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Epidural Clonidine Depresses Sympathetic Nerve Activity in Humans by a Supraspinal Mechanism

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Background: **Epidural administration of the α_2-adrenergic agonist clonidine induces hypotension. Animal experiments have indicated a possible spinal mechanism through activation of α_2-adrenergic receptors on sympathetic preganglionic neurons, resulting in a decrease of efferent sympathetic activity. However, the pharmacokinetic behavior of epidural clonidine, the high lipid solubility of the drug, and the apparent sedative side effects also indicate a possible supraspinal mechanism. To test this hypothesis, the effect of epidural and intramuscular clonidine on efferent sympathetic nerve activity to the leg was studied with microneurography.**

Methods: **In 15 healthy volunteers, a lumbar epidural catheter was inserted and multiunit postganglionic sympathetic activity was recorded in a skin or muscle fascicle of the peroneal nerve before and after epidural injection of clonidine. Skin blood flow in the hand and in the foot was measured with laser Doppler flowmetry. In six additional experiments, performed at another time, clonidine was given intramuscularly.**

Results: **After epidural injection of clonidine (3 μg/kg) the resting level of skin sympathetic activity decreased to 18 ± 5% (n = 6; $P < 0.001$), muscle sympathetic activity expressed as bursts/min to 41 ± 12% (n = 7; $P < 0.01$), and integrated muscle sympathetic activity to 41 ± 13% (n = 7; $P < 0.01$) of control values after 30 min. However, the capacity for activation of skin sympathetic activity by arousal stimuli and of muscle sympathetic activity by apnea remained. Intramuscular clonidine inhibited both skin sympathetic activity (n = 3) and muscle sympathetic activity (n = 3) to the same extent. Skin blood flow increased whereas blood pressure and heart rate decreased after epidural and intramuscular clonidine.**

Conclusions: **The comparable inhibition of resting sympathetic nerve activity, paralleled by a decrease in heart rate and blood pressure after both epidural and intramuscular clonidine, indicates that epidural clonidine induces a supraspinally evoked general decrease in sympathetic outflow. (Key words: Analgesics, epidural: clonidine. Anesthetic techniques, epidural. Measurement techniques: microneurography. Sympathetic nervous system.)**

THE central antihypertensive agent clonidine is an α_2-adrenergic agonist that possesses pain-relieving properties.[1] It has been administered epidurally for postoperative analgesia[2–7] and in the treatment of cancer pain.[8] The antinociceptive effect is assumed to result from activation of α_2-adrenergic receptors in the dorsal horn of the spinal cord.[9–11] Injected epidurally, clonidine causes a decrease in arterial blood pressure,[4,5,12] but whether this is a central or spinal effect is not known. A possible spinal hypotensive mechanism is indicated by electrophysiologic studies in rats showing that spinal application of clonidine activates α_2-adrenergic receptors on sympathetic preganglionic neurons, resulting in a decrease of efferent sympathetic nerve activity.[13] This notion is supported by hemodynamic studies in sheep[14] and humans.[15] However, the pharmacokinetic behavior[6] and apparent sedative effect of epidural clonidine[3,6] as well as the high lipid solubility of the drug indicate a possibility for a supraspinal mechanism of clonidine when epidurally administered.

Using microneurography, this study was undertaken to reveal whether putative changes in efferent sympathetic nerve activity to muscle and skin in the leg after epidural clonidine (3 μg/kg) could be ascribed to a systemic and thus supraspinal effect. The clonidine dose is within the range used clinically,[2–7] and animal data suggest that it is not likely to produce dangerous side effects.[11,16–18] To distinguish between spinal and systemic effects of the drug, clonidine was injected in-

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tramuscularly in six subjects. Recordings of arterial blood pressure, heart rate, and skin blood flow in arm and leg were used to evaluate possible hemodynamic compensatory mechanisms.

Materials and Methods

Twenty-one experiments were performed with 15 healthy volunteers, aged 24–49 yr. Written informed consent was given by all subjects, and the investigation was approved by the Human Ethics Committee, University of Göteborg.

Recording Muscle and Skin Sympathetic Nerve Activity

Multiunit postganglionic sympathetic activity was recorded with a tungsten microelectrode, with a tip diameter of a few microns, inserted in a muscle or skin fascicle of the peroneal nerve at the fibular head. A reference electrode was inserted subcutaneously 1–2 cm from the recording electrode. When a muscle or skin nerve fascicle was identified, small electrode adjustments were made until a site was found in which sympathetic impulses could be recorded.

