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Notes

Rectal absorption of morphine from controlled release suppositories

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Abstract

The absorption profiles and bioavailability of morphine in human volunteers ($n = 13$) were described after oral administration of MS Contin tablets and rectal administration of a newly developed controlled release suppository. By manipulating the viscosity of fatty suppository base an entirely identical cumulative morphine input could be obtained compared with oral dosing.

Keywords: Morphine; Rectal absorption; Controlled release; MS Contin

Controlled release oral morphine represents an innovation over conventional immediate-release morphine because of its convenient 12 h dosing schedule and ease of administration (Kaiko et al., 1989). Recently, a few studies have suggested that similar analgesia can be achieved in patients with cancer if controlled release oral preparations (MST, MS Contin) have been changed from the oral to the rectal route without major dose adjustment (Maloney et al., 1989; Wilkinson et al., 1992). Rectal administration of the oral dosage form resulted in a relative bioavailability, closely corresponding to the pattern of oral sustained absorption. However, the absorption rate was slower, probably due to differences in the amount of liquid available for tablet dissolution in the rectum vs the stomach and intestine.

Incomplete hydration was also reported in the case of a study with controlled release morphine hydrogel suppositories administered to human volunteers (Cole et al., 1990).

We decided therefore to develop a rectal triglyceride dosage form with the purpose of achieving an entirely similar absorption pattern compared with oral dosing.

Fatty suppositories were prepared (European Patent Office, no 92203989.6) by mixing morphine sulphate pentahydrate (USP) carefully with various amounts (3–6%) of Aerosil R972 (Degussa, U.K.) and a fixed concentration of hydrox-

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ypropylmethylcellulose 4000 (HPMC 4000, Bufa B.V., The Netherlands) and then subsequently mixing with a molten base of Witepsol W25 (Hüls AG, Germany); they were poured into plastic moulds (3 ml) and stored at 4°C. The suppositories possessed a controlled content of 30 mg morphine sulphate. The oral dosage form used in this study was the commercially available MS Contin tablets (Dagra Pharma B.V., The Netherlands) containing 30 mg of morphine sulphate.

Seven male and six female healthy volunteers, aged 19–29 years and weighing 52–82 kg, participated in the cross-over study.

The study protocol was approved by the Institutional Review Board and informed consent was obtained. After an overnight fast the volunteers received a standard light breakfast consisting of one slice of white bread and two slices of currant bread, 150 ml orange juice and 150 ml tea. The lunch was identical. 10 h after the start of the experiment the volunteers were free to eat what they wanted. The experiment started at 08:30 a.m. at which time the volunteers received the suppository rectally, or the MS Contin tablet, together with 100 ml water, orally. All volunteers received cross-over both the suppository and the MS Contin tablet, with a period of at least 4 weeks between the administrations. The volunteers remained in the sitting position during the first 6 h after administration. All volunteers were asked to keep the suppository in for at least 12 h after administration. Venous blood samples were obtained at 0, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h after drug ingestion. Plasma was immediately separated and stored frozen until analyzed. Morphine concentrations were assayed according to an electrochemical HPLC method (Visser and Moolenaar, 1986). With 1.0 ml plasma this method was accurate to concentrations as low as 0.5 ng/ml plasma.

In general, lipid insoluble drugs such as morphine sulphate can only be released from a molten suppository mass by means of a mechanical transportation process such as sedimentation. In this respect it was concluded that the release process includes a flow of particles in the suppository base into the direction of the interface as well as a flow of solute away from the interface (Schoonen et al., 1979). For this reason it can be expected that sedimentation as well as the interface transport is affected by viscosity. Therefore, we made a matrix system of morphine sulphate by adding Aerosil R972 to fix the drug particles in the suppository base. In addition, HPMC 4000 was added in order to increase the viscosity of the aqueous rectum fluid, thereby decreasing the transport rate of morphine sulphate through this layer. In a pilot study ($n = 3$) we examined the influence of the addition of the lipophilic Aerosil R972 on the drainage process of morphine sulphate in vivo (Table 1).

