence of pruritus (60%) than did the bupivacaine + clonidine groups (0%; $P < 0.05$).

Discussion

Initial experience with epidurally administered clonidine was, by ethical necessity, open-label, and designed to define dose-related side effects and tolerance; such studies were not designed to rigorously test efficacy. Subsequent double-blind, placebo-controlled trials assessing analgesic efficacy have yielded conflicting results, probably as a result of differences in study design and patient population. For example, epidurally administered clonidine, 150 μg, produces 3–5 h of analgesia following orthopedic or perineal surgery, as determined by change in pain scores,[2] but the same dose produces no analgesia following

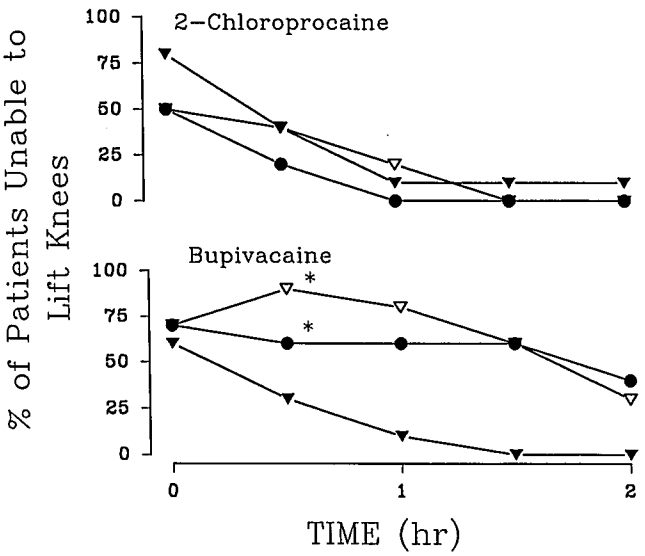

FIG. 4. Motor blockade after epidural injection of saline (▼), low-dose clonidine (▽), or high-dose clonidine (●) in women receiving intraoperative anesthesia from 2-chloroprocaine (*top*) or bupivacaine (*bottom*). Data expressed as percentage of women with motor blockade score ≥ 2. *$P < 0.05$. Curves differ from saline control by Friedman's ANOVA on the entire data set.

TABLE 2. Regression of Sensory Blockade to Pin Prick

Local Anesthetic	Treatment	Initial Level (Dermatome)	Time to Two-segment Regression (min)	Time to Four-segment Regression (min)
Bupivacaine	Saline	T_9	60	90
Bupivacaine	Clonidine-400	T_7*	90	150
Bupivacaine	Clonidine-800	T_8*	75	120
2-Chloroprocaine	Saline	T_{10}	60	90
2-Chloroprocaine	Clonidine-400	T_{10}	45	75
2-Chloroprocaine	Clonidine-800	T_{10}	60	90

Data expressed as median.

* $P < 0.05$ *versus* saline control for initial levels. No significant difference between groups in regression of sensory blockade.

thoracotomy, as determined by iv PCA meperidine usage.[3] Although this difference probably reflects in part the more severe pain following thoracotomy than after other procedures, it may as well be due to differences in definition of analgesia. One can argue that, while changes in pain scores may define a minor analgesic effect quite sensitively, operational definition of treatment to patient comfort by iv PCA is of more clinical significance.

Our initial open-label experience suggested that epidural clonidine doses greater than 500 or 600 μg were necessary for reliable analgesia.[4] To our surprise, 400 and 800 μg doses produced equivalent analgesia in a subsequent placebo-controlled, blinded study of women following cesarean section.[5] However, in the latter study clonidine was injected on admission to the recovery room, and resulted in dramatic prolongation of epidural anesthesia from previously injected bupivacaine. The current study, in which clonidine was injected when pain was perceived, rather than on recovery room admission, confirms this finding, and suggests that 400 μg is an adequate bolus dose in this patient population. That clonidine prolonged motor blockade in the bupivacaine group may reflect the more cephalad sensory level at the time of injection and the tendency to have received more bupivacaine compared to the saline group.

