Further development of a morphine hydrogel suppository

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1 A sustained release monolithic morphine hydrogel suppository (MHS) was developed and administered to five volunteers.

2 The MHS delivered a mean of 55 mg morphine over 12 h. The mean plasma morphine concentration was 15 ng ml⁻¹ from 2 to 12 h after administration.

3 Plasma morphine concentrations were comparable with those reported for the same dose given orally over the same time period.

4 The morphine hydrogel suppository appears to be an effective means of delivering morphine and may be of value in the management of chronic pain.

Keywords morphine hydrogel suppository

Introduction

The rectum is a useful route of drug administration, particularly for sustained release vehicles (de Boer *et al.*, 1982). Sustained release preparations of analgesics are desirable as the avoidance of variations in plasma drug concentration may reduce side effects and improve patient acceptability. A significant proportion of patients with chronic pain are unable or unwilling to take oral medication and a sustained release rectal preparation would be beneficial.

Hydrogels are inert, hydrophilic polymers which can be impregnated with drugs which are released in a controlled fashion on rehydration of the polymer matrix (Graham & McNeil, 1984).

We have previously reported the development of a prototype morphine hydrogel suppository (MHS) (Hanning *et al.*, 1988) and confirmed that it was capable of attaining and maintaining steady plasma concentrations of morphine for up to 12 h. The present study describes the results of an evaluation of a preproduction preparation in normal subjects.

Development and production of the MHS

The hydrogel was prepared by polymerising polyethylene glycol 4000 (K&K Greef Ltd, Croyden), 1,2,6 hexane triol (Aldrich Ltd, Poole) and dicyclohexylmethane 4,4' diisocyanate (Bayer Ltd, Newbury) with anhydrous ferric chloride (FSA Ltd, Loughborough) as a catalyst (Graham & McNeil, 1984; McNeil & Graham, 1984). Molten polyethylene glycol was combined with the other constituents in a fixed stoichiometric ratio and the suppository shape formed by moulding in a cylindrical former. The polymer was then purified before impregnation with morphine sulphate BP (McFarlane Smith Ltd, Edinburgh) by swelling in a solvent until a charge of 100 mg was obtained. The MHS was then dried to remove solvent to give a finished suppository weighing approximately 1.8 g.

A plug of hydrogel with the same swelling characteristics as the MHS was used to cap the centre cavity of the suppository to prevent *in vivo* release of morphine from the inner surface.

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Figure 1 Dimensions of the morphine hydrogel suppository.

A small hole was drilled in the base of the MHS and a length of polyester thread secured by means of a button of reinforced Silastic sheeting (Dow-Corning, Reading) (Figure 1). The thread was intended as a means of removing the MHS at the end of the experimental period or in the event of an adverse effect.

Methods

Five male volunteers aged between 20 and 35 years gave informed written consent to the study which was approved by the local Ethics committee. All gave a full medical history and underwent a physical examination prior to the study. Blood was taken for an automated full blood count and biochemical screen (SMA12). Urine was taken for standard urinalysis (Bililabstix) and screening for drugs of abuse. Subjects were excluded if they displayed any evidence of renal, hepatic or psychiatric disease or had a history of abuse of drugs or alcohol. They were also excluded if they were not within 10% of ideal body weight (Metropolitan Life Insurance Tables). Subjects were observed by a physician and a trained research nurse throughout the study period which was conducted in an in-patient facility.

A venous cannula was inserted in the non-dominant arm and a 10 ml blood sample taken. Baseline measurements of pulse and respiratory rates, arterial blood pressure (sphygmomano-

meter) and oral temperature were taken together with five point verbal rating (VRS) and 10 cm linear analogue scores (LAS) of sedation, nausea and dizziness.

Subjects were questioned to ensure that their rectum had been emptied by recent defaecation. A 100 mg MHS was then inserted by the research nurse with the subject in the right lateral position. A small quantity of water-soluble gel (K-Y jelly) was used to lubricate the MHS. Care was taken to ensure that the MHS was placed just inside the rectum. The MHS was removed 12 h after insertion, examined, weighed and stored at -70°C for measurement of residual morphine.

Blood samples were taken 2, 3, 5, 6, 8, 10, 12, 15, 18 and 24 h after insertion of the MHS for measurement of plasma morphine, morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). Observations were repeated at 2, 4, 6, 8, 10 and 12 h after insertion. Measurements of vital signs were made at 14, 16, 18, 20 and 24 h and the VRS and LAS measured if the subject was awake. Consecutive 12 h urine collections were taken during the study period for measurement of morphine and metabolites.

Subjects were discharged from the study facility when they were alert and symptom-free.

