ANALGESIC EFFICACY OF PERIOPERATIVE BUCCAL MORPHINE

A. R. MANARA, A. R. BODENHAM AND G. R. PARK

SUMMARY

We have studied the effect of regular perioperative administration of buccal morphine sulphate on postoperative analgesic consumption in female patients undergoing lower abdominal surgical procedures. Ten matched pairs of women were allocated randomly to receive either placebo or buccal morphine before operation and at 12-h intervals up to 44 h after operation. Pain was assessed using a visual analogue scale and taste assessed using evaluation forms. Postoperative analgesic requirements were compared using a patient-controlled analgesia system which was set to deliver bolus doses of pethidine without a background infusion. There was no significant difference in pain scores between the two groups. Compared with placebo, buccal morphine did not reduce significantly postoperative pethidine consumption. All patients receiving buccal morphine reported a taste which reduced its acceptability.

KEY WORDS

Morphine sulphate is an effective analgesic when given by the parenteral or oral route [1]. The presence of postoperative ileus and the extensive first pass metabolism of morphine by the gut mucosa and the liver [2] limit the use of oral morphine following surgery. Difficulties in the administration of parenteral opioids result frequently in inadequate postoperative analgesia [3]. Administration of morphine using the buccal route may overcome these problems. Buccal morphine has been shown to be effective in relieving pain after elective orthopaedic surgery [4], in spite of conflicting reports on the pharmacokinetics [4-6].

Placebo-controlled studies of postoperative pain pose ethical difficulties which may be overcome by using a patient-controlled analgesia system (PCAS). This ensures adequate postoperative analgesia for all patients, while allowing comparison of the amount of analgesia demanded after operation by patients receiving an active preparation and those receiving placebo.

We have compared the effect of regular administration of a controlled release formulation of buccal morphine, based on hydrophilic polymers (Napp Laboratories Ltd) [5], with an identical placebo containing no morphine, by assessment of postoperative pethidine consumption delivered by a PCAS. As a previous study [5] indicated that the taste of this formulation may influence its acceptability to patients, we compared also the tastes of active and placebo tablets.

PATIENTS AND METHODS

We studied 20 ASA grade I or II [7] female patients undergoing gynaecological surgery via a Pfannensteil incision. All gave written, informed consent to participate in the study, which was approved by the local Hospital Ethics Committee. The patients were allocated to two groups (A and B) to give 10 pairs matched for age and weight: patients were recruited into group A unless they matched a previously recruited patient, when they

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TABLE I. The taste evaluation form

<table>
<thead>
<tr>
<th>Taste</th>
<th>Non existent</th>
<th>weak</th>
<th>mild</th>
<th>moderate</th>
<th>strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Sweet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Sour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) Salty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d) Bitter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e) Refreshing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(f) Sickly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(g) Metallic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(h) Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please circle the appropriate descriptions

Is the main taste:

- Sweet:
  - Non existent
  - Unbearable
  - Weak
  - Nasty
  - Mild
  - Acceptable
  - Pleasant
  - Moderate
  - Strong
- Sour:
  - Non existent
  - Unbearable
  - Weak
  - Nasty
  - Mild
  - Acceptable
  - Pleasant
  - Moderate
  - Strong
- Salty:
  - Non existent
  - Unbearable
  - Weak
  - Nasty
  - Mild
  - Acceptable
  - Pleasant
  - Moderate
  - Strong
- Bitter:
  - Non existent
  - Unbearable
  - Weak
  - Nasty
  - Mild
  - Acceptable
  - Pleasant
  - Moderate
  - Strong
- Refreshing:
  - Non existent
  - Unbearable
  - Weak
  - Nasty
  - Mild
  - Acceptable
  - Pleasant
  - Moderate
  - Strong
- Sickly:
  - Non existent
  - Unbearable
  - Weak
  - Nasty
  - Mild
  - Acceptable
  - Pleasant
  - Moderate
  - Strong
- Metallic:
  - Non existent
  - Unbearable
  - Weak
  - Nasty
  - Mild
  - Acceptable
  - Pleasant
  - Moderate
  - Strong
- Other (description):

