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International Journal of Pharmaceutics 119 (1995) 223–229

international journal of pharmaceutics

A gamma scintigraphic study of the absorption of morphine from controlled-release tablets

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Received 19 July 1994; revised 16 November 1994; accepted 28 November 1994

Abstract

The gastrointestinal (GI) transit of two morphine controlled-release tablets, with different in vitro dissolution rates, was studied in six healthy male volunteers. The tablets were radiolabelled with indium-111 and their location in the GI tract was determined using gamma scintigraphy. Simultaneously, the absorption of morphine was studied by taking blood samples during a period of 28 h. The study indicates that morphine can be absorbed throughout the entire GI tract. However, the release of the drug from matrix tablets is incomplete or too slow in the distal small intestine and in the colon, resulting in reduced bioavailability of tablets with very prolonged dissolution.

Keywords: Morphine; Absorption; Controlled release; In vitro-in vivo correlation; Gamma scintigraphy; Gastrointestinal transit

1. Introduction

Orally administered morphine is rapidly and completely absorbed (Brunk and Delle, 1974). However, morphine undergoes extensive glucuronidation in the gut wall and liver (Iwamoto and Klaassen, 1977; Dahlström and Paalzow, 1978). This first-pass metabolism leads to a reduced and variable bioavailability. In cancer patients the bioavailability is about 38% with a range from 15 to 64% (Säwe et al., 1981). Investigations in healthy volunteers have resulted in estimates of 20–24% in young individuals and 29% in the elderly (Baillie et al., 1988; Hoskin et al., 1989). The major metabolites are morphine 3-glucuronide and morphine 6-glucuronide, which are present in serum after oral morphine administration (Brunk and Delle, 1974; Yeh et al., 1977). Not only the glucuronides, but also morphine itself, are excreted in the bile and morphine undergoes enterohepatic circulation (March and Elliott, 1954; Peterson and Fujimoto, 1973; Walsh and Levine, 1975; Dahlström and Paalzow, 1978; Hanks et al., 1988).

The half-life of morphine in plasma is short, usually between 1.7 and 4.5 h (Brunk and Delle,

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Elsevier Science B.V.
SSDI 0378-5173(94)00400-5

1974; Stanski et al., 1978; Säwe et al., 1981). There is also a slowly declining terminal phase with a half-life of approx. 15 h (Hasselström and Säwe, 1993). The analgesic effect after intramuscular administration of a 10 mg dose has a duration of 4–6 h (Houde et al., 1960; Jaffe and Martin, 1985). The duration is somewhat longer after oral administration (Houde et al., 1965). Due to the short half-life and short duration of the analgesic effect morphine is administered four to six times daily in order to maintain an adequate analgesic effect. This frequent administration has led to the development of oral controlled-release preparations of morphine, which has increased the dosage interval to 8–12 h (Hanks, 1989). In order to further improve patient convenience, and compliance, a preparation for administration once-a-day would be useful.

To make a once-a-day preparation for a drug with a half-life as short as morphine's, drug release extended over a long time period (15–20 h) is necessary. For such a preparation to have satisfactory bioavailability the active drug needs to be absorbed along the whole GI tract. There are no data in the literature describing the absorption of morphine from different segments of the GI tract.

Gamma scintigraphy is an often used technique for studying the GI transit of solid oral dosage forms (Casey et al., 1976; Daly et al., 1982; Davis et al., 1984). A radioactive marker, such as ^{111}In or ^{99m}Tc, is incorporated into the preparation which allows the in vivo behaviour of the dosage form to be monitored by scintigraphy.

The present investigation studies the absorption of morphine in relation to its location in the GI tract and correlates its absorption rate in vivo with its in vitro dissolution rate.

