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Hemodynamic and Analgesic Profile after Intrathecal Clonidine in Humans

A Dose-Response Study

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Background: **Epidural clonidine produces effective postoperative analgesia in humans. Observed side effects include hypotension, bradycardia, sedation, and dryness of the mouth. A recent clinical study demonstrated that 150 μg intrathecal clonidine administered postoperatively as the sole analgesic agent was effective but produced hypotension and sedation. Animal studies have provided evidence of a biphasic effect on blood pressure after intrathecal clonidine administration, but no data concerning this effect in humans currently exist. This study was performed to evaluate the dose–response hemodynamic and analgesic profiles of intrathecal clonidine administered after a standard surgical intervention, without perioperative administration of additional analgesics, local anesthetics, or tranquilizers.**

Methods: **In a randomized prospective double-blind study, 30 women who underwent elective cesarean section during general anesthesia with thiopental, nitrous oxide, and halothane were studied. Forty-five minutes after tracheal extubation, a lumbar intrathecal puncture was performed, and the patients received 150 (group 1), 300 (group 2), or 450 (group 3) μg clonidine. Postoperative analgesia was assessed on a visual analog scale at rest and after deep cough at standard time points up to 24 h. At the same time points, blood pressure, heart rate, sedation, and respiratory rate also were recorded.**

Results: **Intrathecal clonidine decreased pain in all three groups both at rest and with coughing very shortly after injection, in a dose-dependent fashion. Clonidine 450 and 300 μg reduced pain scores significantly earlier (3rd and 6th min after intrathecal injection respectively), compared with 150 μg clonidine. Pain relief, defined as the time to first request for supplemental analgesic by patients, lasted 402 ± 75 min in group 1, 570 ± 76 min in group 2, and 864 ± 80 min in group 3; significant differences among all groups; $P < 0.01$–0.001). Clonidine reduced mean arterial pressure compared with baseline only in group 1 (21 ± 13%, $P < 0.05$). Delayed hypotension or bradycardia were not encountered after any of the three dose studies. Sedation was evident in all groups, but group 3 patients were significantly more sedated than group 1 and 2 patients. Respiratory rate and motor activity of the lower extremities were unaffected in all three groups (differences not significant).**

Conclusions: **These results demonstrate dose-dependent analgesia after intrathecal clonidine at doses as great as 450 μg. The nearly immediate analgesic effect observed after intrathecal injection of 300 and 450 μg clonidine strongly argues for a spinal rather than a systemic site of action of this α_2-adrenergic agonist. After 300 and 450 μg intrathecal clonidine a relative hemodynamic stability is observed, suggesting a pressor effect at peripheral sites. (Key words: Analgesia: postoperative. Anesthesia, obstetric: cesarean section. Anesthetic techniques: intrathecal. Pain: postoperative. Sympathetic nervous system, α_2-adrenergic receptor agonists: clonidine.)**

This article is accompanied by a Highlight. Please see this issue of ANESTHESIOLOGY, page 27A.

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WIDESPREAD application of opioid-induced spinal analgesia has been limited by side effects such as life-threatening and unpredictable respiratory depression.[1] Spinal clonidine, an α_2-adrenergic agonist, is being extensively evaluated as an alternative to spinal opioids for the control of pain and has been proven a potent analgesic free of some opioid-related, but not all, side effects.[2] To reduce the side effects of epidural clonidine without affecting its analgesic properties, continuous administration after bolus injection or combined ad-

ministration of clonidine with local anesthetics or opioids is advocated.[2]

Experimental data indicate that the analgesic effects of intrathecally administered α_2-adrenergic agonists are mediated spinally through α_2 adrenoceptors located in the superficial layers of the dorsal horn.[3,4] The rationale behind the intrathecal administration of clonidine was to achieve a high drug concentration in the vicinity of the α_2 adrenoceptors in the spinal cord. To date no controlled clinical study has been carried out to evaluate the analgesic effects or side effects of clonidine after all possible routes of administration (systemic, epidural, or intrathecal). Nevertheless, clinical trials of systemic,[5,6] epidural,[6-9] or intrathecal[10-12] administration of clonidine provide evidence that less clonidine is needed intrathecally than epidurally to produce nearly the same analgesic effect with fewer side effects.

The potential for hypotension after spinal clonidine has been noted.[8,9,11,13] The hemodynamic effects of clonidine are complex and depend on factors such as plasma concentration, route of administration, and presence or absence of anesthesia.[11,13-16] In animal studies it has been demonstrated that intrathecal clonidine, at lower doses, has a depressor effect on systemic blood pressure (BP), mediated by spinal α_2 adrenoceptors; but has a pressor effect; and produces marked bradycardia, mediated by peripheral α_2 adrenoceptors, when a larger dose is administered.[17] This effect appears to be mediated by a direct action on the thoracic spinal cord.[18] The only published clinical trial on lumbar intrathecal clonidine administration (150 μg) as a sole analgesic after human surgery documented minimal reduction of mean BP.[11]

The rationale of the current study was to evaluate the dose–response hemodynamic and analgesic effects of intrathecally administered clonidine as a sole analgesic after a standard surgical intervention without administration of additional analgesics, tranquilizers, or local anesthetics before, during, or immediately after the operation.

Materials and Methods

Patient Selection

Written informed consent was obtained, and the study was approved by the Ethics Committee of the local Medical Faculty in accordance with the Helsinki II declaration. Thirty healthy parturient women (ASA physical status 1) undergoing elective first cesarean section were randomly allocated to one of the three treatment groups (n = 10) in a double-blind fashion with the use of coded solutions of the same volume (3 ml). Randomization was performed preoperatively with a table of random numbers. Patients were not included in the study if maternal systemic disease was present. The operations were performed similarly (with regard to type of incision and operative steps; *i.e.*, Pfannenstiel's incision). The characteristics of the groups are summarized in table 1.

