

## Bioavailability of Morphine in Rabbits after Rectal Administration of Suppository Containing Controlled Release Morphine Tablet

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Two kinds of sustained release morphine suppositories have been prepared; one is an oleaginous base suppository (MSC) containing a controlled release morphine tablet (MST: MS Contin), and the other is a hollow-type suppository (MSCH) containing MST and morphine powder packed in its hollow space. *In vitro* release tests and *in vivo* rectal absorption experiments in rabbits were performed. The profiles of morphine release from MST and MSC *in vitro* were similar, and revealed that suppository bases had no effect on the release profile of morphine from the preparation. Morphine release from MSCH was rapid in the early phase, and then enclosed morphine was slowly and continuously released from MST. Pharmacokinetics of morphine from the suppository were compared with the orally administered MST, and it was found that there was no difference in the maximum plasma concentration ( $C_{max}$ ) and the peak time ( $T_{max}$ ) between MSC and MST, but the mean residence time (MRT) of MSC was approximately three times longer than that of MST, and the extent of bioavailability (BA) of MSC was significantly larger than that of MST ( $71.6 \pm 14.2\%$  and  $11.9 \pm 4.0\%$ , respectively).  $C_{max}$  can be altered arbitrarily by changing the morphine content in the hollow space of MSCH. As in the case of MSC, the plasma concentration of morphine from MSCH was maintained.

It is concluded from the above results that MSC is a satisfactory sustained release morphine suppository for the treatment of cancer pain, administering it twice a day, and that MSCH is effective due to its fast analgesic effect and sustained release nature not only for cancer pain but also for surgical operations.

**Keywords** morphine; sustained release; suppository; bioavailability; rabbit; controlled release morphine tablet

It is claimed that the oral route of morphine administration is the most desirable for the treatment of cancer pain from the viewpoint of "quality of life" of the patients.<sup>1)</sup> However, when oral administration is not allowable due to cancerous conditions or side effects, the rectal route is very important for morphine administration to remove pain from the patients. By the rectal route, the first pass effect may be avoided, which can not be escaped from in the case of oral administration, so that the bioavailability (BA) by the rectal route is better as compared to the oral route.<sup>2)</sup> Matsumoto *et al.* reported that a comparable analgesic effect for cancer pain was obtained with a lesser dose of morphine by the hollow-type morphine suppository as by the oral preparation form.<sup>3)</sup> Kawashima *et al.* recently reported that the morphine suppository with an addition of arginic acid had high BA (above 50%) and prolonged rectal absorption in experiments with rabbits.<sup>4)</sup> However, clinically used morphine suppository preparations are not of the sustained release type,<sup>5)</sup> so that more than 3 doses are required per day. Such a dose program is not convenient for either patients or medical practitioners. Thus, a long-term acting morphine suppository is demanded for the sake of patients suffering from chronic pain. Under these circumstances a simple rectal MS Contin tablets (MST) has been used instead of a sustained release suppository, and it has been proved clinically useful.<sup>6)</sup> However, the equivalence of rectal MST and oral MST in the interest of bioavailability concerning plasma morphine levels has never been discussed, or examined.<sup>7)</sup> The authors prepared morphine suppositories (MSC) containing MST, and the preparation was administered to rabbits. It was found that the sustained release nature and BA of the preparation were better than those of the conventional one, and the results were reported previously.<sup>8)</sup> In the present study, hollow-type suppository<sup>9)</sup> (MSCH) containing MST and morphine powder packed

in its hollow space was developed. BA of morphine from MSC and MSCH by rectal administration was compared with that of MST after oral dosing in rabbits.

### Experimental

**Materials** Morphine hydrochloride (JP) was purchased from Takeda Pharmaceutical Ind., Ltd. Controlled release tablets of morphine sulphate (MST: MS Contin) were purchased from Shionogi Pharmaceutical Co., Ltd. Witepsol H-15, and E-75 were obtained from Maruishi Pharmaceutical Co., Ltd. Naloxone hydrochloride, used as the internal standard substance of the morphine assay, was obtained from Sigma Co., Inc. Other reagents were of commercial analytical grade and used without further purification.

