SINGLE-DOSE, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY CROSS-OVER COMPARISON OF EXTRADURAL AND I.V. CLONIDINE IN CHRONIC PAIN

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SUMMARY
We studied 10 patients with chronic back pain who had claimed benefit with a previous extradural dose of clonidine 150 μg combined with local anaesthetic. We compared a single dose of clonidine 150 μg given by either the extradural or i.v. route in a double-blind, randomized, double-dummy and cross-over fashion, with 80% power to detect a difference in the analgesic effect of the two routes. Pain intensity, pain relief, adverse effects, mood, sedation and vital signs were assessed by a nurse observer. I.v. clonidine produced significantly (P < 0.04) greater analgesia than extradural clonidine in one of the five analgesic outcome measures. Clonidine given by either route produced statistically significant sedation and significant decreases in arterial pressure and heart rate. In this study, extradural clonidine had no significant clinical advantages compared with i.v. clonidine; clonidine 150 μg by either route produced a high incidence of adverse effects. (Br. J. Anaesth. 1993; 71: 665-669)

KEY WORDS
Anaesthetic techniques extradural Sympathetic nervous system: clonidine.

The clinical role of clonidine and other alpha2 adrenergic agonists in pain management remains unresolved. Despite the considerable clinical use of clonidine over the past 10 years, there is little evidence from randomized controlled trials to demonstrate its analgesic efficacy when given alone, and the adverse effects with which it is associated may severely limit its usefulness.

The first suggestion of the analgesic effects of clonidine given extradurally in neuropathic pain was reported by Tamsen and Gordh [1]. Since then, several studies have examined the extradural route of administration using both bolus doses [2, 3] and infusions [4]. Several studies showed that clonidine extended the duration of local anaesthesia [5-9] and that it enhanced opioid analgesia in both animals [10-12] and man [13, 14]. There is some evidence of a dose-related response for adverse effects with clonidine [4], but not for analgesic effects [4, 15]. Other routes studied include oral [16], i.v. [17] and transdermal [15]. The placebo-controlled studies available currently in either acute or chronic pain are inconclusive because of conflicting results [2, 6, 16, 18]. The suggestion that clonidine may be effective in neuropathic chronic pain was supported by the finding that some patients had better analgesia with extradural clonidine than with extradural morphine [19].

The aim of this study was to compare the analgesic efficacy and adverse effect profile of i.v. clonidine with extradural clonidine using a double-blind, randomized cross-over design in patients with chronic pain. Negative control (placebo) studies with this class of drugs are subject to methodological problems, primarily because of the presence of overt adverse effects, such as hypotension and sedation. These adverse effects lead to difficulties in maintaining the double-blinding [16, 20]. Positive control studies, using different doses or routes of administration of the test drug, may therefore provide a useful alternative for this class of drug [20], because a similar pattern of adverse effects occurs in all treatment groups, so that analgesic effects can be determined in a more genuinely double-blind way.

PATIENTS AND METHODS
Ethics Committee approval was obtained to recruit patients with chronic back pain attending the Oxford Regional Pain Relief Unit for this single dose, double-blind, double-dummy randomized cross-over study. Patients were selected only if they had constant reproducible pain of moderate or severe intensity below the umbilical region, and if they had previously reported pain relief from an open treatment with extradural clonidine 150 μg combined with local anaesthetic.

Patients were admitted to hospital the day before the study, and after clinical examination a judgement was made as to whether the pain was nociceptive, neuropathic or idiopathic [21]. An extradural catheter was inserted between L2 and L4, using a...
standardized aseptic technique. A test dose of 2% lignocaine 5 ml was given and the position of the catheter confirmed by evidence of sensory or motor block, or both. All clinical examinations and procedures were performed by one investigator (A.J.) assisted by the same nurse (V.K.).

The study began the day after the extradural catheter had been inserted, at least 12 h after the test bolus dose. The study was started only if the pain had returned to baseline intensity, if there was no evidence of residual block and if the pain was of at least moderate pain intensity (categorical pain intensity scale).

Patients received a single dose of clonidine i.v. or extradurally on two separate occasions in randomized order. Treatments were double-blind and double-dummy: on each occasion patients received both an extradural and an i.v. injection, placebo or active. All study treatments were injected over 1 min by the same investigator (A.J.) giving the extradural bolus first. Patients were assessed by one nurse observer (D.C.), using the standard techniques described below. The investigator, nurse observer and patient were not aware of which treatment had been given at any time. Treatments were separated by at least 24 h and the next treatment was given only when the effects of the first had worn off and the pain had returned to baseline intensity. Patients remained in bed throughout each 6-h study period.

At the end of the 6-h study period, patients were free to get out of bed if they were judged to be fully recovered. If they still had pain relief from the study treatment, the time when the pain returned to its normal intensity was recorded. The next morning, patients were reassessed and received the second study treatment, in a manner identical to the first. If patients were still obtaining pain relief after the first treatment, the catheter was removed, they were discharged home and they were asked to return for the second study treatment when the pain had returned to its baseline intensity. This second treatment was then given following the same procedure as the first.