The criteria for recording sympathetic activity in a muscle or skin fascicle were as follows: (1) weak electrical stimulation (0.5–1.5 V, 0.2 s, 1 Hz) through the intraneural electrode elicited involuntary muscle contractions (muscle sympathetic activity [MSA]) or gave rise to skin paresthesia (skin sympathetic activity [SSA]); (2) tapping or stretching of the muscle innervated by the impaled fascicle (MSA) or touch stimuli within the receptive field (SSA) elicited afferent mechanoreceptor discharges; and (3) the neurogram displayed spontaneous intermittent and pulse synchronous bursts (MSA) or activity consisting of irregular bursts of impulses, varying in strength and duration and occurring without obvious relation to heart beats (SSA). Evidence for the sympathetic nature of this activity has been described previously.[19]

The original nerve signal was fed through a band pass filter with a band width of 700–2,000 Hz. Filtered and mean voltage neurograms (obtained by passing the filtered neurogram through a resistance-capacitance integrating network with a time constant of 0.1 s) were stored on an FM tape recorder with records of electrocardiography, skin blood flow, and respiratory movements (Sangamo Sabre VI, Sangamo-Weston Schlumberger, Sarasota, FL). All parameters recorded were displayed on an ink-jet recorder (modified Mingograph 800; Siemens-Elema, Solna, Sweden) with a paper speed of 3 mm/s.

In the quantitative analysis of MSA, which occurs in bursts strictly coupled to the cardiac rhythm, records were divided into 1-min periods. The number of MSA bursts in the mean voltage neurogram were counted by two independent investigators, and the nerve activity was expressed as the average number of bursts per 5-min period. Digitizing board measurements of individual burst amplitudes were made from the chart and the average sum of these amplitudes per 5-min period expressed as integrated sympathetic nerve activity in arbitrary units. Since the SSA recordings contain both sudomotor and vasomotor bursts with highly variable shape and duration, the number of bursts per period does not provide a good measure of SSA. Instead, the area under the neurogram to an added baseline was calculated with a computer program, and SSA was expressed as the average area for 5-min periods.[20]

Skin Blood Flow Measurements

Skin blood flow was monitored continuously using laser Doppler flowmetry (Periflux PF1, Perimed AB, Stockholm, Sweden) with a frequency limit of 4 kHz and a time constant of 0.2 s. Electrical calibration for zero blood flow was made in all recordings. Several gains for the analog output were selectable by switches. The maximum output of a given gain level (defined electrically) was taken as 100%. The analog output of the flowmeter gives no absolute value, but shows relative changes of the flux of erythrocytes.[21–23] The laser Doppler probe was placed on the plantar side of the big toe of the leg used for MSA or SSA recording (n = 18) and on the volar side of the ipsilateral thumb (n = 11). Using a computer program, a mean blood flow was calculated for each minute of the recording and results presented as an average of 5-min periods.

Blood pressure and heart rate were measured automatically every 3–5 min by sphygmomanometry (Nippon Colin, Sphygmomanometer BP-203, Komaki-City, Japan) from the left arm at heart level. Electrocardiography was recorded by surface electrodes on the chest, and respiratory movements were monitored using a strain gauge attached to a rubber strap around the chest.

Procedure

The subjects received no premedication or intravenous fluids. After infiltration of the skin with 3–5 ml

1% lidocaine, epidural puncture was performed at the L2–L3 or L3–L4 interspace, and an epidural catheter was inserted 4–5 cm into the epidural space. With the subjects in a comfortable supine position, continuous recordings of electrocardiography, respiratory movements, blood pressure, heart rate, and skin blood flow were initiated. Subsequently, the peroneal nerve was identified at the fibular head and a recording of MSA or SSA initialized. Baseline sympathetic activity was recorded for 10 min, after which clonidine (3 μg/kg; in 10 ml isotonic saline) was injected through the catheter. Recording of sympathetic activity was continued for 45 min. Blood samples were obtained 15, 30, 45, 60, and 90 min after injection of clonidine epidurally and analyzed for plasma clonidine content using a radioimmunoassay method.[24] The detection limit of clonidine is 10 pg/ml. The intraassay coefficient of variance was 4% and the interassay 8%. The subjects were asked to indicate whether drowsiness was present.

