A DOUBLE-BLIND COMPARISON OF MORPHINE AND BUPRENORPHINE IN THE PREVENTION OF PAIN AFTER OPERATION

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SUMMARY

A double-blind, between-patient comparison has been made of the effects of morphine 10 mg i.v. and buprenorphine 0.3 mg i.v. on the prevention of pain after operation. The drugs were given by the anaesthetist at the end of the operation, and the onset and severity of pain were assessed by a trained nurse. Both drugs caused a significant delay in the appearance of severe pain when compared with the control group, but with buprenorphine the mean delay of 10.5 h was more than twice that of morphine. The only side-effect to occur more frequently after administration of the analgesics was drowsiness, the incidence being greater after buprenorphine than after morphine.

Buprenorphine, a new analgesic drug, is an opiate-like partial agonist-antagonist, related to diprenorphine. Following parenteral administration, it has been shown to have a potency 40-50 times that of morphine. Thus, buprenorphine 0.3 mg produced a degree of displacement of the carbon dioxide response curve similar to that produced by morphine 12.5 mg (Orwin et al., 1976), and buprenorphine 0.4 mg gave better relief of pain after operation than morphine 10 mg, with a longer duration of effect (Dobkin, Esposito and Philbin, 1977).

The purpose of the present investigation was to study the efficacy of buprenorphine 0.3 mg i.v. in decreasing or delaying the onset of pain after major abdominal surgery, and to compare it with morphine 10 mg i.v. An assessment of side-effects was included.

METHOD

The trial was a double-blind, between-patient comparison of buprenorphine 0.3 mg and morphine 10 mg, both drugs being administered i.v. The patients included in the trial were of American Society of Anesthesiologists category I or II and had undergone major abdominal surgery in Akademisch Ziekenhuis, Ghent. All were 55-80 kg in weight and 20-70 yr of age. None had been accustomed to receiving narcotics.

The 51 patients entering the trial were allocated randomly to one of three groups, each of 17 patients. A standard method of anaesthesia was used throughout. Atropine 0.5 mg, droperidol 5 mg and fentanyl 0.1 mg were administered 1 h before operation as premedication. Anaesthesia was induced with methohexitone 1 mg kg⁻¹ and maintained subsequently with nitrous oxide 50% in oxygen plus halothane 0.5-1%. Following the administration of suxamethonium 1 mg kg⁻¹, the trachea was intubated and the lungs were ventilated to maintain normocarbia as judged by the Engstrom nomogram. Muscular relaxation was maintained by the use of pancuronium and antagonized at the end of operation with neostigmine preceded by atropine.

As soon as the patient was able to open his eyes on request after the operation, and before leaving the theatre for the recovery room, the anaesthetist administered the test drugs via an i.v. infusion. One group received no drug at this time, the second group received buprenorphine 0.3 mg and the third group morphine 10 mg. No patient was aware that he had received analgesic medication. Observations, commenced in the recovery room, were made by a trained nurse who was unaware of the patient's group or the medication he had received.

At each observation the patient was asked whether pain was being experienced and, if so, to grade it as mild, moderate or severe. The grades were allocated numerical scores, 0 = none, 1 = mild, 2 = moderate, 3 = severe. Patients withdrawn from the trial because of pain received a score of 3 for the remaining assessments. In order to elicit the incidence of side-effects, each patient was asked also if he had any other complaints, and the occurrence of nausea, vomiting, drowsiness or other complications was noted. Arterial pressure (Riva-Rocci method) and heart rate (palpation) were measured and recorded on each occasion.

Patients asleep at the time of observation were awakened in order to make the assessments. The first observations were made 30 min after the administration of the analgesic (in the control group, after
antagonism of the blockade) then at 30-min intervals for up to 5 h. Any patient suffering, at any time, pain of a degree for which he would normally be given a further dose of an analgesic was withdrawn from the trial and a suitable dose of an opiate given by i.m. injection. The time at which the first i.m. analgesic after operation was given was noted for every patient. No patient was ambulant during the period of observation.

