EFFICACY OF THE EXTRADURAL ADMINISTRATION OF LOFENTANIL, BUPRENORPHINE OR SALINE IN THE MANAGEMENT OF POSTOPERATIVE PAIN
A Double-blind Study

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Shortly after the demonstration of the presence of opioid receptors in the substantia gelatinosa (Cavillo, Henry and Neuman, 1974; Perth, Kuhar and Snyder, 1976; Kitahata et al., 1977; Snyder, 1977), the use of intrathecal and extradural opioids in the management of chronic and acute pain was reported (Yaksh and Rudy, 1976, 1977; Yaksh et al., 1976; Wang, 1977; Wang, Nauss and Thomas, 1979). However, the initial enthusiasm for the use of these techniques in clinical practice was soon tempered by reports of adverse reactions, such as pruritus, vomiting, urinary retention (Reiz and Westberg, 1980; Samii, Chauvin and Viars, 1981), and delayed respiratory depression (Boas, 1980; Christensen, 1980; Davies, Tolhurst-Cleaver and James, 1980; Reiz and Westberg, 1980).

Most of these clinical studies were open and uncontrolled; different doses and different drugs were used and injected at different segmental levels, so that seldom could appropriate comparisons be made. The present study compared the analgesic efficacy and duration of action of two extradurally administered long-acting analgesics, lofentanil and buprenorphine, and compared the findings with those following the administration of physiological saline.

PATIENTS AND METHODS

Choice of analgesic

Although several opioids, agonists as well as agonists/antagonists, have been administered by the extradural route, we were interested in finding a long-acting drug that might be devoid of side effects.

Lofentanil is a new fentanyl derivative. In studies in animals it was 20 times more potent than fentanyl and approximately 6000 times more potent than morphine. Its exceptionally long duration of action (> 24 h) appears to be attributable to persistent occupation of opiate receptor sites (Gommeren and Leysen, 1982). Although lofentanil has been used previously via the extradural route to suppress pain, the results were controversial, and drowsiness and nausea were reported (A. Van Steenberge, personal communication). Before starting the present double-blind study, we performed an open pilot study with lofentanil in 13 patients with postoperative pain after ortho-
paedic surgery. Lofentanil 5 μg in saline 11 ml was administered extradurally (L3–L4). In eight of the 13 patients, analgesia was good and lasted for at least 72 h. In one patient pain recurred after 20 h and in two other patients pain relief was moderately good. In two patients lofentanil was without noticeable effect. All the patients seemed to become sleepy after the injection, but could be aroused easily. There were no other side effects.

Buprenorphine was chosen as the reference drug for the present study since it has been used frequently via the extradural route (Lecron, Levy and Toppet-Balatoni, 1980; Rondomanska, 1980; Carl, Crawford and Wolfe, 1981; Kierkegaard et al., 1981; Zenz et al., 1981).

Patients and technique

Sixty adult patients with postoperative pain after orthopaedic surgery performed under extradural anaesthesia, were selected. The study had been approved by the ethics committee of the Academic Hospital and the patients gave informed consent.

Anaesthesia for the surgical procedure was performed with 2% lignocaine 10 ml with adrenaline 1:80000 mixed with 0.5% plain bupivacaine 10 ml and administered via an extradural catheter inserted at the third lumbar space. Immediately thereafter, a second catheter was inserted three spaces higher and advanced cephalad for 1.5 cm.

Coded 1-ml ampoules containing lofentanil 5 μg (L), buprenorphine 0.3 mg (B) or saline (S) were diluted with saline to a standard volume of 11 ml. As soon as pain occurred in the early postoperative period, patients received the trial drug via the most cephalad catheter. The patients were randomly divided into three groups of 20. Pain intensity as reported by the patients, systolic and diastolic arterial pressures, and heart and respiratory rates were recorded before administration, and at 10, 20, 30, 40 and 60 min and 2, 3, 4, 6, 10, 12, 20, 30, 40 and 72 h after injection. Side effects were sought and recorded. The degree of pain was evaluated using the following scores: no pain, mild pain, moderate pain, severe pain or very severe pain.