Afferent mechanoreceptor discharge (evoked by tapping or stretching the muscle or by stroking the skin area innervated by the impaled fascicle) was tested at intervals and used as a criterion for unaltered electrode position.

In the MSA recordings, maximal voluntary apnea (30–60 s), a procedure that markedly increases muscle sympathetic discharge, was performed intermittently.

Painful transcutaneous electrical stimulation of the median nerve at the contralateral wrist, unexpected sounds or touches, and mental calculations (*i.e.*, serial subtraction of 17 from 1,000 as fast as possible) were used intermittently in the SSA recordings to evoke emotional reactions that would induce arousal with skin sympathetic discharges. The type of stimulus and interval between stimuli were varied to prevent habituation of the response, which is marked when a single type of stimulus is repeated regularly.

At the end of the experiment, a small dose of lidocaine was injected to confirm the epidural position of the catheter.

Intramuscular Clonidine

In six of the subjects, the experiment was repeated at another time with the same dose of clonidine (150 μg/ml) given intramuscularly in the thigh, contralateral to the nerve recording. Apart from not inserting an epidural catheter and with the recording period extended to 90 min after injection, the experimental procedure was unchanged.

Statistics

Values are presented as mean ± SEM. Analysis of variance and Student's *t* test were used for statistical analysis, and $P < 0.05$ was chosen for statistical significance.

Results

Epidural Clonidine

Epidural injection of clonidine resulted in a decrease of spontaneous SSA and MSA in all subjects studied. However, individual bursts of SSA and MSA at rest could reach a high amplitude after clonidine, and the capacity for inducing bursts with arousal stimuli (SSA) or apneas (MSA) remained throughout the experiments (figs. 1 and 2), indicating an unaltered intraneural electrode position.

The individual changes in resting sympathetic nerve activity for all subjects are shown in fig. 3A. The inhibition of SSA and MSA was significant after 10 and 15 min, respectively. Compared to the control period, SSA decreased to 18 ± 5% (n = 6; $P < 0.001$), MSA bursts to 41 ± 12% (n = 7; $P < 0.01$), and integrated MSA to 41 ± 13% (n = 7; $P < 0.01$) after 30 min. In two SSA recordings, the proper position of the electrode was

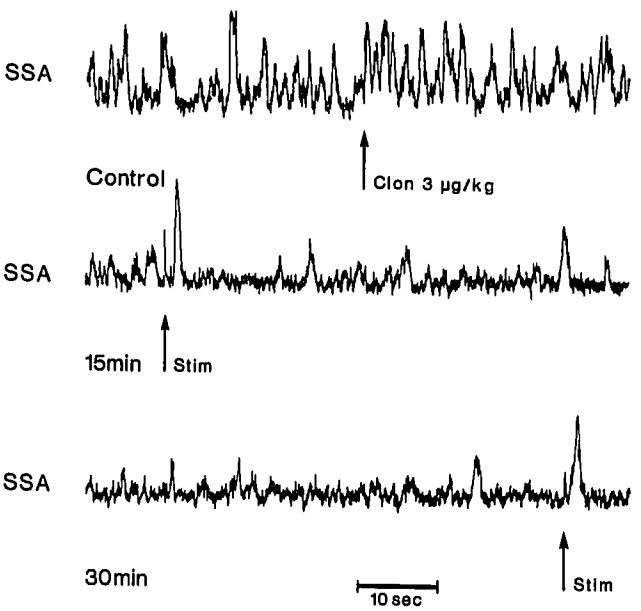

Fig. 1. Skin sympathetic nerve activity (SSA) from the left peroneal nerve in the control situation and 15 and 30 min after epidural clonidine. Resting-level SSA decreased. Note that SSA could be activated by arousal stimuli after 15 min and after 30 min.