All patients received a standard general anaesthetic, which was induced with thiopentone 3–5 mg kg⁻¹ and maintained with nitrous oxide and isoflurane in oxygen (FiO₂ 0.3). Alcuronium was used to provide neuromuscular block and ventilation was controlled according to the Radford Nomogram [8]. Requirement for analgesia during the operation was assessed according to autonomic changes (sweating, lachrymation, heart rate greater than 100 beat min⁻¹ or an increase in systolic arterial pressure of 15 mm Hg above baseline value) and provided by incremental i.v. bolus doses of fentanyl 25 µg. At the end of surgery, residual neuromuscular block was antagonized with neostigmine 2.5 mg and atropine 1.2 mg.

Both groups received postoperative analgesia with bolus i.v. doses of pethidine via a PCAS through an i.v. cannula separate from that used for i.v. fluids. Pethidine was diluted in 0.9% saline to form a 10-mg ml⁻¹ solution. The PCAS was set to deliver a bolus of pethidine 15 mg with a lockout time of 9 min. The PCAS was interfaced with a Hewlett-Packard type 82162A thermal printer to record the times of successful and unsuccessful demands.

Patients completed a 100-mm linear visual analogue scale (VAS) [9, 10] for pain and nausea immediately before taking the buccal tablets, on arrival in the anaesthetic room and at 1, 2, 3, 4, 8, 24, 36 and 48 h after surgery. The two ends of each line were defined as no pain and worst ever pain for the pain scale and no nausea and vomiting for the nausea scale. Pupil size was assessed at the same time by comparison with a pupil chart (1–8 mm). Sleeping patients were not disturbed after operation. Taste evaluation forms (table I) were completed on arrival in the anaesthetic room and 48 h after operation.

Student's unpaired t test was used to compare patient data and consumption of pethidine. Pain scores were analysed using the Wilcoxon rank sum test. Statistical significance was defined as
$P < 0.05$. Analysis of variance in pethidine consumption in the first 8 h after operation indicated that, based on 20 patients, the study would have a power of 75\% to detect a difference (at the 5\% level) of 50 mg in pethidine consumption between the two groups.

**RESULTS**

There was no significant difference in age or weight of the patients between the groups (table II) and intraoperative requirements for fentanyl also were similar for both groups (median 50 g, range 0–100 g) (table II).

Pethidine consumption was not significantly different between the groups in the first 8 h after operation or in the remaining 12-h periods (fig. 1). There was no difference between the groups in the cumulative consumption of pethidine at these time intervals (fig. 1).

There was no significant difference in pain scores between the groups at 18, 36 and 48 h. Few patients completed the VAS in the first 4 h after operation and the results for this period were not analysed (table III). Three patients in the active group and one in the placebo group vomited, but there was no significant difference in nausea score between the two groups. The baseline modal pupil size was 4 mm in both groups and varied ±1 mm from baseline in all patients throughout the study.

All patients receiving the active buccal morphine preparation reported a taste from their tablet. Eight described the taste as moderately or strongly bitter; the remaining two patients in the group described the taste as metallic and sour.

<table>
<thead>
<tr>
<th>Time after op. (h)</th>
<th>Active group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65 (54-71)</td>
<td>56 (51-69)</td>
</tr>
<tr>
<td>(n = 3)</td>
<td>(n = 3)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>40 (34-50)</td>
<td>63 (55-75)</td>
</tr>
<tr>
<td>(n = 5)</td>
<td>(n = 3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>20 (11-56)</td>
<td>81 (33-86)</td>
</tr>
<tr>
<td>(n = 5)</td>
<td>(n = 4)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>24 (0-66)</td>
<td>45 (27-85)</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>(n = 4)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>22 (0-61)</td>
<td>37 (16-58)</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(n = 4)</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>25 (0-57)</td>
<td>22 (13-41)</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(n = 9)</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>11 (0-25)</td>
<td>18 (0-23)</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(n = 7)</td>
<td></td>
</tr>
</tbody>
</table>
One patient removed a tablet at 5 h because of the bitter taste; a further patient retained the tablets only for the purpose of the study. Only two patients reported a taste from the placebo tablet: one reported a moderate, nasty sickly taste and a second patient reported a mild, acceptable bitter taste. In both groups the tablets stayed in place or moved about only slightly in 18 patients. The other two patients reported marked movement of the tablet.

