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Bioavailability of a morphine suppository is increased after intracolostomal administration in colostoma-constructed rabbits

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Abstract

This study was performed to assess the pharmacokinetics of morphine and its major metabolites after its rectal or colostomal administration in rectal-resected (ROP) or colostoma-constructed (SOP) rabbits, respectively. The pharmacokinetics of morphine, morphine-3-glucuronide (M3G), and M6G in normal rabbits appeared to be similar to those in human, judging from their plasma concentration–time profiles and the susceptibility of morphine to first-pass metabolism. In SOP, but not ROP, rabbits, the plasma concentrations of morphine, M3G and M6G were significantly increased compared with those in normal rabbits. The AUC of morphine and its metabolites, and the *F* value of the former in the SOP group were greater than those in the control group, while the elimination half-life ($t_{1/2}$) values were comparable in the two groups. In addition, the disposition of morphine and its metabolites after intravenous (i.v.) administration to SOP rabbits was almost the same as that in normal rabbits, suggesting that an increase in the rate of absorption of morphine in SOP rabbits was not due to inflammation at the absorption site caused by operation, but probably due to its increased solubility in loose stools. Therefore, great attention should be paid when morphine suppositories are intracolostomally administered to colostoma-constructed patients.

Keywords: Palliative care; Pharmacokinetics; Morphine suppository; Metabolism; Colostoma; Rabbit

1. Introduction

The standard therapy regimens for tumors, especially solid tumors including colorectal ones, consist mainly of surgical operation, chemotherapy and radiotherapy (Buyse et al., 1988; Scheithauer et al., 1993; Douilard et al., 2000). Although these therapies lead to superior outcomes, there are a number of patients with progressive tumors who suffer from pain due to infiltration and/or metastasis of the tumors. Therefore, together with such therapies or at the terminal stage, palliative care is important for the maintenance of a patient's QOL (World Health Organization, 1996).

Morphine is the most important, strong opioid analgesic presently available, and its use is increasing. The guidelines of WHO for pain management recommend its oral administration. However, when oral administration is difficult due to nausea, vomiting or ileus, morphine is administered intravenously, subcutaneously or intrarectally. The bioavailability of rectally administered morphine has been shown to

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be higher than that of orally administered morphine, which is thought to be due to the avoidance of hepatic first-pass elimination with this route (Glare and Walsh, 1991). Thus, considering a patient's QOL, the rectal route is one of the most useful ones.

On the other hand, rectal administration may be difficult or even impossible in patients in whom the rectum has been excised, or in whom it is diseased. When those patients complain of pain, the colostomally administered morphine suppositories has been suggested. However, to our knowledge, there has been only one case report on the bioavailability of morphine suppositories given colostomally, but consistent results were not obtained, that is, the bioavailability of morphine increased in some patients, but decreased in others, and the reason for this discrepancy was not fully clarified (Højsted et al., 1990). Thus, a systematic study on the bioavailability of colostomally administered morphine suppositories has not been performed yet.

Therefore, in this study, we examined the pharmacokinetics of morphine after administration of morphine suppositories intrarectally and intracolostomally to rectal-resected (ROP) and colostoma-constructed (SOP) rabbits, respectively, which have been demonstrated to be very useful model animals (Nagasawa et al., 2001, 2002). Furthermore, to evaluate the effect of difference of the administration routes on metabolism of morphine, we determined the disposition of the two major inactive and active metabolites of morphine, morphine-3-glucuronide (M3G) and M6G, respectively.

2. Experimental section

2.1. Materials

Pure morphine hydrochloride was obtained from Shionogi & Co., Ltd. (Osaka, Japan). M3G and M6G were kind gifts from Mr. Syu Yuasa (Department of Pharmacy, Nagoya Memorial Hospital, Nagoya, Japan). Nalbuphine powder (Internal standard for HPLC) and Witepsol H-15 were purchased from Sigma (St. Louis, MO, USA) and Maruishi Pharmaceutical Co., Ltd. (Osaka, Japan), respectively. All the other chemicals were commercial products of reagent grade.

2.2. Animals

Male Japanese white rabbits (Japan SLC Inc., Hamamatsu, Japan) were used. All experiments were approved by the Experimental Animal Research Committee of Kyoto Pharmaceutical University, and were performed according to the Guideline for Animal Experimentation of Kyoto Pharmaceutical University.

In the intravenous (i.v.), intrarectal (i.r.), and intracolostomal (i.s.) administration experiments, animals had free access to water and were fasted overnight (about 24 h) prior to the experiments.