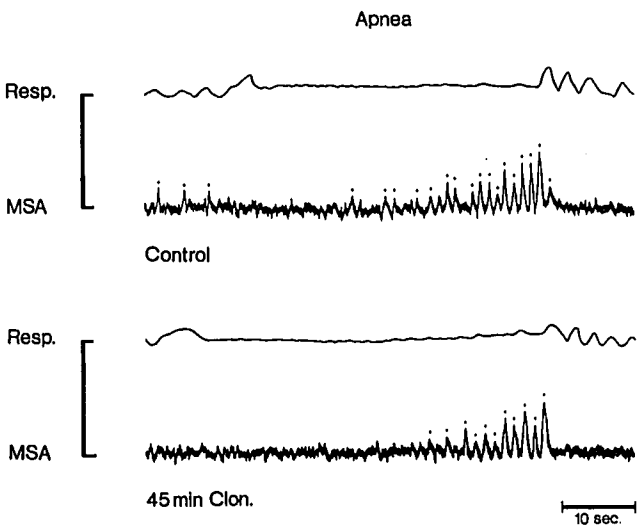

Fig. 2. Respiratory movements and muscle sympathetic nerve activity (MSA) recorded from the left peroneal nerve in the control period and 45 min after epidural clonidine. Resting-level MSA decreased, but the activation of MSA by apnea was unaffected. Bursts of MSA are identified by small dots.

lost between 30 and 40 min after clonidine administration. However, in the remaining four subjects and in all the MSA recordings, only minor further decrease of nerve activity was observed up to 45 min. Simultaneous with the decrease in sympathetic nerve activity, skin blood flow (fig. 4) increased in the foot (n = 12; $P < 0.05$) but not significantly in the hand (n = 7).

Blood pressure and heart rate started to decrease within 15 min after epidural clonidine (fig. 5). All subjects except one indicated drowsiness after a mean of 17 min (range 10–29), and the majority fell asleep during short periods of the experiment. Plasma clonidine concentrations are shown in fig. 6.

Intramuscular Clonidine

Sixty and 90 min after intramuscular injection of clonidine, plasma concentrations were comparable to those achieved after epidural injection (fig. 6). Individual changes in resting sympathetic nerve activity for all subjects are shown in fig. 3B. Compared to the control period, SSA decreased to an average of 16% (n = 3), MSA bursts to 42% (n = 3), and integrated MSA to 30% (n = 3) after 90 min. Skin blood flow (fig. 4) increased in the foot (n = 6; $P < 0.05$) but not significantly in the hand (n = 4). Blood pressure and heart rate were decreased significantly after 30 min (fig. 5). The subjects indicated drowsiness after 15–30 min.

Discussion

This study shows that both epidural and intramuscular clonidine result in an inhibition of spontaneous SSA and MSA to the leg, parallelled by a decrease in blood pressure and heart rate, an increase in skin blood flow, and sedation.

The fact that sympathetic inhibition in the epidural experiments appeared concomitant with sedation could suggest that sympatho-inhibition was induced by sedation *per se*. However, the resting level of SSA (which depends on the thermoregulatory state) does not decrease during sleep.§ Resting MSA is altered during sleep[25] but the MSA decrease during light sleep is small (approximately 10% decrease in stage 2 sleep). Thus, sedation *per se* cannot explain the sympatho-inhibition following epidural clonidine.

The clonidine-induced sedation, on the other hand, indicates a supraspinal effect of the drug when epidurally administered. Since several previous time control studies[26,27] during long-lasting microneurographic experiments have shown unaltered heart rate and blood pressure, the fact that the decrease in sympathetic discharge to the leg is accompanied by parallel reductions in blood pressure and heart rate suggests that these effects are part of a supraspinally elicited general inhibition of sympathetic outflow. If the sympatho-inhibition recorded in the leg had been a regional response to a spinal effect of clonidine, heart rate would have increased during hypotension due to baroreceptor reflex mechanisms, as seen during lower limb sympatho-inhibition after lumbar epidural anesthesia.[28,29] Furthermore, the plasma concentrations show that the concentration range for the antihypertensive effect of clonidine (0.5–2 ng/ml)[30] is reached 15–30 min after epidural administration of the drug, proving the possibility for systemic (*i.e.*, supraspinal) effects. Finally, the finding that intramuscular clonidine, resulting in comparable plasma concentrations, inhibits SSA and MSA to the same extent as in the epidural experiments supports the notion of a supraspinally evoked decrease in sympathetic outflow.

The discrepancy between skin blood flow changes in hand and foot after epidural clonidine could indicate an effect of the drug also at the level of the spinal cord. However, this difference in skin blood flow responses

§ Elam M, Noll G, Wallin BG: Unpublished observations. 1991.