Anesthesia

After induction of anesthesia with thiopental (6 mg/kg) and paralysis with atracurium (0.3 mg/kg), the trachea was intubated and anesthesia was maintained with oxygen–nitrous oxide, supplemented with halothane not exceeding 0.5 vol%.[11] No additional analgesics or tranquilizers were administered during or immediately after the operation. Intraoperatively 1,000 ml Ringer's lactate was administered routinely. All patients received 40 ml/kg Ringer's lactate solution for the first 24 h postoperatively.

Assessment of Postoperative Pain

Assessment of pain was made on a visual linear analog scale (VAS) of pain intensity. Each patient was presented with a line 100 mm long and was told that the left end represented no pain and the right end the worst

Table 1. Patient Data

	Group 1 (150 μg clonidine)	Group 2 (300 μg clonidine)	Group 3 (450 μg clonidine)
Age (yr)	28 ± 5	29 ± 5	29 ± 5
Weight (kg)	75 ± 9	76 ± 8	75 ± 8
Height (cm)	164 ± 8	163 ± 9	165 ± 7
Duration of surgery (min)	43 ± 8	44 ± 10	41 ± 6

Values are mean ± SD. There were no significant differences between groups.

pain imaginable. They then were asked to make a mark on the line to indicate the intensity of their pain. Each pain assessment was immediately followed by a second one, in which the patient was asked to cough deeply and then mark another parallel line (pain with coughing).[11] Pain scores with coughing on the visual analog scale were recorded to assess the influence of pain relief produced by intrathecal clonidine on early postoperative mobilization. Changes in pain intensity after each assessment were estimated as changes in pain both at rest and with coughing and as percentages of baseline pain intensity scores, with the following equation:

$$\frac{\text{baseline pain score} - \text{pain score after intrathecal administration}}{\text{baseline pain score}} \times 100$$

Sensory level to pin prick and temperature were assessed immediately after pain score assessments.

Postoperative Analgesia

Intrathecal puncture and administration of the coded test substance was performed 45 min after tracheal extubation for all patients in a double-blind fashion. Observations were started immediately before intrathecal injection (0 min, baseline). The coded test substance (clonidine hydrochloride 150 μg/ml) in group 1 (n = 10) was 150 μg (~ 2 μg/kg), in group 2 was (n = 10) 300 μg (~ 4 μg/kg), and in group 3 (n = 10) was 450 μg (~ 6 μg/kg), diluted as needed to 3 ml volume in normal saline. Intrathecal injections were performed with a 25-G disposable spinal needle inserted with the patient in lateral position. The needle was inserted at interspace L2–L3 or L3–L4 depending on the body habitus, and correct placement of the needle tip within the subarachnoid space was confirmed by aspiration of cerebrospinal fluid before and after injection.

Duration of the analgesia was defined as the time until the patient made the first request for supplemental analgesia. When additional analgesia was demanded, the patient received 50 mg intravenous meperidine and left the study.

Postoperative Measurements

Data were recorded after the administration of the intrathecal medication in the 1st h; at 3, 6, 10, 15, 20, 30, 45 and 60 min; every hour up to 6 h; at 2-h intervals between 6 and 12 h; and then every 6 h up to 24 h. The person who obtained the analgesic and hemodynamic measurements was the same for every subject.

Hemodynamic and respiratory data at 0 min (immediately before intrathecal injection) also were compared. BP (systolic, diastolic, and mean) and heart rate (HR) were measured oscillometrically (Dinamap, Critikon, Tampa, FL). HR was additionally monitored electrocardiographically for the first 3 h after injection. Respiratory depression was considered present when the respiratory rate decreased to less than 9 breaths/min.

The occurrence of nausea, vomiting, or pruritus was noted during each assessment. Somnolence was scored at each interval on the following scale: 1 = awake and alert; 2 = awake but drowsy, responding to verbal stimulus; 3 = drowsy but rousable, responding to physical stimulus; and 4 = unrousable, not responding to physical stimulus.

Statistical Analysis

Results are reported as means ± standard deviation. Although presented in some cases for clarity as percent changes from baseline (mean ± SEM), all data analyses were performed on raw data. Intergroup comparison of patient characteristics, baseline hemodynamics, and baseline visual analog pain scores were made with Student's *t* test for unpaired data. Statistical comparisons for interval data (hemodynamic variables and pain scores) between groups were performed by two-way analysis of variance for repeated measures and at each time by one-way analysis of variance (Kruskall–Wallis). When only two groups were compared with each other the Mann–Whitney *U* test for comparisons at each time was used. Intragroup analysis of pain scores, hemodynamic parameters, and respiratory rate were performed on raw data by one-way analysis of variance for repeated measures, followed by a *post hoc* Scheffé's test for comparison with baseline. Duration of analgesia in the three groups was compared by the Kaplan-Meier method and a log-rank test. Ordinal data (scores of sedation and dryness of mouth) were analyzed with Friedman's two-way analysis of variance. Differences were considered significant when $P < 0.05$.

Results

Demographic data and duration of surgery were not significantly different among the three groups (table 1). Neither baseline pain and sedation scores nor hemodynamic and respiratory data differed significantly among the groups (tables 2 and 3).

Table 2. Comparison of Postoperative (baseline) Pain Scores and Duration of Analgesia after Intrathecal Clonidine Injection between the Three Groups

	Pain at Rest		Pain of Coughing		Duration of Analgesia (min)
	Baseline (mm)	Maximal Pain Relief (%)	Baseline (mm)	Maximal Pain Relief (%)	
Group 1 (150 μg clonidine)	70 ± 14 (53–90)	98 ± 2 (94–100)	81 ± 10 (63–100)	86 ± 16 (42–96)	402 ± 75* (240–480)
Group 2 (300 μg clonidine)	68 ± 14 (47–85)	98 ± 2 (95–100)	82 ± 11 (65–100)	92 ± 7 (72–100)	570 ± 76† (420–660)
Group 3 (450 μg clonidine)	70 ± 15 (49–92)	97 ± 4 (86–100)	82 ± 10 (66–100)	94 ± 5 (85–100)	864 ± 80† (660–900)

Values are mean ±SD (range).

