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Epidural Epinephrine and Clonidine

Segmental Analgesia and Effects on Different Pain Modalities

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Background: It is not known whether epidural epinephrine has an analgesic effect *per se*. The segmental distribution of clonidine epidural analgesia and its effects on temporal summation and different types of noxious stimuli are unknown. The aim of this study was to clarify these issues.

Methods: Fifteen healthy volunteers received epidurally (L2-L3 or L3-L4) 20 ml of either epinephrine, 100 µg, in saline; clonidine, 8 µg/kg, in saline; or saline, 0.9%, alone, on three different days in a randomized, double-blind, cross-over fashion. Pain rating after electrical stimulation, pinprick, and cold perception were recorded on the dermatomes S1, L4, L1, T9, T6, T1, and forehead. Pressure pain tolerance threshold was recorded at S1, T6, and ear. Pain thresholds to single and repeated (temporal summation) electrical stimulation of the sural nerve were determined.

Results: Epinephrine significantly reduced sensitivity to pinprick at L1-L4-S1. Clonidine significantly decreased pain rating after electrical stimulation at L1-L4 and sensitivity to pinprick and cold at L1-L4-S1, increased pressure pain tolerance threshold at S1, and increased thresholds after single and repeated stimulation of the sural nerve.

Conclusions: Epidural epinephrine and clonidine produce segmental hypoalgesia. Clonidine bolus should be administered at a spinal level corresponding to the painful area. Clonidine inhibits temporal summation elicited by repeated electrical stimulation and may therefore attenuate spinal cord hyperexcitability. (Key words: Analgesia, epidural. Sympathetic nervous system, α_2 -adrenergic agonists: clonidine. Sympa-

thetic nervous system, catecholamines: epinephrine. Pain, experimental. Central temporal summation.)

STIMULATION of α_2 -adrenoreceptors located in the spinal cord produces antinociception.¹ Therefore, epidurally administered adrenergic agonists have the potential to produce segmental analgesia.

The addition of epinephrine to local anesthetics or opioids may enhance epidural analgesia.²⁻⁵ This effect may be the result of reduced vascular uptake of local anesthetics⁶ and opioids,⁴ which increases their concentration at the neural targets. Epinephrine is an α -adrenoreceptor agonist and produces antinociception when administered intrathecally in animals.^{7,8} An early report described the efficacy of intrathecal epinephrine as a sole analgesic for labor in humans.⁹ Analgesia after intrathecal administration does not necessarily imply analgesia after epidural administration. Systemic absorption,¹⁰ dura penetration, and metabolism¹¹ may affect the spinal bioavailability of epidurally administered epinephrine. Segmental hyposensitivity to ice and pinprick has been observed after epidural epinephrine in one volunteer.⁴ However, the effect of epinephrine has not been investigated in a randomized controlled fashion, so presently it is not known whether epidural epinephrine has *per se* an analgesic action.

Several investigations have shown the efficacy of the α_2 -adrenoreceptor agonist clonidine when administered epidurally for the management of postoperative¹²⁻¹⁶ and chronic¹⁷⁻²⁰ pain. Epidural clonidine produces analgesia to cold pain test in the foot, but not in the hand,²¹ which strongly suggests a spinal action. However, the segmental distribution of analgesia is not known, and the effects of epidural clonidine on different types of noxious stimuli and on temporal summation have not been investigated. Temporal summation occurs when the repetition of a peripheral stimulus causes increased pain perception. Increased and prolonged firing of dorsal horn neurons after repeated stimulation²² (central

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sensitization) is probably the mechanism underlying temporal summation. Central sensitization is likely to play an important role in the physiopathology of acute and chronic pain syndromes, such as postoperative and neuropathic pain.²³

We have investigated the effects of epidurally administered epinephrine and clonidine on different types of experimentally induced painful and nonpainful stimuli applied on different dermatomes. The aims were to assess the segmental spread of analgesia, to identify the types of stimulation inhibited by epidural epinephrine and clonidine, and to investigate the effects of these drugs on temporal summation.

Materials and Methods

Anesthetic Procedure

We studied 16 healthy volunteers. Exclusion criteria were a history of alcohol abuse or intake of psychotropic drugs, the intake of opioids or nonsteroidal antiinflammatory drugs in the past 2 weeks, the intake of other analgesics or sedatives in the past 24 h, coagulation abnormalities, pregnancy, or fever. The study was approved by the local ethics committee, and written informed consent was obtained from all volunteers. The investigation was conducted with a randomized, double-blind, placebo-controlled, cross-over design. All randomizations were performed by drawing lots.

The volunteers fasted for at least 6 h and were not premedicated. Electrocardiograph, noninvasive blood pressure (one measurement every 5 min), and hemoglobin oxygen saturation using pulse oximetry (SpO_2) were monitored with a Hellige Servomed monitor (Hellige AG, Freiburg, Germany). Expired carbon dioxide was monitored continuously *via* a nasal catheter with a Hewlett Packard M 1025B anesthetic gas analyzer (Hewlett Packard, Andover, USA). A peripheral intravenous cannula was inserted, and 4 ml/kg Ringer's lactate was rapidly infused, followed by $2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$.

