MORPHINE SULPHATE SLOW RELEASE

Comparison with i.m. Morphine for Postoperative Analgesia

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There has been increasing interest in recent years in the administration of opioids by non-parenteral routes in the treatment of postoperative pain (Ellis et al., 1982; Fell, Chmielewski and Smith, 1982; Derbyshire et al., 1984; Hanning et al., 1984). Previous studies from this department have demonstrated that acceptable postoperative analgesia can be achieved by the administration of slow release morphine sulphate tablets (MST) at approximately 6-hourly intervals. Such treatment has been compared with conventional intermittent i.m. morphine (Fell, Chmielewski and Smith, 1982) and with 6-hourly sublingual buprenorphine (Derbyshire et al., 1984). To date, however, oral MST and morphine i.m. have not been compared in a double-blind, double-dummy investigation.

The present study was designed to provide further information on the use of MST for postoperative analgesia. There were several objectives. First, comparison of MST with morphine 4-hourly i.m. provides a more stringent comparison of the efficacy of MST than was undertaken in previous studies. Second, since a single dose of MST releases morphine over at least a 7-h period (Vater et al., 1984), there is a potential risk of cumulative with 4- or 6-hourly dose regimens. In order to examine this particular question, blood was sampled at the beginning and end of the assessment period for measurement of serum morphine concentrations. Third, since previous studies of MST assessed analgesia only at 24 and 48 h after surgery, an opportunity was taken to assess analgesia in the early postoperative period.

SUMMARY

Eighty patients undergoing abdominal surgery were studied after operation. Morphine was administered regularly every 4 h by either the i.m. (morphine sulphate 10 mg) or the oral route (MST Continus 20 mg) in a double-blind double-dummy trial. Both MST and i.m. morphine provided satisfactory postoperative analgesia, but significantly greater amounts of supplementary i.m. morphine were required in the MST group. More adverse effects were reported by the patients in the i.m. morphine group. The mean serum morphine concentration in 12 patients in the MST group was 1.7 ng ml⁻¹ at 08.00 h and 19.5 ng ml⁻¹ at 16.00 h on the 1st day after operation, suggesting impaired gastric emptying in the early postoperative period. It is therefore recommended that further studies of the bioavailability of MST in the early postoperative period be undertaken before any recommendations are made regarding its routine use for pain relief at that time.

PATIENTS AND METHODS

Eighty patients about to undergo cholecystectomy, hysterectomy or herniorrhaphy gave informed consent to participate in this study which had been approved by the District Ethical Committee. All patients were within the age range 18–65 yr and only those without significant respiratory or cardiovascular dysfunction were included in the study. No patient was receiving opioids at the time of admission to hospital.

Patients were allocated randomly to receive postoperative analgesia with either i.m. (morphine sulphate, Evans Medical Limited) or oral (MST Continus, Napp Laboratories) morphine sulphate. Matched dummies of either wax matrices (for the i.m. morphine group) or 5% dextrose ampoules
COMPARISON OF SLOW RELEASE AND I.M. MORPHINE

(for the oral morphine group) were packed with the appropriate active drug in coded boxes labelled for each patient. The nurses administering the morphine and the observers were unaware of the route of administration of active drug until the end of the study.

Anaesthesia. Patients were premedicated with diazepam 10 mg by mouth 1–2 h before surgery. Anaesthesia was induced with thiopentone and maintained with 66% nitrous oxide in oxygen, supplemented by either morphine (up to 10 mg) or papaveretum (up to 20 mg) and a volatile agent (halothane or enfurane), if required. Morphine sulphate was given i.v. to any patient complaining of pain in the recovery room before transfer to the ward. This dose was not included in the calculation of the amount of postoperative analgesic administered.

Upon return to the ward, patients received tablets and an injection every 4 h. The doses (1 ml i.m., 2 tablets orally) were halved or omitted if the nursing staff considered that the patient was oversedated. Supplementary doses (escape doses) of morphine i.m. were available to the patient upon request and recorded.