If pain relief was unsatisfactory (very severe, severe or moderate pain) 40 min after injection, 0.25% bupivacaine 15 ml with adrenaline 1:200000 was given via the lower catheter, the result was coded as “no effect” and these patients were withdrawn from the study (early withdrawal). At that time, the two catheters were removed in all patients. If “unsatisfactory pain relief” was noted subsequently, the patient received pentazocine 45 mg i.m. and was withdrawn from the study at that point (late withdrawal).

Statistical analyses were by the Kruskal–Wallis test and \( P < 0.05 \) was considered significant.

RESULTS

The three groups of 20 patients were comparable for age, weight and height (table I). The distribution of the sites of operation is shown in table II. The time between the last injection of local anaesthetic during surgery and the injection of the trial drug was 259 ± 16 min (mean ± SEM) for L, 271 ± 16 min for B and 274 ± 28 min for S.

The distributions of the pain scores at the various times of assessment are shown in figures 1, 2 and 3.
EXTRADURAL LOFENTANIL OR BUPRENORPHINE

Fig. 1. Pain evaluation after placebo (n = 20). ■ = No pain; □ = mild pain; * = moderate pain; • = severe pain; □ = very severe pain; ▲ = unsatisfactory pain relief; stippling = no effect. (Key applies to figures 2, 3 also.)

Fig. 2. Pain evaluation after buprenorphine (n = 20).

Fig. 3. Pain evaluation after lofentanil (n = 20).
No statistical differences existed between the three groups immediately before the administration of the test drug. The onset of analgesia was observed generally between 10 and 20 min for lofentanil and buprenorphine, with a gradually increasing effect. At 40 min after injection, 12 (S), seven (B) and one (L) patients reported no effective pain relief (severe or very severe pain) and were excluded from the rest of the study (early withdrawal). Another patient (L) complained of unsatisfactory pain relief just after the extradural catheter had been removed, was given the i.m. analgesic and rated as unsatisfactory. The analysis of the cumulative numbers of patients reporting unsatisfactory or no pain relief (table III) is in favour of lofentanil (significant difference between S and L, and B and L).

At 12 h, seven (S), six (B) and 16 (L) patients and at 30 h seven (S), five (B) and 11 (L) patients still had mild or no pain, confirming the long duration of action of lofentanil. The differences in degree of pain between placebo and lofentanil and between buprenorphine and lofentanil were statistically significant at several time intervals (table IV), each time in favour of lofentanil. There were no significant differences between any groups after 30 h.

**TABLE IV.** *Statistical evaluation of pain evaluation before and after extradural administration (Mann-Whitney U test)*

<table>
<thead>
<tr>
<th>Time after extradural administration</th>
<th>Before extradural</th>
<th>20 min</th>
<th>40 min</th>
<th>1 h</th>
<th>3 h</th>
<th>6 h</th>
<th>12 h</th>
<th>20 h</th>
<th>30 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo v. lofentanil</td>
<td>0.598</td>
<td>0.007</td>
<td>0.003</td>
<td>0.006</td>
<td>0.004</td>
<td>0.008</td>
<td>0.017</td>
<td>0.057</td>
<td>0.239</td>
</tr>
<tr>
<td>Buprenorphine v. lofentanil</td>
<td>0.797</td>
<td>0.01</td>
<td>0.011</td>
<td>0.018</td>
<td>0.012</td>
<td>0.017</td>
<td>0.007</td>
<td>0.022</td>
<td>0.14</td>
</tr>
<tr>
<td>Buprenorphine v. Placebo</td>
<td>0.797</td>
<td>0.617</td>
<td>0.33</td>
<td>0.394</td>
<td>0.626</td>
<td>0.914</td>
<td>0.776</td>
<td>0.695</td>
<td>0.695</td>
</tr>
</tbody>
</table>

**FIG. 4.** Respiratory rate (mean ± SEM) after injection of placebo (dotted columns), buprenorphine (open columns) and lofentanil (cross-hatched columns) (*n* = 20 each).
No distinct cardiovascular or respiratory depression was noted at any time in the three groups. A transient period of bradypnoea (respiratory rate of 12 b.p.m.) lasting for 30 min occurred in one (L) patient, 90 min after injection. Mean respiratory rate was sometimes marginally higher in the S group than in the B and L groups (fig. 4), but no statistically significant differences were noted.