Pain at rest = visual analogue scale score at rest; Pain on coughing = visual analogue scale score after deep cough. Intergroup comparison of pain scores (two-way ANOVA); all groups differ significantly with each other ($P < 0.001$). Intergroup comparison of duration of analgesia (Kaplan—Meier analysis and log-rank test): all groups differ significantly with each other: *$P < 0.01$ for comparisons between groups 1 with group 2; †P 0.001 for comparisons between groups 1 and 2 with group 3.

Onset of analgesia in all three groups was evident very shortly after intrathecal injection (figs. 1B and 2B). Reduction of pain scores at rest occurred significantly earlier in a dose-dependent fashion (fig. 1B). Group 2 patients (300 μg) experienced significantly lower pain scores between 6 and 20 min than did group 1 ($P < 0.01$, fig. 1B). Pain scores in group 3 patients (450 μg) differed significantly between 3 and 20 min compared with those in group 1 patients ($P < 0.001$, fig. 1A). After this initial 20 min period and until 180 min pain score reduction was similar in all three groups. After 240 min, the pain scores of patients in groups 2 and 3 were significantly lower than those of patients in group 1 up to 300 min ($P < 0.01$). Finally, the pain scores of patients in group 3 were significantly lower than those of group 2 patients between 360 and 480 min ($P < 0.05 - P < 0.01$, respectively) (figs. 1A and 2A). Similar results were observed for pain scores after deep cough (figs. 2A and 2B).

Duration of analgesia, as determined by the time elapsed before the first supplemental analgesic request by patients, lasted 402 ± 75.1 (range 240–480 min) in group 1,570 ± 76.2 min (range 420–660 min) in group 2, and 864 ± 80.1 min (range 660–900 min) in group 3 ($P < 0.001$, fig. 3 and table 2).

No segment spread of analgesia was detected.

Table 3. Comparison of Hemodynamic Variables after Intrathecal Clonidine Injection between the Three Groups

Variable	Group	Baseline	Lowest Subsequent Mean Value Level Observed	% Change	Time Observed† (min)
Systolic arterial pressure (mmHg)	150 μg clonidine	119 ± 14	102 ± 20	−14 ± 9 (NS)	T90
	300 μg clonidine	123 ± 12	107 ± 12	−11 ± 6 (NS)	T420
	450 μg clonidine	122 ± 13	108 ± 10	−9 ± 7 (NS)	T60
Diastolic arterial pressure (mmHg)	150 μg clonidine	76 ± 9	58 ± 13	−25 ± 11*	T90
	300 μg clonidine	77 ± 9	65 ± 10	−14 ± 11 (NS)	T300
	450 μg clonidine	77 ± 7	67 ± 11	−13 ± 8 (NS)	T120
Mean arterial pressure (mmHg)	150 μg clonidine	90 ± 11	71 ± 13.0	−21 ± 13*	T90
	300 μg clonidine	89 ± 10	75 ± 16	−13 ± 8 (NS)	T20
	450 μg clonidine	89 ± 8	77 ± 5	−11 ± 6 (NS)	T60
Heart rate (beats/min)	150 μg clonidine	77 ± 9	67 ± 8	−12 ± 12 (NS)	T120
	300 μg clonidine	77 ± 9	67 ± 7	−13 ± 8 (NS)	T120
	450 μg clonidine	78 ± 6	66 ± 10	−13 ± 13 (NS)	T120

Values are mean ± SD. NS = not significant.

* $P < 0.05$ for comparisons with baseline (one-way ANOVA, post hoc test).

† After intrathecal puncture.

