COMPARISON OF BUPRENORPHINE-HYOSCINE AND PAPAVERETUM-HYOSCINE AS PREMEDICANTS FOR GYNAECOLOGICAL SURGERY

J. W. SEAR and J. I. ALEXANDER

SUMMARY
Buprenorphine 0.3 mg and papaveretum 20 mg, both combined with hyoscine 0.4 mg, were used as premedicants in female patients undergoing laparoscopy or abdominal hysterectomy. The effects were compared. It was found that the increase in drowsiness and tranquility was greater following buprenorphine than that following papaveretum. A low frequency of nausea was reported in the buprenorphine-hyoscine group of patients who had undergone hysterectomy. The analgesic effects of the drugs, in these doses, appeared to be similar in degree and duration.

Buprenorphine is a potent analgesic drug and may be administered for the relief of pain after major surgery (Hovell and Ward, 1977; McQuillan, 1976; Edge, Cooper and Morgan, 1979). Its anxiolytic and sedative properties make it suitable also for preoperative medication (Rolly and Versichelen, 1976).

Since it is a partial opioid agonist, the result of the interaction of buprenorphine with other opioid agonists will depend upon the relative concentrations of each drug (Rance, 1979) and will alter according to the strength of the first drug and the method of, and interval following, its administration. It may antagonize the effects of other opioid analgesics given before or during operation if used only in the postoperative period (de Castro, 1979). Buprenorphine may also interact with sedative drugs, such as the benzodiazepines, and potentiate their effect. Thus, its use in the period after operation may be more effective when associated with its use before surgery.

A previous study suggested that when used alone as a premedicant, buprenorphine was associated with a moderate frequency of side-effects such as salivation and nausea (Sear, Cartwright and Alexander, 1979). However, an opioid premedicant is usually combined with an anticholinergic agent such as atropine or hyoscine. The present study seeks to compare the efficacy of buprenorphine-hyoscine premedication with that of a standard regimen, namely papaveretum and hyoscine.

PATIENTS AND METHODS
One hundred and twenty-nine patients undergoing gynaecological surgery took part in this double-blind parallel-group comparison. The hospital Ethics Committee gave approval for the study, and the patients gave informed verbal consent. All patients included in the study (ASA grades I or II) were aged between 20 and 70 yr and weighed from 45 to 90 kg. Patients, who were receiving currently, or had received in the recent past, treatment for anxiety or depression, were excluded from the study. Premedication with papaveretum 20 mg and hyoscine 0.4 mg, or buprenorphine 0.3 mg and hyoscine 0.4 mg was given i.m. 1 h before surgery. Each patient was suitable for either premedicant and random allocation was made. Anaesthesia was induced with thiopentone 3–4 mg kg$^{-1}$ or Althesin 60 μg kg$^{-1}$ and after neuromuscular blockade by alcuronium 0.25 mg kg$^{-1}$, the trachea was intubated. Anaesthesia was maintained (intermittent positive pressure ventilation) with 66% nitrous oxide in oxygen, supplemented by halothane (0.5–1% as necessary).

No analgesic agents were given to the patients during operation. The minute ventilation was sufficient to maintain normocapnia as determined by nomogram (Nunn, 1960). All the surgery was performed by one surgeon, thereby decreasing interpatient variability. At the end of the operation, residual neuromuscular blockade was reversed with neostigmine 0.04 mg kg$^{-1}$ preceded by atropine.


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0.02 mg kg⁻¹. Measurements and recordings of arterial pressure (by oscillotonometry), heart rate and respiratory rate were made before premedication, just before induction of anaesthesia, immediately after surgery and at the 1st, 2nd and 3rd hours in the postoperative period.

Assessment of the hypnotic and anxiolytic effects of the premedicants was made by one of three independent observers unaware of the premedication, by simple questioning of the patients before premedication and 1 h after premedication but before surgery. Scoring was 0–3 for anxiety (0 = nil, 1 = slight, 2 = moderate, 3 = severe) and 0–3 for drowsiness (0 = alert, 1 = drowsy, 2 = very drowsy, 3 = sleeping).

For analysis of results, the patients were divided into two subgroups depending on the surgery undertaken: minor = laparoscopy for infertility or sterilization, and major = total abdominal hysterectomy. Each patient had been informed that pain might be experienced after the operation and that analgesics would be available without delay if requested. Furthermore, it was the practice of the nurses in the recovery room and the ward to question the patients frequently regarding their level of comfort. Following surgery, the patients received analgesia as required and the time from premedication to the first administration of analgesia following hysterectomy was noted. The frequency of the side-effects of nausea, vomiting, dizziness, sweating, vasoconstriction and dreaming was noted.

Statistical methods

These were used to compare separately the effects of the two premedication regimens in patients undergoing laparoscopy and abdominal hysterectomy. Ages and weights were compared between premedicant groups by a one-way analysis of variance. The times between premedicant and the induction of anaesthesia, and the times from premedication to the first administration of analgesia following hysterectomy, were compared using the Mann–Whitney U test. Anxiety and drowsiness scores were compared for each drug treatment separately between assessments, before premedication and before induction of anaesthesia, using the Wilcoxon matched pairs signed ranks test. Differences between groups were assessed using the Mann–Whitney U test. The frequency of unwanted effects in each treatment group was compared using the Fisher exact probability or Pearson's Chi-squared test as appropriate.