To minimize the risk of infection, bleeding, and perforation of the dura, no epidural catheter was inserted; only a single-shot injection was performed. For the same reasons, the three punctures were not performed at the same interspace, but one of two randomized schedules were followed: L2-L3, L3-L4, and L2-L3, or L3-L4, L2-L3, and L3-L4, with an interval of at least 1 week between sessions. All punctures were performed in the sitting position, with the median approach, using a 18-gauge Tuohy needle. They were done by the same anes-

thesiologist, who had previously performed more than 2,000 epidural blocks. The epidural space was identified by loss of resistance, injecting no more than 2 ml of 0.9% saline. Only a clear feeling of loss of resistance was considered as identification of the epidural space.

Each volunteer received, in a random order, an epidural injection of 20 ml of either epinephrine, 100 μg , clonidine, 8 $\mu\text{g}/\text{kg}$, (Catapresan®, Boehringer, Basel, Switzerland) or saline, 0.9%, on three different days. Epinephrine and clonidine were diluted with 0.9% saline. The dose of 100 μg epinephrine was chosen because it is probably the dose most frequently used in association with local anesthetics for epidural anesthesia. The dose of 8 $\mu\text{g}/\text{kg}$ clonidine was chosen because it roughly corresponds to the dose providing pain relief in postoperative patients.^{12,15} A test dose of 5 ml of the epidural solution was first injected. After 4 min, the remaining dose was administered in increments of 5 ml every 60 s. Each 5-ml bolus was injected over 15–18 s. Before each injection, the syringe was detached from the needle to exclude intravascular or intrathecal placement. During this time, blood pressure was measured every 2 min. After injection of the last bolus, the volunteers were placed in the supine position.

Atropine, 0.5 mg, was injected intravenously if the heart rate was less than 45 beats/min. The volunteers scored sedation on a 10-cm visual analogue scale (VAS), where 0 = fully fit and 10 = hardy able to keep the eyes open. Blood pressure, heart rate, SpO_2 , end-tidal carbon dioxide, and sedation scores were recorded before and 30, 60, 90, and 120 min after the epidural injection and each time before the beginning of the test series.

Testing Procedure

The three sessions were planned for each subject at the same time of the day. The volunteers first tried all tests for training. Then baseline recordings of all tests were performed. After the epidural injection, the test series were performed 30, 60, 90, and 120 min after the administration of the total volume of the solution investigated. In each series, the tests were performed in the following order: pain rating after electrical stimulation, pinprick, cold, pressure pain tolerance, and single and repeated electrical stimulation of the sural nerve. In all threshold determinations, the mean of two values was calculated. The test series lasted approximately 15 min.

Pain Rating (VAS) after Electrical Stimulation. Copper stainless steel dull pins (diameter, 1.2 mm;

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length, 2 mm) were applied on the left side to the skin of the following dermatomes: S1 (foot, just distal to the lateral malleolus); L4 (5 cm above a line drawn from the middle of the patella to the anterior superior iliac spine); L1 (anterior superior iliac spine); T9 (5 cm from the median line, on a horizontal line passing 3 cm above the umbilicus); T6 (5 cm from the median line, on a horizontal line passing 2 cm above the xiphoid process); T1 (elbow, on the medial epicondyle); forehead (1 cm above the middle of the eyebrow). A 25-ms, train-of-five, 1-ms, square-wave impulse (perceived as a single stimulus) was delivered from a computer-controlled constant current stimulator (University of Aalborg, Denmark). Subjective pain detection threshold, defined as the current intensity eliciting a distinct pricking pain, was determined at each dermatome tested in a randomized order before the epidural injection by increasing the current intensity from 1 mA in 1-mA intervals. For pain rating, which was the variable analyzed, a stimulus of an intensity of 1.8 times the baseline pain threshold (determined only before the epidural injection) was delivered at each dermatome tested in a randomized order. After each stimulation, the volunteers rated the perceived pain on an electronic 10-cm VAS. Before each rating series, two stimuli at two random dermatomes were delivered for training.

Pinprick and Cold. Sensitivity to pinprick and cold were tested at the aforementioned dermatomes, on the left side, 2 cm from the sites where the pin electrodes were applied. Pinprick was performed by pricking the skin twice with an interval of about 0.3 s, using a 21-gauge sharp-bevel needle. Cold sensitivity was tested with gel bags (Physiopack, Fisch Laboratories, Vibraye, France) kept in a freezer, and applied to 4 cm² skin surface for 2 s. Response was defined as *hyposensitivity* when subjects did not feel any sensation or when they felt only a sensation of touch or *light* pinprick (cold).

Mechanical Pressure. Pressure pain tolerance threshold was determined on the center of the pulp of the third and fourth left toes (S1), 3 or 4 cm above the xiphoid process (T6), and at the left and right ear lobes, in a randomized order. An electronic pressure algometer (Somedic AB, Stockholm, Sweden),²⁴ whose probe had a surface area of 64 mm², was used. The pressure was increased from 0 at a rate of 30 kPa/s to a maximum pressure of 1000 kPa. *Pain tolerance threshold* was defined as the point when the volunteer did not want the pressure to be increased further. If the tolerance threshold was more than 1000 kPa, this value was con-

sidered as tolerance threshold. The mean of the two measurements at each dermatome was calculated.