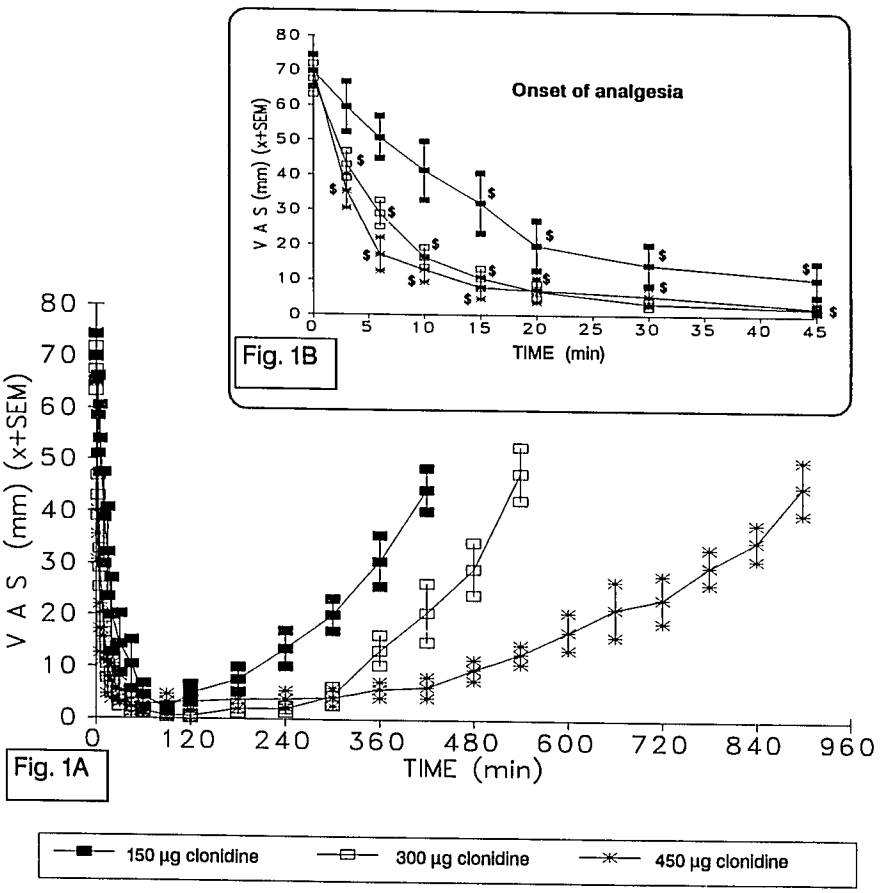

Fig. 1. Changes in visual analog pain scores (mean ± SEM) until 960 min after 150, 300, and 450 µg intrathecal clonidine (groups 1, 2, and 3, respectively). Onset of analgesia in all three groups was evident very shortly after intrathecal injection (*B*). Significant pain score reductions compared with baseline were observed between 15 and 300 min in group 1, between 3 and 480 min in group 2, and between 3 and 840 min in group 3 ($*P* < 0.05, *A* and *B*). Comparisons between groups 1 and 2 revealed significant differences between 6 and 20 min (*B*) and between 240 and 300 min (*A*; *P* < 0.01). Comparisons between groups 1 and 3 revealed significant differences between 3 and 20 min (*B*) and between 240 and 300 min (*A*; *P* < 0.001). Comparisons between groups 2 and 3 revealed significant differences at 6 min (*B*) and between 360 and 540 min (*A*; *P* < 0.05 − 0.01). Between 20 and 180 min, pain score reduction was similar in all three groups (*A*).

Intragroup up comparisons revealed a reduction of arterial BP (systolic, diastolic, and mean) only in group 1 ($P < 0.05$), whereas a nonsignificant fluctuation was noticed throughout the study in the other two groups (fig. 4 and table 3). Compared with baseline, mean arterial BP in group 1 was significantly lower between 90 and 360 min ($P < 0.05$), with a maximum decrease (21 ± 13%, $P < 0.05$) recorded at 360 min after intrathecal administration (fig. 4A and table 3). The maximum reduction in mean arterial BP was observed at 20 min in group 2 (13 ± 8%, difference not significant) and at 60 min in group 3 (11 ± 6%, difference not significant) (table 3). A delayed hypotensive effect was not observed in any of the groups studied up to 24 h after intrathecal clonidine administration.

Compared with baseline, clonidine in the three dose regimens studied did not reduce HR (fig. 5 and table 3). No patient in any group was treated for bradycardia (HR < 56 beats/min):

All patients were awake and alert immediately before intrathecal puncture (figs. 6A–6C). Intrathecal clonidine produced sedation in all groups studied. Patients in group 3 were significantly more sedated than were groups 1 and 2 at 15, 90, 120, and 360 min and more sedated than group 2 at 420 min ($P < 0.05$–0.001, fig. 6). Patients in group 2 were not significantly more sedated than patients in group 1 (figs. 6A and 6B).

All patients in the three groups studied reported dryness of mouth after intrathecal clonidine administration.

Discussion

Clonidine produces its antinociceptive, cardiovascular, and sedative effects by sometimes opposing actions[17] at multiple sites.[19,20] These actions depend on the site of administration[6,11,21,22] the dose,[7–9,17,22] and the concomitant administration of other drugs.[23–25]

Knowledge of possible hemodynamic side effects after intrathecal administration of α_2-adrenergic agonists provides guidelines for safe and extensive use of this therapy in clinical anesthetic practice. Animal and