Table 1
Rectal absorption profile of morphine ($n = 3$) during 3 h after administration of fatty suppositories containing various amounts of Aerosil R972

Plasma morphine (ng/ml) at time (h)	0% Aerosil	3% Aerosil	6% Aerosil
0.5	12.3	3.4	0.5
1.0	23.4	6.5	1.4
2.0	17.1	5.8	2.5
3.0	11.7	5.4	2.9

A substantial decrease in absorption rate of morphine was observed for such increased viscosity. Our results suggest that there is an optimum

Table 2
Mean absorption characteristics of morphine (mean ± S.D.) calculated from the individual ($n = 13$) plasma morphine curves following rectal and oral administration of 30 mg morphine sulphate

Plasma morphine (ng/ml) at time (h)	Oral, MS Contin	Rectal, supp.
0.5	7.5 ± 2.3	8.2 ± 5.7
1.0	11.1 ± 2.8	11.2 ± 5.8
2.0	11.6 ± 3.6	10.3 ± 3.4
3.0	9.4 ± 1.8	8.2 ± 2.3
4.0	8.3 ± 1.7	7.4 ± 2.4
6.0	5.0 ± 1.3	5.9 ± 2.5
8.0	2.9 ± 1.0	3.7 ± 2.5
12	0.6 ± 0.6	1.3 ± 1.8
24	0.0 ± 0.0	0.0 ± 0.0
C_{max} (ng/ml)	12.5 ± 3.5	13.0 ± 4.7
T_{max} (h)	1.54 ± 0.52	1.96 ± 1.51
AUC_{0-8} (ng ml h^{-1})	58.6 ± 11.2	58.4 ± 16.0

Table 3
Cumulative input of morphine (fraction of dose absorbed, mean ± S.D.) after administration of MS Contin tablets, a suppository with a controlled release profile (C.R.) and a morphine suppository without additives (W.A.)

Time (h)	Oral, MS Contin	Rectal, supp. (C.R.)	Rectal, supp. (W.A.)
0.5	0.06 ± 0.02	0.06 ± 0.04	0.09 ± 0.03
1.0	0.12 ± 0.03	0.12 ± 0.07	0.22 ± 0.05
2.0	0.19 ± 0.05	0.18 ± 0.07	0.33 ± 0.07
3.0	0.22 ± 0.04	0.20 ± 0.06	0.34 ± 0.08
4.0	0.24 ± 0.04	0.22 ± 0.07	0.34 ± 0.07
6.0	0.26 ± 0.05	0.26 ± 0.07	0.34 ± 0.05
8.0	0.26 ± 0.05	0.27 ± 0.08	[a]
12	0.25 ± 0.05	0.28 ± 0.09	[a]
24	0.25 ± 0.05	0.28 ± 0.09	[a]

[a] Not measured.

in the concentration added: in the case of a doubling of the amount of Aerosil R972 used, the pronounced increase of viscosity cannot be overcome in vivo by the prevailing pressure of the rectal wall (Moolenaar and Schoonen, 1980).

The main goal of our study was to develop a rectal dosage form for morphine sulphate which results in a plasma profile comparable with that of the orally administered MS Contin tablet.

Table 2 presents mean morphine plasma levels and absorption data after administration of MS Contin tablets and the newly developed fatty suppository with Aerosil R972 and HPMC 4000.

The similarity between the two plasma curves is clear. For none of the absorption parameters could a statistically significant difference be observed. The absorption profiles of morphine, plotting the cumulative input against time, were also calculated from the plasma data using numerical deconvolution as described by Proost (1987). As a reference, pharmacokinetic data following intravenous administration of 10 mg morphine hydrochloride were used (Brunk and Delle, 1974).

Table 3 clearly demonstrates the sustained release of morphine from the suppository when the cumulative input values are compared to the values of a morfine Witepsol suppository without additives (Moolenaar et al., 1988). The absorption profile reveals that the major part of morphine is released during the first 2 h, followed by a slower release from 2 to 6 h after administration. After 6 h no significant release occurs.

The total amount of morphine absorbed from the suppositories was 28% on average, entirely identical compared after oral dosing with the MS Contin tablets (Table 1). This low value of the relative bioavailability and the interindividual variations in morphine plasma concentrations can be explained by the high first-pass kinetics of morphine (Hoskin et al., 1989). No significant difference in the rectal absorption pattern between male and female volunteers could be observed. Furthermore, no discomfort following application of the rectal dosage form was reported by the volunteers. Apart from a tempory sedation and fatigue, none of the volunteers suffered from any side-effect. It might thus be concluded that the newly developed suppository is safe and suitable for further clinical testing.

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