In the oral (p.o.) administration experiments, rabbits were pretreated by the method described by Maeda et al. (1977). Briefly, rabbits were fed with a special diet, which was prepared by removing alfalfa from a commercial solid diet (RC4; Oriental Yeast Co., Ltd., Tokyo, Japan), for a week of conditioning before the p.o. study. After being fasted overnight with water ad libitum, a rubber stomach tube, 25 cm in length and 5 mm in external diameter with a large hole on the side of the tip, was inserted into the stomach, and then 50 ml of warmed saline (37 °C) was instilled. The fluid in the stomach was then withdrawn by suction with a syringe. This procedure was repeated until the fluid withdrawn contained hardly any solid material. After gastric lavage, the rabbits were allowed water ad libitum and muzzled to prevent coprophagy during the night.

2.3. Animal operation

In the experiments involving ROP or SOP rabbits, the rabbits were surgically operated on as reported previously (Nagasawa et al., 2001, 2002). Briefly, under pentobarbital anesthesia (50 mg/kg, i.v.), midline laparotomy was performed. The arteries and veins in the mesorectum governing the resected rectum portion (approximately 10 cm length from 10 cm from the anus) were ligated, and then the portion in which the governing vessels had been ligated was resected. In ROP rabbits, the upper (oral side) and lower (anal side) ends resulting from the resection were occluded by the Albert–Lembert method. On the other hand, in SOP rabbits, after resection of the rectal portion, the remaining lower end (anal side) was ligated, and a colostoma was constructed using the upper end (oral side) at the abdomen midline following the Hartmann

method. After the operation, the rabbits were allowed water ad libitum and fasted overnight, the experiments being performed on the next day. After the experiments, an autopsy was performed, the leakage of rectal contents, the blood circulation and the pathological condition of the operated portion being examined.

2.4. Animal experiments

An i.v. bolus of an aqueous morphine solution (20 mg/ml/kg) was injected via an ear vein (20 mg/kg). In the p.o. administration experiments, the same morphine solution as in the case of i.v. administration was administered orally via gastric intubation (40 mg/kg). A morphine suppository (40 mg/kg), which was prepared using Witepsol H-15 as a suppository base as for the clinical formulation, was inserted into the rectum (normal and ROP rabbits) or colostoma (SOP rabbits), and then the anus or colostoma was immediately closed with adhesive (Aron Alpha®) to prevent expulsion of the suppository. This procedure resulted in no detectable leakage of the rectal contents during the experimental period. In all cases, blood samples (approximately 1.0 ml) were collected directly from an ear vein in heparinized disposable plastic syringes at 0.083, 0.25, 0.5, 1, 2, 4 and 6 h after each dose. The samples were immediately centrifuged, and the plasma fractions obtained were stored at −20 °C until the assay.

2.5. Sample purification

The plasma samples obtained were purified by the method reported by Mason et al. (1991) with slight modifications. Sep-Pak® Plus C_{18} cartridges (Waters, Milford) were used to prepare samples for HPLC analysis. Briefly, prior to use, the cartridges were primed with 2 ml methanol followed by 2 ml water. To a 200 μl sample, 800 μl water, 250 μl aqueous nalbuphine solution (internal standard), 1 ml 0.2 M borate buffer (pH 9.0), and 200 μl 0.1 M pentane-1-sulphonic acid were added. The samples and standards were then passed through the cartridges and the eluate discarded. This was followed by washing through 5 ml water to remove molecules of greater polarity than morphine, M3G, M6G and nalbuphine. Finally, 1 ml methanol, which was used to extract the morphine, M3G, M6G and nalbuphine, was passed through the cartridge, the eluate being collected for analysis. The methanol was evaporated under a stream of nitrogen gas at 60 °C. The dried residue was then reconstituted in 100 μl of the mobile phase described below, and 20 μl of which was injected into the HPLC column. The extraction efficiencies for morphine, M3G and M6G were 90% or more (data not shown).