**Preparation of Suppository** Sustained release MSC containing MST (10 mg of morphine sulphate) was prepared by the following procedures: an equal amount of Witepsol H-15 and E-75 was melted at 40–45°C, and 1.8 ml of the melt was poured into a 2.25 ml plastic mold and allowed to cool at room temperature for 10 min. Then, 0.3 ml of a suppository base of lower than 35°C was poured on the mold. One MST was placed in the melt, and the mixture was allowed to cool at room temperature for another 1 h to solidify the suppository. MSCH containing MST and morphine hydrochloride powder was prepared as follows: an equal amount of Witepsol H-15 and E-75 was melted at 40–45°C, and 1.7 ml of the melt was poured into a 2.25 ml plastic mold, and one MST was placed in the melt. The hollow-type suppository preparation plug of vinyl silicon<sup>10)</sup> was immediately equipped with the mold. After allowing it to cool for 1 h at room temperature, the plug was removed, and thus created a hollow space that was filled with 10 or 5 mg of powdered morphine hydrochloride. Then, a suppository base below 35°C was added up to 2.25 ml to the mold, and it was cooled for another 1 h after enclosing the tail of the suppository. MSCH containing 10 or 5 mg morphine hydrochloride in its hollow space is hereafter termed MSCH-10 or MSCH-5 (Fig. 1).

**Release Test *in Vitro*** The release test of morphine from the preparation was performed using a cell (PTSW type, Pharma Test, Germany) according to a rotating dialysis cell method.<sup>11)</sup> In the releasing phase, 1000 ml of 0.1 M phosphate buffer, pH 7.4, was placed, and 5 ml of phosphate buffer, pH 7.4, was placed in the release cell. The stirring speed of the releasing phase and rotation of the release cell was 25 rpm, and temperature of the releasing phase was maintained constant ( $37 \pm 0.1^\circ\text{C}$ ). Durapore HVLP, 0.45  $\mu\text{m}$ , (Japan Millipore Ltd.), was used for membrane.

Releasing phase, 1 ml, was collected periodically after placing the suppository or tablet in the device, and an equal volume of solution was supplemented to the phase immediately after sampling. The amount of morphine released was determined spectrophotometrically at 285 nm.

**Drug Administration** The experimental animal was male albino rabbit of 2.5–3.0 kg body weight. For dosing by the venous route, after fasting for 48 h, 1 ml of morphine hydrochloride, 10 mg/ml, was injected in the marginal ear vein. For dosing by the oral route, after fasting for 48 h with a neck fixer to prevent ingestion of feces, and after washing the stomach, one controlled release morphine tablet was administered by means of an oral catheter. For dosing by the rectal route, after fasting for 48 h with a neck fixer, one suppository was administered, and the anus was closed by a clip to prevent spilling of the suppository. In any case of the dosing route, 1 ml blood specimens were collected from the ear veins before and after administration at certain intervals. The specimens were centrifuged at 3000 rpm for 10 min at 4 °C to separate the plasma, which was then kept frozen at –40 °C until analysis.

**Measurement of Morphine in Plasma** Morphine in the plasma was assayed with 0.5 ml of the plasma specimen by high performance liquid chromatography (HPLC). Using naloxone hydrochloride as the internal standard substance, an electrochemical detector was used to detect the morphine peak. Procedure and conditions used for HPLC analysis were as reported previously.<sup>8)</sup>

**Pharmacokinetic Analyses** Morphine levels in plasma were analyzed by the Moment method<sup>12)</sup> for pharmacokinetic purposes using the following parameters: the maximum plasma concentration ( $C_{max}$ ), peak time ( $T_{max}$ ), mean residence time ( $MRT$ ), area under the curve of plasma concentration ( $AUC_{0-\infty}$ ) and extent of bioavailability ( $BA$ ).  $AUC_{0-\infty}$  was calculated from the plasma concentration data by means of the trapezoidal rule. Rate of absorption of morphine and cumulative absorption rate were calculated for oral and rectal groups by the deconvolution method.<sup>13)</sup>

**Statistical Analyses** Statistical comparison of the mean parameters was performed using the Student's *t*-test.

**Results**

**Release of Morphine from Suppositories and Tablets *in Vitro*** Time-course of *in vitro* morphine release from MST, MSC and MSCH are shown in Fig. 2. Morphine release from MSC and MST was almost constant up to 6 h of testing, and the morphine releasing profile from MSC and MST was similar. Rapid morphine release was

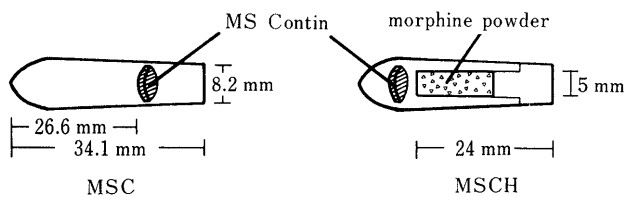


Fig. 1. Schematic Illustration of MSC and MSCH Suppositories

observed *in vitro* from MSCH-10 up to 1 h, and then a slow and constant releasing profile was observed.

