Brachial plexus block with bupivacaine: effects of added alpha-adrenergic agonists: comparison between clonidine and epinephrine

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The effects of clonidine and epinephrine, administered into the brachial plexus sheath, were evaluated in 60 patients who underwent surgery of the upper limb. All patients received 40 to 50 ml of 0.25% bupivacaine, injected into the brachial plexus sheath, using the supraclavicular technique. The patients were randomly allocated to two groups so that 30 patients received 150 μg clonidine hydrochloride (Group I), and 30 received 200 μg epinephrine (Group II). The quality and the duration of analgesia were assessed as well as the possible side-effects. The block produced with the addition of clonidine was longer (994.2 ± 34.2 vs 728.3 ± 35.8 min) and superior to that with epinephrine ($P < 0.001$). No major side-effects were recorded. We conclude that the injection of clonidine into the brachial plexus sheath is an attractive alternative to epinephrine to prolong the duration of analgesia following upper limb surgery under conduction anaesthesia.

Les effets de l'addition d'agents agonistes alpha-adrénergiques à la bupivacaïne lors de blocs du plexus brachial ont été évalués chez soixante patients ayant une intervention chirurgicale sur le membre supérieur. L'ensemble des patients a reçu 40 à 50 ml de bupivacaïne à 0.25% pour réaliser un bloc du plexus brachial par voie sus-claviculaire. Les patients du groupe I (n = 30) recevaient par la même voie 150 μg de clonidine, ceux du groupe II (n = 30) 200 μg d'adrénaline. La durée et la qualité de l'analgésie sont ensuite étudiées ainsi que les éventuels effets adverses. Une différence statistiquement significative a été retrouvée en ce qui concerne la durée d'analgésie qui était supérieure dans le groupe clonidine (994,2 ± 34,2 min vs 728,3 ± 35,8 min ; $P < 0.001$). Aucun effet adverse majeur n'est retrouvé. Les auteurs concluent à l'intérêt particulier de la clonidine pour prolonger la durée d'analgésie après chirurgie du membre supérieur réalisée sous anesthésie régionale.

Key words

ANAESTHETIC TECHNIQUES: regional, brachial plexus;
ANALGESIA: postoperative;
SYMPATHETIC NERVOUS SYSTEM: clonidine.

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Presented in part at the 16th Annual Meeting of the American Society of Regional Anesthesia, Cincinnati, USA, April 4–7, 1991.

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Accepted for publication 28th May, 1991.

Several techniques have been used to prolong the duration of regional anaesthesia. Besides the continuous infusion of local anaesthetics through catheters and recently opioids as adjuvants to local anaesthetic solutions,[1] the addition of epinephrine appears to be the most widely used.[2] The prolongation of action is generally related to local vasoconstriction which slows down the vascular resorption of local anaesthetics. Vasoconstriction is related to the action of epinephrine on $alpha_1$-type receptors. Nevertheless, this action remains controversial and other mechanisms have been proposed. The existence of alpha-type receptors, which take part in the transmission of nociceptive stimuli at the spinal level, emphasizes a possible direct action of alpha-adrenergic agonists on neural tissues.[3] These receptors are of the $alpha_2$-type.[4–7] Several experimental and clinical studies have shown that $alpha_2$ adrenergic agonists were able to prolong the dura-

tion of action of local anaesthetics and/or to produce analgesia after epidural and intrathecal administration.[8–14] Recent reports also pointed out that clonidine, an alpha$_2$ agonist, may have benefited patients when it was injected at peripheral nerve sites: after femoral nerve blocks with either lidocaine or bupivacaine, the analgesia obtained with clonidine lasted longer than analgesia obtained with epinephrine.[15–16] No information is available on the efficacy and possible side-effects of clonidine injected with bupivacaine for brachial plexus blocks.

The purpose of this randomized double-blind study was to compare the duration of analgesia produced by the addition of clonidine with that produced by epinephrine when injected with bupivacaine into the brachial plexus sheath.

Methods

Sixty patients, ASA physical status I–II, undergoing orthopaedic or traumatological surgical procedures of the upper limbs, were included in this study after approval by the local human investigation and ethics committee. The protocol was fully explained to each patient and each consented to the procedure. All patients were aged 18 yr or more. Excluded from the study were patients with a history of cardiac, respiratory, hepatic and/or renal failure, and women who were pregnant. Patients known to be sensitive or allergic to one of the study medications were also excluded. Patients with the usual contraindications to brachial plexus block, such as clotting disorders and cutaneous infections, were not included in the study.