Single and Repeated (Temporal Summation) Stimulation of the Sural Nerve. After the skin had been degreased, bipolar surface Ag/AgCl-electrodes filled with electrode gel (interelectrode distance, approximately 2 cm) were placed just distal to the right lateral malleolus. Electromyographic (EMG) reflex responses were recorded from the middle of the biceps femoris and the rectus femoris muscles (Ag/AgCl-electrodes). A leg rest was placed under the knee to obtain a 30° semiflexion. Electrophysiologic (flexion reflex) and psychophysical (perception of pain) thresholds were determined. The same type of stimulator used for pain rating was used. The EMG signal was amplified and filtered (1.5–150 Hz) by a Hellige (Hellige AG) single-channel EMG-electroencephalographic (EEG) amplifier. Stimulation and recording were controlled with the NFRsys software (Aalborg University) on a personal computer.

The impulse pattern described previously for pain rating was used. The current intensity was increased from 1 mA in 1-mA intervals until (1) a reflex with an amplitude exceeding 20 μ V for at least 10 ms in the 70- to 200-ms poststimulation interval was detected by the computer program (electrophysiologic single-stimulus threshold), and (2) a pain sensation was evoked (psychophysical single-stimulus threshold). To elicit temporal summation, the previously mentioned stimulus burst was repeated five times with a frequency of 2 Hz.²⁵ The current intensity was increased from 1 mA in 1-mA intervals until a summation threshold was observed. *Summation threshold* was defined as an increase in perception of current intensity during the five stimulations (psychophysical summation threshold) and an increase in the amplitude of the final one or two reflexes above a fixed limit of 20 μ V for at least 10 ms in the 70- to 200-ms poststimulation interval (electrophysiologic summation threshold; fig. 1). For single and repeated stimulation, if the threshold was above a maximal current of 80 mA, the threshold was defined as 80 mA.

Statistics

Categorical and numerical data were analyzed by logistic regression²⁶ and two-factors multivariate repeated-measures analysis,²⁷ respectively. Both methods study the influence of various factors (independent or explanatory variables) on a dependent variable, which is dichotomous for logistic regression (e.g., hyposensitivity and normal sensation of pinprick) and numerical

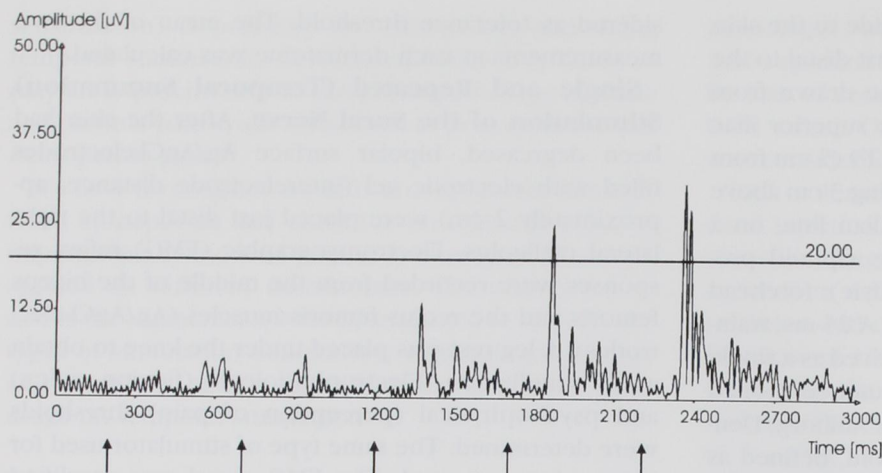


Fig. 1. Nociceptive reflex (EMG response) after repeated electrical stimulation of the sural nerve (temporal summation). Arrows indicate the five stimulations. Although the intensity of the five stimuli is the same, there is a step increase in the amplitude of the reflex response after the third stimulus.

for two-factors multivariate repeated-measures analysis (e.g., pressure pain tolerance threshold). In the latter case, the experimental units were the 45 subject-drug combinations, and the other variables were treated as repeated factors. A P value < 0.05 was considered significant. The software used was SAS version 6.10 (SAS Institute Inc., Cary, NC).

Eleven regression analyses were performed on the following dependent variables: (1) pain rating after electrical stimulation (VAS); (2) pinprick (hyposensitivity and normal sensation); (3) cold (hyposensitivity and normal sensation); (4) pressure pain tolerance threshold (kPa); (5) threshold after electrical stimulation of the sural nerve (mA); (6) pain during epidural injection (yes/no); (7) systolic blood pressure (mmHg); (8) heart rate (beats/min); (9) sedation score (VAS); (10) end-tidal carbon dioxide (vol %); and (11) arterial oxygen saturation (%). Numerical dependent variables were analyzed as the difference between values measured after administration of the epidural solution and basal values.