2.6. HPLC conditions

Morphine, M3G and M6G were assayed under the HPLC conditions described by Glare et al. (1991), and adapted to our laboratory. The HPLC system consisted of a Hitachi 655 pump equipped with a fluorescence spectrophotometer F-1150 (Hitachi, Tokyo, Japan). The analytical conditions were as follows: column, a STR-ODS-II one (5 μm, 250 mm × 4 mm i.d.; Shimadzu, Kyoto, Japan); mobile phase, acetonitrile–10 mM sodium dihydrogen phosphate and 1 mM sodium dodecyl sulfate (pH adjusted to 2.1 with phosphoric acid) (24:76, v/v); and flow rate, 1.0 ml/min. Fluorescence was measured at 210 nm (excitation) and 550 nm (emission). The analysis was carried out at 35 °C for good separation. The retention times under these conditions were 7.9, 10.7, 17.6 and 73.5 min for M3G, M6G, morphine and nalbuphine, respectively. No interference peaks due to endogenous substances were observed for any plasma samples. The ratios of the peak height of each substance to that of the internal standard were plotted against known concentrations of substance, and standard curves were generated by least-squares linear regression analysis. The standard curves obtained for morphine, M3G and M6G were linear over the concentration range of 0.1–20 μg/ml in plasma ($r^2 > 0.999$). The detection limit was generally 0.05 μg/ml and the coefficient of variation was less than 13%.

2.7. Pharmacokinetic analysis

The peak plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) for morphine, M3G and M6G were determined from the actual observed data. The area under the plasma concentration–time curves (AUC) from 0 to 6 h for them was calculated by means of the trapezoidal rule. The bioavailability (F) of morphine was estimated by a standard method based upon the dose and AUC values. The elimi-

nation half-life ($t_{1/2}$) was obtained by dividing ln 2 by the slope of the elimination phase in the plasma concentration–time curve.

2.8. Statistical analysis

Data are expressed as mean ± S.E. Comparisons between groups were made by means of one-way analysis of variance followed by Fisher's Protected LSD test. Differences were considered to be statistically significant when $P < 0.05$.

3. Results

3.1. i.v., p.o. and i.r. administration to normal rabbits

To confirm the validity of rabbits for investigation of the pharmacokinetics of morphine and its metabolites, a morphine solution or suppository was i.v., p.o. or i.r. administered to normal rabbits. As depicted in Fig. 1, the plasma concentrations of morphine after p.o. administration were apparently lower than those after i.v. administration, despite the fact that the i.v. dose was half the p.o. one. On the other hand, the morphine concentrations in the i.r. group were significantly higher than those in the p.o. group, and were almost equal to the concentrations in the i.v. group 2, 4 and 6 h after its administration. For M3G and M6G, contrary to morphine, there were no apparent differences in their concentrations among the administration routes. The F and C_{max} values of morphine after p.o. administration were 5.73% and 0.409 μg/ml, respectively, and those after i.r. administration were 21.6% and 2.37 μg/ml, respectively, being significantly greater than those in the p.o. group (Table 1). There were no differences in the AUC values for M3G and M6G between the i.v., p.o. and i.r. groups, and the ratio of AUC of M3G or M6G to that of morphine (AUC_{M3G}/AUC_M or AUC_{M6G}/AUC_M, respectively) after p.o. administration was significantly greater than that after i.v. administration. On the other hand, the AUC_{M3G}/AUC_M and AUC_{M6G}/AUC_M values in the i.r. group were much lower than those in the p.o. group, and the former value was not significantly different from that in the i.v. group.

3.2. i.r. and i.s. administration to ROP and SOP rabbits

Fig. 2 shows the plasma concentration–time profiles of morphine, M3G and M6G after i.r. or i.s. administration of a morphine suppository (40 mg/kg) in ROP or SOP rabbits, respectively. In the ROP group, the plasma concentrations of morphine and its metabolites were almost the same as those in the normal group. However, after i.s. administration of morphine suppositories to SOP rabbits, the morphine, M3G and M6G concentrations were significantly higher than those after i.r. administration to normal ones. There were no differences in any of the parameters between the normal and ROP groups (Table 2). On the other hand, the C_{max}, AUC and F of morphine, and the C_{max} and AUC of M3G and M6G, but not AUC_{M3G}/AUC_M or AUC_{M6G}/AUC_M, were significantly greater in the SOP group compared with those in the normal group

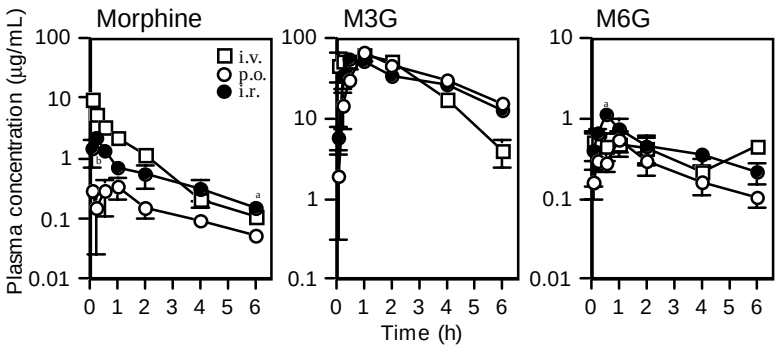

Fig. 1. The plasma concentration–time profiles of morphine, M3G and M6G after i.v. (20 mg/kg), p.o. or i.r. (40 mg/kg) administration of a morphine solution or suppository to normal rabbits. Each point represents the mean ± S.E. for three rabbits. [a] $P < 0.05$, [b] $P < 0.01$ (vs. p.o.).