RESULTS

One hundred and twenty-nine patients were studied. Forty-five underwent hysterectomy (study A) and 84 laparoscopy (study B). The ages and weights of the patients in each of the four subgroups are shown in table I. No significant intergroup differences were found.

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine–hyoscine</td>
<td>48</td>
<td>32.9 ± 1.13</td>
<td>63.8 ± 1.42</td>
</tr>
<tr>
<td>Papaveretum–hyoscine</td>
<td>36</td>
<td>31.2 ± 1.31</td>
<td>63.5 ± 1.63</td>
</tr>
<tr>
<td>Abdominal hysterectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine–hyoscine</td>
<td>20</td>
<td>37.9 ± 2.08</td>
<td>60.3 ± 2.34</td>
</tr>
<tr>
<td>Papaveretum–hyoscine</td>
<td>25</td>
<td>37.4 ± 1.85</td>
<td>62.1 ± 1.81</td>
</tr>
</tbody>
</table>

Study A

Twenty patients received buprenorphine and hyoscine and 25 received papaveretum and hyoscine. The time between the administration of the premedicant and the preoperative assessment was comparable for the two premedicant groups (mean buprenorphine = 72 min; mean papaveretum = 77 min). The scores for anxiety and drowsiness before premedication and at the preoperative assessment are shown in table II. There was significantly more drowsiness following premedication in both treatment groups, but there was no statistical difference in the increases in score between the treatment groups. However, the assessment of anxiety before operation showed a significant decrease (premedication to pre-induction (P<0.01)) for those patients receiving buprenorphine and hyoscine but not for those receiving papaveretum and hyoscine. The decrease in anxiety in the buprenorphine group, using the individual patient differences, was significantly greater than that in those patients receiving papaveretum (P < 0.02). However, the anxiety score before treatment was greater in the patients who received buprenorphine.

The unwanted effects following premedication before and after operation are shown in table III. Following the operation, the only significant difference between the treatment groups was a greater frequency of nausea in those patients receiving papaveretum and hyoscine (P<0.01).

Requirements for analgesia after operation were
TABLE II. Mean scores, determined as in text, for anxiety and drowsiness following assessments before premedication and before induction of anaesthesia

<table>
<thead>
<tr>
<th>Anxiety</th>
<th>Drowsiness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal hysterectomy (n = 45)</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine–hyoscine (20)</td>
<td>1.30</td>
</tr>
<tr>
<td>Papaveretum–hyoscine (25)</td>
<td>0.56</td>
</tr>
<tr>
<td>Laparoscopy (n = 84)</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine–hyoscine (48)</td>
<td>0.65</td>
</tr>
<tr>
<td>Papaveretum–hyoscine (36)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

TABLE III. Frequency of unwanted effects, assessed before and after operation, in 20 patients receiving buprenorphine and 25 patients receiving papaveretum, and hyoscine. All patients were undergoing abdominal hysterectomy. **P < 0.01; (Pearson's Chi-squared test)

<table>
<thead>
<tr>
<th>Unwanted effect</th>
<th>Before operation</th>
<th>After operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Buprenorphine–hyoscine</td>
<td>Papaveretum–hyoscine</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dreaming</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Number of patients</td>
<td>20</td>
<td>25</td>
</tr>
</tbody>
</table>

comparable for the two treatment groups. Of the patients receiving buprenorphine and hyoscine as premedication, 80% (n = 16) required postoperative analgesics at a mean time interval from premedication of 9.6 h (range 2.5–18.8). Of those receiving papaveretum and hyoscine, 88% (n = 22) received analgesics at a mean time interval of 8.5 h (range 3.8–16.0).

Study B
Of the 84 patients studied, 48 received buprenorphine and hyoscine. The time from administration of premedication to the induction of anaesthesia was comparable in the two treatment groups (mean buprenorphine–hyoscine = 82 min; mean papaveretum–hyoscine = 79 min). In the buprenorphine–hyoscine treatment group, there were significant increases in the drowsiness scores (P < 0.01) and decreases in the level of anxiety before operation (P < 0.01) following premedication (table II). The hypnotic effects of buprenorphine and hyoscine were greater (using the individual score differences) than for papaveretum and hyoscine (P < 0.05). There was no significant decrease in anxiety in the papaveretum–hyoscine group. Following operation, there were no significant differences in the frequency of unwanted effects between the two treatment groups. None of the patients in either group required analgesia after operation.

Cardiovascular and respiratory effects
For all patients, premedication resulted in clinically insignificant decreases in systolic and diastolic arterial pressures (table IV). In those patients undergoing hysterectomy, premedication with buprenorphine–hyoscine resulted in faster heart rates before operation (P < 0.01) and immediately after operation (P < 0.05) than with papaveretum–hyoscine. This was coupled with the higher anxiety scores before premedication and be-
fore operation in this group, and may, therefore, reflect the increase in sympathetic drive present in these patients.