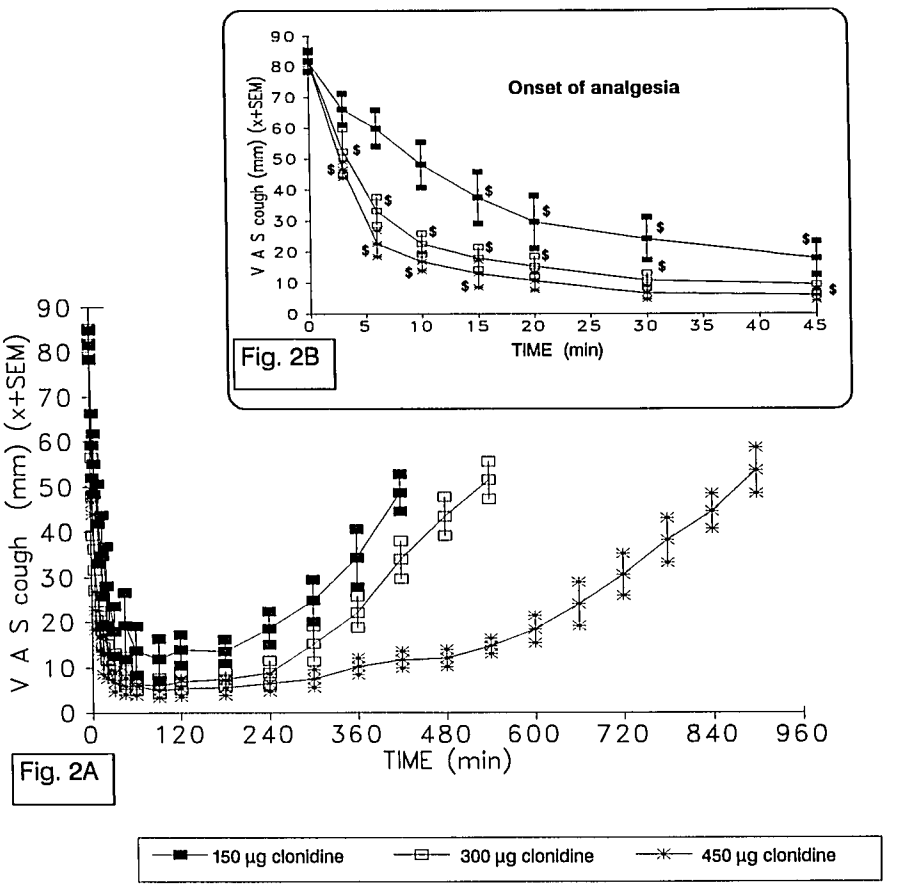

Fig. 2. Changes in visual analog pain scores after deep cough (mean ± SEM) until 960 min after 150, 300, and 450 µg intrathecal clonidine (groups 1, 2, and 3, respectively). Onset of analgesia was evident very shortly after intrathecal injection (*B*). Significant reductions in pain score during coughing compared with baseline were observed between 15 and 300 min in group 1, between 3 and 480 min in group 2, and between 3 and 840 min in group 3 ($\$P < 0.05$, *A* and *B*). Intergroup comparisons between groups 1 and 2 revealed significant differences between 6 and 20 min (*B*) and between 240 and 300 min (*A*; $P < 0.01$). Comparisons between groups 1 and 3 revealed significant differences between 3 and 20 min (*B*) and between 240 and 300 min (*A*; $P < 0.001$). Comparisons between groups 2 and 3 revealed significant differences at 6 min (*B*) and between 360 and 540 min (*A*; $P < 0.05 - 0.01$). Between 20 and 180 min, pain score reduction was similar in all three groups (*A*).

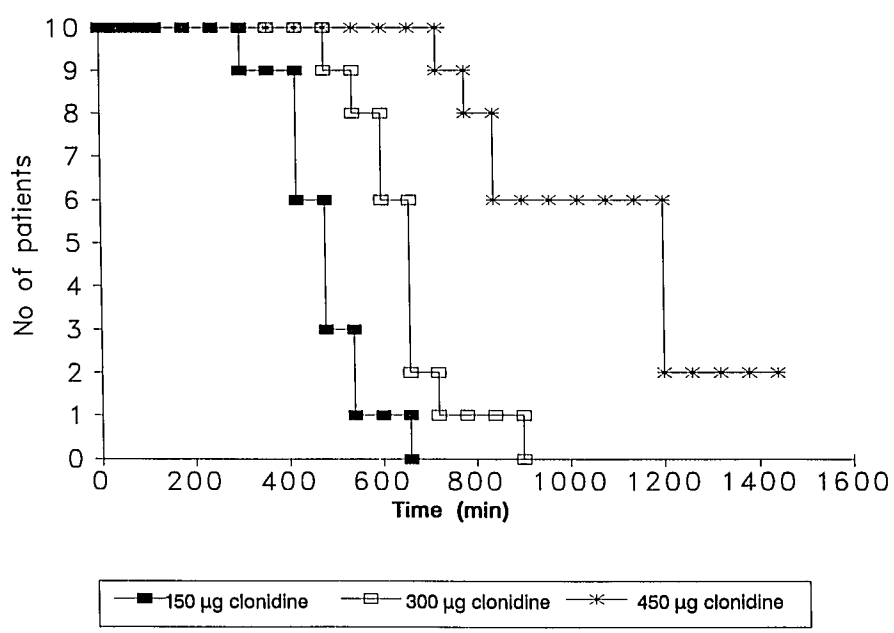

Fig. 3. Log-rank curves. Number of patients not requesting analgesia after intrathecal clonidine administration (filled squares = 150 µg; open squares = 300 µg; asterisks = 450 µg clonidine). At a patient's first request for additional analgesia, the study for that patient was terminated. The log-rank curves representing the three doses studied are significantly different ($P < 0.001$). Duration of analgesia was 402 ± 75.1 min (range 240–480 min) in group 1, 570 ± 76.2 min (range 420–660 min) in group 2, and 864 ± 80.1 min (range 660–900 min) in group 3 ($P < 0.001$).

