THE MORPHINE HYDROGEL SUPPOSITORY

A New Sustained Release Rectal Preparation

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The most widely practised technique for the relief of postoperative pain is the i.m. injection of an opioid administered on an intermittent “on-demand” basis. It is generally accepted that the failure to anticipate pain and the variations in the plasma drug concentration associated with this technique result in poor analgesia and frequent side-effects, and that the continuous administration of an appropriate drug is preferable.

The rectal route of administration is suitable for sustained release preparations [1], but is not often considered by British physicians [2]. A new, monolithic sustained-release morphine hydrogel suppository (MHS), capable of attaining and maintaining analgesic or near-analgesic blood concentrations of morphine has been developed, and then evaluated in three pilot studies in patients with postoperative pain.

DEVELOPMENT OF THE MORPHINE HYDROGEL SUPPOSITORY

Hydrogels

Hydrogels are crystalline-rubbery compounds based on cross-linked ethylene oxide [3]. They are insoluble in water, biologically inert and hydrophilic. In the dehydrated form they are firm and can be moulded and shaped. When hydrated they swell to two to four times the original volume and become soft and rubbery. They can be impregnated with water- or alcohol-soluble drugs which are released on rehydration in a reproducible and predictable manner. The rate of release is determined by the chemical composition of the hydrogel and its rate of rehydration, the surface area and thickness of the block of hydrogel and the concentration of drug within the matrix. Early studies using prostaglandin E_{2} confirmed that predictable release profiles could be obtained, and that particular preparation has been used to facilitate cervical ripening in labour [4]. An additional benefit was the improved temperature stability of the prostaglandin in the hydrogel matrix.

Pharmacokinetic theory suggests that the attainment of a steady blood concentration of a drug with a constant infusion requires a time equal to four to five times the elimination half-life \( T_{1/2} \) of the drug. The \( T_{1/2} \) for morphine is 2–3 h and, consequently, an initial bolus of morphine is required in order to accelerate the attainment of a steady-state concentration. Thus the ideal release profile should incorporate both a bolus and a continuous release of morphine in order to ensure a rapid onset of action.

SUMMARY

The morphine hydrogel suppository (MHS), a monolithic sustained release rectal preparation, has been developed and evaluated in three pilot studies. Two release profiles have been prepared. The first, MHS(B), has a high initial release rate followed by a constant release for the remainder of a 12-h period. The second, MHS(S), has the same constant release rate for 12 h. MHS(B) is intended to attain and maintain analgesic or near analgesic plasma concentrations of morphine, and MHS(S) to maintain that concentration for successive 12-h periods. The pilot studies suggest that MHS may be of value in the management of postoperative pain.
A number of hydrogel configurations were tested in vitro for a suitable release profile [5]. The most suitable was a hollow cylinder with closed ends (fig. 1). The concentration of morphine was arranged to be greatest at the outer and inner surfaces, giving the release profile closest to that thought to be ideal (fig. 2). The choice of bolus and constant-release dose was complicated by the paucity of information on the rectal bioavailability of morphine. An estimated dose of a 10-mg bolus and a constant release of 4 mg h\(^{-1}\), to err on the side of safety, was chosen. The bolus and release rate achieved in vitro were 11.4 mg and 4.1 mg h\(^{-1}\). A silicone rubber collar was fitted to the base of the suppository to anchor a thread which could enable the device to be withdrawn in the event of overdose. This and subsequent developments were evaluated in the series of pilot studies outlined below. The initial study showed that a greater dose was required and that some flexibility in dosage would be advantageous.

Prototype MHS (II)

The total dose and rate of release of morphine were increased by equilibrating the hydrogel at 37 °C. (The solubility of morphine increases with temperature, allowing a higher concentration to be achieved.) The overall size of the suppository was increased and the shape changed to a smoother outline. Two half suppositories (fig. 3) were joined by a short length of hydrogel rod. One half was drilled through the closed end to take a withdrawal thread. Two different strengths of half suppository were prepared, giving boluses of 6 mg and 10 mg and infusion rates of 2.5 and 3.6 mg h\(^{-1}\), respectively. Three different strengths of suppository were thus available by joining two halves with a rod of hydrogel, giving single doses of 12, 16 and 20 mg, infusion rates of 5, 6.1 and 7.2 mg h\(^{-1}\) and total contents of 76, 103 and 130 mg morphine, respectively.