2. Materials and methods

2.1. Preparations

Two morphine hydrochloride controlled-release (CR) tablets (A and B), containing insoluble paraffin as the principal inert matrix former, were used in the study. The two tablets had different in vitro dissolution rates which are presented in Fig. 1. The insoluble polymeric material is considered to give a coherent and porous matrix in which the drug is dispersed and the release rate should thus be diffusion controlled according to Higuchi (1963). Consequently, the release rate should be dependent on the diffusion coefficient of the drug in the fluid, the solubility of the drug (at the actual pH), the concentration of drug in the tablet, and the porosity and tortuosity of the tablets.

The release rate was virtually pH independent at low pH levels but decreased at higher levels due to the reduced solubility of morphine (pK_a value 8.1 at 35°C) (see Fig. 2).

The tablets were radiolabelled with a colloid of [^{111}In]indium chloride. They had an activity of 4 MBq (0.11 mCi) when administered. An unlabelled aqueous solution of morphine hydrochloride was used as a reference preparation.

2.2. Subjects

Six healthy male volunteers (age, 35–60 years; weight, 62–90 kg; and height, 168–182 cm) participated in the study after giving their informed consent. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee at Lund University, Sweden. Approval to administer the radiolabelled preparations was obtained from the National Board of Health and Welfare.

2.3. In vivo study

The study followed a non-randomized, crossover design. Three subjects started with the solu-

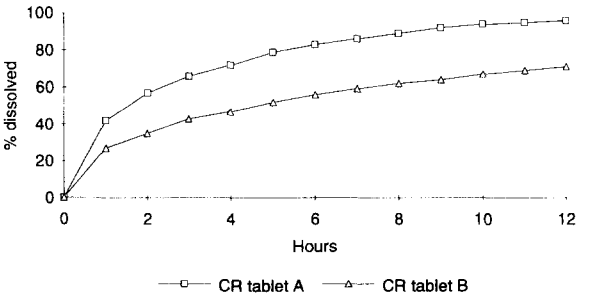

Fig. 1. In vitro dissolution rates at pH 6.8 (USP XX, basket/paddle method, 50 rpm) of the CR tablets.

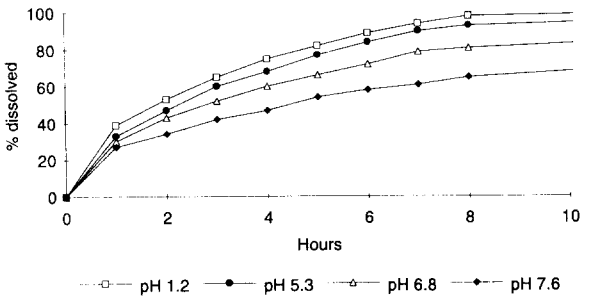

Fig. 2. In vitro dissolution rates at different pH levels for CR tablet A.

Table 2
Mouth-to-caecum transit time (h)

Subject	CR tablet A	CR tablet B
1	2.0	5.0
2	5.0	5.0
3	–	3.4
4	4.0	5.9
5	5.0	10.0
6	3.5	4.0
Median	4.0	5.0
Range	2.0–5.0	3.4–10.0

tion followed by CR tablets A and B. The other three started with CR tablet A followed by tablet B and then the solution. There was a wash-out period of 1–2 weeks between the study sessions.

The subjects fasted from 10:00 p.m. on the night before each study day. At about 7 a.m. the following morning the relevant preparation was swallowed with 300 ml of orange juice (used to mask the bad taste of the solution). The tablets were given in a dose of 20 mg morphine hydrochloride and the dose of the solution was 10 mg. 1.5 h after drug administration a light standardized breakfast was served provided that the tablets had left the stomach at that time. All meals during the first 12 h after administration were standardized.

Five ^{57}Co anatomical reference markers were attached to the subjects in connection with the measurements. These were performed using two parallel coupled gamma cameras (Nuclear Chicago Pho/Gamma HP) mounted with high-energy collimators. The energy window (30%) was placed symmetrically over the 245 keV photon peak. Simultaneous collection of data from the gamma cameras was performed in a computer (PDP 11/34, Gamma 11 V3.1) where they were stored as 64 × 64 matrix images. Images of 60–120 s duration were taken when the tablets were swallowed and thereafter immediately after each blood sample. These were collected at predetermined intervals up to 12 h, and then at 24 and 28 h after administration.