Study treatments and randomization codes were prepared and supplied by the Pharmacy Department at the Churchill Hospital. All treatments were prepared on the day of the study, under aseptic conditions. Treatments were presented as two, pre-filled 10-ml syringes, identified only by patient name, study number (1-10), route of administration (i.v. or extradural) and occasion (1 or 2). The treatment code was kept in the pharmacy in a sealed envelope which was opened after the study was completed. Patients received two single-dose injections, extradural and i.v. on two separate occasions, of clonidine 150 μg (Catapres, Boehringer Ingelheim) or placebo (normal saline).

Assessments

Before study treatment. Baseline assessments were made for current pain using a categorical verbal rating scale for pain intensity (severe = 3; moderate = 2; mild = 1; no pain = 0), by an eight-word scale (Tursky scale; randomly placed words ranging from "no pain" to "excruciating", scored 0-7) and by a visual analogue scale of pain intensity (VASPI: 100-mm line labelled "no pain" at one end and "the worst possible pain" at the other end). Mood was measured with a visual analogue scale (VASMOOD: 100-mm line labelled "worst I could feel" at one end and "the best I could feel" at the other end). Sedation was measured with a categorical scale (asleep = 3; moderately drowsy = 2; mildly drowsy 1; alert = 0). If patients were sleeping then they were woken at each assessment time. Heart rate, arterial pressure and oxygen saturation of arterial blood were measured (Hewlett-Packard GMBH 78352C).

After study treatment. Pain intensity, mood, sedation and vital sign measurements were repeated at 30, 60, 90, 120, 240 and 360 min after the end of the i.v. and extradural injections. Pain relief was also assessed at these times using a categorical verbal rating scale (none = 0; slight = 1; moderate = 2; good = 3; complete = 4) and a visual analogue scale (VASPR: 100-mm line labelled "no relief" at one end and "complete pain relief" at the other). Observed and volunteered adverse effects were recorded. Patients were asked "is there anything else bothering you, or has the treatment upset you in any way?"

At the end of the study, both the patient and the nurse made an overall global rating of the treatment. Patients were asked "how effective was the treatment today?". This was rated as poor = 0; fair = 1; good = 2; very good = 3; excellent = 4. The nurse made her rating before the patient, to avoid bias. After the second study period, patients were asked which treatment they preferred "1 or 2?".

Statistical analysis

It was estimated that at least 10 patients would be necessary to achieve power of 80% with alpha level of 0.05 (two-tailed) and beta level of 0.2 to detect a difference of 40% between the two routes of administration on the primary outcome measure, TOTPAR.

The sum of the pain intensity difference from the categorical pain intensity scale, the visual analogue scale for pain intensity and the Tursky 8 word score were calculated [22] to derive SPID, VASSPID and WORDSPID, respectively. Total pain relief was calculated from the categorical scale for pain relief (TOTPAR) and from the visual analogue scale for pain relief (VASTOTPAR). The area under the curve for mood against time (AUCMood) was calculated.

Comparisons were tested using the Wilcoxon rank test and were considered statistically significant if \( P < 0.05 \). Results are presented as median and range.

Results

The study took place between December 1991 and February 1992. Ten patients were studied (table I). Patient No. 4 had pain at two separate sites; these were assessed independently. Results are therefore presented for 11 pain sites. All patients received both of the study treatments and no patient withdrew from the study. Two of the patients had relief...
EXTRADURAL AND I.V. CLONIDINE IN CHRONIC PAIN

TABLE I. Patient details

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Site</th>
<th>Duration (months)</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>M</td>
<td>Arachnoiditis</td>
<td>Back and leg</td>
<td>306</td>
<td>Neuropathic</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>F</td>
<td>Arachnoiditis</td>
<td>Back and leg</td>
<td>120</td>
<td>Neuropathic</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>M</td>
<td>Paraparesis</td>
<td>Back</td>
<td>360</td>
<td>Neuropathic</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>M</td>
<td>Arachnoiditis</td>
<td>Back and leg</td>
<td>23</td>
<td>Neuropathic</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>F</td>
<td>Arachnoiditis</td>
<td>Leg</td>
<td>480</td>
<td>Neuropathic</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>M</td>
<td>Arachnoiditis</td>
<td>Leg</td>
<td>264</td>
<td>Nociceptive</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>F</td>
<td>Osteoarthritis spine</td>
<td>Leg</td>
<td>240</td>
<td>Nociceptive</td>
</tr>
<tr>
<td>8</td>
<td>58</td>
<td>M</td>
<td>Myelopathy</td>
<td>Back</td>
<td>24</td>
<td>Neuropathic</td>
</tr>
<tr>
<td>9</td>
<td>42</td>
<td>M</td>
<td>Idiopathic back pain</td>
<td>Back</td>
<td>6</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>10</td>
<td>59</td>
<td>M</td>
<td>Arachnoiditis</td>
<td>Leg</td>
<td>30</td>
<td>Neuropathic</td>
</tr>
</tbody>
</table>