Table 1
Pharmacokinetic parameters of morphine, M3G and M6G after i.v., p.o. and i.r. administration of a morphine solution or suppository in normal rabbits

	Parameter	i.v. (20 mg/kg)	p.o. (40 mg/kg)	i.r. (40 mg/kg)
Morphine	C_{max} (μg/ml)	–	0.409 ± 0.0994	2.37 ± 0.365[b]
	T_{max} (h)	–	0.278 ± 0.121	0.208 ± 0.0420
	AUC (μg h ml^{-1})	7.49 ± 1.38	0.859 ± 0.196	3.24 ± 0.739[a]
	F (%)	100 ± 18.4	5.73 ± 1.31	21.6 ± 4.93[a]
M3G	C_{max} (μg/ml)	–	71.8 ± 13.2	63.3 ± 7.42
	T_{max} (h)	–	1.33 ± 0.333	0.750 ± 0.144
	AUC (μg h ml^{-1})	194 ± 20.0	209 ± 18.8	183.9 ± 27.7
	AUC_{M3G}/AUC_M	29.3 ± 9.24	258 ± 33.1[†]	61.0 ± 8.80[c]
M6G	C_{max} (μg/ml)	–	0.561 ± 0.135	1.18 ± 0.160
	T_{max} (h)	–	1.33 ± 0.333	0.521 ± 0.188[a]
	AUC (μg h ml^{-1})	1.84 ± 0.845	1.42 ± 0.0731	2.71 ± 0.575
	AUC_{M6G}/AUC_M	0.256 ± 0.103	1.77 ± 0.263[†]	0.896 ± 0.180[*,b]

Each value represents the mean ± S.E. of three experiments. [*] $P < 0.05$, [†] $P < 0.001$ (vs. i.v.). [a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$ (vs. p.o.).

(Table 2). The $t_{1/2}$ values of morphine in the normal, ROP and SOP groups were 1.87 ± 0.15 h, 1.91 ± 0.18 h and 1.55 ± 0.12 h, those of M3G 2.43 ± 0.05 h, 1.76 ± 0.31 h and 2.21 ± 0.76 h, and those of M6G 2.66 ± 0.34 h, 1.86 ± 0.21 h and 1.25 ± 0.18 h, respectively, and there were no differences in these values among the three groups.

3.3. i.v. administration to normal and SOP rabbits

In order to determine whether or not the increases in the plasma concentrations of morphine and its metabolites after i.s. administration to SOP rabbits were due to physiological effects of the operation, a morphine solution was i.v. administered to normal and SOP rabbits. No apparent differences in the plasma concentrations of morphine, M3G and M6G were observed between the control and SOP groups (data not shown), and the pharmacokinetic parameters also showed no significant differences between both the groups (Table 3). Moreover, the $t_{1/2}$ values of morphine, M3G and M6G in the normal group were 0.982±0.033 h, 1.21±0.27 h and 3.94 ± 1.24 h, respectively, and those in the SOP group 1.02 ± 0.05 h, 1.88 ± 0.15 h and 1.21 ± 0.06 h, respectively, no significant difference in these values being observed between the normal and SOP groups.

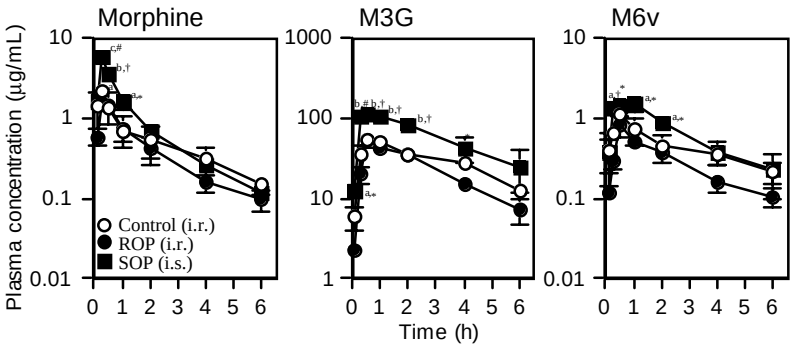

Fig. 2. The plasma concentration–time profiles of morphine, M3G and M6G after i.r. or i.s. administration of a morphine suppository (40 mg/kg) to normal, ROP or SOP rabbits. Each point represents the mean ± S.E. for three rabbits. The data for the normal group were cited from Fig. 1. [a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$ (vs. normal). [*] $P < 0.05$, [†] $P < 0.01$, [#] $P < 0.001$ (vs. ROP).