Table 1
Gastric emptying time (h)

Subject	CR tablet A	CR tablet B
1	0.5	2.0
2	0.5	1.0
3	12.0 [a]	1.5
4	0.5	1.5
5	1.0	3.0
6	1.0	1.0
Median	0.75	1.5
Range	0.5–1.0 (12.0 [a])	1.0–3.0

[a] Non-fasting

2.4. Determination of morphine and morphine 6-glucuronide in serum

Serum concentrations of morphine and its 6-glucuronide metabolite (M6G) were determined using an LC method with UV/EC detection (Svensson et al., 1982; Svensson, 1986). The limits of quantification were 0.6 ng/ml (morphine) and 2.3 ng/ml (M6G). The precision was 9.7% at 2 ng/ml and 4.6% at 11 ng/ml for morphine; and 6.1% at 13 ng/ml and 4.6% at 64 ng/ml for M6G.

2.5. Calculations

Standard bioavailability parameters (AUC_{0-28h}, C_{max} and t_{max}) were calculated. The relative bioavailability (F_{rel}) of the CR tablets was calculated as $AUC_{tablet}/(AUC_{solution} \times 2)$. The curve width at half the C_{max} concentration (W_{50}) was used as a measure of the flatness of the serum concentration profile. The ratio $AUC_{M6G}/AUC_{morphine}$ was calculated on a molar basis. The in vivo dissolution rates of the CR tablets were

calculated using numerical deconvolution (Langenbucher, 1982).

Since gamma scintigraphic measurements were performed discontinuously, the exact arrival time in the small and large intestine, respectively, could not be determined. Instead the maximum gastric emptying time (corresponding to the first appearance in the small intestine) and the maximum time to reach the ileo-caecal junction (mouth-to-caecum transit times) were recorded.

2.6. Statistics

The mean relative bioavailability (F_{rel}) of each of the CR tablets, and the 90% confidence interval, were calculated after log transformation of the AUC data. Comparison of t_{max} data was performed using Wilcoxon's signed rank test. Comparisons of the $AUC_{M6G}/AUC_{morphine}$ ratios, and the W_{50} data were carried out with a paired t-test. A p value of less than 0.05 was considered statistically significant.

3. Results and discussion

3.1. Gastrointestinal transit

The GI transit times are presented in Table 1 (gastric emptying) and Table 2 (mouth-to-caecum), respectively. In one subject (no. 3) the tablet (CR tablet A) had not been emptied from the stomach 4 h after administration although he had been given extra water and was laid down on his right side. It was decided to let him eat lunch at that time which resulted in the tablet remaining in the stomach until 12 h after administration.

The transit times observed for the tablets in this study are generally in agreement with those earlier observed in similar studies where the transit time through the small intestine had been shown to be about 2–4 h during different conditions (Khosla and Davis, 1989; Khosla et al., 1989; Davis et al., 1990). One exception is subject no. 5 (CR tablet B) with a small-intestinal transit time of approx. 7 h.

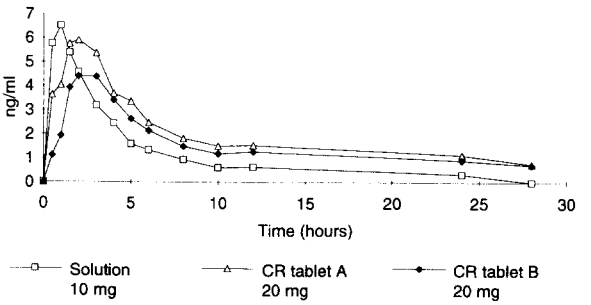

Fig. 3. Mean serum concentrations of morphine.