All patients fasted for six to eight hours before surgery. Premedication consisted of flunitrazepam 1 to 2 mg orally 60 to 90 min before anaesthesia. An 18-gauge cannula was inserted into a vein of the contralateral forearm. Brachial plexus block was performed using the supraclavicular technique with 0.25% bupivacaine. The volume of bupivacaine was determined according to the body weight (BW) of the patients; 40 ml (100 mg) if BW $<$ 60 kg, 45 ml (112.5 mg) if 60 $<$ BW $<$ 75 kg, 50 ml (125 mg) if BW $>$ 75 kg. The patients were randomly allocated to two groups of thirty patients each. One of the two adrenergic agonists studied was mixed with the local anaesthetic solution in the same syringe. Patients in Group I (n = 30) received 0.2 mg epinephrine (E) and those in Group II (n = 30) received 0.15 mg clonidine (CLO). The amount of liquid added to the local anaesthetic solution was small (1 ml) so that it could not affect the concentration of bupivacaine. Two experienced staff anaesthetists were involved in this double-blind study: one prepared the anaesthetic solution and performed the brachial plexus block while the other, unaware of the anaesthetic solution in use, evaluated the study variables. None of the patients received intravenous medications that could induce sedation.

The following criteria were assessed in the operating room: (i) the time to onset of sensory blockade (SB) according to a three-point score (O: no block; SBI: sensory blockade with persistence of touch; SB2: complete sensory blockade); (ii) the time to onset of motor blockade (MB) according to a three-point scale (0: no block; MB1: motor blockade in at least three nerve territories of the upper limb; MB2: complete motor blockade). Using an automatic blood pressure measuring device, systolic (BPs) and diastolic (BPd) blood pressure and heart rate (HR) were measured throughout the experiment especially before anaesthesia (T0) and at 10, 15 and 30 min (T10, T15, T30). The quality of analgesia was assessed during surgery, in the recovery room and in the surgical ward every 15 min according to a three-point scale: 1, good or very good analgesia; 2, tolerable pain; 3, unsatisfactory or no analgesia. The existence of good analgesia was used to determine the duration of analgesia. If the patient began to experience pain, it was considered that the analgesic action of the drug had terminated. We also considered the nurse's assessment of the patient's comfort and the time from injection into the brachial plexus sheath to the request of the patient for analgesia. All medications prescribed during the immediate postoperative period were recorded. Contingent adverse effects were also noted with special attention to haemodynamic modifications and sedation which were studied every 15 min as well as the quality of analgesia.

Data were expressed as means ± SEM and compared using ANOVA test and Student's t test. Significance was assumed if $P < 0.05$.

Results

There were no significant differences between the two groups regarding sex, height and weight of the patients and in the duration of surgery (Table I). Similar surgical procedures were performed on both Group I and II patients. All patients had an adequate anaesthetic block for their surgery. The different stages of the onset of motor and sensory blockades were recorded and there were no differences for these variables between patients who received epinephrine and those who received clonidine (Table II). Conversely, the total duration of satisfactory analgesia was longer in Group II than in Group I (728.3 ± 35.8 vs 994.2 ± 34.2 min; $P < 0.001$) (Table III). No differences were noted at any time concerning blood pressure and heart rate. Table IV resumed these variables during the first thirty minutes of the experiment. No side-effects were noticed in either group. In particular, no sedation was found in patients who received clonidine.

TABLE I Patient characteristics and duration of operations (mean ± SEM)

	Group I	*Group II*
Sex		
Male	17	15
Female	13	15
Height (cm)		
Mean	166.9 ± 1.6	163.9 ± 3.6
Range	153–180	144–188
Weight (kg)		
Mean	64.03 ± 2.2	66.3 ± 2
Range	48–97	47–87
Duration of operation (min)		
Mean	64.3 ± 7.3	85.2 ± 10.7
Range	15–165	15–230

TABLE II Time to onset of sensory and motor blockades (minutes) (means ± SEM) (SB: sensory blockade; MB = motor blockade)

	Group I	*Group II*
SB1		
Mean	13.0 ± 1.4	15.3 ± 1.2
Range	5–45	5–30
SB2		
Mean	27.2 ± 2.4	32.2 ± 2.3
Range	10–50	10–65
MB1		
Mean	17.9 ± 2.8	18.5 ± 2.1
Range	5–70	5–60
MB2		
Mean	25.8 ± 3.2	31.2 ± 3.9
Range	10–100	10–120

