Central Effects of Epidural and Intravenous Clonidine in Patients
Anesthetized with Enflurane/Nitrous Oxide

An Electroencephalographic Analysis

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Epidural clonidine produces regional anesthesia as well as sedation and a decrease in anesthetic requirements. To assess these effects, the electroencephalogram (EEG) was recorded after epidural or intravenous (iv) injection of clonidine during enflurane/N₂O anesthesia. Eighteen ASA physical status I women undergoing vaginal hysterectomy were allocated randomly to receive epidural clonidine (8 µg · kg⁻¹ in 4 ml over 2 min) and iv saline (10 ml over 14 min); or epidural saline (4 ml over 2 min) and iv clonidine (8 µg · kg⁻¹ in 10 ml over 14 min); or epidural saline (4 ml over 2 min) and iv saline (10 ml over 14 min). The level of anesthesia was kept constant beginning 10 min before and until 44 min after epidural injection. EEG power spectral analysis was performed throughout the study period using a 2-min average of 8–9-s epochs. Clonidine significantly reduced EEG total power only after epidural administration (P < 0.05). Relative power increased in the 6 band in both the epidural and iv clonidine groups (P < 0.001). The depression of the total EEG power after epidural injection could be explained neither by systemic absorption alone nor by hemodynamic variations. It may represent the contribution of the direct spinal action of this α₂-adrenergic agonist to general anesthesia. (Key words: Anesthetic techniques: epidural; intravenous. Monitoring; electroencephalography. Sympathetic nervous system, α₂-adrenergic agonists: clonidine.)

LARGE DOSES of epidural clonidine alone relieve postoperative surgical pain.1 Experimentally, the α₂-adrenergic agonists modulate the pain perception at a spinal level.2–5 In humans, however, a central effect sufficient to alter the perception of pain has been suggested.6,7 Using electroencephalographic (EEG) recording,8 this study was designed to investigate the existence of a central effect of clonidine.

Materials and Methods

Eighteen women, ASA physical status I, undergoing elective vaginal hysterectomy were studied. All patients gave informed consent to participate in this study, which was approved by the institutional Medical Ethics Committee. All patients were between 45 and 55 yr of age, were free from neurologic or cardiovascular diseases, and were not taking any medications.

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ANESTHESIA

No premedication was administered. Immediately before general anesthesia, an epidural catheter was inserted at the L1–L2 or L2–L3 interspace and its position verified by injection of 3 ml bupivacaine 0.5% with 1/200,000 epinephrine. After 5 min, another 5 or 6 ml bupivacaine 0.5% plus epinephrine was injected. In all patients, 20 min after the last injection, segmental anesthesia was confirmed at the T10 level by loss of thermal sensitivity.

General anesthesia was induced with propofol 2 mg · kg⁻¹ and alfentanil 0.5 mg. Atracurium 0.4 mg · kg⁻¹ was given for muscle relaxation. After tracheal intubation, the lungs were mechanically ventilated. Anesthesia was maintained with N₂O (inspiratory fraction 0.5) in O₂ and enflurane.

All patients received Ringer's lactate. No glucose-containing fluid was administered. To prevent hypothermia, infusion fluids were warmed to 38°C, and a warming mattress was used.

STUDY PROTOCOL

The study protocol began after completion of surgery and at least 1 h after the epidural injection of bupivacaine. Anesthesia was prolonged for 1 h, during which the N₂O inspiratory fraction (0.5) and the enflurane end-expiratory concentration (0.7%) (Datex Capnomac®, Helsinki, Finland) were kept constant. Mechanical ventilation was adjusted to maintain stable end-tidal CO₂ concentrations (31–32 mmHg) because variations of arterial CO₂ tension were recently reported to influence the EEG.9 Intravenous (iv) fluid administration was increased for any decrease in arterial pressure greater than 10% of the baseline value. Surgical muscle relaxation was maintained by injection of additional atracurium (0.2 mg · kg⁻¹).

Arterial blood gases were measured at the beginning and the end of the experiment. SPO₂ was monitored during the entire procedure.