The independent (explanatory) variables included in the analyses of the aforementioned dependent variables were drug (placebo, epinephrine, or clonidine) for all analyses; dermatome where the stimulus was applied for the regressions on pain rating, pinprick, cold, and pressure pain tolerance; time (30, 60, 90, and 120 min after injection) for all analyses except for pain during injection (no time course), pinprick, and cold (risk of overfitting because of low frequency of positive outcomes); type of stimulus (single or repeated) and type of response (psychophysical or electrophysiologic) for the regression on threshold to electrical stimulation of the sural nerve. Potential interaction between drug, der-

matome, and time have been investigated by including pairwise products of these variables (e.g., drug \times dermatome) in the analyses (except for pinprick and cold, to avoid overfitting). For the analyses of pinprick and cold, data were stratified according to the sensitivity of subjects to the tests. All data collected from each subject in all three sessions, including all tests performed on all dermatomes at all times, were tabulated according to the response (*i.e.*, hyposensitivity/normal sensation) in a 15 (subjects) \times 2 (response) table. The subjects with similar frequencies of hyposensitivity to pinprick (cold) were grouped. Four groups for pinprick and two groups for cold were identified and included in the analyses as dummy variables. Because of the relatively low frequency of patients with hyposensitivity to pinprick and cold, in the regressions on these two variables, the dermatomes had to be grouped into two dummy variables: forehead-T1-T6-T9 and L1-L4-S1.

Results

One volunteer was not enrolled because of abnormal prothrombin time. Of the 16 volunteers enrolled, one could not participate in two sessions because of fever and was excluded from the analysis. The remaining 15 (10 men) had a median age of 25 yr (range, 21–31 yr), a body weight of 71 kg (range, 52–86 kg), and a body height of 179 cm (range, 163–191 cm). Blinding frequently was impossible for clonidine because of the sedative effect caused by this drug.

Analgesia

Clonidine, compared with placebo, significantly reduced pain rating after electrical stimulation, and its

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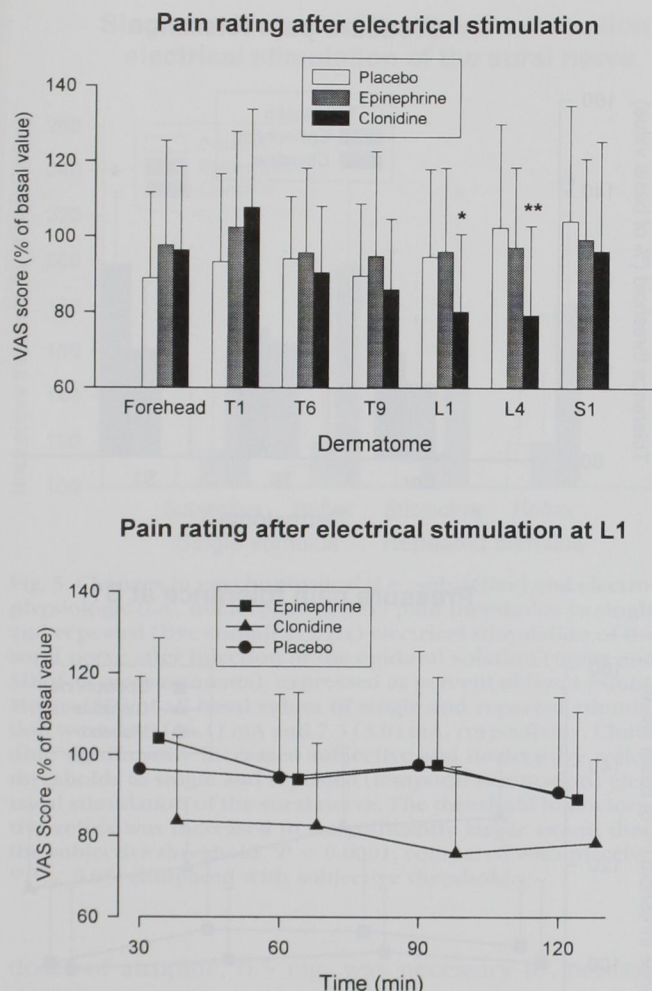


Fig. 2. The two graphs show changes in pain rating after electrical stimulation recorded after injection of the epidural solution at all dermatomes tested (mean and SD of all measurements) (top) and at L1 (mean and SD of measurements at each time; bottom), expressed as percent of basal values. Mean (SD) of all basal values was 4.2 (1.8) cm. Mean (SD) of current intensity delivered was 10.3 (8.0) mA. Clonidine, compared with placebo, significantly reduced pain rating after electrical stimulation, and its effect depended on the dermatome tested (P values of the variables drug \times dermatome and dermatome < 0.05 and < 0.005 , respectively). When the dermatomes were separately analyzed, the effect of clonidine was significant at L1 and L4, compared with forehead. * $P < 0.05$; ** $P = 0.067$ (borderline significance).

effect depended on the dermatome tested. When the dermatomes were separately analyzed, the effect of clonidine was significant at L1 and L4 compared with forehead (fig. 2, top). The effect did not change significantly during the testing procedure (variable time was not significant with any test used).

Epinephrine caused hyposensitivity to pinprick in

40% of subjects ($P < 0.0001$; placebo as reference) at the dermatomes L1–L4–S1 ($P < 0.0001$; group forehead–T1–T6–T9 as reference) (fig. 3, top). No significant effect of epinephrine was found with the other tests used.