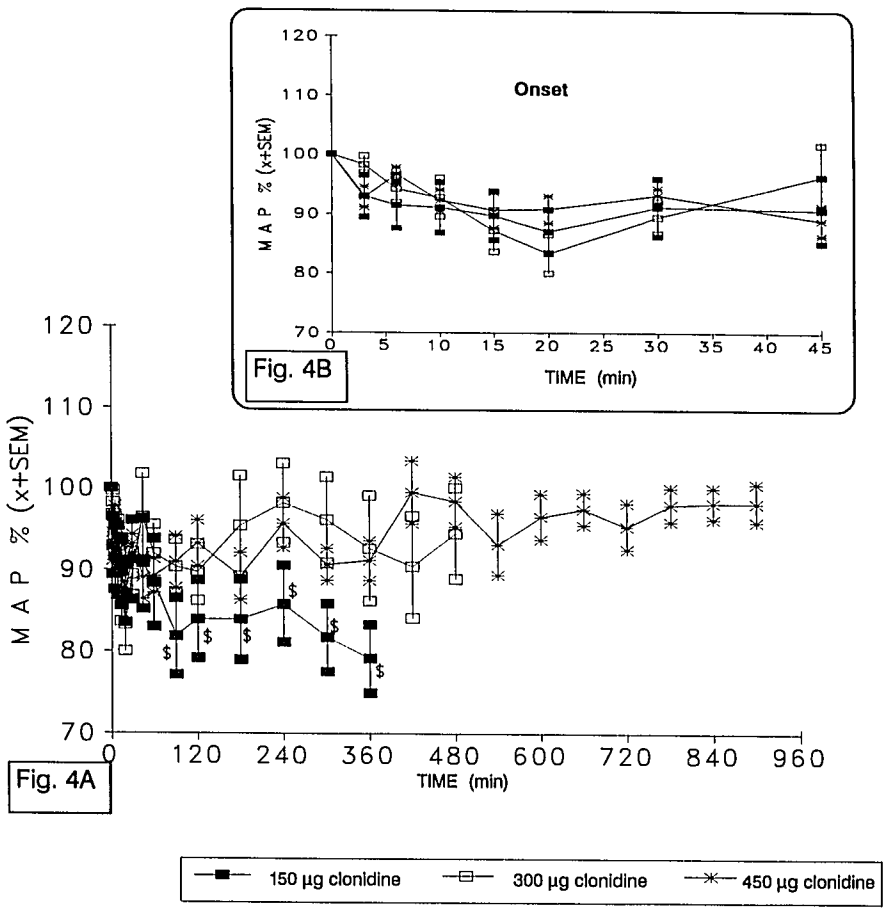

Fig. 4. (*A* and *B*) Changes in mean arterial blood pressure (MAP) after 150, 300, and 450 µg intrathecal clonidine (groups 1, 2, and 3, respectively). Results are expressed as percentage change from baseline (mean ± SEM). Statistics were performed on raw data. In group 1, MAP decreased significantly from 90 to 360 min in comparison with baseline ($P < 0.05, one-way analysis of variance and *post hoc* Scheffé's test) (*A*). In groups 2 and 3, MAP did not differ significantly in comparison with baseline throughout the study period. Vertical statistics revealed significant differences only at 360 min between groups 1 and 2 and groups 1 and 3 (Mann–Whitney *U* test) ($P < 0.05) (*A* and *B*).

clinical studies have demonstrated that spinal (epidural and intrathecal) administration of α_2-adrenergic agonists decreases BP or HR or both.[8,11,13,17,26] This is the first dose–response study of intrathecal clonidine administration in humans. The current data demonstrate a relative hemodynamic stability after 300 and 450 µg intrathecal clonidine. Furthermore, intrathecal clonidine as a sole analgesic, in a dose-dependent fashion up to 450 µg, significantly reduced postoperative pain scores almost immediately after injection. These analgesic effects strongly argue for a spinal rather than a systemic site of action of clonidine. In addition, this study demonstrates that less clonidine is needed intrathecally than epidurally or systemically to produce a strong analgesic effect of up to 14 h duration and with fewer hemodynamic side effects.

Hemodynamic Effects

Clonidine induces different hemodynamic effects after systemic or spinal administration. Systemically administered clonidine produces a biphasic effect on BP: in smaller doses, actions probably at brainstem sites decrease BP, whereas in larger doses BP increases as a result of direct peripheral vasoconstriction.[27]

Solomon *et al.*[17] demonstrated in rats that lumbar intrathecal clonidine decreases BP at lower doses, mediated by a spinal α_2-adrenergic mechanism, whereas at higher doses it increases BP by action at peripheral α_1 and α_2 adrenoceptors. Castro and Eisenach[14] documented in an experimental study in sheep that the same clonidine dose (300 µg) administered *via* three routes (intravenous, lumbar epidural, and intrathecal) produced significantly different hemodynamic effects: intravenous clonidine increased BP immediately after injection; lumbar intrathecal injection decreased BP significantly after 10 min; and epidural clonidine decreased BP significantly only 2 h after injection. The authors do not provide body weight data of the animals studied.[14] If one takes in account that the body weight of the sheep studied is the same as that reported by

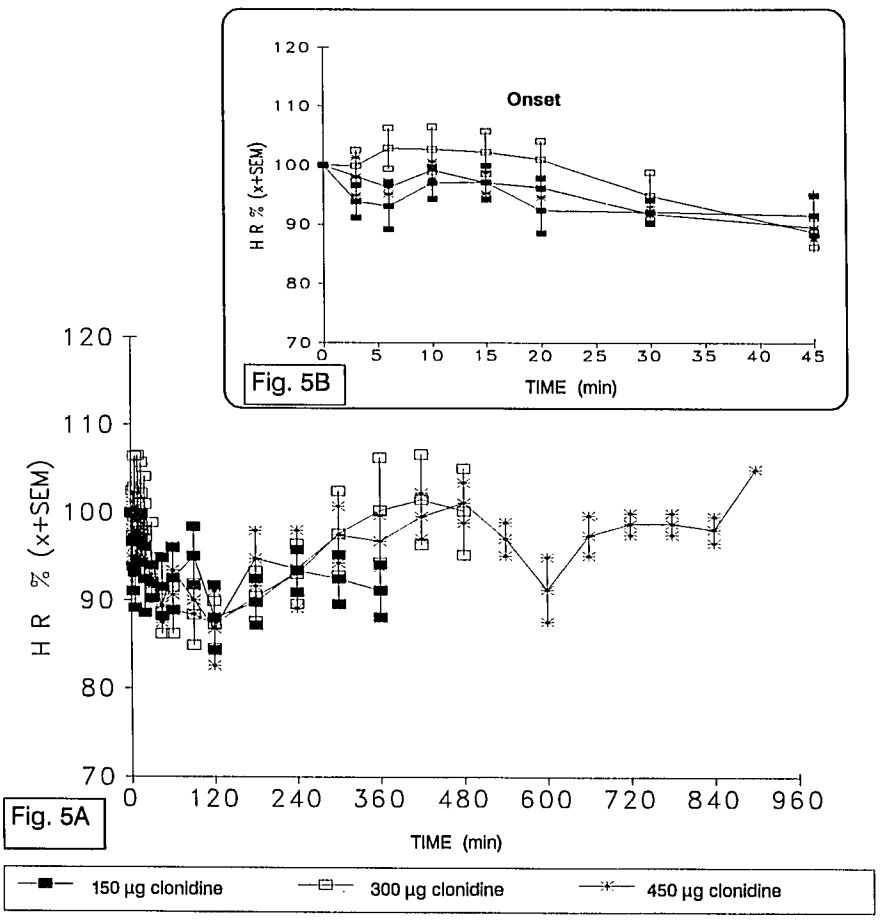

Fig. 5. (*A* and *B*) Changes in heart rate (HR) after 150, 300, and 450 µg intrathecal clonidine (groups 1, 2, and 3, respectively). Results are expressed as percentage change from baseline (mean ± SEM). Statistics were performed on raw data. No significant differences in HR were found among the groups.