TABLE III Total duration of effective analgesia (min) (mean ± SEM $P < 0.0001$)

	Group I	*Group*
Mean	728.3 ± 35.8	994.2 ± 34.2
Range	400–1035	720–1440

TABLE IV Systolic (BPs) and diastolic (BPd) blood pressures (mmHg) and heart rate (HR) (bpm) (mean ± SEM)

	Group I	*Group II*
T0		
BPs	135.2 ± 3.5	127.7 ± 6
BPd	69.2 ± 2.1	72.5 ± 2.4
HR	74.4 ± 2.34	75.1 ± 2.8
T10		
BPs	128.4 ± 3.3	125.1 ± 3.7
BPd	66.3 ± 2.1	68.4 ± 2.3
HR	76.6 ± 2.5	74.1 ± 2.7
T15		
BPs	128.1 ± 3.4	125.7 ± 4.2
HR	74.5 ± 2.3	75.4 ± 3.6
T30		
BPs	128.4 ± 2.4	122.8 ± 3.8
BPd	66.3 ± 1.8	66.6 ± 2.4
HR	73.7 ± 2.3	71.2 ± 2.23

Discussion

This study demonstrated that, when clonidine was added to bupivacaine and injected into the brachial plexus sheath, it resulted in longer analgesia than when epinephrine was added. However, it was difficult to define the exact duration of analgesia following bupivacaine with either clonidine or epinephrine. Indeed, we relied on our patients' tolerance to pain to define the end of analgesia, and this end-point varied markedly among patients. Nevertheless, these results are in agreement with those obtained by Goldfarb *et al.*[15] using clonidine with bupivacaine for femoral nerve blocks. The mechanism of action for such a potentiation of analgesia remains controversial and poorly understood.

Clonidine, an imidazole compound, has long been used as an anti-hypertensive agent that produces reductions in blood pressure and heart rate. These effects result from central and peripheral alpha$_2$ agonist activity. There is a reduction in sympathetic nervous system outflow[17] which involves the endogenous opioid system[18] and an impairment of peripheral adrenergic neurotransmission by activation of inhibitory presynaptic alpha$_2$ receptors,[19] which leads to increased parasympathetic nervous system activity. Clonidine has also been shown to have alpha$_1$ agonist properties,[20] so that its mechanism of action and effects are complex.

Clonidine has been shown to produce analgesia in animals and humans via a non-opiate action on the alpha$_2$ receptors of the dorsal horn of the spinal cord.[5,21–23] However, the mechanism of the prolongation of local anaesthetic action by clonidine when injected at peripheral nerve sites is not known. We postulate three possible mechanisms. First, clonidine may interfere with the vascular resorption of local anaesthetics by producing vasoconstriction. Alpha$_2$ receptor stimulation produces vasoconstriction in dogs,[24] cats[25] and pigs[26] but not in monkeys.[27] However, the alpha$_2$ effects are different in various animal species and also on different types of blood vessels.[28] There is a different distribution of the two types of alpha-adrenoceptors between arteries and veins. Myers *et al.*[29] have shown a reduction in nerve blood flow caused by epinephrine, but we are not aware of any

similar study with clonidine. The effect of clonidine on spinal cord blood flow is contradictory. Eisenach and Grice showed that the epidural injection of clonidine (17 to 25 $\mu g \cdot kg^{-1}$) did not modify spinal blood flow in sheep[30] but Gordh *et al.*[31] showed a reduction of 25 to 35% after epidural clonidine (10 to 30 $\mu g \cdot kg^{-1}$). Boico *et al.* have shown in humans that intrathecally administered clonidine (150 μg) did not modify the vascular resorption of bupivacaine.[32] Thus, it is unlikely that clonidine, in the dosages we used, could affect the pharmacokinetic behaviour of local anaesthetics.

Secondly, clonidine may have a direct action on neural tissues, especially at the spinal level. Experimental studies have shown the existence of alpha$_2$ pre- and postsynaptic adrenergic receptors in the substantia gelatinosa of the dorsal horn of the spinal cord.[5,33–35] At this level, alpha$_2$ adrenergic agonists are responsible for a reduction in the release of substance P from primary afferent neurons.[36,42] This effect is caused by a cell membrane hyperpolarization resulting from enhanced potassium conductance.[38]