Prototype MHS (II)

The need to continue the administration of morphine beyond the first 12 h necessitated the development of an MHS with a different release profile since repeated administration of the bolus
MORPHINE HYDROGEL SUPPOSITORY

Two strengths of suppository were prepared. The "high" dose MHS(B) contained morphine 130 mg released as a 16-mg single dose, followed by a constant release of 6.9 mg h\(^{-1}\) and the matching MHS(S) had a similar constant release rate and contained morphine 120 mg. The "low" dose (MHS(B)) contained morphine 105 mg with single dose and constant release of 10 mg and 5.5 mg h\(^{-1}\), respectively. The low dose MHS(S) contained morphine 100 mg at the appropriate release rate.

EVALUATION OF PROTOTYPE MHS

Patients and Methods

The prototype MHS were evaluated in a series of pilot studies. The studies were approved by the District Ethical Committee and all patients gave their informed consent.

Pilot study I

Prototype MHS(I) were administered to four healthy patients (two male) of mean age 39.5 yr (range 22–54) and mean weight 79 kg (67–89)[6].

The suppositories were administered 2–12 h before surgery and further analgesia provided with pethidine i.m. on demand. Venous blood samples were drawn before insertion and 30, 60, 90, 120, 180 and 240 min thereafter and, subsequently, at least every 240 min up to 720 min. Plasma morphine concentrations were determined by high pressure liquid chromatography (HPLC)(7).

The suppositories were readily and painlessly inserted and removed and the patients were unaware of them whilst in situ. The plasma morphine concentrations attained are shown in figure 4. There was considerable variation between the subjects, although there was a general impression of the attainment of a plateau 2 h after administration which was maintained for the subsequent 10 h.

A further patient underwent excision of the rectum for carcinoma 12 h after the administration of an MHS(I). Histological examination of the mucosa adjacent to the suppository showed no abnormality.

The concentrations of morphine attained were less than those usually associated with adequate analgesia.

Pilot study II

Twelve otherwise healthy patients (five male) about to undergo a surgical procedure normally requiring postoperative opioid analgesia were studied (8). An MHS (II) selected according to the patient's weight and proposed operation was administered 2 h before surgery. Patients weighing less than 50 kg received the lowest strength, those from 50 to 70 kg the median strength and those more than 70 kg the highest strength. Anaesthesia was induced and maintained by conventional techniques, further intraoperative analgesia being provided with fentanyl at the anaesthetist's discretion. Additional postoperative analgesia was given as pethidine at the discretion of the nursing staff.

Venous blood samples were drawn before insertion of the MHS(II) and then 30, 60, 90, 120,

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FIG. 4. Plasma morphine concentrations with time in four patients following the administration of a prototype MHS(I).
240, 360, 480 and 720 min thereafter, and plasma morphine concentrations were measured by HPLC. Technical difficulties with the assay resulted in plasma morphine concentrations being available for only nine subjects.

The demographic data, operation and dose of morphine administered are shown in table I. The suppositories were easily and painlessly inserted. The fully hydrated suppository was undetectable in situ by the patient. Plasma morphine concentrations (table II) were slightly greater than with the first prototype and showed a similar time course. No formal estimations of analgesia or nausea were undertaken, but it was noted that only three patients required additional intra- and postoperative opioid drugs. All three were undergoing upper abdominal surgery. Only one patient, who underwent cholecystectomy, complained of nausea of severity sufficient to merit the administration of an antiemetic drug.

**Pilot study III**

The third pilot study was designed to examine the changes in plasma morphine concentration during the period following the change from an MHS(B) to an MHS(S)[9]. Linear analogue scores (LAS) for pain, nausea, sedation and dizziness were also recorded. A similar group of patients receiving conventional analgesia (intermittent i.m. injection of morphine) were similarly studied in an open design to provide some basis for comparison.

Eighteen healthy women undergoing abdominal hysterectomy were allocated randomly to receive analgesia by either MHS or i.m. morphine for the first 24 h after surgery. Those receiving MHS and weighing more than 70 kg were given the “high” dose; the “low” dose was given to those patients who weighed less than 70 kg.

The MHS(B) was administered 2 h before operation and the MHS(S) 12 h later. Further analgesia was provided with i.m. pethidine 75–100 mg as required. The i.m. morphine group received morphine 10 mg 1 h before surgery and the same dose on demand in the postoperative period. Both groups also received an antiemetic before and after the surgical procedure, as required. The anaesthetic technique was standardized, fentanyl being given as required.