3.2. Bioavailability

The mean serum concentration profiles of morphine for the three preparations studied are depicted in Fig. 3. The corresponding profiles for M6G are shown in Fig. 4.

The pharmacokinetic parameters determined are listed in Table 3. Compared to the solution, CR tablet A (with the faster dissolution) had a relative bioavailability of 100.2% with a 90% confidence interval of 81.1–123.8%. CR tablet B, on

Table 3
Pharmacokinetic parameters for morphine

	CR tablet A 20 mg	CR tablet B 20 mg	Solution 10 mg
C_{max} (ng/ml) [a]	6.8 ± 2.6	4.9 ± 1.7	6.9 ± 2.9
t_{max} (h) [b]	1.5 (0.5–3.0)	3.0 (1.75–4.0)	0.75 (0.5–1.75)
AUC (ng ml^{-1} h) [a]	56.0 ± 19.3	46.0 ± 21.7	30.1 ± 15.2
F_{rel} (%) [c]	100.2 (81.1–123.8)	76.4 (59.4–98.3)	–
W_{50} (h) [b]	4.23 ± 1.24	4.74 ± 1.62	2.64 ± 0.58
M6G/morphine ratio	3.81 ± 2.36	4.95 ± 2.65	4.03 ± 2.36

[a] Mean ± S.D.
[b] Median (range).
[c] Mean (90% confidence interval).

the other hand, had a reduced bioavailability of 76.4 (59.4–98.3)%. Only for CR tablet B did the t_{max} data differ significantly from those for the solution. The W_{50} values were not significantly higher for either of the CR tablets than for the solution. The small sample size makes finding significant differences problematic. It is likely that a larger sample size would have given significant differences in W_{50}. However, the small differences observed show that this kind of matrix tablet formulation only moderately flattens the serum concentration profiles compared to a solution.

The M6G/morphine ratio was not significantly different for the three treatments. The ratios are comparable to those previously found during long-term treatment in cancer patients (Säwe et al., 1983; McQuay et al., 1990) and after single-dose administration to normal volunteers (McQuay et al., 1987).

Linear system analysis (deconvolution and convolution) can be used to investigate a number of biopharmaceutical and pharmacokinetic processes. Depending on the choice of weighting function (unit impulse) and response function different input functions such as drug absorption rates can be estimated (see Möller, 1989). If the weighting function is the serum concentration profile after an oral solution and the response function is that of a solid oral dosage form, then the resulting input function directly represents the in vivo dissolution rate, i.e., the difference between the unit impulse and the delayed process (Hanano, 1967; Nogami and Hanano, 1967; Cutler, 1981).

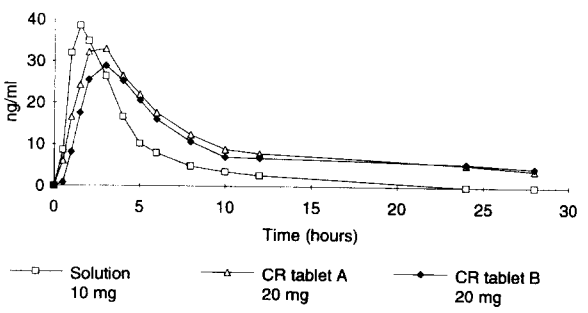

Fig. 4. Mean serum concentrations of morphine 6-glucuronide.

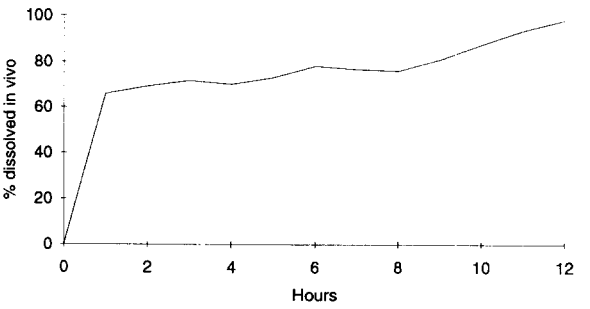

Fig. 5. Example of a subject where absorption ceased a few hours before the tablet reached the ileo-caecal junction (mouth-to-caecum transit time: 3.5 h).