**Comparison of Plasma Concentration–Time Profiles of Morphine after Rectal Administration of MSC and MSCH-10** Plasma concentration–time profiles of morphine after oral MST and rectal MSC and MSCH-10 are shown in Fig. 3. Pharmacokinetic parameters are shown in Table I. Plasma morphine levels after oral MST reached a maximum in about 2 h, and declined rapidly after 4 h. Plasma

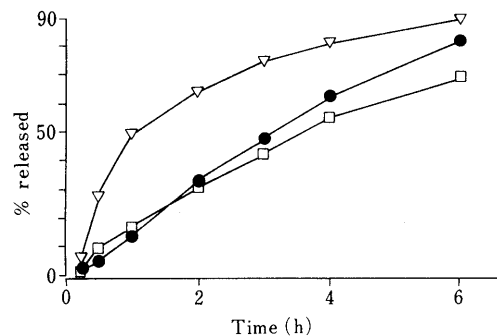


Fig. 2. *In Vitro* Release Profiles of Morphine from MST, MSCH-10 and MSC

▽, MSCH-10 (10 mg morphine HCl + 10 mg morphine sulphate); ●, MSC (10 mg morphine sulphate); □, MST (10 mg morphine sulphate). Each point represents the mean of three experiments.

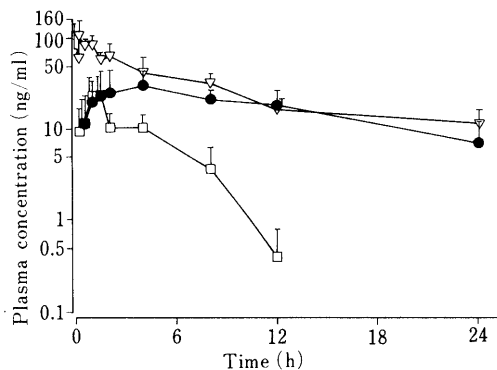


Fig. 3. Plasma Concentration–Time Profiles of Morphine after Oral Administration of MST and Rectal Administration of MSCH-10 and MSC

▽, MSCH-10 (10 mg morphine HCl + 10 mg morphine sulphate); ●, MSC (10 mg morphine sulphate); □, MST (10 mg morphine sulphate). Each point represents the mean ± S.E. of four rabbits.

TABLE I. Pharmacokinetic Parameters of Morphine after Oral and Rectal Administration in Rabbits

Parameters	Route of administration			
	Oral	Rectal		
		MSC	MSCH-10	MSCH-5
Dose (mg/rabbit)	10	10	20	15
$C_{max}$ (ng/ml)	30.9 ± 19.0	34.4 ± 18.7	142.8 ± 47.4	54.8 ± 18.9
$T_{max}$ (min)	127.5 ± 78.9 <sup>e)</sup>	172.5 ± 78.9 <sup>e,g)</sup>	25.0 ± 23.5	52.5 ± 28.7
$MRT$ (min)	218.1 ± 61.6 <sup>b,d,f)</sup>	650.3 ± 109.7	630.9 ± 133.5	556.5 ± 121.8
$AUC_{0-\infty}$ ( $\mu\text{g} \cdot \text{min}/\text{ml}$ )	5.5 ± 1.4 <sup>c)</sup>	27.2 ± 10.1	44.7 ± 12.4	26.7 ± 12.6
$AUC_{0-\infty}^{i.v.}$ ( $\mu\text{g} \cdot \text{min}/\text{ml}$ )	47.4 ± 6.4	38.3 ± 12.2	53.2 ± 2.6	43.3 ± 3.7
$BA^a$ (%)	11.9 ± 4.0 <sup>b,d,g)</sup>	71.6 ± 14.2 <sup>e,g)</sup>	42.0 ± 11.3	40.1 ± 15.3