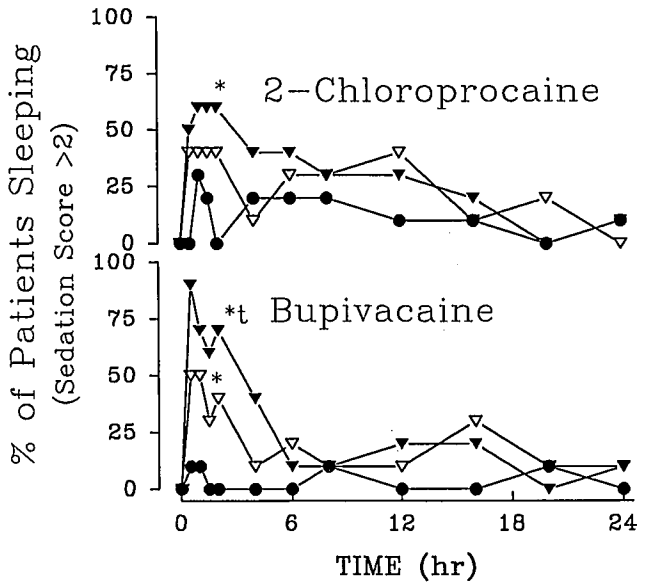

FIG. 5. Sedation following epidural injection of saline (▼), low-dose clonidine (▽), or high-dose clonidine (●) in women receiving intraoperative anesthesia from 2-chloroprocaine (*top*) or bupivacaine (*bottom*). Data expressed as percentage of women with sedation score ≥ 3. *$P < 0.05$ *versus* saline control by Friedman's ANOVA on entire data set. †$P < 0.05$ *versus* high-dose clonidine–bupivacaine group.

Although, in agreement with its lipid solubility, epidurally administered clonidine produces only brief analgesia following bolus injection, there have been few examinations of continuous epidural infusions of clonidine to produce sustained analgesia. An infusion rate after cesarean section of 20 μg/h, but not 10/μg, decreases iv PCA morphine use.[5] When combined with epidural morphine, 18-μg/h clonidine decreases the need for supplemental opioids after abdominal surgery.[6] Compared to a previous study of similar design,[5] the current study suggests that epidural clonidine infusion at 40 μg/h decreases iv PCA use following cesarean section more than does 10 or 20 μg/h, without altering the incidence of side effects. That iv PCA morphine usage dose not completely stop following epidural clonidine injection does not mean that clonidine is a poor analgesic. For example, in a study of similar design,§ epidural morphine 5 mg, believed to be an excellent analgesic therapy following cesarean section, decreased iv PCA usage by only 44%, compared to the 62% reduction following high-dose clonidine after bupivacaine in this study.

2-Chloroprocaine antagonizes the analgesic action of the α_2-adrenergic agonist clonidine as it does the opioid agonists fentanyl[7,8,10] and morphine.[9] The only previous investigation of 2-chloroprocaine and intraspinally injected α_2-adrenergic agonists demonstrated a reduction in the duration of labor analgesia following epidurally administered bupivacaine plus fentanyl and epinephrine when 2-chloroprocaine was previously injected.[8] Com-

§ Barber M: Personal communication. Abstract presented at the 23rd Annual Meeting of the Society of Obstetric Anesthesia and Perinatology, 1991.

parison with previous studies suggested that 2-chloroprocaine was interfering with the actions of both the opioid fentanyl and the adrenergic agonist epinephrine, although this was not rigorously tested.