**RESULTS**

There were no significant differences between the three groups in respect of age, sex and weight (table I). The operations performed, mainly operations on the uterus, stomach and kidney, and their duration were similar in the three groups.

**TABLE I. Patient distribution, sex, age and weight**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Male</th>
<th>Female</th>
<th>Mean age (yr)</th>
<th>Mean weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>17</td>
<td>9</td>
<td>8</td>
<td>50.1 ± 3.9</td>
<td>65.5 ± 2.2</td>
</tr>
<tr>
<td>Morphine 10 mg</td>
<td>17</td>
<td>8</td>
<td>9</td>
<td>46.7 ± 3.8</td>
<td>63.8 ± 2.8</td>
</tr>
<tr>
<td>Buprenorphine 0.3 mg</td>
<td>17</td>
<td>8</td>
<td>9</td>
<td>50.5 ± 4.7</td>
<td>65.0 ± 2.7</td>
</tr>
</tbody>
</table>

The mean pain scores are displayed in table II and figure 1. The control group behaved as expected, all except two patients requiring an analgesic within 2 h. Buprenorphine 0.3 mg produced a remarkable degree of pain control during the period of observation. Throughout, the buprenorphine group had lower mean pain scores than the control group and the difference was significant ($P<0.001$). The i.v. administration of morphine 10 mg was less successful in delaying the onset of pain after surgery. At no time were the mean pain scores of this group as low as those of the buprenorphine group although the differences between the two treated groups were not significant for up to 1 h. From that time, the differences were significant ($P<0.05$) for at least 4 h.

Table III provides an assessment of the combined duration and intensity of the analgesic effect of each drug. In the buprenorphine group only two patients required a second dose of analgesic during the 5-h period of observation. The shorter duration of action of morphine was demonstrated by the increase in the number of patients in that group requiring a second injection of analgesic in the last hour of observation. A comparison of the numbers of patients withdrawn from the study showed a significant difference between the buprenorphine and morphine groups only at 5 h (chi-square test).

The time of the administration of the first i.m. injection of an analgesic was recorded for all patients and it was possible to calculate the mean time interval between the end of the operation and this injection for each group.

**TABLE III. Cumulative totals of patients withdrawn from the trial because of pain**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
<th>210</th>
<th>240</th>
<th>270</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0</td>
<td>3</td>
<td>13</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Morphine 10 mg</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine 0.3 mg</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE IV. Mean time between the end of operation and administration of first i.m. analgesic**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>Mean time (min)</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>17</td>
<td>80</td>
<td>±14</td>
</tr>
<tr>
<td>Morphine 10 mg</td>
<td>17</td>
<td>307</td>
<td>±80</td>
</tr>
<tr>
<td>Buprenorphine 0.3 mg</td>
<td>16</td>
<td>637</td>
<td>±75</td>
</tr>
</tbody>
</table>

The results demonstrated a large difference between the control group and both treatment groups, and between the two treatment groups. One patient who received buprenorphine did not require a subsequent i.m. injection of an analgesic.
MORPHINE AND BUPRENORPHINE FOR POSTOPERATIVE PAIN

3.0
2.0
1.0

GROUP MEAN PAIN SCORES
CONTROL
MORPHINE
BUPRENORPHINE

TIME (min) 0 30 60 90 120 150 180 210 240 270 300

Fig. 1. Mean pain scores against time for the three groups.

Cardiovascular effects (table V)

Only two observations of significance were noted in the cardiovascular indices measured. A systolic arterial pressure of 50 mm Hg was observed 1 h after operation in a female who had received morphine. The rapid infusion of the appropriate fluids corrected this. A heart rate of less than 50 beat min\(^{-1}\) for the first 90 min after operation was noted in a female who had received buprenorphine. The patient received atropine 0.5 mg and neostigmine 2.5 mg at the end of operation. No treatment was required.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean heart rate (beat min(^{-1}))</th>
<th>Mean systolic pressure (mm Hg)</th>
<th>No. of observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>79.9 ± 1.8</td>
<td>119.5 ± 4.2</td>
<td>39</td>
</tr>
<tr>
<td>Morphine 10 mg</td>
<td>82.5 ± 1.6</td>
<td>114.9 ± 2.1</td>
<td>119</td>
</tr>
<tr>
<td>Buprenorphine 0.3 mg</td>
<td>81.0 ± 1.4</td>
<td>127.5 ± 1.9*</td>
<td>158</td>
</tr>
</tbody>
</table>

* Significantly greater mean systolic arterial pressure than in morphine group.