The difference in heart rates between the buprenorphine–hyoscine and papaveretum–hyoscine treatment groups in patients undergoing laparoscopy was not significant. Clinical assessment of the ventilatory depressant effects of the two premedicants showed them to be similar in both duration and effect.

**DISCUSSION**

Buprenorphine is an oripavine derivative, which has been shown in man and in experimental animals to have a high potency, limited agonist–partial antagonist effect, and to have a low dependence liability. It may be administered either sublingually or parenterally. Following i.m. injection to patients in pain, the onset of relief is evident within 30 min. The analgesic properties of the drug have been used previously to supplement 75% nitrous oxide in oxygen (Kay, 1980) and to induce sleep as part of a technique of analgesic anaesthesia (de Castro and Parmentier, 1976). Our previous open study compared buprenorphine 0.3 mg with morphine sulphate 10 mg both given alone i.m. as premedication (Sear, Cartwright and Alexander, 1979). It showed buprenorphine not only to be more soporific and to have a longer duration of action than morphine, but also to be associated with a greater frequency of side-effects such as nausea, giddiness and double-vision. Other workers (Kay, 1978; Hovell and Ward, 1977) have shown that buprenorphine has a longer duration of action than morphine in these doses and Orwin, Orwin and Price (1976) found that buprenorphine 0.3 mg was equivalent to 13.3 mg of morphine sulphate in terms of peak respiratory depression. Papaveretum is the most commonly prescribed narcotic analgesic drug in the Bristol and Weston Health District and 20 mg, containing 10 mg of morphine base, is equivalent to 13.3 mg of morphine sulphate. The combination, papaveretum and hyoscine, is the most commonly prescribed premedicant but appears, in some respects, to be inferior to the combination of buprenorphine and hyoscine. Since actions of pure agonists may oppose those of partial agonist–antagonists, it is logical to use drugs of a single type throughout an anaesthetic technique.

The lack of clinically obvious respiratory depression following this dose of buprenorphine confirms the findings of other workers (Rolly and Versiche-
In our patients, the changes in arterial pressure and heart rate with both papaveretum and buprenorphine, combined with hyoscine, were clinically insignificant.

The mean anxiety scores before premedication were dissimilar. Of the patients undergoing laparoscopy, those receiving buprenorphine–hyoscine were less anxious than the others, but the scores were similar. Of those undergoing hysterectomy, those receiving buprenorphine–hyoscine were more anxious and those receiving papaveretum–hyoscine were less anxious than the patients for laparoscopy. The assessment was made before the patient was allocated, by random selection, to a drug sub-group so that this difference could not have been related to the choice of premedicant. All those who had anxiety presently or recently treated by drugs had been excluded from the study and there were no other factors in the patients’ histories which account for this difference. However, in each operation sub-group, the decrease in anxiety was greater in those patients receiving buprenorphine–hyoscine.

Thus, the combination of buprenorphine and hyoscine results in suitable premedication and the side-effects of drowsiness and tranquillity offer possible advantages in the preoperative management of an anxious patient.

REFERENCES


COMPARAISON DES ASSOCIATIONS

BUPRENORPHINE–HYOSCINE ET PAPAVERETUM–HYOSCINE COMME PREMEDICATION DANS LA CHIRURGIE GYNECOLOGIQUE

RESUME

La buprénorphine 0,3 mg et le papaveretum 20 mg tous deux associés à 0,4 mg d’hyoscine, ont été utilisés comme agents de prémédication chez des patientes devant subir des coelioscopies ou des hysterectomies par voie haute. Les effets ont été comparés. Nous avons trouvé que la somnolence et la sédation étaient plus grandes après buprénorphine qu’après papaveretum. Nous n’avons retrouvé qu’un faible pourcentage de nausées dans le groupe buprénorphine–hyoscine des patientes qui avaient subi une hysterectomie. Les effets analgésiques des agents semblaient comparables, à ces doses, à la fois en intensité et en durée.

EIN VERGLEICH VON BUPRENORPHIN–HYOSCIN UND PAPAVERETUM–HYOSCIN BEI DER PRÄMEDIKATION FÜR GYNÄKOLOGISCHE OPERATIONEN

ZUSAMMENFASSUNG

Se usaron 0,3 mg de buprenorfina y 20 mg de papavereto, ambos combinados con 0,4 mg de hioscina como agentes de premedicación en pacientes femininas sometidas a una laparoscopia o una histerectomía abdominal. Se llevó a cabo una comparación de los efectos. Se comprobó que el aumento de la modorra y de la tranquilidad era mayor después de la buprenorfina que después del papavereto. Se informó de una baja frecuencia de nauseas en el grupo de pacientes con buprenorfina que habían sido sometidas a histerectomía. Los efectos analgésicos de las substancias, en esas dosis, parecen ser análogos tanto en grado como en duración.