Each value represents the mean ± S.D. ( $n=4$ ). a) Extent of bioavailability:  $BA = \{(AUC_{0-\infty}/\text{dose}) / (AUC_{0-\infty}^{i.v.}/\text{dose})\} \times 100$ . b) Significantly different from MSC ( $p < 0.01$ ). c) Significantly different from MSC ( $p < 0.05$ ). d) Significantly different from MSCH-10 ( $p < 0.01$ ). e) Significantly different from MSCH-10 ( $p < 0.05$ ). f) Significantly different from MSCH-5 ( $p < 0.01$ ). g) Significantly different from MSCH-5 ( $p < 0.05$ ).

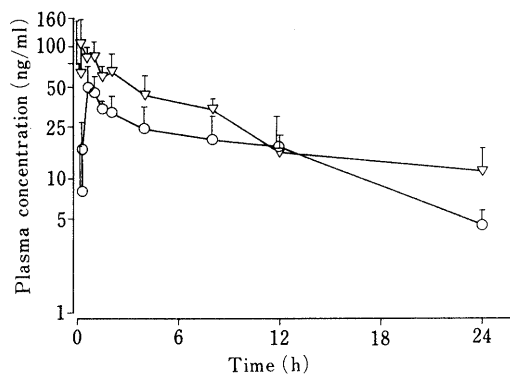


Fig. 4. Plasma Concentration-Time Profiles of Morphine after Rectal Administration of MSCH-10 and MSCH-5

▽, MSCH-10 (10 mg morphine HCl+10 mg morphine sulphate); ○, MSCH-5 (5 mg morphine HCl+10 mg morphine sulphate). Each point represents the mean  $\pm$  S.E. of four rabbits.

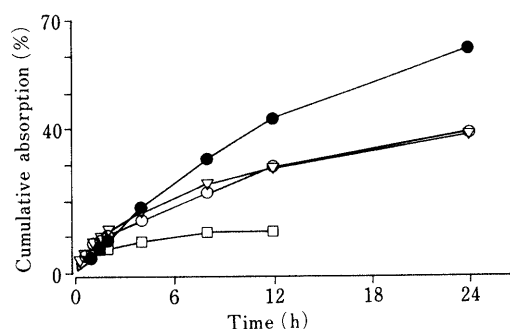


Fig. 5. Cumulative Absorption-Time Profiles of Morphine after Oral Administration of MST and Rectal Administration of MSC, MSCH-10 and MSCH-5

●, MSC (10 mg morphine sulphate); ▽, MSCH-10 (10 mg morphine HCl+10 mg morphine sulphate); ○, MSCH-5 (5 mg morphine HCl+10 mg morphine sulphate); □, MST (10 mg morphine sulphate). Each point represents the mean of four rabbits.

morphine levels after 12 h of administration were as low as 0.4 ng/ml in average.

After rectal MSC, plasma morphine levels reached a maximum in 2–4 h, and disappearance henceforth was slow. Plasma morphine levels after 12 h were  $18.7 \pm 7.7$  ng/ml, about a half of  $C_{max}$ . On the other hand, in the case of MSCH-10,  $T_{max}$  was significantly shorter, but the plasma concentration-time profile after 4 h was similar to that of MSC, and  $MRT$  was not significantly different from that in the case of MSC.  $BA$  was  $42.0 \pm 11.3\%$  for MSCH-10, and  $71.6 \pm 14.2\%$  for MSC, being significantly larger. Comparing the pharmacokinetic parameters, MSC and MSCH-10 showed obviously longer  $MRT$  and larger  $BA$  than oral MST.

**Change in Plasma Morphine Levels due to Difference in Morphine Amount in the Hollow Space of MSCH** Plasma morphine levels after rectal administration of MSCH-10 and MSCH-5 are shown in Fig. 4. Up to 4 h after rectal administration, plasma morphine levels were always lower in the case of MSCH-5 than in MSCH-10. However, after 4 h, the plasma concentration-time profile was similar in both cases, and  $BA$  was also comparable ( $42.0 \pm 11.3\%$  and  $40.1 \pm 15.3\%$ , respectively).

