International Journal of Pharmaceutics, 33 (1986) 249–252
Elsevier

IJP 01099

Short Communications

Rectal absorption of methadone from dissolution-promoting vehicles

Frits Moolenaar, Bert G. Kaufmann, Jan Visser and Dirk K.F. Meijer

Department of Pharmacology and Pharmacotherapeutics, Subfaculty of Pharmacy, State University of Groningen (The Netherlands)

(Received 22 April 1986)
(Accepted 11 May 1986)

Key words: Methadone – Rectal absorption – Suppository – Micro-enema

Rectal absorption conditions of methadone were found to be strongly dissolution rate-limited (Moolenaar et al., 1984). Although the pK_a of methadone ($pK_a = 9.2$) in relation to the prevailing pH in the human rectum (pH = 7.5–8.0) in itself provides favourable rectal absorption conditions, the free base precipitates from solutions of pH higher than 7. It can be argued therefore that in spite of a rather fast release profile in vitro in the case of fatty suppositories, and complete dissolution in the case of aqueous micro-enemas, soon after rectal administration partial precipitation of the methadone base from the rectal dosage forms is likely to occur. As a consequence, the C_{max} and AUC_{0-8h} values were found to be significantly ($P < 0.05$) lower compared with the oral route of administration.

Recently we concluded that in the case of slightly soluble drugs the driving force for rectal absorption can in principle be enhanced by adding solvents which improve the solubility at rectal pH circumstances (Vromans and Moolenaar, 1985). In addition, an optimum concentration of the solvent added could be established.

In the present investigation a cross-over study in healthy volunteers was designed to investigate rectal absorption conditions of methadone from dissolution-promoting vehicles including suppository bases. For rectal use, solutions of methadone were prepared containing 10.0 mg of methadone HCl (Ph.Eur., Brocacef, Maarssen, The Netherlands) dissolved in respectively 5 ml of distilled water (pH = 6.0), in 5 ml of a mixture of glycofurol (Merck) and water (1 : 1, pH = 8.0) and in 5 ml of a mixture of glycofurol and water (1 : 4, pH = 8.0). The pH was adjusted with 0.01 N NaOH. The solutions were administered as micro-enemas, using a 5.0 ml plastic disposable syringe (B-D, Luer-lok TIP) with a plastic application tube. Fatty suppositories were prepared by mixing methadone HCl (particle size < 125 μm) carefully with lactose (Ph.Eur., particle size < 180 μm, 100 mg a suppository) and subsequently with a molten base of Witepsol H15 (Interpharm), poured into brass moulds (2 ml) and stored at 4°C. The weight of the suppositories was adjusted exactly to 1.80 g possessing a controlled content of 10.0 mg methadone HCl. Macrogol suppositories were prepared by mixing methadone HCl with a molten base of PEG 1540, poured into brass moulds (2 ml) and stored at 4°C. The weight of

Correspondence: F. Moolenaar, Department of Pharmacology and Pharmacotherapeutics, Subfaculty of Pharmacy, State University of Groningen, Ant. Deusinglaan 2, NL-9713 AW Groningen, The Netherlands.

the suppositories was adjusted to exactly 2.3 g possessing a controlled content of 10.0 mg methadone HCl.

The oral dosage form consisted of 10.0 mg methadone HCl dissolved in 50 ml water. Six healthy students, aged 22–29 years, and weighing 54–82 kg, participated in the cross-over study. No drugs were taken for two weeks prior to or during the 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 3 h from that time. The volunteers were asked to remain recumbent. Venous blood samples were obtained 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8 and 24 h after drug ingestion. Plasma was immediately separated and stored at − 20°C until analyzed by means of HPLC analysis (Moolenaar et al., 1984).

The mean absorption characteristics calculated from the individual absorption curves are summarized in Table 1. Typical plasma methadone concentration–time profiles after rectal and oral administration of the various dosage forms for two subjects are shown in Fig. 1. It appears that the addition of the solvent glycofurol to the rectal methadone solution has a pronounced effect on the initial rectal absorption rate of methadone (Table 1, Fig. 1a). Compared with the pure aqueous rectal dosage form, the 20% glycofurol micro-enema did produce significantly ($P < 0.05$) higher plasma levels during the first 2 h after administration. Also the t_{max} and C_{max} values indicate that a substantial increase in the driving force for absorption occurred. Compared with oral dosing it also appeared that absorption proceeds significantly ($P < 0.05$) more rapidly during the first hour after administration.