The role of alpha$_2$ adrenoceptors in the mechanism of the neurotransmission of pain is confirmed by the selective antagonism of the antinociceptive effect of intrathecally applied alpha adrenergic agonists by intrathecal yohimbine.[23] These effects on the modulation of pain are dependent on specific non-opiate receptors system but obviously there is some relationship between the various biochemical systems acting in the process of pain transmission.[40] Thus, Ossipov *et al.*[6] have suggested that the alpha$_2$ agonist system is located downstream from the opiate system and that opioids stimulate specific opioid receptors which in turn could stimulate alpha$_2$ receptors. In the same way, supraspinal inhibitory pathways could act on dorsal horn alpha-2 adrenoceptors.[43] It has been suggested recently that alpha-2 adrenergic agonists produce analgesia by activating cholinergic neurons within the spinal cord.[44] Finally, clonidine may act on peripheral nerve alpha-adrenoceptors and interfere at the presynaptic level with the spinal neurotransmission of pain, and/or through a post-synaptic alpha$_2$ specific effect either direct or via the release of endogenous opioids.[45] This hypothesis deserves further study to determine whether alpha adrenoceptors in addition to opioid receptors[46,47] are present in peripheral nerve endings.

Thirdly, clonidine may induce analgesia via a systemic mechanism, after vascular resorption and secondary distribution to the brainstem. Indeed, clonidine has been documented to induce same analgesia when administered orally, transdermally, intramuscularly or intravenously.[14,48–51] However, the observation that there were no significant haemodynamic effects in our patients makes this suggestion unlikely. Despite the fact that the absence of relationship between plasma clonidine concentrations and analgesia has been documented in the literature, further studies may be necessary to measure plasma clonidine concentrations following injection at peripheral nerve sites.

No side-effects were noted in any of our patients. There were no changes in blood pressure or heart rate throughout the study. Also, drowsiness, which is often associated with the use of clonidine,[14] was not apparent in our patients.

In conclusion, we have shown that the addition of clonidine produced a longer duration of analgesia than epinephrine when injected with bupivacaine into the brachial plexus sheath. This was not associated with major side-effects. These findings are in agreement with recent reports of the potentiation of mepivacaine and lidocaine with clonidine in brachial plexus analgesia.[52,53] Therefore, clonidine is an attractive option to prolong analgesia in the postoperative period in patients undergoing surgical procedures under conduction anaesthesia.

References

1 *Viel EJ, Eledjam JJ, de La Coussaye JE, d'Athis F.* Brachial plexus block with opioids for postoperative pain relief: comparison between buprenorphine and morphine. Regional Anesthesia 1989; 14: 274–8.

2 *Cousins MJ, Bridenbaugh PO.* Neural blockade. *In*: Cousins MJ, Bridenbaugh PO (Eds.). Neural blockade in Clinical Anesthesia and Management of Pain. Philadelphia, JB Lippincott, 1987; 111–44.

3 *Collins JG, Kitahata LM, Matsumoto M, Homma E, Suzukawa M.* Spinally administered epinephrine suppresses noxiously evoked activity of wide-dynamic-range neurons in the dorsal horn of the spinal cord. Anesthesiology 1984; 60: 269–75.

4 *Fletwood Walker AM, Mitchell R, Hope PS, Molony V, Igoo A.* An alpha 2 receptor mediates the selective inhibition by noradrenaline of nociceptive responses of identified dorsal horn neurones. Brain Res 1985; 334: 243–54.

5 *Sullivan AF, Dashwood MR, Dickenson AH.* Alpha 2 adrenoceptor modulation of nociception in rat spinal cord: location, effects and interactions with morphine. Eur J Pharmacol 1987; 138: 169–77.

6 *Ossipov MH, Suarez LJ, Spaulding TC.* Antinociceptive interactions between alpha 2 adrenergic and opiate agonists at the spinal level in rodents. Anesth Analg 1989; 68: 194–200.

7 *Luttinger D, Ferrari R, Perrone MH, Haubrich DR.* Pharmacological analysis of alpha 2 adrenergic mechanisms in nociception and ataxia. J Pharmacol Exp Ther 1985; 232: 883–9.

8 *Yaksh TL, Reddy SVR.* Studies in the primate of the

analgesic effects associated with the intrathecal action of opiates, alpha-adrenergic agonists and baclophen. Anesthesiology 1981; 54: 451–67.

9 *Kitahata LM.* Spinal analgesia with morphine and clonidine. Anesth Analg 1989; 68: 191–3.

10 *Racle JP, Benkhadra A, Poy JY, Gleizal B.* Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. Anesth Analg 1987; 66: 442–6.