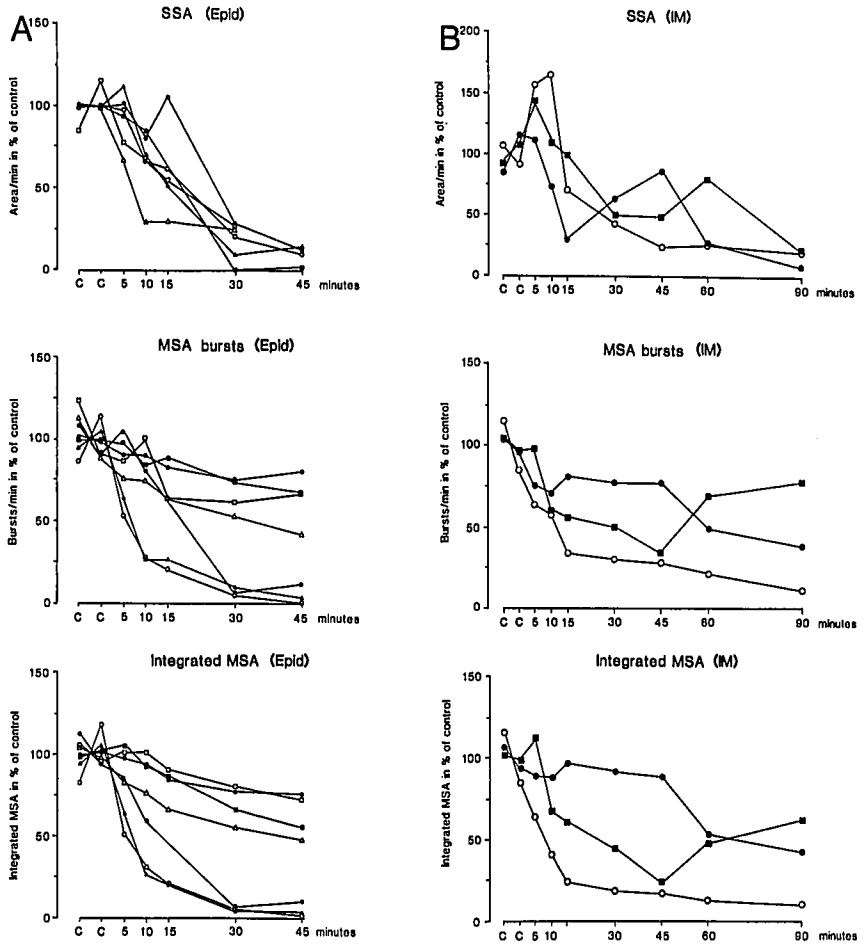

Fig. 3. (*A*) Quantitative analysis of SSA (area under the neurogram) from six subjects, of MSA expressed as bursts/min, and of integrated MSA from seven subjects after epidural clonidine. Values are given as an average for 5-min periods in a percentage of the mean value during the 10-min control period. In two SSA recordings, no 45-min value was achieved because the proper position of the electrode was lost between 30 and 40 min after clonidine. (*B*) Quantitative analysis of SSA (area under the neurogram) from three subjects (different y-axis), of MSA expressed as bursts/min, and of integrated MSA from three subjects after intramuscular clonidine. Values are given as an average for 5-min periods in a percentage of the mean value during the 10-min control period. C = control.

was similar after intramuscular clonidine, making such a partly spinal mechanism of action less likely. Regional differences in neural control of skin blood flow was demonstrated recently in a human study.[31] The present finding of different skin blood flow responses after clonidine administration supports the notion of spatial differentiation of skin sympathetic outflow.

In a previous study of untreated hypertensive patients, MSA was recorded before and after an intravenous bolus injection of clonidine.[32] In three subjects with low resting MSA, sympathetic activity increased after clonidine, whereas in four subjects with higher resting MSA, the activity decreased. In the present study, performed on healthy individuals, MSA decreased in all