Venous blood samples were drawn and LAS

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Operation</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>Morphine dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tubal ligation</td>
<td>F</td>
<td>45</td>
<td>66</td>
<td>103</td>
</tr>
<tr>
<td>2</td>
<td>Gastrectomy</td>
<td>M</td>
<td>65</td>
<td>75</td>
<td>130(FP)</td>
</tr>
<tr>
<td>3</td>
<td>Varicose vein stripping</td>
<td>F</td>
<td>48</td>
<td>105</td>
<td>130</td>
</tr>
<tr>
<td>4</td>
<td>Scaphoid graft</td>
<td>M</td>
<td>34</td>
<td>85</td>
<td>130</td>
</tr>
<tr>
<td>5</td>
<td>Tubal ligation</td>
<td>F</td>
<td>40</td>
<td>47</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>Spinal fusion</td>
<td>M</td>
<td>78</td>
<td>76</td>
<td>130</td>
</tr>
<tr>
<td>7</td>
<td>Coracoid transfer</td>
<td>M</td>
<td>24</td>
<td>80</td>
<td>130</td>
</tr>
<tr>
<td>8</td>
<td>Vagotomy and pyloroplasty</td>
<td>F</td>
<td>53</td>
<td>66</td>
<td>103(FP)</td>
</tr>
<tr>
<td>9</td>
<td>Excision of rhinophyma</td>
<td>M</td>
<td>63</td>
<td>84</td>
<td>103</td>
</tr>
<tr>
<td>10</td>
<td>Cholecystectomy</td>
<td>F</td>
<td>35</td>
<td>70</td>
<td>103(FPN)</td>
</tr>
<tr>
<td>11</td>
<td>Extraction of molar teeth</td>
<td>M</td>
<td>25</td>
<td>85</td>
<td>103</td>
</tr>
<tr>
<td>12</td>
<td>Mastectomy</td>
<td>F</td>
<td>68</td>
<td>71</td>
<td>103</td>
</tr>
</tbody>
</table>

**Table II. Plasma morphine concentrations (ng ml⁻¹) following the administration of an MHS(II) in nine patients**

| Time (min) | 30 | 60 | 90 | 120 | 240 | 360 | 480 | 720 |
|------------|----|--|--|--|--|--|--|--|--|
| Mean       | 3.0| 5.3| 7.8| 8.9| 15.3| 16.5| 17.3| 16.9|
| SEM        | 1.0| 1.3| 1.7| 1.7| 2.3 | 2.5 | 2.4 | 1.5 |
| Range      | 0–7.5| 0–11.0| 0–13.7| 1.2–16.8| 5.0–25.5| 6.7–30.5| 9.7–31.8| 13.3–26.2 |
completed at 4, 12, 13, 14 and 24 h after the commencement of the study in both groups. No attempt was made to co-ordinate i.m. injections and sample times. Patients were also asked to complete an LAS for their average and maximum pain at the end of the study period.

Eight patients received MHS and 10 received i.m. morphine. One patient given MHS was withdrawn from the study following a hypotensive episode after a dose of pethidine: the MHS was removed and a full recovery ensued with i.v. fluid replacement. Two patients given i.m. morphine were withdrawn: one because a hysterectomy was not performed and the other for a presumed reaction to morphine.

There was no significant differences between the groups with regard to age or weight.

The plasma concentrations of morphine are shown in figure 5. The plasma concentrations of morphine were maintained during the change from MHS(B) to MHS(S) without any consistent pattern of an increase or diminution. The concentrations achieved with MHS were less than those achieved with i.m. morphine, although with less scatter, as would be expected.

The mean LAS for pain were less in the MHS group than the i.m. morphine group (table III). The LAS for maximum pain was significantly less for the MHS group than for the i.m. morphine groups ($P < 0.05$) (Rank Sum Test).

The MHS group received a mean of 4.2 doses of pethidine (range 1–5) and the i.m. group a mean of 4.5 doses of morphine (range 3–6).

The mean LAS for nausea were also less in the MHS group. The MHS group required significantly fewer doses of antiemetic (mean 2.4 range 0–7) than the i.m. morphine group (mean 5.4 range 4–7) ($P < 0.01$, Student’s $t$ test).