**Time-Course of Cumulative Absorption Rate** Cumulative absorption rates of morphine after oral MST and rectal MSC and MSCH are shown in Fig. 5. After oral

MST, the cumulative absorption rates in 4 and 12 h were 8.6% and 11.3%, respectively, and during 4–12 h after administration absorption was negligible. On the other hand, in the case of MSC, the cumulative absorption increased linearly up to 12 h. In the case of MSCH, the cumulative absorption was more rapid than that of MSC up to 2 h, and thereafter the rate of increase lowered up to 12 h, but a constant increase was observed. The cumulative absorption rate up to 24 h was obviously higher in MSC than in MSCH.

## Discussion

In the present study, influences of the suppository bases on the morphine release from the MSC containing MST, and  $BA$  of rectal MSC and oral MST were examined. In addition, the usefulness of MSCH with rapid onset of the effect and long-term maintenance of the effect were examined.

*In vitro* release experiments revealed that the release profile of MSC and MST was almost the same, and the effect of the suppository bases on the morphine release from MSC was negligible. By including MST in the oleaginous base suppository, convenience and effectiveness of the dosage form has been improved. From MSCH-10, containing morphine in the hollow space of the suppository, morphine was released rapidly, as in the case of Watanabe's report<sup>9)</sup> of releasing water-soluble drugs from hollow-type suppository, and thereafter slow and long-term release of morphine from MST followed. *In vitro* release experiments showed no difference in MSC and MST, but *in vivo* experiments showed an obvious difference of plasma morphine levels after oral MST and rectal MSC. MST is so constructed that long-term releasing is maintained, but after an oral dose, it rapidly loses the constant releasing ability. Hiraga *et al.* reported that oral administration of MST in man showed comparable elimination half life ( $t_{1/2}$ ) after 6 h of administration, which was almost the same in the case of the oral administration of morphine solution.<sup>14)</sup> Thus, it is hard to maintain controlled release after 6 h of oral MST. By oral route, MST loses its controlled release property because the controlled release matrix structure is broken within a short time in the digestive organ. Therefore, the rectal route of MST is more favorable than the oral route as far as the controlled release is concerned.  $BA$  of MSC was proved to be better than that of MST in the present experiment, contrary to the report in man by Kaiko *et al.*<sup>7)</sup> in which  $BA$  of oral MST and rectal MST were not different. The  $BA$  of morphine by rectal administration is influenced by various factors: the contents in the rectum,<sup>5b,15)</sup> the position in the rectum of the preparation,<sup>16)</sup> the hepatic and extrahepatic metabolism<sup>5c,17,18)</sup> and the release rate of morphine from the preparation.<sup>4)</sup> In this case, the discrepancy seems to be mainly due to the rectal stool amounts and the absorption part in the rectum, not due to animal strains. In our study, the first pass effect, which could not be neglected by the oral route, could be avoided by the rectal route. When MSC was rectally administered, melted base and tablet were separated, which was different from the conventional morphine suppository preparations, and the tablet, preserving controlled release matrix structure, stayed at the

lower rectum, not being dispersed upward with the suppository base.

As anticipated from the results of *in vitro* release experiments, the *in vivo* release of morphine from MSCH-10 was sharp, and after 4 h release became very slow, and after 12 h the plasma level was the same as in the case of MSC. As shown in Fig. 4, the amount of morphine of the hollow space in the suppository could control the  $C_{max}$ . It is particularly useful to use after surgical operation for the rapid onset of an analgesic effect. The  $C_{max}$  is controlled by altering the morphine amount in the hollow space, which may contribute to the avoidance of side effects due to a rapid increase in morphine concentration in the plasma. *BA* after MSCH-10 or MSCH-5 was significantly small as compared to that after MSC, and the reason may be that morphine packed into the hollow space of MSCH was released from the melted base rapidly, and as the base was dispersed upward of the rectum, a part of the morphine might have undergone the first pass effect. On the other hand, contained MST remained in the lower rectal part maintaining its matrix structure, and comparing it with *in vitro* releasing experiments, in which mechanical destruction accelerates releasing, longer and constant release might be accomplished.

In conclusion, a better analgesic effect can be expected by rectal MSC, compared to oral MST, and twice a day dosing is sufficient for the treatment of cancer pain. MSCH is also a useful morphine suppository for not only chronic anti-pain treatment, but also for the acute, and post-operation treatment of pain. The clinical application of MSC and MSCH should be repeated to evaluate its usefulness.

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