EXTRADURAL OPIOIDS FOR POSTOPERATIVE ANALGESIA

A double-blind comparison of pethidine, fentanyl and morphine

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SUMMARY

Pethidine 50 mg, fentanyl 100 μg and morphine 2 mg administered to the extradural space, were compared in the treatment of pain following surgery. All three drugs produced a rapid decrease in pain scores as assessed using a visual linear analogue, morphine being the least effective. Fentanyl had a relatively short duration of action (2 h), whereas morphine appeared to be the longest acting. It is suggested that the best relief of pain would be obtained by incremental doses given extradurally. All drugs produced an increase in sedation, but there was no respiratory depression as assessed by \( P_{\text{aCO}_2} \) measurement.

Following its initial use in patients with chronic pain (Behar et al., 1979), increasing use has been made of extradural morphine in patients suffering from pain after surgery (Cousins et al., 1979; Torda, 1979; Bailey and Smith, 1980; Bromage, Camporesi and Chestnut, 1980; Graham, King and McCaughey, 1980; Magora et al., 1980; Reiz and Westberg, 1980; Wolfe and Davies, 1980). Although these authors reported excellent analgesia of long duration with minimal side-effects, others have found extradural morphine disappointing in the treatment of postoperative pain. McClure and colleagues (1980) showed no difference between the pain relief produced by morphine and a placebo 20 min after administration.

Initial experience with the technique in this department was obtained in the management of pain in patients following major hepato-biliary surgery. In eight patients, pethidine 100 mg in normal saline 10 ml was injected via an extradural catheter inserted in the mid-thoracic region. Although analgesia followed rapidly, all patients became heavily sedated, two being unrousable, and there was a marked decrease in respiratory rate, although apnoea did not occur. Significant analgesia in these patients lasted from 3 to 6 h, as assessed using a visual linear analogue scale.

Since these experiences with extradural pethidine differed from work already published it was decided to institute a double-blind study of the effectiveness of three opioid drugs: pethidine, fentanyl and morphine, in patients with pain after surgery.

PATIENTS AND METHODS

Studies were carried out on 60 patients (33 male and 27 female) in whom extradural catheters had been inserted after the induction of anaesthesia. The catheters were introduced into the mid-thoracic region for upper abdominal surgery and the lower thoracic or lumbar region for lower abdominal operations. Informed consent was obtained from each patient. Premedication was with appropriate doses of papaveretum and hyoscine and the anaesthetic consisted of an i.v. induction followed by the administration of a competitive neuromuscular blocking drug, tracheal intubation and ventilation of the lungs with 70% nitrous oxide in oxygen. Small amounts of halothane or enflurane were added to deepen anaesthesia if necessary, but i.v. analgesic drugs were not given. Following antagonism of the neuromuscular blockade at the end of the procedure, the patients were transferred to the recovery room or intensive care unit where the studies were carried out.

Pain was assessed using a visual linear analogue scale as first described by Bond and Pilowsky (1966). The patient placed a mark on the line corresponding to the degree of pain experienced and the distance (in millimetres) from the left hand edge of the line to the mark was taken as the pain score. The method was explained to each patient on the day before surgery, and anyone unable to understand was not included in the trial. Pain was assessed before the administration of the drug at
the patient's first request for analgesia, at 5, 10, 20, 30 and 60 min after administration and at hourly intervals thereafter. Any patient who requested additional analgesia received it immediately in the form of i.m. or i.v. papaveretum and thereafter was excluded from analysis of the results.

At each assessment heart rate, arterial pressure and respiratory rate were recorded. In 38 patients (12 each in the morphine and fentanyl groups and 14 who had received pethidine) an arterial cannula had been inserted for monitoring purposes during surgery, and in these patients samples of arterial blood were taken for measurement of $P_{a\text{CO}_2}$. An attempt was made to assess the degree of sedation scored: 0 = awake and alert; 1 = awake but drowsy; 2 = drowsy but rousable; 3 = unrousable.

The drugs, which were free of preservative, were prepared in the hospital pharmacy in identical coded ampoules. They contained pethidine 50 mg, fentanyl 100 $\mu$g or morphine 2 mg, all in normal saline 10 ml. They were administered in a random fashion such that 20 patients received each drug. The dose of pethidine was chosen in the light of our initial experience with the drug. The doses of morphine and fentanyl were chosen on the basis of those commonly reported by other authors (Wolfe and Nicholas, 1979; Chayen, Rudich and Borrine, 1980; McClure et al., 1980; McQuay et al., 1980). It was considered unethical to incorporate a placebo when the time of onset of analgesia was uncertain.

### RESULTS

The operations performed, the number of patients who received each drug in the operative groups and their mean ages and weights are shown in table I. One patient, following herniorrhaphy, was extremely restless and voluble in the recovery room and unable to record the amount of pain experienced. He was given an analgesic solution, which was later shown to be morphine, and although he became calmer and apparently had relief of pain, was still unable to co-operate and was excluded from the trial. All remaining patients were able to co-operate with the method of assessment of pain.