EEG recording was begun after surgery was completed (T−10). Ten min later (T0), patients received, in a double-blind and randomized fashion, one of the following:

• epidural clonidine 8 µg · kg⁻¹ (4 ml) over 2 min and an iv infusion of saline over 14 min: group 1 (n = 6)
• epidural saline (4 ml) over 2 min and iv clonidine 8 µg · kg⁻¹ (10 ml) over 14 min: group 2 (n = 6).

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- epidural saline (4 ml) over 2 min and iv saline (10 ml) over 14 min: group 3 (n = 6).

Saline or clonidine was injected intravenously using an electronic infusion pump (Terumo®; Tokyo, Japan). Epidural saline or clonidine was injected over 2 min.

The study considered EEG recordings from 10 min before (T−10) until 44 min (T44) after the beginning of the epidural and iv injections (T0).

**Electroencephalographic Analysis**

During the study period, two channels of the EEG were recorded continuously from F3-P3 and F4-P4 (international 10–20 system), using Ag–AgCl collodion-attached disc electrodes, filled with electrode jelly. Electrode impedance was maintained at less than 2 kΩ. The EEG signal was amplified 20,000 times and compressed using an OTE Biomedica Berg Fourier Analyzer 1264 (Firenze, Italy). A power-spectral analysis was performed using partially overlapping 8–9-s epochs producing power spectra with a resolution of 0.5 Hz. The spectral bands of 0.5–3.0 Hz (δ band), 3.0–8.0 Hz (θ band), 8.0–13.0 Hz (α band), and 13.0–30.0 Hz (β band) and the total power of 0.5–32 Hz were analyzed. The values were averaged from 2-min samples of EEG. The analyzer printed the spectral power of the frequency bands listed above. Artifacts of greater than 32 Hz frequency were directly eliminated by the system. The artifacts under this frequency were identified by a proportional threshold device that zeroed the tracing for 0.5 s whenever a sudden excess voltage occurred. The number of identified artifacts was visualized on the printer numeric strip. An equalizer high-pass filter (4 Hz, 6 db/octave) was used to suppress the lower frequencies, which otherwise would have had disproportionate weighting in the spectral analysis.19

**Statistical Analysis**

For EEG statistical analysis we considered only values produced by the dominant hemisphere (F3-P3 in all patients). In order to suppress the intersubject variation in EEG spectral power analysis, the 2-min sample of EEG before the start of epidural and iv injection (T0) was established as baseline and expressed as 100%. The other values were expressed as a percentage of this baseline value. The relative power of each band was expressed as a percentage of total power.

Evolution of the spectral analysis over the time was evaluated by one way univariate analysis of variance with repeated measures (CSS Statistica, Statsoft, Tulsa, OK). Intergroup differences were analyzed by Tukey’s least significant difference test and confirmed by contrast analysis. Baseline values of the EEG during equilibration period, demographic data, and blood gases values were analyzed by analysis of variance. Changes of hemodynamic

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**Fig. 1.** Evolution of EEG total power (0.5–32.0 Hz) with time. Raw data (A) and percentage change from baseline period (B) after epidural or intravenous (iv) injection of clonidine (8 μg·kg⁻¹) or saline. Results are mean ± SD. One way univariate ANOVA with repeated measures, Tukey least significant difference test, and contrast analysis.

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<th>Raw Data (A)</th>
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<td>Epi./iv</td>
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data over time were evaluated using Tukey’s test. A P value of less than 0.05 was considered significant.

Results

All three groups of six patients were comparable for age, weight, and height. Blood gases were within normal range, with mild hypocapnia, and they did not differ among groups.

Clonidine or placebo was injected at 86 ± 16 min after the last bupivacaine injection.

The postoperative course was uneventful for all patients.

Electroencephalographic Analysis

Each 2-min average of the EEG spectral data from 18 patients was considered. Because of the profound muscle relaxation and the lack of any stimulation, no artifact was detected.

The effects of clonidine on the total EEG power are summarized in figure 1. There were no statistically significant differences among the three groups in the baseline values (T–10, T–2, T0) (P = 0.43). After injection of clonidine or saline, the depression in total EEG power was significant only in the epidural group (figs. 1A and 1B).

Theta Power was well maintained in both clonidine groups (fig. 2). Relative theta power was significantly greater in the two clonidine groups than in the saline group (fig. 3) (epidural vs. saline P < 0.001; iv vs. saline P = 0.004; epidural vs. iv P = 0.49). Baseline differences in the proportion of the relative theta power were noted among the three groups, although these were not statistically significant (P = 0.13).