Median 57
Range 40-77

TABLE II. Analgesia scores (mean (range)) (10 patients—11 pain sites). * Significant difference between routes (Wilcoxon Test). † Two patients could not distinguish the treatments

<table>
<thead>
<tr>
<th></th>
<th>Extradural</th>
<th>I.V.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPID</td>
<td>3 (-2.5 to 6)</td>
<td>2 (-1 to 10)</td>
</tr>
<tr>
<td>TOTPAR</td>
<td>4 (0-14.5)</td>
<td>6 (0-16)</td>
</tr>
<tr>
<td>VASSPID</td>
<td>58 (-54 to 300)</td>
<td>117 (-43 to 323)</td>
</tr>
<tr>
<td>VASTOTPAR</td>
<td>60 (0-416)</td>
<td>58 (0-428)</td>
</tr>
<tr>
<td>WORDSPID</td>
<td>0 (-6 to 9)</td>
<td>* 2 (-3 to 16)</td>
</tr>
<tr>
<td>AUCMOOD</td>
<td>-6 (-328 to 48)</td>
<td>-56 (-267 to 164)</td>
</tr>
</tbody>
</table>

Patient global 0 (0-2) | 1 (0-2)
Nurse global 0 (0-1)  | 1 (0-2)
Treatment preferred† 5 | 3

AUCMOOD scores were small for both treatments, with no significant difference between the routes. The global ratings by both the patient and the nurse were poor, with no significant difference between routes. Two patients could not distinguish between relief obtained from the two treatments; three preferred the i.v. clonidine and five preferred the extradural dose.

There was a significant increase from baseline in the mean sedation scores for clonidine by both routes: at 60, 90, 120 and 180 min for the extradural route and at 30, 60, 90, 120 and 180 min for i.v. administration. The maximum change (from alert at baseline to moderately drowsy) occurred at 90 min for both routes. There was no significant difference between the routes.

There was no significant change in mean oxygen saturation scores from baseline for clonidine by each route, but a significant decrease in heart rate with extradural clonidine at 60, 90, 120, 180, 240, 300 and 360 min and with i.v. clonidine at 90, 120 and 360 min. Maximum change (18% difference from mean baseline) was at 90 min after extradural clonidine and at 120 min after i.v. administration. There was no significant difference between the routes. There was a significant decrease in the mean systolic and diastolic arterial pressures at all assessment times for both treatments. Maximum change (20%, difference from mean baseline) was at 90 min for both routes. There was no significant difference between the routes.

Adverse effects

The incidence of adverse effects was high for both treatments. Eight patients experienced adverse effects from extradural clonidine and seven from i.v. clonidine. Seven patients had adverse effects with clonidine by both routes (patients Nos 1, 2, 3, 4, 5, 8, 10); two patients had no adverse effects from either route (patients Nos 7 and 9) and one patient had adverse effects from the extradural route only (patient No. 6). Only one patient reported the adverse effects to be unacceptable, and did so for both treatments (patient No. 5). Three patients had more than one adverse effect after extradural clonidine (patients Nos 2, 3, 9) and three patients had more than one adverse effect after i.v. clonidine (patients Nos 4, 5, 10).

Adverse effects occurred earlier with i.v. (30 min)
than with extradural. The most common adverse effect was dry mouth, affecting seven patients for both routes. Other adverse effects were headaches, feeling hot, dizziness, sweating and shaking. In those patients who were affected, many of the effects were continuous and persisted throughout the study.

DISCUSSION

This study suggests that there is no advantage to be gained by giving clonidine by the extradural route compared with giving it by the i.v. route. Although only 10 patients were studied, the methods were sufficiently sensitive to detect a significant difference in one measure of analgesia—i.v. clonidine gave greater analgesia than extradural clonidine. A similar trend was seen with the other measures.

Similar results have been reported in postoperative pain—an i.m. dose of clonidine was indistinguishable from an extradural dose in a parallel group design [23]. This is analogous with the finding that there was no clinical advantage with extradural fentanyl compared with the same dose given by the i.v. route [24, 25].

The finding of no clinical advantage for extradural clonidine over parenteral clonidine in postoperative pain, taken with our results from chronic pain patients, raises at least two points. First, the pain relief which resulted from clonidine by each route in this study was poor (fig. 1). It might be argued that the dose of clonidine (150 µg) was insufficient to produce effective analgesia. However, this dose did produce adverse effects, suggesting that, if larger doses were to be found to produce better analgesia, the associated adverse effects would nevertheless preclude the use of the drug. Second, if extradural clonidine does not have any analgesic advantage over the same dose given parenterally, why is extradural rather than i.v. clonidine being used?

Such considerations would argue against the use of clonidine as the sole analgesic in postoperative pain. Similarly, for chronic pain patients, single doses of extradural clonidine alone do not appear to produce lasting benefit. Although in this study patients were selected because of claimed benefit from a previous open dose of extradural clonidine combined with local anaesthetic, in all but two the pain had returned to baseline after extradural clonidine alone within 24 h. There may nevertheless be a role for clonidine in combination with a local anaesthetic agent or opioid, or both, because of known synergism between them [26].

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