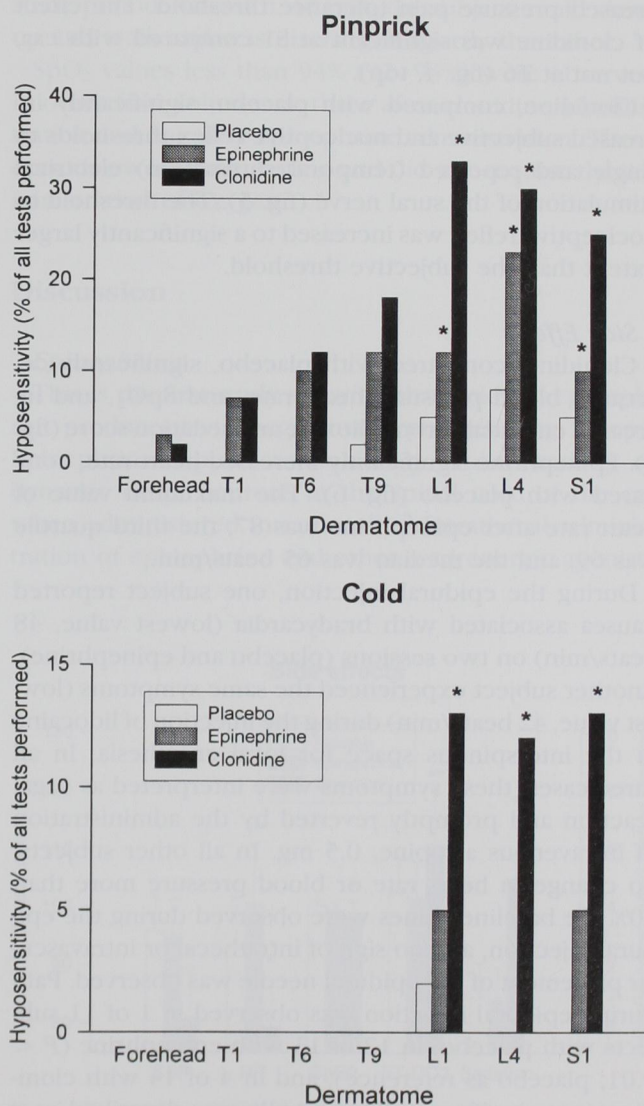


Fig. 3. The two graphs show the percent of tests wherein subjects reported hyposensitivity to pinprick (top) and cold (bottom), expressed as percent of all tests performed at each dermatome at all times after administration of the epidural solution. All subjects had a normal perception of pinprick and cold at all dermatomes before injection. Epinephrine caused hyposensitivity to pinprick in 40% of subjects ($P < 0.0001$, placebo as reference) at L1–L4–S1 ($P < 0.0001$, forehead–T1–T6–T9 as reference). Clonidine caused hyposensitivity to pinprick in 40% and cold in 33% of subjects ($P < 0.0001$ in both analyses, placebo as reference) at L1–L4–S1 ($P < 0.0001$ in both analyses, forehead–T1–T6–T9 as reference). * $P < 0.0001$.

Clonidine caused hyposensitivity to pinprick in 40% and cold in 30% of subjects ($P < 0.0001$ in both analyses; placebo as reference) at the dermatomes L1-L4-S1 ($P < 0.0001$ in both analyses; forehead-T1-T6-T9 as reference; fig. 3).

Clonidine, compared with placebo, significantly increased pressure pain tolerance threshold. The effect of clonidine was significant at S1 compared with ear, but not at T6 (fig. 4, top).

Clonidine, compared with placebo, significantly increased subjective and nociceptive reflex thresholds to single and repeated (temporal summation) electrical stimulation of the sural nerve (fig. 5). The threshold to nociceptive reflex was increased to a significantly larger extent than the subjective threshold.

Side Effects

Clonidine, compared with placebo, significantly decreased blood pressure, heart rate, and SpO_2 , and increased end-tidal carbon dioxide and sedation score (fig. 6). Epinephrine significantly increased heart rate, compared with placebo (fig. 6). The maximum value of heart rate after epinephrine was 87; the third quartile was 69, and the median was 65 beats/min.

During the epidural injection, one subject reported nausea associated with bradycardia (lowest value, 48 beats/min) on two sessions (placebo and epinephrine). Another subject experienced the same symptoms (lowest value, 42 beats/min) during the injection of lidocaine in the interspinous space for local anesthesia. In all three cases, these symptoms were interpreted as vagal reaction and promptly reverted by the administration of intravenous atropine, 0.5 mg. In all other subjects, no change in heart rate or blood pressure more than 20% the baseline values were observed during the epidural injection, and no sign of intrathecal or intravascular placement of the epidural needle was observed. Pain during epidural injection was observed in 1 of 11 subjects with placebo, in 12 of 13 with epinephrine ($P < 0.01$; placebo as reference), and in 4 of 14 with clonidine (not significant). This usually was described as a feeling of pain pressure, which gradually decreased after injection and disappeared within 2–5 min. Data are not complete for all 45 sessions because this effect was not expected and was therefore not recorded on the first sessions.