In the iv group, the relative theta power increase reached a plateau after 18 min. In the epidural group, 34 min was required (fig 3).

Hemodynamic data (heart rate and mean arterial blood pressure) are presented in figure 4. Clonidine significantly reduced heart rate (P < 0.001) and mean arterial pressure (P < 0.001) in both the epidural (from 75 to 60 beats·min⁻¹ and from 78 to 72 mmHg) and in the iv group (from 75 to 63 beats·min⁻¹ and from 79 to 69 mmHg). No differences were found between these two groups. Heart rate was significantly reduced 14 min after injection in both groups (epidural P = 0.02, iv P = 0.04).

**Fig. 2.** Percentage change from baseline period for power in the δ (0.5–3.0 Hz) (A), θ (3.0–8.0 Hz) (B), α (8.0–13.0 Hz) (C) and β (13.0–32.0 Hz) (D) bands after intravenous or epidural injection of clonidine (8 µg·kg⁻¹) or saline. Results are mean ± SD.
Mean arterial blood pressure decreased 14 min \( (P = 0.01) \) after epidural and 28 min \( (14 \text{ min after the end of the infusion}) \) after iv injection \( (P < 0.01) \).

**Discussion**

Our results demonstrate that under stable enflurane/\( \text{N}_2\text{O} \) anesthesia, both epidural and iv clonidine cause significant changes in total EEG power as well as in the EEG power spectrum. These changes are in all likelihood a drug effect because mean arterial blood pressure and oxygenation were maintained within the normal range and because clonidine only modestly \( (28\%) \) reduces the cerebral blood flow by interacting with the central adrenergic regulator system.\(^ {11,12} \) Furthermore, dexmedetomidine, a selective \( \alpha_2 \)-adrenergic agonist that produces a reduction of more than 45\% in cerebral blood flow in dogs despite an increase in arterial pressure, did not affect cerebral metabolic rate for \( \text{O}_2 \) or mean sagittal sinus \( \text{PO}_2 \), excluding global cerebral ischemia.\(^ {13} \)

EEG activity is generated by the synaptic potential of the pyramidal cells. The dendrites of these cells receive inputs of generalized and specific thalamocortical projections. Thus, the EEG is a suitable quantitative measure of drug effect: if a change occurs during steady-state anesthesia, it suggests that some change is occurring in the responsiveness of the brain.\(^ {8} \)

Clonidine, a centrally acting \( \alpha_2 \)-adrenergic agonist, enhances the depth of halogenated anesthesia by reducing the noradrenergic neurotransmission and by a specific anesthetic action mediated by the postsynaptic \( \alpha_2 \) receptors.\(^ {14} \) The majority of central noradrenergic neurons originate in the locus coeruleus and in the lateral pontine reticular formation.\(^ {15,16} \) They either ascend to innervate the thalamus, the hypothalamus, the basal telencephalon, and the entire neocortex, or they also descend to the dorsal spinal horn. With its extensive distribution, the central noradrenergic system is implicated in neuronal modulation over a large part of the brain and influences the electrophysiologic responses of cerebral cortical neurons.\(^ {17,18} \) Clonidine, by promoting the cellular \( K^+ \) efflux, hyperpolarizes the norepinephrine-containing neurons and inhibits their spontaneous firing rate.\(^ {14} \) This inhibition may explain the decrease of the total EEG power illustrated by the current study. Animal (rat) experimentation has demonstrated, by means of single-unit recording techniques, that low-dose iv clonidine \( (6.5 \mu g \cdot kg^{-1}) \) totally inhibited the spontaneous firing of brain norepinephrine-containing neurons in the locus coeruleus.\(^ {19} \)

Shift of the processed EEG signal toward the \( \delta \) range \( (0.5-3 \text{ Hz}) \) has been interpreted as a deepening of anesthesia with opioids,\(^ {20,21} \) propofol,\(^ {22} \) or \( \text{N}_2\text{O}. \)\(^ {23} \) A \( \delta \) shift of the EEG spectral analysis after oral premedication \( (5 \mu g \cdot kg^{-1}) \) with clonidine as described in this study has already been reported by Ghignone et al.\(^ {24} \)