On the other hand, the 50% glycofurol micro-enema did *not* result in an increased absorption profile, in spite of the fact that the same favourable pH and solubility circumstances were created. This remarkable phenomenon may be explained by the fact that, by adding solvents to an aqueous drug system in attempts to improve the solubility profile, one has to consider at the same time a decreased diffusion flow of the drug (Kakemi et al., 1965). The diffusion flow, in a previous study represented by the mass transport coefficient K, was found to be strongly dependent on the concentration of the particular solvent used (Vromans and Moolenaar, 1985). In the present study we found that the K value of methadone was substantially reduced depending on the concentrations of glycofurol added (Table 2). It can be argued therefore that in vivo a faster absorption pattern may be expected with a lower con-

TABLE 1
ABSORPTION CHARACTERISTICS OF METHADONE HCl (MEAN + S.D.) AFTER RECTAL AND ORAL ADMINISTRATION OF 10.0 mg METHADONE HCl TO HEALTHY VOLUNTEERS

Plasma methadone (ng/ml) at time (h)	Oral solution	Rectal solution			Suppositories	
		0% Glycofurol	20% Glycofurol	50% Glycofurol	Witepsol W15	PEG 1540
0.5	4 ± 2	8 ± 3	15 ± 6	4 ± 2	2 + 2	3 + 1
1.0	12 ± 4	14 ± 4	25 ± 8 *	17 ± 5	6 ± 5	12 ± 4
1.5	22 ± 8	17 ± 4	28 ± 8 *	23 ± 6	11 ± 5	27 ± 6
2.0	32 ± 10	20 ± 4	31 ± 7 *	25 ± 7	13 ± 4	32 ± 6
3.0	32 ± 9	21 ± 4	29 ± 6	25 ± 5	16 ± 4	29 ± 6
4.0	30 ± 5	22 ± 4	26 ± 6	27 ± 6	15 ± 4	28 ± 6
6.0	23 ± 3	19 ± 4	21 ± 4	24 ± 4	13 ± 3	24 ± 5
8.0	20 ± 5	17 ± 4	21 ± 4	21 ± 4	12 ± 3	20 ± 4
24.0	–	13 ± 3	14 ± 5	13 ± 4	8 ± 4	16 ± 3
n	5	8	4	4	7	4
C_{max} (ng/ml)	37.3 ± 6.9	23.6 ± 3.6	32.6 ± 5.1	28.1 ± 4.3	15.9 ± 4.9	35.1 ± 8.9
t_{max} (h)	2.8 ± 0.8	3.2 ± 0.5	2.1 ± 0.6	3.8 ± 0.9	3.3 ± 1.2	2.6 ± 0.7
AUC_{0-8} (ng/ml/h)	188 ± 26	145 ± 32	192 ± 28	175 ± 30	100 ± 35	186 ± 28

* Significantly different from the aqueous rectal solution.