Systolic blood pressure less than 90 mmHg (lowest value, 77 mmHg) was observed in five subjects, always after administration of clonidine. These values were slowly reached, *i.e.*, no case of sudden hypotension was

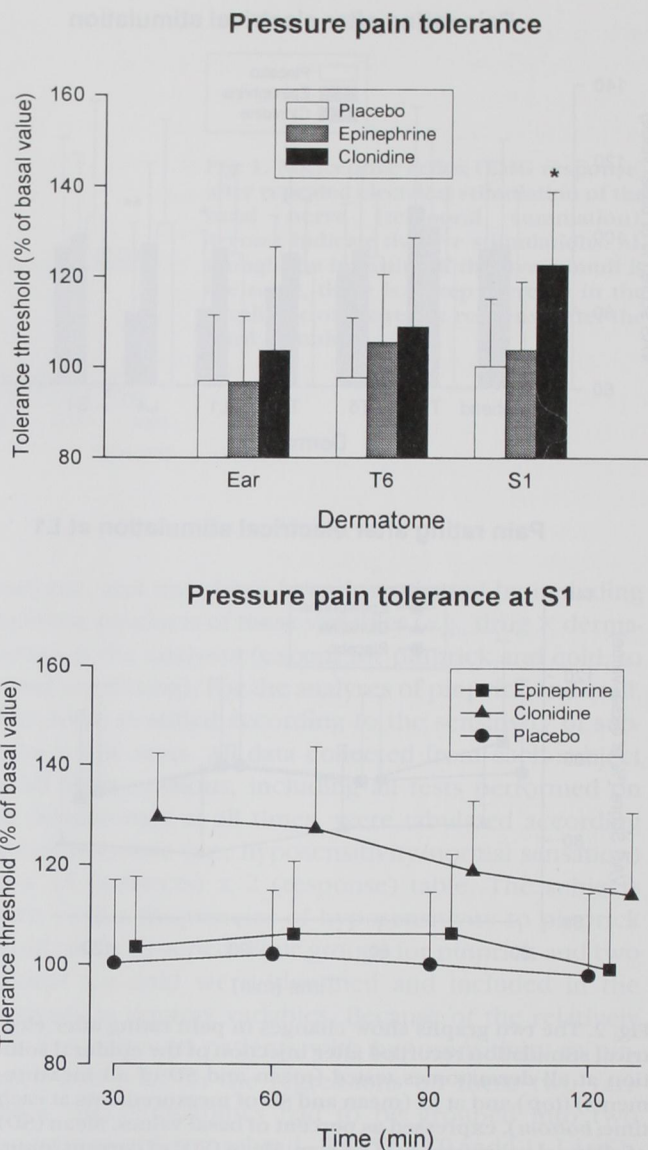


Fig. 4. The two graphs show changes in pressure pain tolerance threshold recorded after injection of the epidural solution at all three dermatomes tested (mean and SD of all measurements) (top) and at S1 (mean and SD of measurements at each time) (bottom), expressed as percent of basal values. Mean (SD) of all basal values was 622 (187) kPa. Clonidine, compared with placebo, significantly increased pressure pain tolerance threshold ($P < 0.01$). The effect of clonidine was significant at S1, compared with ear, but not at T6. * $P < 0.01$.

observed. Ephedrine was never administered. Atropine was administered intravenously in two subjects after clonidine administration because of bradycardia. The lowest value was 37 beats/min, observed after the end of the experiment. The intravenous injection of three

Single and repeated (temporal summation) electrical stimulation of the sural nerve

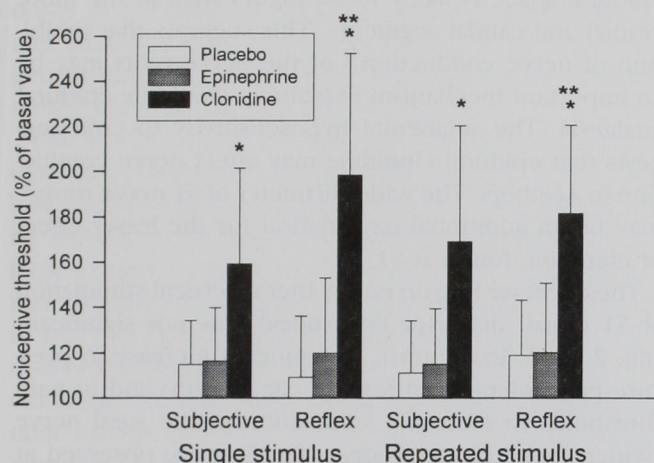


Fig. 5. Changes in psychophysical (*i.e.*, subjective) and electro-physiologic (*i.e.*, nociceptive reflex) pain thresholds to single and repeated (five stimuli at 2 Hz) electrical stimulation of the sural nerve after injection of the epidural solution (mean and SD of all measurements), expressed as percent of basal values. Means (SD) of all basal values of single and repeated stimulation were 13.9 (16.1) mA and 7.3 (3.0) mA, respectively. Clonidine significantly increased subjective and nociceptive reflex thresholds to single and repeated (temporal summation) electrical stimulation of the sural nerve. The threshold to nociceptive reflex was increased to a significantly larger extent than the subjective threshold. * $P < 0.0001$, compared with placebo. ** $P < 0.05$, compared with subjective threshold.

doses of atropine, 0.5 mg, was necessary to increase the heart rate above 45 beats/min.