The mean pain scores at each assessment are shown in table II. There was no significant difference between the pain scores in the control period. Following injection of the opioid drug there was a prompt and significant decrease in the pain scores in each group, the maximum decrease being achieved within 20–30 min. The mean pain scores in the pethidine group were significantly less than in those given morphine at 10, 20, 30 and 60 min ($P<0.05$, 0.01, 0.01 and 0.05 respectively; Student's $t$ test); while in the fentanyl group the score was significantly less than in the morphine group at 30 min ($P<0.05$). Ten patients who had received pethidine, nined given fentanyl and four given morphine recorded zero pain score at some stage during the study. These were all recorded within 1 h of the administration of the drug, but only lasted for a maximum of 30 min in the fentanyl group and 20 min in the morphine group. Total

<table>
<thead>
<tr>
<th>Operations performed</th>
<th>Analgesic</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Pethidine</td>
</tr>
<tr>
<td>Upper abdominal</td>
<td></td>
</tr>
<tr>
<td>Hepato-biliary</td>
<td>7</td>
</tr>
<tr>
<td>Gastric</td>
<td>1</td>
</tr>
<tr>
<td>Small bowel</td>
<td>2</td>
</tr>
<tr>
<td>Vascular</td>
<td>—</td>
</tr>
<tr>
<td>Adrenalectomy</td>
<td>1</td>
</tr>
<tr>
<td>Lower abdominal</td>
<td></td>
</tr>
<tr>
<td>Gynaecological</td>
<td>2</td>
</tr>
<tr>
<td>Colectomy</td>
<td>2</td>
</tr>
<tr>
<td>Vascular</td>
<td>3</td>
</tr>
<tr>
<td>Herniorrhaphy</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Mean age ± SEM (yr)</td>
<td>52.6 ± 3.12</td>
</tr>
<tr>
<td>Mean weight ± SEM (kg)</td>
<td>64.2 ± 3.2</td>
</tr>
</tbody>
</table>
analgesia occurred for a significant time in only two patients, both given pethidine (2 h and 5 h respectively).

By 2 h there was an increase in pain score in all groups, being most marked in those given fentanyl, and at this time the mean pain score in these patients was significantly greater than in those who received pethidine. By 4 h, 15 of the fentanyl group had been withdrawn from the study as they had received further analgesia. There was little increase in pain scores in the morphine group after 2 h and only a small increase in those who had received pethidine. Apart from the 4-h recording in the fentanyl group, the pain scores at each time of assessment were significantly lower than the control values for that particular group.

The results are complicated by the fact that patients were withdrawn progressively from the trial as they required additional analgesia, so that the mean pain scores alone could be misleading. Table III shows the pattern of the withdrawal of patients in a cumulative fashion. At 3 h, significantly more patients who had been given fentanyl than had received pethidine had been withdrawn (P < 0.01, Fisher's exact test), but the difference between morphine and fentanyl did not quite reach statistical significance. By 4 h, the majority of patients in the fentanyl group had been withdrawn, the number remaining in the other groups being significantly greater. By 7 h, more of the patients who had received pethidine and been withdrawn compared with the morphine group, although the difference was not statistically significant. Table IV shows the number of patients at each time of assessment in whom the pain scores were 50% or less of the control values. These results, taken with the pattern of withdrawal, indicate that fentanyl had a relatively short duration of action when given to the extradural space whereas, of the three agents, morphine produced the longest effect.

The changes in respiratory rate, PaCO2, and degree of sedation are shown in figure 1. There was a decrease in respiratory rate following each drug, being least with morphine, but it was significantly less than control values from 5 min to 2 h in the
pethidine group, and at 20 min in those given fentanyl. There were no significant changes in $P_{aO_2}$. An increase in sedation was immediately obvious, being maximum at 30 min with each drug, and persisting for 3 h. At no stage did any patient become unrousable or give cause for concern.

No significant changes occurred in heart rate or arterial pressure during the study, and no patient complained of nausea, vomiting or itching. No sensory or motor loss was detected at any stage.

**DISCUSSION**

All three drugs used in this study produced a rapid and significant decrease in pain scores when injected into the extradural space. However, the duration of action differed from that reported by other workers in that it was much shorter. The pain scores alone cannot be the only factor to be taken into account when looking at the duration of action because of the progressive withdrawal of patients from the study as they required additional analgesia. When looked at in this way, fentanyl appeared to produce satisfactory analgesia for about 2 h, while morphine appeared to have the longest duration of action.

Doubt must be raised as to the reliability of taking the duration of action of an analgesic drug, in these circumstances, as the time to the next administration of a narcotic agent. This cannot be equated with the time by which further relief of pain is required. The administration of additional analgesia depends on the patient requesting further medication and on the availability of a trained nurse. Cousins and colleagues (1979) measured pain relief using a visual linear analogue scale and found that the mean duration of action of pethidine 100 mg, given extradurally for the relief of pain after operation, was 6 h. McClure and co-workers (1980), using a similar method of assessment, found extradural morphine 2 mg and 5 mg to be disappointing in the treatment of pain following surgery and to be ineffective when used immediately after operation.

