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Bioavailability of morphine from suppositories

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Rectal absorption conditions for morphine hydrochloride from aqueous solutions have been found to be highly dependent on pH, which may be explained as being due to pH partioning (Moolenaar et al., 1985). It was concluded that for single-dose therapy with morphine, especially when a rapid analgesic effect is required, a rectal solution adjusted to a pH in the range of 7–8 will provide an entirely adequate dosage form. Both the absorption rate and the bioavailability are greatly improved compared with orally administered morphine.

Very little is known about the pharmacokinetic behaviour of the drug suspended in suppositories. From a study with 10 patients with pain secondary to cancer, it was concluded that plasma concentrations of morphine, following single 10 mg doses of morphine sulphate in a suppository, were certainly not less favourable than after oral dosing (Ellison and Lewis, 1984). However, the composition of the dosage forms was not mentioned, the rate of absorption was not established, and surprisingly, the oral solution dosage form used resulted in a relatively slow absorption profile. In contrast to the above, from clinical experience it was concluded that 2–2.5 times more morphine was commonly needed rectally than orally (Lipman and Anderson, 1984).

In the present investigations, a cross-over study in healthy volunteers was designed to investigate rectal absorption conditions of morphine hydrochloride from well-defined fatty suppositories. To establish differences in relative rate and extent of absorption, a comparison was made with an orally administered solution of morphine hydrochloride.

Fatty suppositories were prepared by mixing morphine HCl (Ph. Eur., Brocacef; particle size 80% smaller than 45 μm) carefully with lactose (Ph. Eur., particle size smaller than 180 μm), in order to ensure content uniformity, and then subsequently mixed with a molten base of Witepsol H 15 (Interpharm), they were poured into brass moulds (2 ml), and stored at 4°C. The suppositories did possess a controlled content of 10.0 mg morphine HCl.

The oral dosage form consisted of 10.0 mg morphine hydrochloride dissolved in 100 ml water. Seven healthy students, aged 21–28 years and weighing 62–81 kg, participated in the cross-over study. The study protocol was approved by the Institutional Review Board and informed consent was obtained. The experiments were initiated at 09.00 h. Food was not allowed for the next 6 h. The volunteers were asked to lay down during this period. Venous blood samples were obtained at 0,

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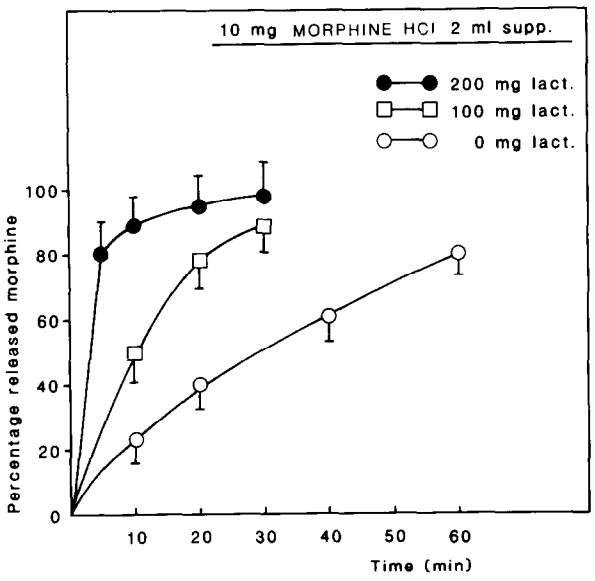

Fig. 1. Effect of lactose on release rate of morphine HCl (mean ± S.D.) from Witepsol H15.

0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 24 h after drug ingestion. Plasma was immediately separated and stored at 20 °C, until analyzed. Morphine was assayed by electrochemical HPLC method (Todd et al., 1982). With 1.0 ml plasma samples the method was accurate to concentrations as low as 0.5 ng/ml plasma.

Since the amount of morphine HCl (10 mg) which has to be suspended is extremely low in relation to the fatty base (2 ml), the inert excipient lactose was used. The purpose is to achieve mixing of the drug with lactose before morphine HCl is levigated with the molten base, in order to achieve a proper content uniformity. In vitro release measurements of morphine hydrochloride from the suppository, using a release apparatus as described previously (Schoonen et al., 1976), showed a transport which was highly dependent on the amount of lactose used (Fig. 1). It is well known, that for drugs readily soluble in water: (a) release from the molten suppository is largely determined by the rate of presentation of the drug particles to the lipid/water interface; and (b) particle size reduction gives rise to a decrease of release and absorption rate.

Since the commercial quality of morphine HCl used consisted of relatively small particles (80% smaller than 45 μm), it is not surprising that a hampered in vitro release of morphine particles was observed. It was intriguing to discover that the addition of crystalline lactose particles decreased the interfacial resistance. One might argue that the intensively mixed blend of lactose and morphine HCl, results in agglomeration of particles creating favourable particle transport in the molten suppository. However, when suppositories were prepared by mixing morphine HCl with the molten triglyceride base, and subsequent cautious addition of lactose, identical release profiles were obtained.