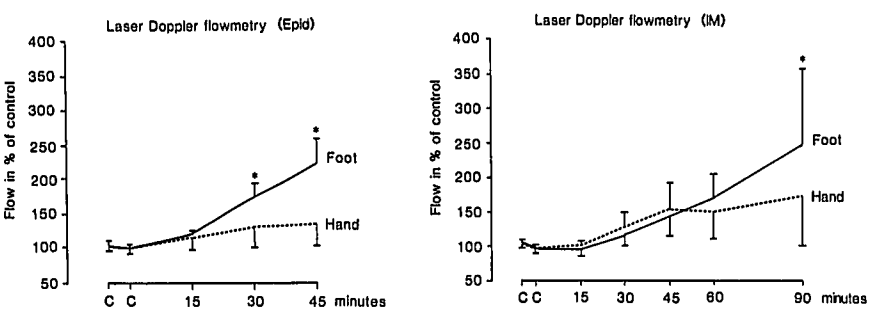

Fig. 4. Changes in skin blood flow in the foot (n = 12) and hand (n = 7) after epidural clonidine (*left*) as well as in the foot (n = 6) and hand (n = 4) after intramuscular clonidine (*right*). Values are presented as an average of 5-min periods. C = control.

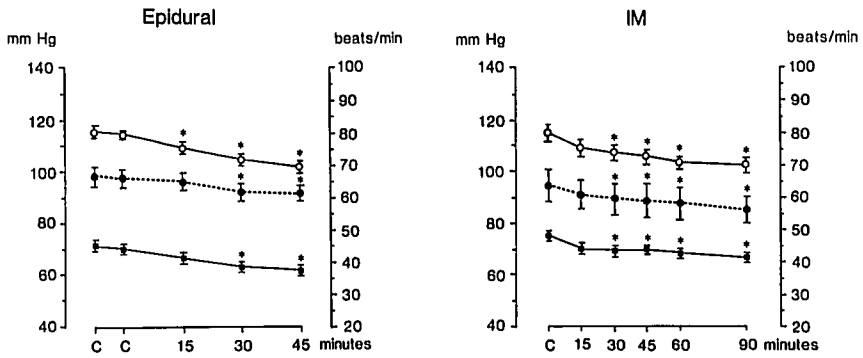

Fig. 5. Changes in systolic and diastolic blood pressure as well as heart rate after epidural (*left*) and intramuscular (*right*) clonidine (3 μg/kg). C = control.

subjects after epidural or intramuscular clonidine, regardless of the level of resting MSA. Although differences between hypertensive and normotensive subjects might explain the inconsistency between these two studies, the discrepancy indicates the need for further investigation of MSA changes after intravenous clonidine.

The capacity for activation of SSA by arousal stimuli and of MSA by apnea remained essentially unaltered, although the variability and habituation of such activations make exact quantification difficult, especially in sedated subjects. These findings may explain the observations in an animal study in which intrathecal clonidine led to a decrease in adrenal vein epinephrine concentration during rest but did not suppress the dynamic response of adrenal epinephrine during nociceptive stimulation.[33] Interestingly, oral administration of clonidine recently was shown[34] to have minimal effects on the more standardized cold pressor test activation of MSA,[35] indicating a remaining sympatho-excitatory capacity despite the marked inhibition of resting MSA induced by clonidine.

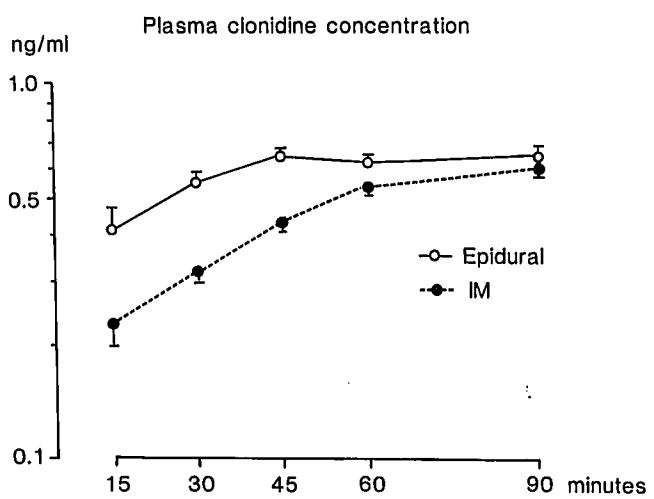

Fig. 6. Plasma concentrations after epidural (n = 7–14) and intramuscular (n = 6) clonidine (3 μg/kg).

The positive effect of epidural clonidine in relieving neurogenic pain has been emphasized by several authors.[1,8,36] A large number of experimental and clinical studies suggest a relationship between certain neuropathic pain syndromes and the activity of the sympathetic nervous system. Abnormal or increased sympathetic nerve activity has been assumed to induce/maintain pain, but to what extent the sympathetic involvement is contributory or fundamentally causal remains uncertain.[37–39] Against this background, the sympatho-inhibitory effect of epidural clonidine might be useful in these pain syndromes.