No complications were seen that could be attributed to the extradural opioids, and the frequency of complications following extradural morphine would seem to be lower than by conventional routes of administration (Reiz and Westberg, 1980). The most serious side-effect was respiratory depression. In all our patients there was a decrease in respiratory rate, but this was never a problem and there was no depression of ventilation, as judged by change in $P_{aCO_2}$. However, there has been a number of reports of severe respiratory depression and coma following the use of extradural opioids, although the timing of the depression appears to vary. In most instances it occurred within 45 min of administration (Glynn et al., 1979; Scott and McClure, 1979; Boas, 1980; Welch, 1981), although in some it was delayed for 4–6 h (Christensen, 1980; Reiz and Westberg, 1980). Glynn and colleagues (1979) showed that the respiratory depression coincided with high c.s.f. concentrations of pethidine and suggested that this, combined with the effects of the narcotic premedication given some time earlier, could be the cause. This early occurrence of respiratory depression after extradural administration is in marked contrast to that seen after intrathecal opioids, where several hours often elapse before any serious effects are seen (Glynn et al., 1979; Lolios and Andersen, 1979; Davies, Tolhurst-Cleaver and James, 1980). Glynn and co-workers (1979) have commented on the fact that there is virtually no information on the rate of removal of drugs from c.s.f. and that many factors such as changes in posture, coughing and vascular pulsations would affect c.s.f. flow and hence the movement of any contained narcotics.

Systemic absorption of extradural opioids is unlikely to be a major factor in the production of analgesia. Yaksh and Rudy (1976) produced
potent analgesia in rats with intrathecal morphine and showed that the latter was confined to the spinal cord. Cousins and colleagues (1979) measured blood and c.s.f. concentrations of pethidine after extradural administration and found that the onset of pain relief coincided with high c.s.f. concentrations while the blood pethidine concentrations were below the analgesic value. However, systemic effects do occur, as indicated by the increase in sedation observed following all three drugs and which was maximum at 30 min. Bromage, Camporesi and Chestnut (1980) found less central depression following extradural opioids than after approximately the same dose of opiate i.v.

There is considerable enthusiasm for the use of extradural opioids in the treatment of all types of pain. There is no doubt that they produce rapid relief of pain, but the duration of action found here was much shorter than that reported by others. This may be related to the method of assessment of the pain. It is also interesting to note that Husemeyer, O'Conner and Davenport (1980) found extradural morphine to be ineffective in relieving pain in labour. Of the drugs used in this study, pethidine appeared to be the most effective and morphine the least, but this is probably a matter of dosage. More effective analgesia could probably have been obtained with morphine by titrating the extradural dose against the demands of the patients (Bromage, Camporesi and Chestnut, 1980). The duration of action of fentanyl was relatively short and a continuous infusion, with which excellent results have been reported (Bailey and Smith, 1980), would be more appropriate.

Serious side-effects do occur at a variable time after the administration of extradural opioids, and they are potentially lethal. Little is known of the factors that contribute to the appearance of severe respiratory depression. Despite the many advantages that this technique appears to offer, more work needs to be done to elucidate these factors and at the moment the authors are not prepared to use extradural opioids for analgesia after surgery unless the patient is under constant expert surveillance.

ACKNOWLEDGEMENTS

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REFERENCES


OPIACES PAR VOIE EXTRADURALE POUR ANALGESIE POSTOPERATOIRE: COMPARAISON À DOUBLE INCONNUE DE LA PETHIDINE, DU FENTANYL ET DE LA MORPHINE

RESUME
On a comparé 50 mg de pethidine, 100 μg de fentanyl et 2 mg de morphine administrés dans l’espace extradural, pour le traitement de la douleur faisant suite à une intervention chirurgicale. Ces trois agents ont entraîné une rapide diminution de la douleur, estimée à l’aide d’un analogue linéaire visuel, la morphine étant le produit le moins efficace. Le fentanyl a eu une durée d’action relativement courte (2 h), alors que la morphine semble avoir été l’agent ayant la plus longue durée d’action. L’auteur est d’avis qu’un meilleur soulagement de la douleur pourrait être obtenu par des doses croissantes administrées par voie extradurale. Tous les produits ont accru la sédation, mais il n’y a eu aucune dépression respiratoire comme on a pu en juger par la mesure de la $P_{\text{a}CO_2}$.

OPIACES EXTRADURALES PARA ANALGESIA POSOPERATIVA: UNA COMPARACIÓN DE DOBLE ANONIMATO DE LA PETIDINA, EL FENTANIL Y LA MORFINA

SUMARIO
A la cavidad extradural se le administraron 50 mg de petidina, 100 μg de fentanilo y 2 mg de morfina, cuyos efectos se compararon en el tratamiento del dolor después de la operación quirúrgica. Las tres drogas produjeron una rápida disminución de los umbrales de dolor, según evaluación efectuada mediante una analogía lineal y visual. El fentanilo presentó una actividad relativamente corta (2 h), mientras que la morfina pareció ser la más duradera. Se sugiere que el mejor alivio del dolor se obtendría incrementando las dosis administradas extraduralmente. Todas las drogas produjeron un incremento de la sedación pero no hubo depresión respiratoria según los evaluación llevada a cabo por la medición de la $P_{\text{a}CO_2}$. 