Assessment. All assessments were undertaken by two observers (A.B. and P.A.P.): the analgesia regimens and procedures were divided evenly between both. Linear analogue scales (LAS—10 cm horizontal lines) were used for the assessment of pain, sedation, nausea and dizziness. Peak expiratory flow rate (PEFR) was measured at each assessment (Wright Peak Flow Gauge). Overall acceptability was assessed by means of a questionnaire (Ellis et al. 1982) (table II). The LAS and use of the Peak Flow Gauge were explained to the patient before surgery and a control PEFR was recorded using the best of three attempts.

At 08.00 h on the 1st day after operation, at 2-hourly intervals thereafter until 18.00 h, patients were asked to rate pain, sedation, nausea and dizziness on the LAS and a PEFR was recorded. At 18.00 h a "Patient Satisfaction" questionnaire was completed. At 09.00–10.00 h on the 2nd day after operation, a final PEFR was measured and the questionnaire completed again.

Serum morphine concentrations were measured in 12 patients (nine hysterectomy, two cholecystectomy, one herniorrhaphy). Blood was sampled at 08.00 h and at 16.00 h (2 h after a regular dose of morphine) on the 1st day after operation. Serum was separated after coagulation and stored at −18 °C until required for measurement of morphine concentrations using high pressure liquid chromatography with electrochemical detection (Aitkenhead et al., 1984).

Analysis of data was undertaken using Student's t test, paired or unpaired, as appropriate for data with an expected normal distribution, Wilcoxon Rank Sum test for data from the linear analogue scores, and Chisquared test (with Yates' correction) for other data. P < 0.05 was taken as the level of statistical significance.

RESULTS

Data from the three types of operation have been combined, since exclusion of the hernia group (n = 10) and separate analysis of the hysterectomy and cholecystectomy groups did not alter the pattern of results. There were no differences between the two groups in respect of age, sex or smoking status. However, the MST group were taller and heavier than the i.m. morphine group (table I).

Mean pain score was greater in the MST group at 08.00 h (fig. 1) and mean nausea score was greater in the i.m. morphine group at 10.00 h (fig. 2), but otherwise there were no significant differences between the groups in respect of pain, nausea, sedation or dizziness. There was a consistent trend for the MST group to exhibit a lower incidence of unwanted effects as shown by the summated side effect scores (fig. 3).

Mean PEFR was 45% of the preoperative control value at the first assessment period. There was an improvement toward the control value

| TABLE I. Demographic data (mean±SEM). **P < 0.05 |
|------------------------|------------------------|
|                        | MST (n = 39)           | Morphine i.m. (n = 35) |
|------------------------|------------------------|
| Age (yr)               | 43 (1.7)               | 46 (1.8)               |
| Male/female            | 7/32                   | 5/30                   |
| Height (cm)            | 166 (1.2) **           | 162 (1.1)              |
| Weight (kg)            | 70 (2.1) **            | 63 (1.3)               |
| Smokers                | 16                     | 13                     |
| PEFR (litre min⁻¹)     | 460 (14)               | 447 (13)               |
| Time to first assessment (h) | 19 (0.4)           | 19 (0.4)               |
| Operation              |                        |                        |
| Cholecystectomy        | 14                     | 12                     |
| Hysterectomy           | 20                     | 18                     |
| Herniorrhaphy          | 5                      | 5                      |
during the 1st and 2nd days after operation, but there were no significant differences between groups at any assessment point and therefore data have been pooled to provide figure 4. There was a significant negative correlation between linear analogue pain score and percentage change in PEFR ($r = -0.42, P < 0.001$) although there was considerable scatter about the line of best fit (fig. 5).

More supplementary morphine was required in the MST than in the i.m. group (table II). The number of extra doses administered was significantly greater in the group receiving MST; 10 (25%) of the MST group required supplementary analgesia in the first 12 h after operation compared with six in the i.m. morphine group ($P < 0.05$, Chi squared test). Thirteen extra doses of analgesia were administered to the MST group and six to
the i.m. morphine group within the first 24 h ($P < 0.05$, Chi squared test). This suggests that the MST group in general received less analgesia than the i.m. group from the regimen under investigation. This is also supported by the observation that the number of times the prescribed dose of morphine and placebo was reduced differed between groups (table II). In the first 12 h nine and 17 patients received reduced doses (MST and i.m. morphine, respectively), whereas in the second 12-h period the numbers were 30 and 37, respectively. When these numbers are combined,
Fig. 5. Scatter diagram: linear analogue pain scores (mm) plotted against peak expiratory flow rate (litre min⁻¹) during 1st day after operation in all patients. Line of best fit derived by analysis of least squares \( r = -0.42, P = < 0.001 \).