Eisenach *et al.* elsewhere (~ 45 kg mean weight),[28,29] one can assume that the dose used by Castro and Eisenach[14] in sheep was ~ 7 µg/kg, which is close to the dose administered in group 3 (450 µg, ~ 6 µg/kg) of the current study in humans. In contrast to Castro and Eisenach, we did not observe a depressor effect on BP after lumbar intrathecal administration of 6 µg/kg clonidine.

If the experimental data in awake sheep are applicable to humans, who, in addition, are in postoperative pain, the results of a later experimental study performed in awake sheep by Eisenach and Tong[18] confirm the results of our clinical study. These authors studied the same intrathecal clonidine dose used previously by Castro and Eisenach[14] (300 µg, ~ 7 µg/kg, although again, body weight data are not provided). They demonstrated that thoracic but not lumbar or cervical intrathecal clonidine decreased BP, whereas a pressor effect of BP was documented after intrathecal administration of 1,500 µg (~ 33 µg/kg) at all spinal levels.[18] Finally, the authors demonstrated that an intermediate intrathecal clonidine dose of 750 µg (~ 17 µg/kg) injected at all spinal levels (lumbar, thoracic, and cervical) had no effect on BP.[18]

The majority of experimental studies concerning intrathecal administration of clonidine suggest the existence of a safe dose range below and above which depressor or pressor hemodynamic effects may be observed in humans. In the current study, immediate depressor effects on BP were encountered only after 150 µg intrathecal clonidine, and neither pressor nor depressor effects, immediately or delayed, were observed after 300 and 450 µg. Therefore, clonidine doses > 300 µg and at least ≤450 µg may be within the window of hemodynamic stability after this route of administration.

Castro and Eisenach[14] furthermore documented that 300 µg clonidine injected in the lumbar epidural or

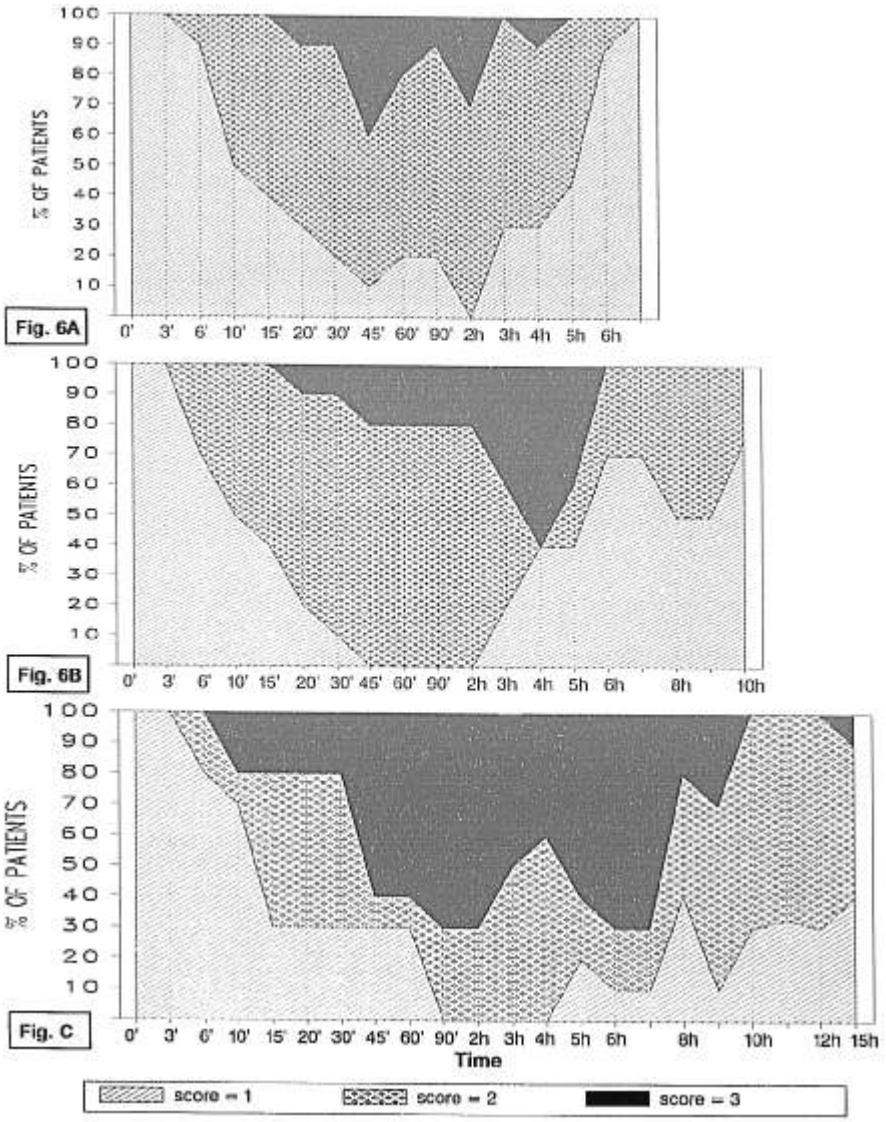

Fig. 6. Sedation scores after administration of 150 (*A*), 300 (*B*), and 450 (*C*) μg intrathecal clonidine (groups 1, 2, and 3, respectively). Scores: 1 = awake and alert; 2 = awake but drowsy, responding to verbal stimulus; 3 = drowsy, but rousable, responding to physical stimulus; and 4 = unrousable, not responding to physical stimulus. Intrathecal clonidine produced sedation in all groups. Patients in group 3 were significantly more sedated than those in groups 1 and 2 at 15, 90, 120, and 360 min and more sedated than group 2 at 420 min ($P < 0.05$–0.001). Patients in group 2 were not significantly more sedated than were patients in group 1.