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

12 *Bonnet F, Boico O, Rostaing S et al.* Extradural clonidine analgesia in postoperative patients. Br J Anaesth 1989; 63: 465–9.

13 *Tamsen A, Gordh T.* Epidural clonidine produces analgesia. Lancet 1984; 2: 231–2.

14 *Bonnet F, Boico O, Rostaing S, Loriferne JF, Saada M.* Clonidine-induced analgesia in postoperative patients: epidural versus intramuscular administration. Anesthesiology 1990; 72: 423–7.

15 *Goldfarb G, Ang ET, Debaene B, Galet C, Jolis P.* Duration of analgesia after femoral nerve block with bupivacaine: effect of clonidine added to the anesthetic solution. Anesthesiology 1989; 71: A 643.

16 *Goldfarb G, Ang ET, Debaene B, Delefosse D, Jolis P.* Duration of analgesia after femoral nerve block with lidocaine: effect of clonidine added to the anesthetic solution. Anesthesiology 1989; 71: A 644.

17 *Wing LMH, Reid JL, Hamilton CA, Sever P, Davies DS, Dollery CT.* Effects of clonidine on biochemical indices of sympathetic function and plasma renin activity in normotensive man. Clin Sci 1977; 53: 45–53.

18 *Kunos G, Farsang C, Ramirez-Gonzalez MD.* Beta-endorphin: possible involvment in the anti-hypertensive effect of central alpha-receptor activation. Science 1981; 211: 82–4.

19 *Langer SZ, Cavero J, Massingham R.* Recent developments in noradrenergic neurotransmission and its relevance to the mechanism of action of certain hypertensive agents. Hypertension 1980; 2: 372–82.

20 *Kiowski W, Hulthen UL, Ritz R, Buhler FR.* Alpha 2 adrenoceptor-mediated vasoconstriction of arteries. Clin Pharmacol Ther 1983; 34: 565–9.

21 *Bentley GQ, Copeland IW, Stan J.* The action of some alpha adrenoceptor agonists and antagonists in antinociceptive test in mice. Clin Exp Pharmacol Physiol 1977; 4: 405–19.

22 *Reddy SVR, Maderdrut L, Yaksh TL.* Spinal cord pharmacology of adrenergic agonist-mediated antinociception. J Pharmacol Exp Ther 1980; 213: 525–33.

23 *Howe JR, Wang JY, Yaksh TL.* Selective antagonism of the antinociceptive effect of intrathecally applied alpha adrenergic agonist by intrathecal prazosin and intrathecal yohimbine. J Pharmacol Exp Ther 1983; 224: 552–8.

24 *Sakakibara Y, Fujiwara M, Maramatsu I.* Pharmacological characterization of the alpha adrenoreceptors of the dog basilar artery. Naunyn Schmiedebergs' Arch Pharmacol 1982; 319: 1–7.

25 *Madgett IC, Langer SZ.* Characterization of smooth muscle alpha adrenoceptors and responses to electrical stimulation in cat isolated perfused middle cerebral artery. Naunyn Schmiedebergs' Arch Pharmacol 1983; 323: 24–32.

26 *Busija DW, Leffler CW.* Exogenous norepinephrine constricts cerebral arterioles via alpha 2 adrenoceptors in new born pigs. J Cereb Blood Flow Metab 1987; 7: 184–8.

27 *Hayashi S, Park MK, Kuehl TJ.* Postsynaptic alpha adrenoceptors in baboon cerebral and mesenteric arteries. J Pharmacol Exp Ther 1985; 235: 113–21.

28 *Mey JD, VanHoutte PM.* Uneven distribution of postjunctionnal alpha 1 and alpha 2 like adrenoceptors in canine arterial and venous smooth muscle. Circ Res 1981; 48: 875–84.

29 *Myers RR, Heckmann HM.* Effects of local anesthesia on nerve blood flow: studies using lidocaine with and without epinephrine. Anesthesiology 1989; 71: 757–62.

30 *Eisenach JC, Grice SC.* Epidural clonidine does not decrease blood pressure or spinal cord blood flow. Anesthesiology 1988; 68: 335–40.

31 *Gordh T, Feuk U, Norlen K.* Effects of epidural clonidine on spinal cord blood flow and regional and central hemodynamics in pigs. Anesth Analg 1986; 65: 1312–8.

32 *Boico O, Bonnet F, Mazoit JX, Darmon JL, Catoire P, Rey B.* Effects of epinephrine and clonidine on pharmacokinetics of spinal bupivacaine. Anesthesiology 1989; 71: A646.