However, in our study the dissolution of the drug from the CR tablets occurs in part in regions of the GI tract where we currently have no knowledge whether drug absorption is possible. What appears as incomplete in vivo dissolution might also represent a lack of absorption from that segment. In most of our subjects (five out of six) dissolution (absorption) appeared to already have ceased 1–2 h before the tablet reached the ileo-caecal junction, as shown in Fig. 5. In this subject there is virtually no dissolution/absorption during the interval 1–8 h although the tablet did not reach the ileo-caecal junction until 4 h after administration. This indicates poor dissolution/absorption even in the distal parts of the small intestine, something which is also supported by the generally reduced bioavailability (approx. 75%) of the slower of the two tablets. The increase seen from 8 h and onwards is most likely due to the enterohepatic circulation.

The data from these five subjects do not allow us to distinguish between poor dissolution and poor absorption. However, in one of the subjects in vivo dissolution and absorption continued long after the tablets had reached the ileo-caecal junction (Fig. 6). Although in the case illustrated the mouth-to-caecum transit time was only 2 h, the CR tablet administered had a relative bioavailability of 110%. This indicates that morphine can be absorbed from the large intestine and that the reduced absorption observed in most subjects is related to a slow or incomplete release of the drug from the dosage form. Also, the fact that

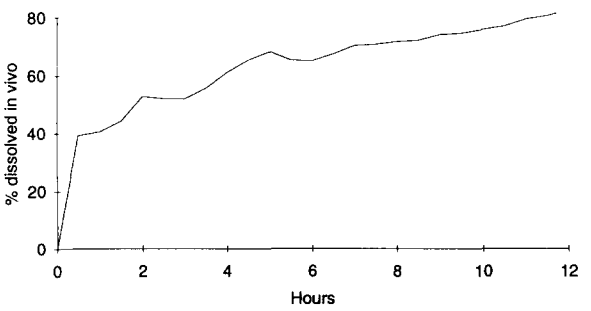

Fig. 6. Example of a subject with continuing absorption throughout the GI tract (mouth-to-caecum transit time: 2 h).

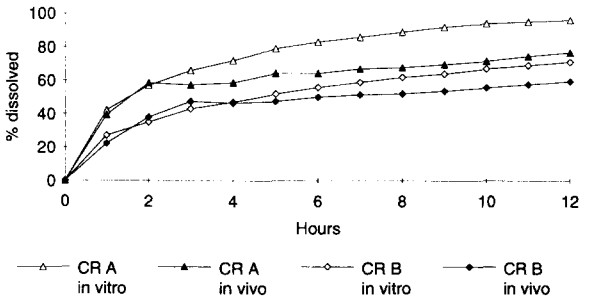

Fig. 7. Comparison of in vivo and in vitro (pH 6.8) dissolution rates for the two CR tablets.

morphine undergoes enterohepatic circulation, where the glucuronides are deconjugated in the caecum and morphine reabsorbed, further supports that morphine can be absorbed from the large intestine, at least in its most proximal parts.

Fig. 7 shows the relationship between the mean dissolution rates in vitro and in vivo for the two tablets. The correlation appears to be relatively good during the first hours but as the in vivo dissolution stops or decreases after a few hours a direct correlation is no longer seen.

4. Conclusions

The study has shown that morphine can be absorbed from both the small and large intestine in humans. However, matrix controlled-release tablets show limited absorption from both the large intestine and distal parts of the small intestine. This is probably due to incomplete release of the active drug from the tablets. Thus, CR tablets of a conventional type are not suitable for once daily administration of morphine.

Acknowledgements

We are grateful to Ms Heidi Forsmo Bruce for performing the serum analyses, to Ms Maritta Chefrad for the preparation of the CR tablets, and to Professor Lennart Paalzow for comments on the manuscript.

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