intrathecal space produces plasma concentrations similar to those after intravenous injection after the first 10–20 min. They also observed a clear correlation between plasma concentration and BP only after intravenous clonidine injection: BP was decreased at concentrations < 2 ng/ml and an increased BP at concentrations > 2 ng/ml.[14] Therefore it is possible that plasma concentrations are not advantageous in predicting the BP effect after intrathecal clonidine administration in humans. The authors also suggested that their pharmacokinetic results in sheep would predict, more accurately than preliminary reports in humans,[7] the effective epidural clonidine dose in humans to be 6–15 μg/kg.[14] This prediction was later confirmed by several clinical studies.[8,9,32]

Oral clonidine has been reported to produce severe bradycardia in hypertensive patients with resting bradycardia or with sinoatrial or atrioventricular nodal dysfunction or in patients taking agents slowing HR or cardiac conduction, because of a direct cardiac and central mechanisms.[31] Epidural clonidine in a dose range of 100–900 μg significantly decreases HR between 19 and 24% 113 min after administration in postoperative patients.[8] Similar results have been reported after epidural administration of clonidine in patients with cancer[32] and in healthy volunteers.[19,20] Of

176 patients in clinical studies evaluating epidural clonidine in the postoperative setting,[6-9,23,26,30,33,34] severe dysrhythmia developed in 4: in 1, atrial fibrillation developed after 100 μg epidural clonidine,[8] and 3 other patients received atropine for severe bradycardia.[6,9]

In the current study, the maximal reduction of HR was 12–13% (difference not significant) in all groups studied and coincided 120 min after administration. Despite the small sample size, none of these 30 patients required any therapeutic intervention, indicating that the intrathecal doses studied may not produce excessive bradycardia as a result of direct cardiac or central action, at least in young and healthy patients. Furthermore, delayed bradycardia due to cephalad spread by rostral circulation in cerebrospinal fluid or by systemic absorption and central redistribution after intrathecal administration was not detected in the observation period.

Analgesic Effects

Experimental data provide evidence that the antinociceptive effects of intrathecal α_2 agonists in animals are mediated by spinal α_2 adrenoceptors: (1) α_1- and α_2-adrenergic receptors are present in the superficial layers of the dorsal horn[4]; (2) only the intrathecal administration of α_2 but not of α_1 antagonists reversed antinociception produced by intrathecal clonidine in rats[17,35]; and (3) intravenous administration of α_2 antagonists had no effect on the antinociceptive effect of intrathecal clonidine.[17,28,35] These antinociceptive effects of intrathecally administered α_2-adrenergic agonists have been produced in a variety of species and in a wide variety of pain models.[3,36].

The results of this first dose–response study in humans showed that intrathecally administered clonidine produces nearly immediately a significant reduction of postoperative pain scores in a dose-dependent fashion 3, 6, and 15 min after administration of 450, 300, and 150 μg, respectively. We have previously documented in a placebo-controlled study that 150 μg intrathecal clonidine (*i.e.*, the lowest dose used in the current study) reduces postoperative pain scores significantly compared with placebo by 20 min after injection.[11] This strongly argues for a spinal rather than a systemic site of action for this α_2-adrenoceptor agonist. Nevertheless, experimental data demonstrate that clonidine produces analgesia when directly injected in the locus ceruleus as well.[37] We therefore cannot exclude delayed supraspinal analgesic effects, which may account for the long duration of analgesia observed after 300 and 450 μg intrathecal clonidine as a result of rostral spread or systemic absorption and central redistribution. On the other hand, the high lipid solubility of clonidine and the rapid absorption and elimination in cerebrospinal fluid argue against a residence time long enough for extensive rostral distribution.[14]

Clinical studies suggest that the effective dose of epidural clonidine for postoperative pain relief is ≥3 μg/kg.[7-9] An intrathecal clonidine dose of 2 μg/kg produces a strong analgesic effect of 6 h median duration, establishing this dose as the smallest effective dose for postoperative analgesia.[5,11]

The duration of analgesia in the current study was dose-dependent: 450 μg intrathecal clonidine produced postoperative analgesia of approximately 14 h duration, the longest ever reported after a bolus[6,8,26] or bolus plus continuous[9,30] administration of clonidine *via* any route (systemic,[5,6,30] epidural,[6,8,9,26,30] or intrathecal[10,11]).

Side Effects

Sedation has been documented after systemic,[5,20,22,30] epidural,[6,8,9,30] or intrathecal[10,11] administration of clonidine in humans. Experimental data show that the sedative–hypnotic effect of α_2-adrenergic agonists is caused by actions primarily in the locus ceruleus.[38] In the current study, sedation was not significantly different between the two groups receiving 150 and 300 μg of intrathecal clonidine. Only patients who received 450 μg intrathecal clonidine were significantly more sedated than both other groups. Because hemoglobin oxygen saturation or arterial blood gases were not measured, we cannot exclude the possibility that the intense sedation observed in group 3 could produce hypoxemia, especially in high-risk patients, although we did not encounter significant reduction in the respiratory rate. Quantitation of the sedative effect is difficult because observations were based on an arbitrary scale. The observation that intrathecal clonidine produced sedation in the 1st h after administration of 150–450 μg argues toward a supraspinal action *via* systemic absorption rather than rostral spread.[14]

In conclusion, whereas sedation may be a considerable side effect after larger doses (450 μg), hypotension is the main side effect only after smaller doses (< 300 μg) of intrathecal administration of clonidine. However, we did not observe delayed hypotension, considering the fluid preload administered perioperatively, or even a net pressor effect after 300 and 450 μg in-

trathecal clonidine. Therefore these two doses may be considered hemodynamically stable in the postoperative setting and are smaller than the dose that produces a net pressor effect in humans after intrathecal administration.

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