Fifteen minutes after injection of clonidine, one subject manifested an episode of apnea, as detected by the alarm system of the gas analyzer (which was activated after 30 s of apnea), associated with a decrease in SpO_2 to 80%. No sign of upper airway obstruction was observed. He was arousable by verbal command and could spontaneously breathe. After 2–3 s, however, he fell asleep and apnea manifested again. He had to be continuously aroused and incited to breathe. Because the subject was arousable and cooperative, the study was normally performed. Because the apnea episodes were associated with arterial oxygen desaturation (SpO_2 around 90%), a nasal probe was inserted, and oxygen, 2 l/min, was administered. The apnea episodes became less frequent and shorter at 2 h, 50 min after the administration of clonidine. No apnea episode occurred after 3 h, 5 min, and the respiratory frequency was 10–15 breaths/min. The administration of oxygen was discontinued after 3 h, 15 min. Since the beginning of oxygen admin-

istration and after its discontinuation, SpO_2 remained in the range of 95–99%. The end-tidal carbon dioxide was 4.7–5.4 vol% during the experiment (*i.e.*, until 2 h after injection) and reached the maximum value of 6.5 vol% after 2 h, 55 min (while deeply sedated). The sedation score was 8.5–9.3 cm during the 120-min study period. After 4 h, 40 min, the subject could stand up and walk and was discharged shortly thereafter.

SpO_2 values less than 94% (92–93%) were observed in other four volunteers, three after clonidine administration and one after epinephrine administration. These episodes were short-lasting and did not require the administration of oxygen.

Discussion

Epinephrine

This is the first study showing that epidural epinephrine produces *per se* segmental hypoalgesia (fig. 3, top). Epinephrine suppresses noxiously evoked activity of dynamic range neurons in the spinal cord of the cat when administered intrathecally.⁸ Intrathecal administration of epinephrine and other α -adrenergic agonists

Side effects

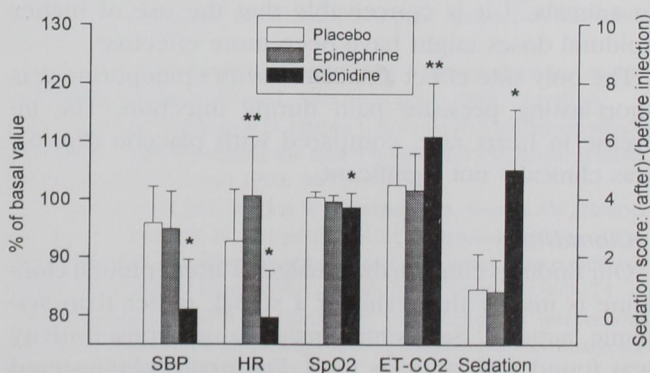


Fig. 6. Changes in systolic blood pressure (SBP, mmHg), heart rate (HR, beats/min), arterial oxygen saturation (SpO_2 , %), end-tidal carbon dioxide (ET- CO_2 , vol %), and sedation score (visual analogue scale, 0–10 cm) after injection of the epidural solution (mean and SD of all measurements), expressed as percent of basal values. Because of the different range of sedation score, this parameter is expressed as the arithmetic difference between values measured after injection of the epidural solution and basal values. Clonidine, compared with placebo, significantly decreased SBP, HR, and SpO_2 , and increased end-tidal CO_2 and sedation score. Epinephrine significantly increased heart rate, compared with placebo. * $P < 0.0001$. ** $P < 0.001$.

in rats produces antinociception, which can be antagonized in a competitive fashion by α - but not by β -antagonists.⁷ Epinephrine and norepinephrine produce a hyperpolarization of primary afferent terminals in the isolated frog spinal cord, which is antagonized by α_2 - but not by α_1 - or β -antagonists.²⁸ Thus, absorption into the cerebrospinal fluid and binding to α_2 -adrenoreceptors²⁹ is the most likely mechanism explaining epinephrine-induced segmental hypoalgesia after epidural administration.

Segmental hypoalgesia was observed only with pinprick and only in 40% of subjects. No effect was found with the other tests used. Thus, the analgesic effect of epidural epinephrine, 100 μ g, appears modest, and can only be detected by a weak painful stimulus, such as pinprick. Systemic absorption¹⁰ and metabolism by spinal meningeal catechol-O-methyl transferase¹¹ may limit the spinal bioavailability of epidurally administered epinephrine. Further, epinephrine binds to an equal extent to the α_2 - and α_1 -adrenoreceptors, whereas clonidine has a selectivity ratio α_2/α_1 of 200:1.³⁰ Hypoalgesia to pinprick could not be detected in a relatively high proportion of subjects. This may be the result of factors preventing epinephrine from reaching the α_2 -adrenoreceptors in an adequate concentration, hyposensitivity to α_2 -adrenergic agonists, poor sensitivity of the pinprick test, or inadequate dose. Because the antinociceptive effect of intrathecal epinephrine is dose-dependent in animals,^{7,8} it is conceivable that the use of higher epidural doses might have been more effective.