Side-effects (table VI)

Drowsiness was the most frequently recorded side-effect, being reported in 54% of the assessments made on the control group and more frequently in the other two groups. Nausea and vomiting were recorded in all groups. No difference in the frequency of nausea and vomiting was demonstrated in the two analgesic groups, the number of episodes being small for both treatments.

<table>
<thead>
<tr>
<th>Group</th>
<th>Drowsiness</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>No. of observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>21 (54%)</td>
<td>2 (5%)</td>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td>Morphine 10 mg</td>
<td>75 (63%)</td>
<td>6 (5%)</td>
<td>1</td>
<td>119</td>
</tr>
<tr>
<td>Buprenorphine 0.3 mg</td>
<td>119 (75%)</td>
<td>5 (3%)</td>
<td>1</td>
<td>158</td>
</tr>
</tbody>
</table>

DISCUSSION

This trial was of unusual design in that, instead of testing the analgesic efficacy of the medications against established postoperative pain, the analgesics were given at the end of operation in order to delay the
onset of pain. This approach has two major advantages. First, it was considered ethical to include a control group, as these patients were treated according to established practice and there was no question of giving a placebo to a patient in pain. Second, the method shortened the period of observation required by the assessor when compared with the methods of treating established pain. The i.v. administration of the narcotic produced a greater effect more rapidly and for a shorter duration than did i.m. injection and, by giving the injection before the onset of pain, eliminated also waiting for pain to occur, administering an analgesic, and waiting for its effect to develop.

The most likely disadvantage of the method is the necessity to select, for the trial, patients who will certainly develop pain after operation. A control group is obligatory to demonstrate this. In this study all except one patient did require eventually an i.m. opiate to control pain following surgery. The one patient who did not, received buprenorphine and was given an oral analgesic 18 h after operation. One further disadvantage of the method is that it makes comparison of cardiovascular and respiratory effects between the groups difficult, as there are no suitable measurements before medication. This study demonstrated a significant difference in mean systolic arterial pressures between the groups receiving morphine and buprenorphine, but as neither group differed significantly from the control, and there were no premedication values for comparison, this finding is of little value. However, De Castro and Parmentier (1976) reported that buprenorphine 0.8 mg administered i.v. after anaesthesia increased heart rate, systolic arterial pressure, central venous pressure and right intra-ventricular pressure. Peripheral vasodilatation was decreased.

The present study confirmed that 0.3 mg (mean 4.6 μg kg⁻¹) of buprenorphine is a suitable dose for the treatment of pain after operation. Dobkin (1977) concluded that 0.3 mg (mean 4.8 μg kg⁻¹) was the optimal dose to treat pain after surgery by i.m. injection, and Hovell (1976) found that i.m. buprenorphine 4 μg kg⁻¹ was more effective in treating pain after operation than were buprenorphine 2 μg kg⁻¹, pentazocine 0.6 mg kg⁻¹ or pethidine 1 mg kg⁻¹. Hovell reported also a 75% frequency of drowsiness after buprenorphine 4 μg kg⁻¹, the same as in this series.

This series confirms also the opinion of Dobkin (1977) that the duration of pain relief with buprenorphine is substantially longer than with other strong analgesics tested previously. De Castro and Parmentier (1976), although not studying postoperative pain, noted that patients remained pain-free for up to 48 h following anaesthesia, including fentanyl, and buprenorphine after operation.