Table 2
Pharmacokinetic parameters of morphine, M3G and M6G after i.r. or i.s. administration of a morphine suppository (40 mg/kg) in normal, ROP or SOP rabbits

	Parameter	Normal (i.r.)[1]	ROP (i.r.)	SOP (i.s.)
Morphine	C_{max} (μg/ml)	2.37 ± 0.365	1.81 ± 0.480	5.84 ± 0.158$^{\#,c}$
	T_{max} (h)	0.208 ± 0.0420	0.313 ± 0.0630	0.25
	AUC (μg h ml^{-1})	3.24 ± 0.739	2.51 ± 0.836	5.81 ± 0.265^{*,b}
	F (%)	21.6 ± 4.93	16.7 ± 5.58	38.7 ± 1.77^{*,b}
M3G	C_{max} (μg/ml)	63.3 ± 7.42	58.6 ± 10.8	140 ± 7.60$^{\#,c}$
	T_{max} (h)	0.750 ± 0.144	0.625 ± 0.125	0.938 ± 0.387
	AUC (μg h ml^{-1})	184 ± 27.7	147 ± 13.6	382 ± 56.9^{†,c}
	AUC_{M3G}/AUC_M	61.0 ± 8.80	74.1 ± 17.4	66.3 ± 10.8
M6G	C_{max} (μg/ml)	1.18 ± 0.160	0.833 ± 0.224	1.72 ± 0.324^{a}
	T_{max} (h)	0.521 ± 0.188	0.625 ± 0.125	0.688 ± 0.188
	AUC (μg h ml^{-1})	2.71 ± 0.575	1.75 ± 0.302	4.40 ± 0.520^{*,b}
	AUC_{M6G}/AUC_M	0.896 ± 0.180	0.848 ± 0.228	0.759 ± 0.088

Each value represents the mean ± S.E. of three experiments. $^{*}P < 0.05$, $^{\dagger}P < 0.01$, $^{\#}P < 0.001$ (vs. i.v.). $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ (vs. p.o.).
[1] Data were cited from Table 1.

Table 3
Pharmacokinetic parameters of morphine, M3G and M6G after i.v. administration of a morphine solution to normal and SOP rabbits

	Parameter	Normal[1]	SOP
Morphine	AUC (μg h/ml)	7.49 ± 1.38	4.54 ± 1.08
M3G	C_{max} (μg/ml)	61.7 ± 9.55	65.0 ± 6.49
	AUC (μg h ml^{-1})	194 ± 20.0	165 ± 22.1
	AUC_{M3G}/AUC_M	29.3 ± 9.24	41.2 ± 10.0
M6G	C_{max} (μg/ml)	0.567 ± 0.159	0.966 ± 0.283
	AUC (μg h ml^{-1})	1.84 ± 0.845	1.42 ± 0.325
	AUC_{M6G}/AUC_M	0.256 ± 0.103	0.364 ± 0.112

Each value represents the mean ± S.E. of three experiments.
[1] Data were cited from Table 1.

4. Discussion

In human, because of great first-pass metabolism via mainly hepatic UDP-glucuronyl transferase, about 55% of the absorbed morphine is metabolized to M3G, about 10% to M6G and about 10% to other metabolites, and so the bioavailability of morphine has been reported to be 20–40% (Glare et al., 1991). It has been indicated that in the case of i.r. administration of a morphine suppository, its bioavailability is increased to about 53%, resulting from the partial avoiding of first-pass metabolism (Jonsson et al., 1988). In this study, when a solution of morphine at the dose of 40 mg/kg was orally administered to normal rabbits, the plasma concentrations were apparently lower than those after i.v. administration with the dose of 20 mg/kg, and the F value was estimated to be 5.7% (Fig. 1 and Table 1). On the other hand, the F value of morphine after i.r. administration of a suppository with the dose of 40 mg/kg was calculated to be 22%, which was significantly greater than that after p.o. administration (Table 1), being approximately equal to the value in rabbits reported previously (Matsumoto et al., 1993). In addition, the AUC_{M3G}/AUC_M or AUC_{M6G}/AUC_M value in the p.o. group was significantly greater than those in the i.v. and i.r. groups (Table 1), indicating that the first-pass metabolism after p.o. administration is avoided partially on i.r. administration. It has been reported that the metabolism of morphine to M3G is the main metabolic pathway in both human and rabbit, and this was found to be true in this study (Fig. 1 and Table 1).

