Difference in Rectal Absorption of Morphine from Hollow-Type and Conventional Suppositories in Rabbits

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The bioavailability of morphine after rectal administration using three types of suppositories containing morphine hydrochloride (10 mg) in different added forms was evaluated in rabbits. Three types of suppositories were constructed with a base material (Witepsol H-15): a conventional suppository containing morphine hydrochloride mixed with a base material, a hollow-type suppository containing morphine in an aqueous solution in its cavity, and a hollow-type suppository containing morphine as a powder (hydrochloride salt) in its cavity. The plasma concentrations of morphine and its metabolites, morphine-3-glucuronide (M-3-G) and morphine-6-glucuronide (M-6-G), were determined.

The mean $AUC_{0-\infty}$ of morphine after rectal administration of the hollow-type suppository containing powdered morphine was significantly higher than that after the administration of a conventional suppository, whereas the mean $AUC_{0-6}$ of M-3-G was lower than that after administration of a conventional suppository. The mean $AUC_{0-\infty}$ of M-6-G by a hollow-type suppository containing powdered morphine was higher than that by a conventional suppository. Although the mean $AUC_{0-\infty}$ ratio of M-3-G to morphine after administration of a conventional suppository was three times larger than that of a hollow-type suppository containing powdered morphine, the mean $AUC_{0-\infty}$ ratios of M-6-G to morphine after use of the three types of suppositories were all approximately 1.0.

This study demonstrates that the hollow-type suppository containing powdered morphine is a more effective rectal dosage vehicle than the conventional suppository.

Keywords: morphine; rectal administration; hollow-type suppository; morphine-3-glucuronide; morphine-6-glucuronide; rabbit

Introduction

Morphine has been employed as an analgesic for the treatment of severe chronic pain associated with malignant disease. Many researchers have examined the clinical effectiveness of rectally administered morphine as an aqueous solution or suppository. Furthermore, the rectal administration of morphine was studied as a convenient dosage vehicle with which the first-pass metabolism could be partially avoided. The metabolites of morphine-3-glucuronide (M-3-G) and morphine-6-glucuronide (M-6-G) occur in significant quantities after morphine administration. Recent reports describing the analgesic activity of M-6-G in humans suggest that bioavailability studies of morphine should include the examination of glucuronides. The exact quantitative significance of M-3-G and M-6-G after rectal administration has not been defined, and the differences in bioavailability and disposition of morphine, M-3-G and M-6-G occurring after rectal administration of suppositories containing different forms (powder, aqueous solution) of morphine have not been examined.

The effect of the added form in the rectal dosage vehicle on absorption and metabolism of morphine is by no means proven, but may be very important from the standpoint of bioavailability. However, only a few studies on this effect have been reported. In a previous paper, we reported that rectal morphine administration, delivered as powder in a hollow-type suppository, was more effective in cancer patients than oral administration. In the present study, to evaluate the effect of the added form of morphine in a suppository on the rectal absorption and hepatic metabolism of morphine, the pharmacokinetics of morphine and its glucuronides after rectal administration using three types of suppositories containing morphine in different added forms were investigated in rabbits.

Materials and Methods

Morphine hydrochloride was purchased from Takeda Chemical Ind., Ltd. (Osaka, Japan). M-3-G and M-6-G were obtained as a gift from Kyushu University (Fukuoka, Japan). Nalorphine hydrochloride was supplied from Dainippon Pharmaceutical Co., Ltd. (Osaka, Japan). Witepsol H-15 (H-15, Hüls Troisdorf, Germany) was used as the base. All other chemicals were of analytical grade.

Preparation of Suppository

Conventional suppositories were prepared by the fusion method. An amount (10 mg) of morphine hydrochloride was melted with a melted H-15 base and then dispersed by sonication. The mixtures were quickly poured into steel molds and allowed to solidify at room temperature.

Hollow-type suppositories were constructed using H-15 by the fusion method, as described in a previous report. To elucidate the difference in effect of the added form of morphine on bioavailability, H-15 containing triglyceride without other excipients was used. When the morphine hydrochloride was used as a powder (morphine powder), it was accurately weighed and added to each cavity. When the morphine hydrochloride was used in solution (morphine solution), each suppository containing 10 mg of morphine hydrochloride was dissolved in isotonic NaCl solution (0.5 ml).