The etiology of 2-chloroprocaine's antagonism of intraspinal analgesics is not clear. Long-acting inhibition of both opioid and α_2-adrenergic analgesia argue against an action of 2-chloroprocaine itself or a receptor-specific antagonist phenomenon. One could argue that 2-chloroprocaine produces less dense epidural anesthesia than does bupivacaine, allowing more nociceptive stimulation of the spinal cord during surgery and hence plastic changes in spinal cord nociceptive processing leading to increased postoperative pain.[12] Clinical experience argues against this hypothesis, as does the study in labor cited above.[8] Alternatively, 2-chloroprocaine or, more likely, a metabolite could activate a spinal excitatory system and antagonize intraspinally applied analgesics.[13] Against this argument are the observations that, compared to bupivacaine, iv morphine usage is increased after 2-chloroprocaine anesthesia for cesarean section for only the first few hours,[14] yet the antagonism of intraspinal opioids and α_2-adrenergic agonists is much longer-lasting.

A more plausible explanation for 2-chloroprocaine's antagonism of intraspinal analgesia is the presence of disodium ethylenediamine tetraacetic acid (EDTA), found only in commercial preparations of Nesacaine-MPF®. Relevance of disodium EDTA is supported by two observations. First, high local concentrations of the calcium chelator, disodium EDTA, may produce local effects by reducing extracellular calcium. This may explain hind limb myoclonus observed following intrathecal disodium EDTA administration in animals[15] and severe low back pain following epidural administration of 2-chloroprocaine with disodium EDTA in humans.[16] We have observed anecdotally, as has been reported,[16] that iv calcium administration reverses this back pain. Second, extracellular calcium is important to the analgesic actions of spinally administered opioid and α_2-adrenergic agonists, with inhibition of analgesia by calcium blockade and potentiation by calcium itself.[17] Whereas it should be noted that 2-chloroprocaine inhibits analgesia but not side effects produced by opioids and α_2-adrenergic agonists, this does not necessarily argue against a calcium-chelation mechanism, since the role of calcium in the generation of these side effects has not been determined.

The current study adds to previous investigations defining the safety and side effects produced by epidurally administered clonidine in the postoperative setting. The most worrisome side effect, hemodynamic depression, is rarely of significant degree; occurs within the first 1–2 h following injection; responds readily to iv fluid, ephedrine, or atropine therapy; and is not exacerbated by continuous infusion in healthy postoperative patients. However, cardiovascular safety of this therapy in patients with cardiac or pulmonary pathology remains to be determined. Unlike opioids, clonidine produces minor respiratory effects,[18] and unlike benzodiazepines,[19] does not enhance opioid-induced respiratory depression.[20] Mild hypoxemia in our patient at the peak time of clonidine-induced sedation suggests patients should be closely monitored following bolus clonidine administration. As would be expected, iv PCA morphine but not epidural clonidine was associated with pruritus. The only patient with a slow respiratory rate in this study received only iv PCA morphine and not clonidine.

The ultimate usefulness of epidural clonidine analgesia following cesarean section or other surgery will be determined by large comparative studies. Although clonidine offers unique advantages in certain pain syndromes, such as intractable cancer pain,[21,22] neuropathic pain,[23,24] and reflex sympathetic dystrophy¶ in the postoperative setting, aside from the lack of respiratory depression, it appears to have few definite advantages over traditional opioid therapy. Whether exploitation of synergistic interactions between α_2-adrenergic agonists and opioids,[25] local anesthetics,[26] or cholinergic systems,[27] or development of more selective α_2-adrenergic agonists of differing lipid solubility will suggest unique advantages for this class of compounds is unknown.

In summary, epidural clonidine analgesia following cesarean section is inhibited by previously injected 2-chloroprocaine. After bupivacaine anesthesia, epidural clonidine 400 μg produces analgesia equivalent to 800 μg while causing less sedation, and continuous infusion of 40 μg/h is well tolerated and reduces the need for supplemental morphine. Epidural clonidine therapy may decrease blood pressure and heart rate, and intense sedation following bolus administration may lead to intermittent upper respiratory tract obstruction. Whether the advantages of this nonopioid therapy for postoperative pain outweigh these side effects or can be minimized by combination drug therapy is now under investigation.

¶ Personal observations.

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