EXTRADURAL CLONIDINE DOES NOT POTENTIATE ANALGESIA PRODUCED BY EXTRADURAL MORPHINE AFTER MENISCECTOMY

E. J. VAN ESSEN, J. G. BOVILL AND E. J. PLOEGER

SUMMARY

We have studied the ability of clonidine to potentiate morphine analgesia in 28 patients (ASA I) after meniscectomy under general anaesthesia. One hour after surgery, morphine 3 mg (n = 10), clonidine 75 μg (n = 8) or morphine 3 mg plus clonidine 75 μg (n = 10) was injected extradurally. Morphine alone and in combination with clonidine produced similar and significant analgesia as assessed by verbal analogue pain scores. Pain scores did not decrease significantly in patients given clonidine alone. There were statistically, but not clinically significant decreases in systemic arterial pressure after morphine alone and clonidine alone. No patient developed sensory or motor block. One patient given morphine alone developed retention of urine. It is concluded that, in the dose used in this study, clonidine did not potentiate the analgesia produced by extradural morphine.

KEY WORDS
Anaesthetic techniques: extradural. Analgesics: morphine, clonidine.

Clonidine is a partial α₂-adrenoceptor agonist that produces analgesia when administered systemically, intrathecally and extradurally [1-3]. Analgesia produced by clonidine and other α₂-adrenoceptor agonists is independent of the endogenous opioid system, as it is not antagonized by naloxone [4-6], but is antagonized by the α₂-antagonist yohimbine [7]. Nonetheless, there is evidence for interactions between the two systems. Supraspinally administered morphine results in the release of noradrenaline within the spinal cord [8, 9]. In the rat, yohimbine attenuates the antinociceptive effect of both clonidine and morphine [10]. Antinociceptive interactions between opioids and α₂-adrenoceptor agonists at the spinal cord level in rats have been demonstrated [6, 11, 12]. This suggests that the spinal administration of a combination of an α₂-adrenoceptor agonist and an opioid should produce greater analgesia than each alone. This would be beneficial in reducing dose requirements and thus the risk of side effects from both drugs.

Clonidine potentiates the analgesia produced by morphine in animals [6, 12, 13]. The combination of clonidine and morphine extradurally given 18 h after surgery to patients who had undergone oesophagostrectomy resulted in a potentiation of the intensity, but not the duration of analgesia [14]. The purpose of our study was to determine if a similar interaction exists between extradurally administered clonidine and morphine in patients with pain after knee surgery.

PATIENTS AND METHODS

Twenty-eight patients, ASA class I, undergoing arthroscopy followed by arthrotomy with meniscectomy under general anaesthesia, participated in the study, which was approved by the local medical Ethics Committee. Informed written consent was obtained from each patient. None of the patients was taking analgesics before operation.

All patients were given atropine 0.5 mg i.m. 30 min before arriving in the operating theatre. Anaesthesia was induced with thiopentone 3-5 mg kg⁻¹ and maintained with 70% nitrous oxide in oxygen and halothane to a maximum...
inspired concentration of 2%. Patients breathed spontaneously via a face mask throughout anaesthesia. During anaesthesia the ECG and heart rate were monitored continuously and systemic arterial pressure recorded non-invasively (Dinamap) at 5-min intervals. During surgery Ringer's solution was infused at a rate of 5–7 ml kg⁻¹ h⁻¹. At the end of surgery, anaesthesia was discontinued and the patient transferred to the recovery room.

In the recovery room patients were allocated at random to one of three groups, using a computer-generated table of random numbers. One hour after the end of surgery a Tuohy needle was inserted into the extradural space at the L2–3 interspace and a test dose of lignocaine 2 ml with adrenaline 5 µg ml⁻¹ injected. Then morphine sulphate 3 mg in saline 10 ml (group I), morphine sulphate 3 mg plus clonidine 75 µg in saline 10 ml (group II) or clonidine 75 µg in saline 10 ml (group III) was injected, and the needle withdrawn. The drugs were prepared by a nurse who took no further part in the study. Drugs were administered by one of the investigators (E.v.E.) who was unaware of the drug given. He was responsible also for all observations during the study.

Pain, pinprick and touch sensation, motor power and ventilatory frequency were recorded before and 30, 60, 90, 120, 180, 240, 300 and 360 min after drug administration. Pain was assessed using a verbal analogue scale: patients were asked to state the degree of pain on a scale from 0 (no pain) to 10 (worst possible pain). Pinprick and touch sensation were compared between the area around the knee of the non-operated leg and the shoulder area. They were classified as positive if sensation at the knee was less than that at the shoulder. Motor power was assessed by asking the patient to bend the knee on the non-operated side against pressure applied by the observer. This was recorded as unchanged (compared with pre-drug power), diminished or absent. ECG and heart rate were monitored continuously and arterial pressure recorded non-invasively (Dinamap) at 5–15 min intervals.