Animal Experiments

Male albino rabbits weighing 2.8—3.3 kg were fasted for 24 h prior to each experiment, but water was given freely. The suppository was administered into the rectum according to the method described in our previous paper. For intravenous bolus and oral administrations, 10 mg morphine hydrochloride was dissolved in isotonic NaCl solution. After administration, blood samples were taken from the marginal ear vein at predetermined intervals and centrifuged at 3000 rpm for 15 min. The plasma layer was stored at −30°C until analysis.

Measurement of Morphine in Plasma

The concentrations of morphine and its metabolites, M-3-G and M-6-G, in the plasma were simultaneously determined by the method of Svensson et al. with a slight modification, as follows: 0.5 ml of plasma was added to a test tube containing 50 μl of nalorphine hydrochloride solution (50 μg/ml). Then, this mixture was passed through a solid-phase (SepPak C$_18$, Millipore) system that had been washed with 2 ml of distilled water, and 3 ml of 5% acetone. Morphine and its metabolites were eluted with 4 ml of 70% methanol. The high-performance liquid chromatographic condition was as described below. A HPLC was assembled from the following components: LC-6A constant-flow pump (Shimadzu), SIL-9A sample injector (Shimadzu), TSK-gel ODS-120T column (15 cm x 4.6 mm i.d.; Tosoh), SPD-6A UV detector (210 nm, 0.005 AUFS; Shimadzu) and L-ECD-6A electrochemical...
detector (0.8 V; Shimadzu). The mobile phase was a 10 mM sodium dihydrogen phosphate buffer at pH 2.1 (adjusted with phosphoric acid) containing 1 mM sodium dodecyl sulfate-acetonitrile (75:25). The flow rate was 1 ml/min. The eluate was evaporated to dryness at 60°C under a stream of nitrogen gas. The residue was dissolved with 200 μl of the mobile phase, and 50 μl of the solution was injected into the HPLC system. The lower limits of detection for morphine, M-3-G and M-6-G in plasma were 1, 30 and 10 ng/ml, respectively.

**Pharmacokinetic Analysis** The peak plasma concentration (C_{peak}), the peak plasma concentration time (t_{max}), and the area under the plasma concentration-time curve (AUC) were obtained from each plasma concentration-time curve. AUC_{0→6} was calculated according to the trapezoidal rule.

The relative systemic bioavailability of rectal or oral administration (F_{rect/oral}) was calculated using the following equation:

\[ F_{\text{rect/oral}} = \frac{\text{AUC}_{\text{rect/oral}}}{\text{AUC}_{\text{i.v.}}} \times \frac{(D_{\text{int}})}{D_{\text{rect/oral}}} \]

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D is the dose of morphine hydrochloride; the subscripts rect, oral and i.v. refer to rectal, oral and intravenous administration, respectively.

The fraction (f_ab) of the administration dose which bypasses the liver following rectal administration of morphine hydrochloride to rabbits based on plasma concentration was calculated according to the method of de Boer et al.\(^{13}\)

\[ f_{ab} = \frac{F_{\text{rect}} - F_{\text{oral}}}{1 - F_{\text{oral}}} \times 100 \]

(2)

Statistical analysis was performed using the one-way ANOVA, and the differences were assumed to be significant when p < 0.05.

**Results and Discussion**

**Intravenous and Oral Administration of Morphine Hydrochloride** The mean plasma concentration–time curves of morphine and its glucuronides after intravenous and oral administration at a dose of 10 mg are illustrated in Figs. 1A and B, respectively. These pharmacokinetic parameters are summarized in Table I.

After intravenous administration, the concentration of morphine rapidly decreased, whereas the concentration of M-3-G, the main metabolite, remained at significantly high levels compared to that of morphine. Therefore, the metabolism of morphine to morphine glucuronides proceeded extremely rapidly. Although M-3-G and M-6-G after oral administration were found to be present in quantities similar to those observed after intravenous administration of morphine, the mean AUC_{0→6} of morphine after oral administration was significantly low compared to that of intravenous administration. The relative bioavailability for oral administration was approximately 6%. This is thought to be due to the extensive first-pass metabolism after oral administration. This result generally agrees with the findings of others that the bioavailability was low after oral administration in rabbits\(^{6}\) and humans.\(^{6}\)

**Rectal Absorption of Morphine from Conventional Suppository** To evaluate the avoidance of first-pass metabolism from rectal administration, a conventional suppository containing 10 mg of morphine hydrochloride was administered into the rectum of rabbits. The mean plasma concentration–time curves of morphine and M-3-G are given in Figs. 2A and B, respectively. These pharmacokinetic parameters are summarized in Tables I and II.