Measurement of morphine and metabolites

Venous blood was collected into heparinised polypropylene tubes, centrifuged immediately and the plasma stored at -70°C until analysis. The concentrations of morphine, M6G and M3G in plasma and urine were measured by high pressure liquid chromatography (h.p.l.c.) using electrochemical and fluorescence detection (Joel *et al.*, 1988). The lower limits of detection were 1 ng ml^{-1} , 1 ng ml^{-1} and 5 ng ml^{-1} and the interday coefficients of variation were 5.2%, 6.2% and 4.5% for the assay of morphine, M6G and M3G respectively. Coefficients of variation were calculated from the assays of standard solutions of 10, 20 and 30 ng ml^{-1} for morphine and M6G and 100, 200 and 300 ng ml^{-1} for M3G.

The residual morphine content of the MHS was assayed by swelling in a 2:1 solution of acetonitrile and ethanol, grinding in a blender to ensure full extraction and subsequent measurement by h.p.l.c.

The *in vitro* release rate of morphine was determined by swelling in 900 ml water at 37°C buffered to pH 7.9 with a phosphate buffer in a Caleva 8-ST USP dissolution apparatus stirred at 50 rev min^{-1} . The central cavity of the MHS was plugged with a silicone elastomer to ensure that release only occurred from the outer surface, mimicking the *in vivo* release. The dissolution

media was pumped continuously with a peristaltic pump through the measuring chamber of a u.v. spectrophotometer (Philips Analytical PU8620) set at 210 nm.

The areas under the concentration curves from time zero to 24 h (AUC (0,24)) for morphine and metabolites were calculated using the linear trapezoidal method.

Results

The MHS used were found to contain a total of 103.2 mg of morphine sulphate. The *in vitro* release profile is shown in Figure 2 and was approximately 20 mg h⁻¹ for the first hour and 10 mg h⁻¹ for the next 8 h.

The demographic data and the dose of morphine administered to the five subjects (A–

Figure 2 *In vitro* release profiles of three morphine hydrogel suppositories. Total morphine content 103.2 mg.

Table 1 Demographic data and morphine dose

Subject	Age (years)	Weight (kg)	Height (m)	Morphine dose (mg)
A	28.4	74	1.75	58.9
B	23.1	76	1.81	53.6
C	20.3	59.5	1.64	—
D	32.4	83.5	1.83	44.0
E	22.5	73	1.78	62.8

Figure 3 Plasma concentrations of morphine with time in five subjects (—○— A, —●— B, —△— C, —▲— D, —□— E).

E) are shown in Table 1. All completed the study period and were fit for discharge after 24 h.

The plasma concentration-time profiles for morphine and its metabolites in each of the volunteers are shown in Figures 3, 4 and 5. The urinary excretion of morphine, M6G and M3G and the AUC (0,24) for each subject is given in Table 2.

Insertion of MHS was satisfactory in four volunteers (ABCE) and could not be detected by them when *in situ*. One subject (D) complained of discomfort which persisted throughout

Figure 4 Plasma concentrations of morphine-6-glucuronide with time in five subjects (—○— A, —●— B, —△— C, —▲— D, —□— E).

Table 2 AUC(0,24) and urinary excretion of morphine (M), M6G and M3G

Subject	AUC (0,24) (ng ml ⁻¹ h)			Urinary excretion (mg)					
	M	M6G	M3G	M		M6G		M3G	
				0–12	12–24	0–12	12–24	0–12	12–24
A	337	964	6418	1.54	1.54	5.59	8.26	21.3	29.1
B	271	711	4186	1.37	0.37	5.52	2.12	19.4	8.6
C	347	998	7609	1.19	3.05	4.36	8.39	16.0	37.5
D	114	381	2532	1.2	0.42	4.24	2.3	14.5	9.7
E	190	767	6458	0.96	1.24	4.28	6.92	16.0	28.2

Figure 5 Plasma concentrations of morphine-3-glucuronide with time in five subjects (—○— A, —●— B, —△— C, —▲— D, —□— E).

the study period. Examination of the MHS on removal showed that the base was poorly hydrated. The residual morphine content was greater and the average plasma morphine and metabolite concentrations less than those in other subjects. This was the only MHS removed intact. All of the others fragmented and in all subjects but one (C) were completely retrieved. In this subject less than 50% of the MHS was retrieved and he had morphine and metabolite concentrations consistently greater than the other subjects during the second 12 h period. Although well at 24 h and considered fit for discharge at approximately 10.00 h, he subsequently reported that he slept for most of the rest of the day.

Sedation was noted by all subjects, mainly during the early part of the study. The mean LAS was 2.3 cm (range 0–3.8) and was never sufficiently severe to prevent normal activities (watching television, reading, eating). Three subjects complained of nausea at one time point and one vomited after eating. Two complained of dizziness. At no time were the symptoms disabling and no treatment was required.