**TABLE II. Postoperative data (mean ± SEM).** *P* < 0.05 for 24-h combined data

<table>
<thead>
<tr>
<th></th>
<th>MST (n = 39)</th>
<th>Morphine i.m. (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean additional dose of morphine (mg)</td>
<td>4.1 ns (1.1)</td>
<td>1.7 (0.6)</td>
</tr>
<tr>
<td>Total No. additional doses of morphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 12 h</td>
<td>10 **</td>
<td>6</td>
</tr>
<tr>
<td>Second 12 h</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total No. reduced doses of morphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 12 h</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Second 12 h</td>
<td>30</td>
<td>37</td>
</tr>
<tr>
<td>Mean dose of anti-emetic administered: prochlorperazine (mg)</td>
<td>24.5 ns (3.7)</td>
<td>24.1 (3.2)</td>
</tr>
</tbody>
</table>

The 39 reduced doses in the MST group were significantly fewer than the 54 reduced doses in the i.m. morphine group (chi squared 4.57, *P* < 0.05).

Table III shows the results of the “Patient Satisfaction Questionnaire” from the 1st day after operation. The results obtained on the 2nd day after operation are similar and have not been included.

Serum morphine concentrations were measured in 12 patients (table IV). There was a significantly lower serum morphine concentration in the MST group at 08.00 h compared with the data for the i.m. morphine group at the same time, despite the additional administration of a mean dose of 6.4 mg of parenteral morphine in the MST group and the lack of omission of any of the prescribed oral doses (table IV). The concentration of morphine in the MST group at 08.00 h was also significantly smaller than the data for both i.m. and oral morphine at 16.00 h. There was no significant difference between the i.m. and MST group at 16.00 h.

There were six withdrawals from the trial. All these were in the group receiving i.m. morphine. The reasons given were vomiting (three cholecystectomy, one hysterectomy), insufficient analgesia (one hysterectomy) and both insufficient analgesia and vomiting (one hysterectomy). The difference in withdrawal rate was significant.
## DISCUSSION

These results have demonstrated that it was possible to produce acceptable analgesia with MST after abdominal surgery, provided that provision was made for the administration of supplementary parenteral doses of morphine. There was a remarkable similarity in the pain scores seen in the MST group in comparison with the i.m. morphine group. However, if the unwanted effects of morphine (sedation, nausea and vomiting) are summated, differences between the two groups are readily apparent in the earlier part of the 1st day after operation — notably that for similar degrees of analgesia there were fewer side-effects in the MST group.

Our choice of a 4-hourly dose regimen for MST requires some explanation since the long duration of action of MST could permit cumulation. However, the use of a 4-hourly dose facilitated the use of a double-blind double-dummy comparison and, in addition, it was felt that the instruction to nursing staff to halve or omit small doses given frequently permitted finer adjustment of the total dose to meet individual variations in pharmacodynamics.

Although pharmacokinetic studies from our Department have suggested that the bioavailability of MST is 20% following a single dose (Vater et al., 1984), the decision to compare MST 20 mg with i.m. morphine 10 mg was based upon our earlier clinical studies. These suggested a clinically effective ratio of 2:1 MST:morphine for continuing doses over 24–48 h (Fell, Chmielewski and Smith, 1982). The results of the present study also suggest an analgesic ratio closer to 2:1 than to 5:1 for administration over a sustained period of time.

With patient controlled administration, a correlation has been demonstrated between plasma opioid concentration and effective analgesia (mean effective analgesic concentration or MEAC) (Tamsen et al., 1982). Individual patients request additional doses of analgesia when the plasma concentration of opioid decreases below MEAC. Although this is a relatively constant value for the individual, there is a five-fold variation between individuals (Tamsen et al., 1982). In the present study, there was a considerable difference between the mean serum concentrations of morphine in the two groups at 08.00 h and yet the levels of analgesia were similar — that in the MST group (at 08.00 h) being comparable to analgesia provided by i.m. patient-controlled analgesia (Harmer et al., 1983). In addition, the MEAC for morphine is approximately 16 ng ml⁻¹ (HPLC technique) and it is therefore difficult to account for the satisfactory analgesia achieved in the MST group at 08.00 h.