The mean AUC_{0→6} of morphine after the administration of the conventional suppository was two times higher than that following oral administration. The relative bioavailability after rectal administration of the conventional suppository was significantly higher than that following oral administration. The mean AUC_{0→6} of M-3-G after rectal administration was 18 times larger than that of morphine. Data are not shown, but the plasma levels of M-6-G after rectal administration of a conventional suppository were lower than those of M-3-G. Our results in rabbits are in general agreement with results reported by Matsuoka et al.

| Table I. Pharmacokinetic Parameters of Morphine after Intravenous, Oral and Rectal Administrations of Morphine Hydrochloride to Rabbits |
|-------------|----------|--------|--------|--------|
| Route of administration | C_{max} (µg/ml) | t_{max} (min) | AUC_{0→6} (h·µg/ml) | F_{rect/oral} |
| Intravenous | 1.60 ± 0.38 |
| Oral | 0.10 ± 0.06 |
| Suppository | 0.29 ± 0.13 |
| Conventional | 0.37 ± 0.11 |
| Hollow-type | 0.48 ± 0.10 |
| Powder | 0.12 ± 0.07 |
| 0.26 ± 0.06 | 0.49 ± 0.07 |
| 0.31 ± 0.07 | 0.33 ± 0.03 |

a) F_{rect/oral} = \frac{(\text{AUC}_{\text{oral/rect}})}{(\text{AUC}_{\text{i.v.}})} \times \frac{(D_{\text{int}})}{D_{\text{oral/rect}}}, D is the dose of morphine hydrochloride; the subscripts rect and i.v. refer to rectal, oral and intravenous administration, respectively.

--- morphine; --- 3-M-G; --- 6-M-G; ▲ intravenous; ■ oral. Each value represents the mean ± S.E. of four rabbits.

**Fig. 1. Mean Plasma Concentration–Time Curves of Morphine (A) and Its Glucuronides (B) after Intravenous and Oral Administrations of Morphine Hydrochloride to Rabbits**

--- morphine; --- 3-M-G; --- 6-M-G; ▲ intravenous; ■ oral. Each value represents the mean ± S.E. of four rabbits.

**Fig. 2. Mean Plasma Concentration–Time Curves of Morphine (A) and M-3-G (B) after Administration of Three Types of Morphine Hydrochloride Suppositories to Rabbits**

--- morphine; --- 3-M-G; ● hollow-type suppository containing morphine powder; ○ hollow-type suppository containing morphine solution; ● conventional suppository. Each value represents the mean ± S.E. of four rabbits.
al.\textsuperscript{14} Because the plasma M-3-G level was significantly high compared to the morphine level, low relative bioavailability could account for most of the rectally administered morphine which underwent first-pass metabolism, rather than incomplete absorption in the rectum. When oleaginous bases containing drugs spread to the upper part of the rectum, these drugs are subject to hepatic first-pass metabolism after the rectal administration of a conventional suppository.\textsuperscript{1,15} From our results, similar phenomena would occur by the use of an oleaginous base such as H-15. Consequently, the low relative bioavailability (approximately 15\%) of morphine from a conventional suppository may be due to first-pass metabolism in the liver.

Effect of Added Form of Morphine on Rectal Absorption from Hollow-Type Suppository  Previously, we found that hollow-type suppositories offer improved bioavailability of drugs such as propranolol.\textsuperscript{10} We examined the effectiveness of hollow-type suppositories containing morphine in powdered form or solution, in rabbits, with the goal of finding a rectal dosage vehicle that could offer morphine bioavailability superior to that of conventional suppositories. The mean plasma concentrations of morphine and M-3-G obtained after rectal administration of hollow-type suppositories as described above are illustrated in Figs. 2A and B, respectively. These pharmacokinetic parameters are summarized in Tables I and II, respectively.