However, if sympatho-inhibition is the primary goal, the present study indicates that clonidine might as well be administered systemically. The capacity for activation of SSA by arousal stimuli and of MSA by apnea remained, regardless of the degree of clonidine-induced inhibition of resting sympathetic nerve activity. This finding suggests that, if sympathetically maintained pain is elicited mainly by strong sympathetic discharges induced by excitatory stimuli, clonidine (3 μg/kg) may not be expected to have significant analgesic properties in these pain syndromes.

In summary, epidural clonidine inhibits resting sympathetic nerve activity recorded in the leg, but a capacity for transient sympatho-excitation remains. The sympatho-inhibition does not appear to be regional (*i.e.*, induced at the spinal level); rather, it seems to be part of a supraspinally induced general decrease in sympathetic outflow.

References

1. Tamsen A, Gordh T: Epidural clonidine produces analgesia. Lancet 2:231–232, 1984

2. Kalia PK, Madan R, Batra RK, Latha V, Vardhan V, Gode GR: Clinical study on epidural clonidine for postoperative analgesia. Indian J Med Res 83:550–552, 1986

3. Bonnet F, Boico O, Rostaing S, Saada M, Loriferne JF, Toubul C, Abhay K, Ghignone M: Postoperative analgesia with extradural clonidine. Br J Anaesth 63:465–469, 1989

4. Lund C, Qvitzau S, Greulich A, Hjortsø NC, Kehlet H: Comparison of the effects of extradural clonidine with those of morphine on postoperative pain, stress responses, cardiopulmonary function and motor and sensory block. Br J Anaesth 63:516–519, 1989

5. Eisenach JC, Lysak SZ, Viscomi CM: Epidural clonidine analgesia following surgery: Phase I. ANESTHESIOLOGY 71:640–646, 1989

6. Bonnet F, Boico O, Rostaing S, Loriferne JF, Saada M: Clonidine-induced analgesia in postoperative patients: Epidural *versus* intramuscular administration. ANESTHESIOLOGY 72:423–427, 1990

7. Gordh T: Epidural clonidine for treatment of postoperative pain after thoracotomy: A double-blind placebo controlled study. Acta Anaesthesiol Scand 32:702–709, 1988

8. Eisenach JC, Rauck RL, Buzzanell C, Lysak SZ: Epidural clonidine analgesia for intractable cancer pain: Phase I. ANESTHESIOLOGY 71: 647–652, 1989

9. Yaksh TL, Reddy SVR: Studies in the primate on the analgetic effects associated with intrathecal actions of opiates, α-adrenergic agonists, and baclofen. ANESTHESIOLOGY 54:451–467, 1981

10. Murata K, Nakagawa I, Kumeta Y, Kitahata LM, Cillins JG: Intrathecal clonidine suppresses noxiously evoked activity of spinal wide dynamic range neurons in cats. Anesth Analg 69:185–191, 1989

11. Eisenach JC, Dewan DM, Rose JC, Angelo JM: Epidural clonidine produces antinociception, but not hypotension, in sheep. ANESTHESIOLOGY 66:496–501, 1987

12. Glynn C, Dawson D, Sanders R: A double-blind comparison between epidural morphine and epidural clonidine in patients with chronic non-cancer pain. Pain 34:123–128, 1988

13. Guyenet PG, Cabot JB: Inhibition of sympathetic preganglionic neurons by catecholamines and clonidine: Mediation by an alpha-adrenergic receptor. J Neurosci 8:908–917, 1981

14. Eisenach JC, Tong C: Site of hemodynamic effects of intrathecal α_2-adrenergic agonists. ANESTHESIOLOGY 74:766–771, 1991

15. De Kock M: Site of hemodynamic effects of α_2-adrenergic agonists. ANESTHESIOLOGY 75:715–716, 1991

16. Eisenach JC, Grice SC: Epidural clonidine does not decrease blood pressure or spinal cord blood flow in awake sheep. ANESTHESIOLOGY 68:335–340, 1988