**DISCUSSION**

The buccal route may be used to administer drugs which, but for too rapid absorption, would be suitable for sublingual administration [11]. Advantages of the buccal route include avoidance of first pass metabolism, ability to terminate absorption if necessary and convenience of administration [12]. Buccal morphine has been reported to have a greater bioavailability than i.m. morphine [4, 13]. If this is so, buccal preparations might be expected to make a greater contribution to peri- and postoperative analgesia than i.m. morphine [14]. The present study has shown that the buccal morphine preparation did not result in reduction in opioid consumption in either the perioperative or postoperative periods when compared with placebo. Patients in the active and placebo groups demanded similar amounts of pethidine to achieve a similar VAS for pain. This buccal preparation is unlikely, therefore, to be useful clinically in reducing requirements for alternative postoperative analgesia.

These findings are in contrast with those of Bell and colleagues [4], who showed that buccal morphine was effective in relieving pain (as assessed by VAS) after elective orthopaedic surgery. However, reservations have been expressed on the use of VAS in clinical situations [15], when the drug itself may impair the ability of subjects to assess an effect. Objective measures, such as opioid consumption by PCA, may be more sensitive. The differing results of the two studies may reflect the difference in pain after abdominal compared with peripheral orthopaedic surgery. Alternatively, the different formulations of buccal morphine used may have different efficacy, possibly because of differing pharmacokinetics [4, 5].

A recent communication has suggested that the use of a concurrent i.v. infusion of opioid with PCA does not reduce the dose of self-administered analgesic compared with PCA without a concurrent infusion [16]. Marshall and colleagues [17] found also that, after abdominal surgery, patients receiving a low dose i.v. infusion of morphine required as much supplementary morphine as those receiving a placebo infusion. However, the latter study was criticized for using a continuous infusion of morphine in insufficient dosage, resulting in inadequate analgesia and increased side effects [18, 19]. The use of a low dose background infusion of opioid, whether administered i.v. or via the buccal route, may result similarly in inadequate analgesia and not reduce the demands on a PCAS. This would explain the findings in the present study and those reported by Owen and colleagues [16].

All the patients studied were satisfied with their postoperative analgesia, confirming the value of patient controlled analgesia. It is recognized that patients using PCA demand less analgesic than the maximum permissible and appear satisfied, despite a significant amount of pain still present, characteristically between 25–35% on a linear analogue scale. The reason for this may be pharmacological or psychological [20]. This feature is illustrated in the 18–48 h pain scores in the present study.

Although we were concerned initially about inhalation of the buccal tablet by patients with depressed airway reflexes, it was not necessary to remove the tablet in any patient and none was swallowed. However, the complaints of a bitter, metallic, or salty taste by all patients was a significant problem; some patients volunteered that they would never take the preparation again. This problem has been noted previously [5, 14, 21] and supports the concept that most of the morphine dissolves in saliva and is swallowed, rather than being absorbed across the buccal mucosa [5]. The difference in taste between the active tablet and placebo may affect the blindness of future studies unless the placebo is formulated also to taste bitter. The problem of patient acceptability, reports of low plasma concentrations of morphine [5] and low systemic bioavailability of the buccal preparation [6, 22] suggest that this route of administration of morphine has no clinical role at present.

**ACKNOWLEDGEMENTS**

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REFERENCES