The only side effect associated with epinephrine was short-lasting pressure pain during injection. The increase in heart rate, compared with placebo (fig. 6), was clinically not significant.

Clonidine

Our findings confirm that analgesia after epidural clonidine is mainly the result of a spinal, rather than systemic, action.²¹ Segmental analgesia or hyposensitivity was found with all tests used. Epidurally administered clonidine is rapidly absorbed into the cerebrospinal fluid, and the analgesic effect of clonidine correlates with its cerebrospinal fluid concentration.²¹ If absorption into the cerebrospinal fluid with subsequent binding to the α_2 -adrenoreceptors in the spinal cord was the only mechanism explaining the analgesic effect of epidural clonidine, then analgesia at S1 after lumbar administration would be expected to be at least as good as at L1-L4. However, the quality of analgesia was better at L1 and L4 than at S1 (fig. 2, top). The dermatomes

L1-L4 correspond to a spinal level close to the site of injection, wherein the concentration of clonidine in the epidural space is likely to be higher than at the more cranial and caudal segments. This suggests that inhibition of nerve conduction³¹ at the nerve roots may be an important mechanism explaining clonidine epidural analgesia. The segmental hyposensitivity to cold suggests that epidural clonidine may affect nerve conduction in A δ -fibers. The wider diameter of S1 nerve roots³² may be an additional explanation for the lesser effect of clonidine found at S1.

The decrease in pain rating after electrical stimulation at S1 (small diameter electrodes) was not significant (fig. 2, top). In contrast, a significant increase in pressure pain tolerance threshold (fig. 4, top) and in pain thresholds to electrical stimulation of the sural nerve (wider diameter electrodes) (fig. 5) were observed at the same dermatome. These findings suggest that clonidine is less effective in inhibiting short-lasting painful stimuli applied to a small area than long-lasting ones applied to a large area. This may have prevented us from detecting an analgesic effect of clonidine at dermatomes cranial and caudal to L1-L4 using electrical stimulation with small-diameter electrodes.

Epidural clonidine increased subjective and nociceptive reflex threshold to single and repeated stimulation of the sural nerve (fig. 5). Repeated stimulation of the sural nerve is a noninvasive method to investigate temporal summation in humans.²⁵ Nociceptive reflex thresholds to repeated stimulation are increased by isoflurane concentrations used for surgical analgesia,³³ ketamine,³⁴ alfentanil,³⁵ epidural,³⁶ and spinal³⁷ anesthesia. Repeated stimulation may lead to increased and prolonged firing of dorsal horn neurons²² (central sensitization). Spinal hyperexcitability also develops after peripheral nerve lesions³⁸ and is thought to be an important mechanism for neuropathic pain.²³ The inhibition of temporal summation that we have observed suggests that epidural clonidine may contribute to prevent spinal hyperexcitability (preemptive analgesia) and may explain pain relief provided by epidural or intrathecal clonidine in patients with neuropathic pain.^{17-20,39} The electrophysiologic threshold after repeated stimulation is normally close to the psychophysical threshold.²⁵ After clonidine, the former was increased to a significantly larger extent than the latter (fig. 5). This may be the result of the aforementioned effect of clonidine on nerve conduction,³¹ potentially affecting the motor component of the nociceptive reflex. Further, catecholamines depolarize the motoneu-

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rones and depress mono- and polysynaptic reflex discharges through an α -receptor in the spinal cord.⁴⁰ High doses of norepinephrine administered intrathecally in rats produce marked muscle weakness.⁷ These evidences suggest that α -agonists may subclinically affect motor function after therapeutic doses.

Our results confirm the well-known effect of epidural clonidine on arterial blood pressure and heart rate. The low values of blood pressure occasionally observed may be dangerous and may require treatment in elderly or hypertensive patients or in patients with coronary artery disease. The sedative effect of epidural clonidine is also well known and is thought to be mediated by α_2 -adrenoreceptors in the locus ceruleus.⁴¹ The use of clonidine was associated with significantly higher end-tidal carbon dioxide concentrations and lower SpO₂ compared with placebo. Although these effects were quantitatively modest (fig. 6), these findings and the case of severe respiratory depression suggest that patients should be strictly controlled and possibly monitored with at least pulse oximetry. All side effects may be less likely in the presence of pain, which may increase sympathetic output to heart and vessels, and counteract clonidine-induced sedation and respiratory depression.

Conclusions

Epidural epinephrine produces segmental hypoalgesia, which, in addition to its vasoconstrictive properties, provides a rationale for using epinephrine with local anesthetics or opioids for enhancing epidural analgesia.

Epidural clonidine produces segmental analgesia after bolus administration. The deepest effect is observed at the dermatomes corresponding to the site of injection. Clonidine should be administered at a segmental level corresponding to the painful area. Clonidine seems to be more effective in inhibiting long-lasting painful stimuli, applied to large areas, than short-lasting ones, applied to very small areas. Clonidine inhibits temporal summation elicited by repeated electrical stimulation and may contribute to prevent spinal cord hyperexcitability.

Clonidine-induced hemodynamic and respiratory effects may be a concern, particularly in patients with pre- or coexisting cardiovascular or respiratory diseases.

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