17. Gordh T, Prost C, Olsson Y: Evaluation of the toxicity of subarachnoid clonidine, guanfacine, and a substance P-antagonist on rat spinal cord and nerve roots: Light and electron microscopic observations after chronic intrathecal administration. Anesth Analg 65: 1303–1311, 1986

18. Gordh T, Feuk U, Norlén K: Effect of epidural clonidine on spinal cord blood flow and regional and central hemodynamics in pigs. Anesth Analg 65:1312–1318, 1986

19. Vallbo ÅB, Hagbarth K-E, Torebjörk HE, Wallin BG: Somatosensory, proprioceptive, and sympathetic activity in human peripheral nerves. Physiol Rev 59:919–957, 1979

20. Berne C, Fagius J: Skin nerve sympathetic activity during insulin-induced hypoglycaemia. Diabetologia 29:855–860, 1986

21. Holloway GA, Watkins DW: Laser-Doppler measurements of cutaneous blood flow. J Invest Dermatol 69:306–309, 1977

22. Nilsson GE, Tenland T, Öberg PA: Evaluation of a laser Doppler flowmeter for measurement of tissue blood flow. IEEE Trans Biomed Eng 27:597–604, 1980

23. Johnson JM, Taylor WF, Park MK: Laser-Doppler measurement of skin blood flow: Comparison with plethysmography. J Appl Physiol 56:798–803, 1984

24. Arndts D, Stähle H, Förster H-J: Development of a RIA for clonidine and its comparison with the reference methods. J Pharmacol Methods 6:295–307, 1981

25. Hornyak M, Cejnar M, Elam M, Matousek M, Wallin BG: Sympathetic muscle nerve activity during sleep in man. Brain 114:1281–1295, 1991

26. Berne C, Fagius J, Niklasson F: Sympathetic response to oral carbohydrate administration: Evidence from microelectrode nerve recordings. J Clin Invest 84:1403–1409, 1989

27. Kirnö K, Lundin S, Elam M: Effects of intrathecal morphine and spinal anaesthesia on sympathetic nerve activity in humans. Acta Anaesthesiol Scand 37:54–59, 1993

28. Lundin S, Wallin BG, Elam M: Intraneural recording of muscle sympathetic activity during epidural anesthesia in humans. Anesth Analg 69:788–793, 1989

29. Lundin S, Kirnö K, Wallin BG, Elam M: Effects of epidural anaesthesia on sympathetic outflow to the skin. Acta Anaesthesiol Scand 34:492–497, 1990

30. Frisk-Holmberg M: Clinical pharmacology of clonidine. Chest 83:395–397, 1983

31. Oberle J, Elam M, Karlsson T, Wallin BG: Temperature-dependent interaction between vasoconstrictor and vasodilator mechanisms in human skin. Acta Physiol Scand 132:459–469, 1988

32. Wallin BG, Frisk-Holmberg M: The antihypertensive mechanism of clonidine in man: Evidence against a generalized reduction of sympathetic activity. Hypertension 3:340–346, 1981

33. Gaumann DM, Yaksh TL, Tyce GM: Effects of intrathecal morphine, clonidine, and midazolam on the somato-sympathoadrenal reflex response in halothane-anesthetized cats. ANESTHESIOLOGY 73: 425–432, 1990

34. Muzi M, Goff DR, Kampine JP, Roerig DL, Ebert TJ: Clonidine reduces sympathetic activity but maintains baroreflex responses in normotensive humans. ANESTHESIOLOGY 77:864–871, 1992

35. Fagius J, Karhuvaara S, Sundlöf G: The cold pressor test: Effects on sympathetic nerve activity in human muscle and skin nerve fascicles. Acta Physiol Scand 137:325–334, 1989

36. Glynn CJ, Teddy PJ, Jamous MA, Moore RA, Lloyd JW: Role of spinal noradrenergic system in transmission of pain in patients with spinal cord injury. Lancet 2:1249–1250, 1986

37. Bennett GJ: The role of the sympathetic nervous system in painful peripheral neuropathy. Pain 45:221–223, 1991

38. Jänig W: Causalgia and reflex sympathetic dystrophy: In which way is the sympathetic nervous system involved? Trends Neurosci 8: 471–477, 1985

39. Wallin BG, Elam M: Microneurography and autonomic dysfunction, Clinical Autonomic Disorders: Evaluation and Management. Edited by Low P. Boston, Little, Brown, 1992, pp 243–252