Finally, this investigation produced a clinical observation not anticipated in its design. There was no doubt that the patients who had received an i.v. analgesic at the end of operation were more comfortable in the recovery room than those in the control group, who suffered an early onset of severe pain, which continued until an i.m. opiate was administered, and took effect. Anaesthetists, surgeons and nurses have been criticized often for their lack of concern about pain after operation and reluctance to apply adequate therapy early. There seems to be, therefore, a prima facie case for this technique of pain prevention by the anaesthetist in suitable patients, particularly when no potent analgesic has been administered as part of the anaesthetic technique.

Employed as described here, buprenorphine 0.3 mg appears to have advantages over morphine 10 mg, having a rather more intense, and considerably longer duration of effect, with no increase in side-effects other than drowsiness.

ACKNOWLEDGEMENTS

I wish to thank Professor G. Rolly for his co-operation in allowing this trial to proceed, and Dr A. E. Ward of Reckitt & Colman for the supply of buprenorphine and a grant to cover expenses. Assistance with the statistical analyses was given by Mr R. C. Hoare and Mr D. R. Clarke.

REFERENCES


RESUME
On a procédé à une comparaison à double inconnue, entre malades, des effets de la morphine administrée par voie intraveineuse à raison de 10 mg et de la buprenorphine administrée aussi par voie intraveineuse à raison de 0,3 mg, pour la prévention de la douleur après une intervention chirurgicale. Ces médicaments ont été administrés par l'anesthésiste à la fin de l'opération et le commencement de la douleur ainsi que son intensité ont été évalués par une infirmière qualifiée. Les deux médicaments ont causé un important retard dans l'apparition des fortes douleurs par comparaison avec le groupe témoin, mais avec la buprenorphine, le retard moyen de 10,5 h a été supérieur à deux fois celui de la morphine. Le seul effet secondaire qui se soit produit plus fréquemment après l'administration des analgésiques a été la somnolence diurne, son incidence étant plus forte après la buprenorphine qu'après la morphine.

EIN DOPPELBLIND-VERGLEICH ZWISCHEN MORPHIUM UND BUPRENORPHIN ZUR SCHMERZLINDERUNG NACH DER OPERATION
ZUSAMMENFASSUNG
Ein Doppelblind-Vergleich unter Patienten wurde zwischen den Wirkungen von intravenös verabreichten 10 mg Morphinum und 0,3 mg Buprenorphin zur Vermeidung von Schmerzen nach der Operation vorgenommen. Die Drogen wurden vom Narkosearzt nach der Operation verabreicht, und das Einsetzen und der Grad der Schmerzen wurde von einer ausgebildeten Krankenschwester verfolgt. Beide Drogen bewirkten eine wesentliche Verzögerung des Einsetzens starker Schmerzen im Vergleich zur Kontrollgruppe, aber mit einer mittleren Verzögerung von 10,5 Stunden erwies sich Buprenorphin als doppelt so wirksam wie Morphium. Die einzige Nebenerscheinung bei diesen Drogen war Schlafmüdigkeit wobei dies bei Buprenorphin stärker der Fall war als bei Morphium.

COMPARACION DE DOBLE ANONIMATO ENTRE MORFINA Y BUPRENORFINA EN LA PREVENCION DEL DOLOR DESPUES DE UNA OPERACION
SUMARIO
Se ha efectuado una comparación de doble anonimato entre pacientes acerca de los efectos de morfina 10 mg i.v. y buprenorfina 0,3 mg i.v. para la prevención de dolores después de una operación. Las drogas fueron administradas por el anestesista al final de la operación, y tanto el acceso como la intensidad del dolor fueron evaluados por una enfermera recibida. Ambas drogas produjeron una demora significativa en el sufrimiento de dolores intensos en comparación con el grupo de control, pero con buprenorfina la demora media de 10,5 h fue más de dos veces la de morfina. El único efecto colateral que se presentó con más frecuencia después de la administración de analgésicos fue la soñolencia, de mayor intensidad después de la buprenorfina que después de la morfina.