A more likely explanation may be that, as a result of the fast transport of the lactose bulk across the lipid/water interface, the sedimentation flow and the interfacial passage of the small morphine HCl particles is enlarged by a passive convective transport process, initiated by the lactose particles. Schoonen et al. (1979) showed that the sedimentation flow of highly soluble particles is proportional to concentration; this may provide an explanation for the difference in release rate between the suppositories containing 100 and 200 mg lactose.

However, this in vitro phenomenon could not be demonstrated in vivo. Table 1 clearly indicates that no essential difference in absorption rate occurs if morphine HCl suppositories, with or without lactose, were administered to healthy volunteers. From rectal experiments with readily available drugs, such as sodium salicylate, we did observe a proper in vitro/in vivo correlation if release rate differences were due to an interfacial process; for instance, the effect of particle size on rectal release and absorption rate (Schoonen et al., 1980). However, the lactose effect originates from a rate-initiating step in the bulk transport, a phenomenon which is less likely to be observed in vivo. An additional explanation for this in vitro/in vivo discrepancy may be that in vivo the suppository is spreading upward in the direction of the colon, under influence of the abdominal pressure. Small particles (morphine HCl) will be dragged along to a larger part of the lipid/water interface than coarser ones (lactose), resulting in an unequal packing of the bulk in the moving base. As a consequence, it can be expected that this hetero-

geneity results in a decreased effect of lactose on the release process of morphine HCl. Evidently the addition of lactose does not have major consequences for the in vivo absorption rate of morphine HCl in man.

Recently we discovered that rectal absorption of morphine HCl (10 mg) was extremely rapid if the drug was dissolved in water (5 ml) adjusted to pH 7.4, this being the pH which prevails in the human rectum. Maximal plasma concentrations were reached within 30 min after dosing (Ellison and Lewis, 1984) *AUC* values indicated a bioavailability of 55%, exceeding that after oral dosing (35%). In the present study it is obvious that transport of morphine HCl particles from the suppository base is the rate-determining step in the rectal absorption process, resulting in a pronounced lag time in absorption. In this respect, it was intriguing that in all of the five subjects central side-effects were reported 1–2 h after oral dosing, whereas no such effects occurred after rectal dosing with the fatty suppositories. Yet it can be calculated that relative bioavailability 6 h after administration is entirely identical compared with oral dosing (Table 1). Fig. 2 shows typical plasma morphine concentration–time profiles after oral and rectal administration of the various dosage forms for one subject. It can be concluded that for single-dose therapy with morphine, especially when a rapid analgesic effect is required, the rectal solution will provide an attractive alternative dosage form.

TABLE 1

Mean absorption characteristics of morphine HCl (mean ± S.D.) calculated from individual (n = 6) plasma morphine curves following rectal and oral administration of 10 mg morphine HCl

Plasma morphine ($ng \cdot ml^{-1}$) at time (h)	Suppositories		Oral solution
	0 mg lactose	100 mg lactose	
0.25	1.4±0.4	1.8±0.4	9.9 ±3.4
0.50	5.9±1.9	5.4±1.7	10.9 ±3.7
0.75	8.4±2.4	8.6±3.0	8.7 ±2.9
1.0	9.7±2.7	10.2±2.9	7.5 ±2.2
1.5	8.4±2.1	9.5±2.6	6.9 ±1.8
2.0	7.2±1.7	7.5±1.9	5.6 ±1.6
3.0	5.7±1.9	5.1±1.6	3.9 ±0.8
4.0	4.6±1.0	3.6±0.8	1.6 ±0.4
6.0	2.9±0.7	1.9±0.5	0.5 ±0.2
24.0	0.8±0.2	1.0±0.2	–
C_{max} ($ng \cdot ml^{-1}$)	10.3±3.7	10.0±3.5	10.4 ±2.7
T_{max} (h)	1.1±0.3	1.2±0.3	0.49±0.08
AUC_{0-6} ($ng \cdot ml^{-1} \cdot h$)	32.6±5.7	30.2±6.1	24.6 ±5.2

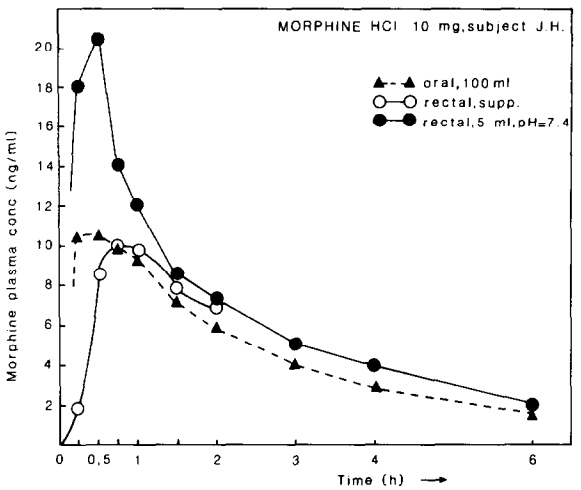

Fig. 2. Typical plasma levels of morphine after rectal and oral administration of 10 mg morphine HCl to one subject.

Rectal dosing with fatty suppositories results in a relative bioavailability, closely corresponding to the pattern of oral absorption. However, the absorption rate is slower, and therefore further studies are required to establish the optimal dosage and dose interval for the relief of moderate to severe pain.

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