There are two possible explanations for this anomaly. First, that satisfactory analgesia at 08.00 h was achieved by a placebo effect. It is known that, after major surgery, some 30% of patients may achieve adequate analgesia without opioids (Beecher, 1959) and that placebos are capable of exerting a very potent analgesic action (Beecher, 1955). It is possible that, in the circumstances of this trial, a potent placebo effect may have been induced.

A second highly speculative reason for the differences between analgesia and serum concentration may be a result of biotransformation. One significant breakdown pathway of morphine is by hepatic conjugation. A major metabolite is morphine-3-glucuronide (M3G) (Boerner, Abbott and Roe, 1975), which is not known to possess any analgesic properties. In addition, a smaller proportion of the administered dose is conjugated to morphine-6-glucuronide (M6G). M6G is thought to be three to four times more...
potent as an analgesic than is free morphine, and to possess a longer half-life, although it may cross the blood–brain barrier slowly. All the administered dose of MST will have passed through the liver before becoming available systemically. It is possible that, in the MST group, some analgesia was provided by M6G. It is difficult to test this hypothesis because of the difficulties inherent in the analysis of M6G, but Svensson and his colleagues (1982) suggested that M6G is the major metabolite of the long term oral administration of morphine.

The very low concentration of free morphine in the MST group at 08.00 h in comparison with the value at 16.00 h and in comparison with the 08.00-h value in the i.m. morphine group is a matter of some concern, since it suggests that there is reduced absorption of MST in the early postoperative period. It has been shown recently that, although morphine administered orally (as MST 20 mg) has no effect on gastric emptying, systemic morphine in a dose of 10 mg causes marked delay in emptying (Park and Weir, 1984). It has been known for some time that anaesthesia (Nimmo, 1984) and systemic opioids delay gastric emptying and it is likely that the low concentration of MST seen in our patients at 08.00 h was produced by the effect of anaesthesia and intraoperative i.v. opioids on systemic absorption. The high concentration of morphine seen in the MST group at 16.00 h is also worrying. If we are comparing 4 mg of available free morphine (MST) with 10 mg (i.m. morphine), the only explanation for the similar concentrations at 16.00 h is that some “dumping” occurred after the delay in gastric emptying had decreased.

The design of our study did not allow us to examine the first 18 h of the postoperative period and we are unable to comment directly on the quality of analgesia before 08.00 h on the 1st day after operation. Nonetheless, the significantly greater number of escape doses of morphine required in the MST group and the significantly higher pain scores at 08.00 h suggest that the analgesia provided by MST alone in the early postoperative period was suboptimal. Only by provision of supplementary doses of morphine did patients in both groups achieve the same level of overall postoperative comfort (table II).

Peak expiratory flow rates were similar in both groups. Our data support earlier work (Spence and Smith, 1971) showing only a slow improvement in lung function during the early postoperative period in spite of analgesia which is rated as acceptable by the patient. A correlation between LAPS and PEFR was demonstrated, confirming earlier studies (Ellis et al., 1982).

Previous studies have suggested that MST may be used to provide satisfactory postoperative analgesia. However, the results of the present study suggest that enthusiasm for this method should be tempered with considerable caution. From our preliminary measurements of plasma morphine concentration, it would appear that there may be little absorption of MST in the period immediately after anaesthesia with systemic opioids. This may produce suboptimal analgesia, but also cause the unacceptable risk of belatedly dumping a large dose of drug from the stomach when gastrointestinal motility increases. However, it should be noted that there was no evidence in the present study for excessive sedation in the MST group in the second 24 h.

These observations regarding dumping of MST are clearly speculative, since we measured plasma morphine in relatively few patients. We would suggest that further studies of the bioavailability of MST in the postoperative period are required before recommendations may be made regarding the routine use to provide analgesia at that time.

REFERENCES