Discussion

Comparison of the plasma morphine concentrations obtained with MHS in the present study with previous work and predictions as to probable analgesic potency are complicated by several factors. Firstly, many early studies assayed morphine with a radio-immunoassay (r.i.a.) with variable cross-reactivity with morphine metabolites and consequent overestimation of morphine concentrations. Secondly, most studies present the maximum plasma concentration (C_{max}) rather than the average although there is a general assumption that overall

analgesic efficacy bears more relation to average than to peak concentrations. Thirdly, the demonstration that M6G is an analgesic (Abbott & Palmer, 1988; Osborne *et al.*, 1988) suggests that the relative production of this compound between different preparations and routes of administration may be important in determining analgesic efficacy.

The plasma morphine concentrations in the subjects studied increased to approximately steady values within 2 to 4 h after administration and were maintained until withdrawal of the MHS. Thereafter they declined rapidly in all the subjects where complete removal was achieved. The average plasma morphine concentration of approximately 15 ng ml⁻¹ compares favourably with other studies. Savarese and colleagues (1986) gave morphine 30 mg twice daily orally as a sustained release preparation (MS-Contin, Purdue-Frederick) or as morphine solution 15 mg 6 hourly to volunteers for 3 days in a randomised cross-over design. Trough and peak plasma morphine concentrations (corrected to be comparable with h.p.l.c. measurements using a factor given by the authors) were 3.5 and 12 ng ml⁻¹, respectively. A similar study using the same dose which compared two different sustained release tablets gave average morphine concentrations of approximately 13 ng ml⁻¹ (Shepard *et al.*, 1988). An r.i.a. was used and the degree of overestimation of plasma morphine compared with h.p.l.c. is unknown but is likely to be of the order of 70%. Osborne and colleagues (personal communication) gave 10 mg morphine as a sustained release preparation (MST, Napp Laboratories) to volunteers in a single dose study. C_{max} and average morphine and M6G concentrations were 4 and 2.5 ng ml⁻¹ and 30 and 10 ng ml⁻¹, respectively, using the same assay as in the present study. There are no studies where a similar dose to that given in the present study (i.e. 50–60 mg) was used. However, if plasma concentrations are assumed to increase in proportion to dose, than it would appear that the average plasma concentration of morphine attained with MHS in this study is approximately equivalent to the same dose given orally in divided doses. A study of patients receiving a mean of 184 mg daily (range 60–600 mg) either as sustained release tablets or oral solution showed mean plasma concentrations (h.p.l.c. assay) of 37 and 34 ng ml⁻¹, respectively (Sloan *et al.*, 1987). Thus a dose of morphine approximately twice the present study resulted in plasma concentrations approximately twice as great.

The ratios between the AUC of morphine and M6G were greater than those reported for single

oral doses of morphine solution or sustained release morphine tablets (Osborne *et al.*, 1987; Poulain *et al.*, 1988). This suggests that there is some bypassing of hepatic metabolism by this method of administration, in agreement with Jonsson and colleagues (1988) who showed a greater rectal bioavailability for morphine than is usually found with oral administration. The effect of any altered pattern of metabolism on analgesic efficacy remains to be determined.

Rectal absorption is likely to be most consistent if the preparation is placed just inside the anal canal. In one subject in this study the MHS was placed too low and hydration was incomplete and discomfort was experienced. An introducer device may be necessary if MHS is to be administered by unskilled care givers.

The ability to remove rectal drug reservoirs such as the MHS offers a valuable margin of safety over oral preparations. Hydrated hydrogel fragments easily and could not be withdrawn using the attached thread in four of the subjects. Complete retrieval of the MHS was possible in three of those subjects. Further development will include improving the means of withdrawal and reinforcing the hydrogel to prevent fragmentation. Plasma morphine concentrations in the subject who retained fragments of the MHS were 9 ng ml^{-1} at the 24 h time point when concentrations in the other subjects were around the limit of detection of the assay. The fragmentation of the MHS would have changed its release profile by increasing the surface area and decreasing the diffusion distances within the

polymer matrix. Nevertheless, the possibility is raised that the MHS may be capable of releasing morphine for 24 h and thus once daily dosing may be practical. Further investigations will be necessary to examine this point.

The present study only examined the absorption of morphine on a single insertion. The increased dose rate during the initial period after insertion suggests the possibility of an increased plasma concentration during this period on second and subsequent insertions. A preliminary study with an earlier prototype MHS suggested that this did not occur (Hanning *et al.*, 1988) but the possibility should be investigated in future studies.

The MHS would appear to be an effective means of delivering morphine at a constant rate from the reservoir of drug over at least 12 h. The present dose reservoir is towards the lower end of the range most commonly required by patients with chronic pain and additional doses will be developed, both greater doses for adult patients and smaller for paediatric patients. The monolithic construction ensures that 'dumping' of the dose is impossible and thus very large doses can be administered with safety. MHS should be useful both for the peri-operative period and for the management of chronic pain.

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