The occurrence of side effects, in particular urinary retention, nausea or vomiting and pruritis were noted. Escape analgesic medication (piviramide 15 mg i.m.) was given when the patient specifically requested additional analgesia or when the nursing staff, using the routine criteria in the recovery room, judged that this was indicated.

### RESULTS

Two patients, both allocated to group III, requested to be withdrawn from the study within 10 min of injection of clonidine, and were not included in the subsequent analysis. The reasons for withdrawal were excessive pain and a request for an alternative form of analgesia in one patient and psychological reasons in the other. No other patients were withdrawn after admission to the study.

The three groups were comparable with respect to age, weight and height (table I). The duration of anaesthesia was significantly (P < 0.05) longer in group I than in groups II and III.

The pain scores before drug administration were compared using unpaired t tests. Other data were analysed by two-way analysis of variance for repeated measures. When indicated, differences within and between the groups were compared using a modified t test and the Bonferroni correction for multiple comparisons [15]. A value of P < 0.05 was considered significant. Data are presented as mean (sd).

### Table I. Patient characteristics (mean (sd))

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>10</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>9:1</td>
<td>8:2</td>
<td>6:2</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>32 (8.0)</td>
<td>32 (12.7)</td>
<td>29 (5.3)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77 (8.5)</td>
<td>71 (10.5)</td>
<td>76 (9.9)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>176 (15.1)</td>
<td>174 (8.5)</td>
<td>178 (8.6)</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>74 (15.0)</td>
<td>57 (16.0)</td>
<td>58 (17.0)</td>
</tr>
</tbody>
</table>

### Table II. Visual analogue pain scores (mean (sd)) (time = 0) and after extradural administration of morphine 3 mg (group I), morphine 3 mg plus clonidine 75 µg (group II), or clonidine 75 µg (group III). *P < 0.01 vs time = 0 min; **P < 0.05 vs group III; † † P < 0.01 vs group III

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.5 (2.2)</td>
<td>5.2 (2.2)</td>
<td>5.3 (1.1)</td>
</tr>
<tr>
<td>30</td>
<td>4.4 (2.0)</td>
<td>3.1 (1.9)**</td>
<td>4.3 (1.4)</td>
</tr>
<tr>
<td>60</td>
<td>3.1 (2.0)</td>
<td>2.8 (2.3)**</td>
<td>4.0 (1.1)</td>
</tr>
<tr>
<td>90</td>
<td>2.5 (1.9)**</td>
<td>2.4 (2.1)**</td>
<td>4.5 (1.1)</td>
</tr>
<tr>
<td>120</td>
<td>2.2 (1.6)**</td>
<td>2.1 (2.0)**</td>
<td>4.8 (1.4)</td>
</tr>
<tr>
<td>180</td>
<td>1.8 (1.4)** † †</td>
<td>2.1 (2.1)** † †</td>
<td>5.3 (1.7)</td>
</tr>
<tr>
<td>240</td>
<td>1.7 (1.5)** † †</td>
<td>1.9 (2.0)** † †</td>
<td>6.3 (1.2)</td>
</tr>
<tr>
<td>300</td>
<td>1.8 (1.3)** † †</td>
<td>2.2 (2.2)** † †</td>
<td>6.3 (0.8)</td>
</tr>
<tr>
<td>360</td>
<td>2.2 (1.5)** † †</td>
<td>2.5 (2.1)** † †</td>
<td>6.3 (1.0)</td>
</tr>
</tbody>
</table>
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were similar between the groups. Pain scores decreased following both morphine alone and the morphine–clonidine combination (table II), but did not differ from the pre-drug score in patients given clonidine alone. Pain scores between groups I and II did not differ. No patient in any of the groups requested or was given rescue medication. Analysis of variance showed that there were no differences between the groups with respect to systemic arterial pressure, heart rate or ventilatory frequency, or within the groups with respect to heart rate or ventilatory frequency. There were, however, significant differences with respect to arterial pressure within groups I and III. In group I (morphine only) systolic and diastolic arterial pressures were significantly \((P < 0.05)\) lower at 4 h (systolic 119 (10.4) mm Hg; diastolic 72 (4.3) mm Hg) compared with control values of 132 (9.4) mm Hg and 82 (6.7) mm Hg, respectively. In group III (clonidine only) diastolic arterial pressure was significantly \((P < 0.05)\) lower at 60 min (72 (14.2) mm Hg) compared with the control value of 84 (7.8) mm Hg. Systolic arterial pressure did not change in this group. There were no changes in arterial pressure in group II.

No changes in pinprick and touch sensation or in motor power were observed in any patient. No patient developed nausea, vomiting or pruritis. None of the patients became sedated. One patient in group I developed retention of urine which required catheterization of the bladder.