After rectal administration of a hollow-type suppository containing morphine solution, the mean plasma morphine concentration rapidly increased, and a higher concentration (0.36 ± 0.11 \(\mu\)g/ml) was obtained at 15 min compared with those obtained in the cases of the hollow-type suppository containing morphine powder and the conventional suppository. These results indicate that the solution was rapidly released to the rectal lumen after the melting of the body of the suppository constructed of H-15, and the morphine was immediately absorbed. We previously reported that a similar result was observed after rectal administration of the hollow-type suppository containing propranolol solution.\textsuperscript{10} The mean relative bioavailability value of the hollow-type suppository containing morphine powder was more than twice as high as that from a conventional suppository. These data suggest that the morphine powder in a hollow-type suppository was quickly dissolved into the rectal fluid after administration and the morphine was rapidly absorbed in the rectum. Furthermore, morphine partly bypasses the liver and is thus only partly subject to hepatic first-pass metabolism.

There are many reports concerning the determination of avoidance of first-pass metabolism.\textsuperscript{13,16,17} A bypass mechanism of first-pass metabolism may depend not only upon the concentration and volume of the drug but also the absorption surface area in the rectum. In the case of a hollow-type suppository containing morphine powder, the topical concentration of morphine in the rectum could be highly maintained and the amount of morphine spreading to the upper part of the rectum, which undergoes hepatic metabolism, would be smaller than that in the case of the conventional suppository. De Boer et al. reported\textsuperscript{13} that it is possible to predict the fraction (\(f_{sh}\)) of the rectal dose which has entered the systemic circulation via a nonhepatic route. This method assumes that the absorption of a drug via oral and rectal routes is complete and that the drug enters the systemic circulation unchanged by either route. The nonhepatic fractions (\(f_{sh}\)) calculated using Eq. 2, which is presented in the Pharmacokinetic Analysis section, are shown in Table III. Almost 30\% of the dose absorbed reaches the systemic circulation via a nonhepatic route on rectal administration of the hollow-type suppository containing morphine powder. Similar results were obtained using the same calculation method in studies on other animals: values of \(f_{sh}\) after rectal administration of a conventional morphine suppository were found to be 14.6\% in rats\textsuperscript{18} and 9.9\% in dogs.\textsuperscript{19} The value of \(f_{sh}\) after administration of the hollow-type suppository containing morphine powder was three times as high as that of the conventional suppository. Thus, a significant difference in rectal absorption of morphine between the conventional and the hollow-type suppository containing morphine powder in rabbits was recognized.

Rectal delivery of the conventional suppository and hollow-type suppositories containing morphine solution and powder resulted in mean M-6-G \(AUC_{0-\text{6}}\) values of 0.28 ± 0.11, 0.34 ± 0.14 and 0.53 ± 0.23 h·\(\mu\)g/ml, respectively. Similarly, Oguri et al.\textsuperscript{20} reported that the urinary excretion of M-3-G after 24 h in the urine was higher than that of M-6-G after subcutaneous administration in rabbits. The mean \(AUC_{0-\text{6}}\) ratios of M-3-G or M-6-G to morphine obtained in this study are summarized in Table IV. The
mean $AUC_{0-\infty}$ ratio of M-3-G to morphine after the administration of the conventional suppository was 23:1, which was three times larger than that of the hollow-type suppository containing morphine powder. Although the mean $AUC_{0-\infty}$ ratios of M-3-G to morphine by rectal administration varied among the three different added forms of morphine, the mean $AUC_{0-\infty}$ ratios of M-6-G to morphine were all approximately 1.0. It is conceivable that the hollow-type suppository containing morphine powder could avoid the first-pass metabolism of morphine in rabbits, unlike the conventional suppository. The difference in $AUC_{0-\infty}$ ratios between M-3-G and M-6-G to morphine may be due to the variation of absorption and metabolism rates of morphine caused by the different morphine forms added in the suppositories.

In this study, the effect of the form of morphine added to the suppository on rectal absorption was evaluated in rabbits. Morphine was more efficiently absorbed, and increased bioavailability was obtained with hollow-type suppositories. Our results suggest that hollow-type morphine suppositories, particularly those containing the powdered form, are superior to conventional suppositories.

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References and Notes


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