There were no significant differences between the groups with respect to sedation or dizziness. All the patients receiving MHS preferred them to injections. One patient who received i.m. morphine preferred injections, another preferred suppositories, and the remainder had no opinion.

**DISCUSSION**

The constant administration of an opioid to provide steady plasma concentrations of the drug should provide better analgesia than intermittent administration in the management of post-operative pain, since the peaks and troughs of plasma concentrations are avoided. The rectum is a suitable site for the administration of drugs, particularly from sustained-release preparations [1]. There is a partial bypassing of first-pass hepatic metabolism, the degree being determined by the anatomical arrangement of the venous drainage in an individual and the position in the rectum of the preparation. Considerable differences in rectal/parenteral availability occur between different individuals, but there is little variation with time within one individual. The rectal/parenteral availability for morphine would appear to be between 0.3 and 0.15; that is, the rectal dose should be three to six times higher than the parenteral dose to achieve similar plasma concentrations [10]. The rate of absorption

![Figure 5](https://academic.oup.com/bja/article-abstract/61/2/221/287278/1)

**Table III.** Mean (SEM) linear analogue scores (cm) for pain following administration of an MHS(B) and an MHS(S) ($n = 7$) and with the intermittent administration of i.m. morphine on demand ($n = 8$).

<table>
<thead>
<tr>
<th>Time after administration (h)</th>
<th>MHS ($n = 7$)</th>
<th>I.m. morphine ($n = 8$)</th>
<th>Average</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>2.4 (0.69)</td>
<td>3.9 (1.4)</td>
<td>3.5</td>
<td>5.9</td>
</tr>
<tr>
<td>8</td>
<td>3.5 (0.89)</td>
<td>5.2 (0.8)</td>
<td>4.1</td>
<td>8.4</td>
</tr>
<tr>
<td>12</td>
<td>3.1 (0.98)</td>
<td>3.6 (1.0)</td>
<td>3.5</td>
<td>5.0</td>
</tr>
<tr>
<td>24</td>
<td>1.9 (0.95)</td>
<td>3.5 (1.1)</td>
<td>4.1</td>
<td>5.0</td>
</tr>
</tbody>
</table>

*P < 0.05
through the rectum is slow compared with i.m. injection and is dependent on the formulation [11]. Rectal administration is thus unsuitable for the management of acute pain, unless it can be foreseen—as with operative and postoperative pain—and is more suited to the management of chronic pain. The ability to remove a suppository readily in the case of an adverse reaction or overdose is an additional margin of safety over oral administration.

The hydrophilic polymer gels (hydrogels) have a number of features which make them suitable vehicles for sustained administration of drugs. They are biologically inert and rehydration and drug release are predictable and reproducible. The variation of drug concentration within the polymer matrix permits differing release profiles. In this case, the ability to release a “bolus” dose followed by a constant release rate is essential for a drug such as morphine with a $T_{1/2}$ of long duration. The monolithic nature of the hydrogel suppositories precludes a sudden release of the contained drug unless the device is divided into many small pieces, thus increasing the surface area. The dehydrated suppositories may be cut with a knife, thus offering the potential of varying the dose to suit individual patients.

These three pilot studies, on progressive developments of the prototype MHS, confirm that the release profile provided is able to maintain analgesic or near analgesic plasma concentrations of morphine for up to 24 h. The attainment of the plateau concentration requires 2–4 h after insertion, thus making the devices unsuitable for the management of acute pain if given alone. The variations between individuals in pain perception, sensitivity to analgesics and rectal absorption make it highly unlikely that one or two strengths of suppository will be able to provide adequate analgesia for more than a few subjects. This is particularly so if the dose errs on the side of safety.

Pain is not necessarily constant throughout the postoperative period and an increase in pain may follow movement, visceral spasm or procedures such as physiotherapy. Constant release devices such as the MHS which provide a “background” concentration of analgesic at an analgesic or sub-analgesic level will also require the addition of small supplementary doses of analgesic to counter these transient increases in pain. The patient may not be spared any injections, but the reduced variation in plasma concentrations may improve overall analgesia and reduce side-effects such as nausea. The pilot studies reported here to tend to confirm this hypothesis, although the number of patients studied and the trial designs preclude confirmation.

Hydrogels are potentially useful vehicles for the programmed sustained release of many drugs. MHS would appear to be a useful addition to our analgesic armamentarium. The preliminary studies suggest that a formal clinical trial is justified. Evaluation of MHS in the management of chronic pain is also appropriate.

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