DISCUSSION

In addition to supraspinal modulation of nociception, opioids also regulate the processing of nociceptive information directly in the spinal cord [16]. This action is mediated via specific opioid receptors and results in selective analgesia without motor or sympathetic block [17]. Several other receptor agonists, including adrenergic amines [4], are involved at the spinal cord level in producing analgesia by modulating afferent nociceptive input or its onward transmission to higher centres, or both. There is theoretical and experimental evidence from animal studies that \(\alpha_2\)-adrenoceptor agonists potentiate opioid analgesia at the spinal cord level [6, 11–13]. In humans, the combined extradural administration of morphine 50 \(\mu\)g kg\(^{-1}\) and clonidine 2 \(\mu\)g kg\(^{-1}\) resulted in significantly better analgesia than that produced by morphine 50 \(\mu\)g kg\(^{-1}\) alone [14]. However, we found that the combination of extradural clonidine 75 \(\mu\)g and morphine 3 \(\mu\)g did not produce greater analgesia than that produced by morphine 3 \(\mu\)g alone. There are several possible explanations why our results are at variance with those of other investigators.

With the exception of the study by Petit and colleagues [14], all the existing experimental evidence that the two antinociceptive systems potentiate each other has been derived from animal studies, mainly in rats. It is possible that there is a species difference for this effect. However, clonidine and morphine act synergistically to produce analgesia after intrathecal injection in monkeys [5], a species much closer in general to humans. In addition, in most of these studies the drugs were administered intrathecally, and in none of the animal studies were they given extradurally.

Bonnet and colleagues [18] found that a single extradural injection of clonidine 2 \(\mu\)g kg\(^{-1}\) provided satisfactory analgesia (but of short duration) in patients who had undergone perianal procedures or surgery on the knee. However, in that study surgery was performed under local anaesthesia with 2% lignocaine plain solution given via an extradural catheter inserted before operation. In addition, some patients also received general anaesthesia with thiopentone and nitrous oxide. We purposely avoided using an extradural catheter, as we were unable to predict, before operation, which patients would progress from arthroscopy to open meniscectomy. Patients undergoing only arthroscopy generally have only mild pain after operation and we felt that it would have been unethical to subject them to unnecessary cannulation of the extradural space. With the exception of a small test dose of lignocaine with adrenaline, to exclude vascular injection, we avoided the use of local anaesthetics. An interaction between amethocaine and clonidine has been demonstrated in humans [19] and this may also apply for lignocaine. A consequence of our not using large doses of local anaesthetics is that we cannot be absolutely certain that our test drugs were injected accurately into the extradural space. The insertion of the Tuohy needle and the extradural injection were, however, carried out by an anaesthetist with many years experience with the extradural technique. When he had any doubt about the position of the needle, the patient was excluded from the study.

We found that extradural clonidine 75 \(\mu\)g did
not result in significant analgesia in our patients. We purposely chose a smaller dose than that used in previous studies in order to test for potentiation. If there is a positive interaction between clonidine and morphine for analgesia, this could be either synergistic or additive. In both cases, we should have expected that the response to the combination would be greater than that of morphine alone. This was not the case. It is possible, of course, that our choice of dose of clonidine was too small to allow for potentiation. Direct application of morphine 5–150 μg to the spinal cord produces a dose-related inhibition of C fibre activity by 57%. This response is unchanged in the presence of small doses (10 μg) of clonidine, but larger doses of clonidine (greater than 50 μg) increase morphine-induced C fibre inhibition to 90% [20].

Postoperative pain may not be the most appropriate model for studying potential interactions between clonidine and morphine. Extradural clonidine has been found to be effective in diminishing chronic cancer and non-cancer pain [21, 22]. This latter pain is transmitted mainly by C afferent fibres, whereas the fast Aδ and Aβ fibres are involved predominantly in the transmission of acute, postoperative pain. In the spinal cord, low doses of both morphine and clonidine produce a selective, dose-dependent inhibition of C fibre evoked activity [20, 23]. Aδ and Aβ fibre activity is reduced only slightly by these drugs, and only by the application of high doses. Neither extradural morphine nor extradural clonidine cause significant interruption of transmission in these fast fibres, as assessed by somatosensory evoked potentials [24, 25]. Extradural clonidine 150 μg was considered unsuitable for the treatment of postoperative pain after abdominal hysterectomy [3]. Clonidine 3 μg kg⁻¹ extradurally lacked clinically significant analgesic effects on severe pain following thoracotomy [26]. Extradural clonidine in doses less than 400 μg was relatively ineffective against acute postoperative pain, and doses greater than 600 μg were required for effective analgesia [27]. Such large doses may result in possibly unacceptable haemodynamic changes. However, Eisenach, Lysak and Viscomi [27] found that the degree of hypotension was greatest with intermediate doses of clonidine (400–600 μg) and least following large doses (700–900 μg). This effect is possibly a result of the predominance of the peripheral α₂-adrenergic receptor-mediated vasoconstriction with the greater doses [28].

In conclusion, we found that the combination of extradurally administered clonidine in combination with morphine did not result in improved analgesia compared with morphine alone. With the doses used in our study, clonidine did not potentiate the analgesic effects of extradural morphine. Furthermore, extradural clonidine 75 μg alone was unsatisfactory for postoperative analgesia.

REFERENCES

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