**Fig. 4.** Evolution of heart rate, mean arterial blood pressure, and total EEG power after epidural or intravenous injection of clonidine \( (8 \mu g \cdot kg^{-1}) \) or saline. Results are mean \( \pm \) SD.
Baseline differences (though not statistically significant) among the three groups in the relative power of the various waves were noted. They may have been due to variations in the depth of anesthesia due to the methodologically arbitrary fixed enflurane concentrations or to N₂O acute tolerance.²⁵

A large dose of epidural clonidine injected at the lumbar level under enflurane/N₂O anesthesia affected central nervous system cortical activity. In awake patients, sedation is a common side effect of epidural clonidine.¹,³,⁶,²⁷ appearing approximately 20 min after injection and lasting 1–3 h. It usually is attributed to a supraspinal effect of clonidine after its vascular absorption.²⁷,²⁸ In this study, epidural clonidine may have increased the level of anesthesia after systemic absorption. Systemic absorption of epidurally administered clonidine is rapid. A pharmacokinetic study using a sheep model disclosed vascular absorption half-times of 10.3 ± 2.8 min after an epidural injection of 300 µg (vs. 5.8 ± 1.9 min iv).²⁹ The sheep model is believed to afford a reliable estimate of the pharmacokinetics of opioids and clonidine in human cerebrospinal fluid (CSF).³⁰,³¹

Vascular absorption of epidurally injected clonidine may only partially account for the observed central effect. In the epidural group, total EEG power was more depressed, and maximal increase in the relative fraction of δ waves arose later. The different speed of clonidine administration between the two groups is unlikely to account for this effect even though epidural clonidine was given over 2 min. A massive vascular absorption can be ruled out by the absence of any hypertensive reaction. Moreover, it is unlikely that normal systemic absorption from the epidural space could induce, on its own, a greater central effect than the same iv dose.

Rostral CSF spread of epidurally administered clonidine could be another explanation for the EEG changes observed. Dural transfer of clonidine to CSF after epidural administration is rapid and extensive. Clonidine concentrations in sheep CSF after redistribution were 1,000 times greater after epidural than after iv injection.²⁹ Clonidine is a highly lipid-soluble compound that shares CSF pharmacokinetics properties with fentanyl. Like morphine and meperidine, fentanyl administered at a lumbar epidural site undergoes rapid (time to maximal concentration = 22.5 ± 13.3 min) cephalad migration, albeit to a small extent.³⁵ It is possible that a small amount of clonidine undergoes similar cephalad migration and reaches the lower brain stem centers. However, clonidine administered iv penetrates the brain very easily,³⁸ and different effects between the iv and epidural routes would be difficult to explain even if epidural cephalad migration of clonidine occurs to some extent.

Epidurally administered α₂-adrenergic agonists have a direct spinal analgesic action that inhibits nociceptive transmission.³⁴ During general anesthesia, nociceptive sensory afference are important determinants of the anesthesia depth.³⁵ Suppression of neurotransmission at the spinal level may be a component of the α₂-adrenergic-induced reduction in volatile anesthetic requirements, as recently suggested by Savola et al.³⁶ using a neonatal rat spinal cord model. In the current study, residual blockade by the local anesthetic may have reinforced this effect. Clonidine potentiates local anesthetic-induced epidural anesthesia.³⁷ Considering the changes of mean arterial blood pressure in the two clonidine groups, epidural clonidine did not, however, accentuate the sympathetic blockade induced by bupivacaine.

A spinal action of clonidine, interrupting loops between the peripheral and the central nervous system and thus reducing the activation of the neocortex, can be proposed as an explanation for this differential effect. The greater EEG suppression in the epidural clonidine group may well be related to diminishing noxious input caused by a deepening level of regional anesthesia. This may be due to clonidine's direct spinal action or to an interaction between local anesthesia and an α₂ agonist effect.³⁸

The difference in effect between the iv and epidural clonidine provides evidence for a EEG depressant effect of epidural clonidine. Although our study cannot clarify the mechanism responsible for this observation, we speculate that it may represent a direct spinal action of the α₂ agonist, which may lead to a greater depth of anesthesia.

References

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