Side effects are shown in table V. Sleepiness was noticed in three (B) and three (L) patients and sweating in one (B) patient. Nausea, vomiting, pruritus or urinary retention were not observed in any of the patients.

**DISCUSSION**

The administration of opioids into the subarachnoid or extradural spaces for postoperative pain relief, has become popular in recent years in the management of postoperative pain. Of the two routes, extradural administration seems preferable, because of the lower risk of infection, the lack of postspinal headache and a lower incidence of side effects. Furthermore, incremental doses can be given via an indwelling catheter. However, most reports mention a failure rate of 10-20%. In an attempt to improve the success rate, the catheter was placed so that the trial drugs were placed at the level of T12-L1, the aim being to have the opioids injected as close as possible to the opioid receptors present in the substantia gelatinosa.

The most appropriate opioid for postoperative pain relief is still open to debate. Theoretically, any opioid except opium or piritramide, could be administered. To date the most widely used drug has been morphine, which produces effective, long-lasting analgesia, but at the expense of a high incidence of side effects.

The ideal drug should have the following characteristics:
- high lipid solubility, inducing fast diffusion into the neural tissues, and little systemic absorption;
- high molecular weight;
- strong binding to receptor protein, thus producing a prolonged effect;
- intense and prolonged intrinsic activity.

Theoretically, at least, the two drugs used in this study seemed to meet most of these characteristics.

Lofentanil had a rapid onset of action and a prolonged effect, and provided adequate pain relief in the majority of patients. No cardiovascular or respiratory depression occurred, confirming our preliminary open study (unpublished results). Three patients were drowsy, in contrast to our initial study in which all 13 patients were sleepy. Buprenorphine was less efficacious in the relief of pain, and its duration of action was shorter than might have been expected (Zenz et al., 1981), although unpredictable activity has been described after extradural administration (Kierkegaard et al., 1981). It is difficult to find a satisfactory explanation for the poorer suppression of pain, with buprenorphine. In most reports the site of injection was below L3-L4 and the drug was given after abdominal or gynaecological surgery. In the present study the drug was placed at T12-L1 and only orthopaedic patients were studied. Combining buprenorphine with a local anaesthetic might be more effective (Lecron, Levy and Toppet-Balatoni, 1980).

The placebo effect was marked in our study. Many studies have shown that about 30–35% of patients report marked pain relief after saline i.m. (Melzack, 1973), a figure close to the 25% found in the present study. McClure and colleagues (1980) compared extradural morphine with saline and found a significant decrease in mean pain score in the placebo group 20 min after injection. In addition, the extradural injection of saline 10 ml (at T10–T11) produced a placebo effect comparable to the analgesia provided by morphine 2 mg injected in the same volume in the lumbar area (Asari et al., 1981). Urbain and McKain (1978) demonstrated that saline 5–10 ml injected intrathecally produced segmental hypoesthesia as well as partial sympathetic blockade. The relatively marked placebo effect after the extradural injection of saline, could, theoretically, be the result of the same modulation of pain perception which results from the intrathecal injection of saline.

Although itching, urinary retention, respiratory
depression, nausea and vomiting are mentioned frequently in the literature, they were not observed in this series of patients. One reason might be the total omission of opioid drugs during the actual anaesthetic.

CONCLUSION
The extradural administration of lofentanil provided effective pain relief of long duration and was significantly better than after buprenorphine in these respects. Its use warrants further study. However, a word of caution about the unrestricted use of lofentanil might be appropriate for the time being, because of its very strong receptor-binding properties and the lack of a suitable antagonist.

REFERENCES