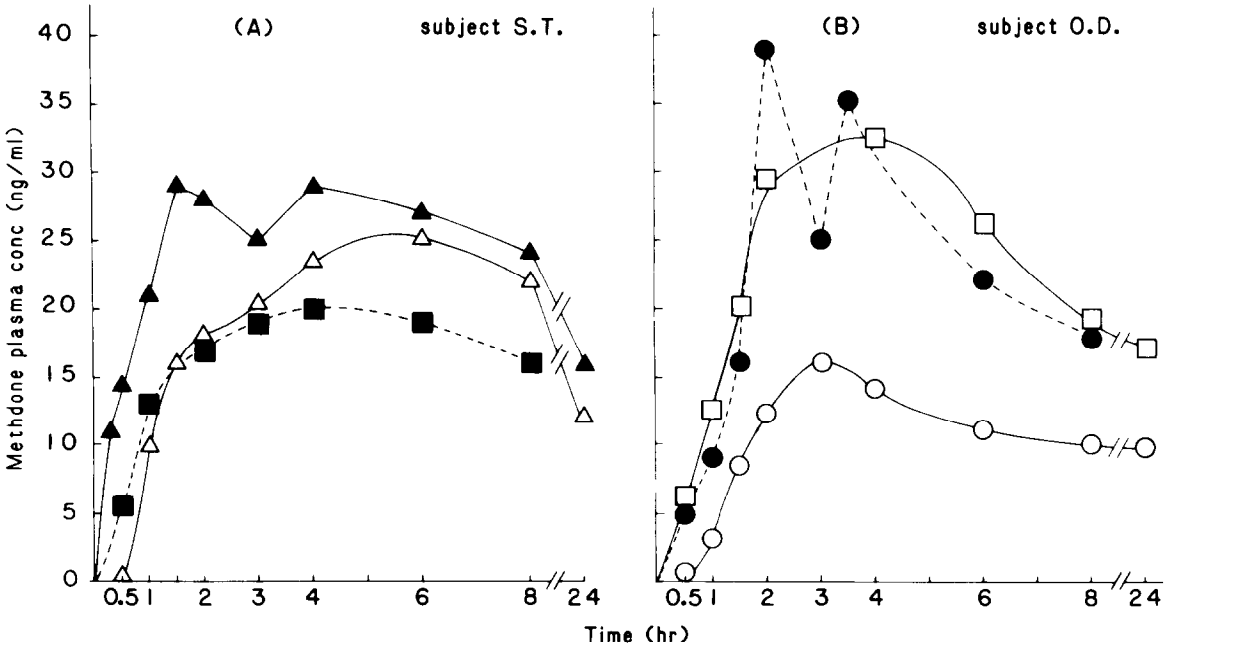

Fig. 1. Typical plasma levels of methadone after rectal and oral administration of 10.0 mg methadone HCl in various dosage forms to two subjects. A: various concentrations of glycofurol in a 5 ml aqueous rectal solution. ■———■, 0%; ▲———▲, 20%; △———△, 50%. B: suppositories vs an oral solution. ●———●, oral solution; ○———○, fatty suppository; □———□, PEG suppository.

centration of glycofurol: in the case of 50% glycofurol the substantial decrease of the K value will counteract the positive effect of the increased solubility on the driving force for absorption. It is likely that this phenomenon mainly plays a significant role during the initial period of the absorption phase, since low molecular weight solvents, such as glycofurol or propylene glycol, will be rectally absorbed to a certain extent, thereby changing the composition of the vehicle administered during the absorption process. Support for this concept can be found in the similar relative bioavailability of the two glycofurol–water micro-enemas 8 and 24 h after administration.

TABLE 2
MASS TRANSPORT COEFFICIENTS (K) OF METHADONE DISSOLVED IN VARIOUS CONCENTRATIONS SOLVENT WATER VEHICLES (% w/w) AT 37°C, USING THE IN VITRO DIFFUSION MODEL AS DESCRIBED IN THE STUDY OF VROMANS AND MOOLENAAR (1985)

% Glycofurol	K methadone
0	1.00
5	0.97
10	0.91
20	0.64
50	0.36

As discussed earlier, rectal dosing with fatty suppositories resulted in a dissolution rate-limited absorption pattern, due to precipitation of the slightly soluble methadone base at rectal pH. In the present study we also observed a rather slow absorption pattern (Table 1, Fig. 1b). An additional factor which may explain the rather unfavourable absorption circumstances is the fact that the methadone base is fairly soluble in the triglyceride vehicle. Thus, in the case of rectal precipitation, a re-uptake of the methadone base in the fatty vehicle may occur, thereby introducing a diffusion controlled release process.

On the other hand, the use of the macrogol PEG 1540 suppository vehicle remarkably increased the rate of methadone absorption (Table 1, Fig. 1b). The mean C_{max}, t_{max} and AUC_{0-8h} were identical compared with oral dosing and did not vary significantly. Obviously more complete

dissolution of methadone by using such a dissolution promoting vehicle has a pronounced influence on the driving force for rectal absorption.

From a therapeutic viewpoint it can be concluded that methadone can be successfully applied rectally. A 20% glycofurol micro-enema (5 ml) should be chosen if a rapid analgesic effect is required. Compared with the oral route of administration rectal dosing of methadone HCl in fatty suppositories gives rise to slow and incomplete absorption due to dissolution rate-limitation and it is uncertain whether such a dosage form can be looked upon as an alternative route of administration in long-term analgesic therapy. On the other hand, a PEG 1540 suppository vehicle (2 ml) provides an adequate rectal dosage form. Absorption rate and relative bioavailability 24 h after administration are entirely identical compared with oral dosing.

References

Moolenaar, F., Fiets, G., Visser, J. and Meijer, D.K.F., Preliminary study on the absorption profile after rectal and oral administration of methadone in human volunteers. *Pharm. Weekblad Sci. Ed.*, 6 (1984) 237–240.

Kakemi, K., Arita, T. and Muranishi, S., Absorption and excretion of drugs. XXVI. Effect of water-soluble bases on rectal absorption of sulfonamides. *Chem. Pharm. Bull.*, 13 (1965) 969–975.

Vromans, H. and Moolenaar, F., Effects of solvents on rectal absorption rate of paracetamol in man: an in vitro approach. *Int. J. Pharm.*, 26 (1985) 5–13.