33 *Unnerstall JR, Kopajitic TA, Kuhar MJ.* Distribution of alpha 2 agonist binding sites in the rat and human central nervous system: analysis of some functionnal, anatomic correlates of the pharmacologic effects of clonidine and related adrenergic agents. Brain Res 1984; 7: 69–101.

34 *Probst A, Cortes R, Palacios JM.* Distribution of alpha 2-adrenergic receptors in the human brainstem: an autoradiographic study using [^{3}H]p-aminoclonidine. Eur J Pharmacol 1985; 106: 477–88.

35 *Howe JR, Yaksh TL, Tyce GM.* Intrathecal 6 hydroxydopamine or cervical hemisection reduces norepinephrine content but not the density of alpha 2 adrenoceptors in the cat lumbar spinal enlargement. NeuroScience 1987; 21: 377–84.

36 *Jeftinijica S, Semba K, Randic M.* Norepinephrine reduces excitability of single cutaneous primary afferent C-fibers in the spinal cord of the cat. Brain Res 1981; 219: 456–63.

37 *Calvillo O, Ghignone M.* Presynaptic effect of clonidine on unmyelinated afferent fibers in the spinal cord of the cat. NeuroSci Lett 1986; 64: 335–9.
38 *North RA, Yoshimura M.* The actions of noradrenaline on neurones of the rat substantia gelatinosa in vitro. J Physiol (London) 1984; 349: 43–55.
39 *Post C, Gordh T Jr, Minor BG, Archer T, Freedman J.* Antinociceptive effects and spinal cord concentrations after intrathecal injections of guanfacine or clonidine in the rat. Anesth Analg 1987; 66: 317–24.
40 *Spaulding TC, Fielding S, Venafro JJ, Harbans L.* Antinociceptive activity of clonidine and its potentiation of morphine analgesia. Eur J Pharmacol 1979; 58: 19–25.
41 *VanGiesbergen PLM, VanDuinkerken E, Sweep CGJ, Wiegant VM, VanRee JM, Dejong W.* Alpha-methyldopa induces a naltrexone-insensitive antinociception and hypomotility in rats. Br J Pharmacol 1990; 99: 467–72.
42 *Spaulding TC, Venafro JJ, Ma MG, Fielding S.* The dissociation of the antinociceptive effect of clonidine from supraspinal structures. Neuropharmacology 1979; 18: 103–5.
43 *Jones SL, Gebhart GF.* Characterization of coeruleospinal inhibition of the nociceptive tail-flick reflex in the rat: mediation by spinal alpha 2 adrenoceptors. Brain Res 1986; 364: 315–30.
44 *Gordh T Jr, Jansson I, Martuig P, Gilberg PG.* Interactions between spinal noradrenergic and cholinergic mechanisms for antinociception. Pain 1987; suppl 4: S408.
45 *Nakamura M, Ferreira SH.* Peripheral analgesic action of clonidine: mediation by release of endogenous enkephalin-like substances. Eur J Pharmacol 1988; 146: 223–8.
46 *Gupta B, Brooks THJ, Tejwani GA, Rattan AK.* Narcotic receptors in human peripheral nerves. Anesthesiology 1989; 71: A 635.
47 *Viel E, Eledjam JJ.* Opiates in regional anesthesia. Ann Fr Anesth Reanim 1990; 9: 42–58.
48 *Bernard JM, Lechevallier T, Pinaud M, Passuti N.* Postoperative analgesia by IV clonidine. Anesthesiology 1989; 7: A154.
49 *Curletta JD, Coyle RJ, Ghignone M.* Systemically administered clonidine enhances postoperative epidural opiate analgesia. Anesth Analg 1989; 68 (Suppl): 66.
50 *Segal IS, Jarvis DA, Duncan SR, White PF, Maze M.* Perioperative use of transdermal clonidine as an adjunctive agent. Anesth Analg 1989; 68 (Suppl): 250.
51 *Gordh T Jr.* A study on the analgesic effect of clonidine in man. Acta Anaesthesiol Scand 1983; 78 (Suppl): 73.
52 *Singelyn FJ, Gouverneur JM.* Duration of block and analgesia after brachial plexus anesthesia with mepivacaine: effect of clonidine added to the anesthetic solution. Anesthesiology 1990; 73: A797.
53 *Wyss E, Karp P, Mons P, Bellhacen R, Alame A, Ruelle JL.* Effects of intramuscular or local clonidine for prolongation of brachial plexus block with lidocaine. Anesthesiology 1990; 73: A821.