On the other hand, although the C_{max} and AUC of M6G were lower than those of morphine with both administration routes, this agreed with the finding that the rate of metabolism of morphine to M6G in rabbit is lower than that in human (Mignat et al., 1995). Overall, it was confirmed that the pharmacokinetic characteristics of morphine including its metabolites in rabbits were almost the same with those in human, and that the use of rabbits was valid for the aim of this study.

When morphine suppositories were administered intrarectally to ROP rabbits, the plasma concentrations and pharmacokinetic parameters of morphine, M3G and M6G were almost the same as those in the control group (Fig. 2 and Table 2). On the contrary, these values in the i.s. group of SOP rabbits were significantly higher than those in the i.r. group of normal ones, while there were no differences in the AUC_{M3G}/AUC_Ms, AUC_{M6G}/AUC_Ms, and $t_{1/2}$ values of morphine, M3G and M6G among the three groups (Fig. 2 and Table 2). These results appeared to indicate that although the pharmacokinetics of morphine and its metabolites were not changed after i.r. administration of morphine suppositories to ROP rabbits compared with the case after i.r. administration to normal rabbits, the i.s. administration to SOP rabbits caused increases in the plasma concentrations of morphine, M3G and M6G due to an increase in the bioavailability of morphine.

Previously we reported that the bioavailability of diclofenac sodium and carbamazepine suppositories decreased in the order of control > ROP > SOP groups, and this is thought to be due to an increase in the extent of first-pass metabolism in the case of the former, and a decrease in the absorption in the upper rectum and colon in the latter (Nagasawa et al., 2001, 2002). Contrary to diclofenac and carbamazepine, morphine is a highly hydrophilic compound, of which the octanol/buffer (pH 7.4) partition coefficient is 1.2 (Interview form). Generally, the water content of feces in the colon is higher than that in the rectum. Furthermore, it has been reported that the absorption of hydrophilic compounds is increased but that of hydrophobic ones is decreased with inflammation at the absorption site (Nagasawa et al., 1994; Satoh et al., 1988, 1990). Taking all the above into consideration, the most plausible explanation for the increased bioavailability of morphine suppositories in SOP rabbits might be an increase in an absorbable form of morphine, which is released from the suppository base and dissolved in water highly present in feces in the colon, and of its membrane permeability. That is to say, the F value, which was expected to decrease due to increasing first-pass metabolism resulting from the absorption in the colon, might be increased in SOP rabbits.

In general, trauma induces a decrease in the serum albumin level and an increase in alfa-1 acid glycoprotein, and alteration of hepatic clearance of drugs (Boucher et al., 1991). In fact, Christe et al. indicated that acute trauma causes the same alterations of these proteins, to which morphine binds, and this results in an increase in morphine bioavailability due to a decrease in its clearance (Christe et al., 1995). However, in this study, we think there was no difference in the level of operative injury between ROP and SOP rabbits, and so the changes in serum proteins can not explain the difference between ROP and SOP rabbits. This was confirmed by the finding that there were no differences in the disposition of morphine and its metabolites between normal and SOP rabbits after i.v. administration of morphine (Table 3). Thus, in this study, trauma resulting from operative injury is not considered to alter the pharmacokinetics of morphine and its metabolites.

Morphine (and M6G) is one of the substrates for P-glycoprotein, which is expressed in the colon (Huwyler et al., 1996; Seelig, 1998; Chin et al., 1989). Piquette-Miller et al. demonstrated that in rat liver during acute inflammation the expression and activity of P-glycoprotein are decreased (Piquette-Miller et al., 1998). Although it is not clear whether or not a similar phenomenon occurs in the colon, which is the absorption site in SOP rabbits, it was speculated that operative inflammation resulted in a decrease in the barrier function handled, at least in part, by P-glycoprotein, and therefore, the bioavailability of morphine was increased. Furthermore, this decrease in P-glycoprotein expression in the colon might explain the results in ROP rabbits. That is to say, it is thought that in ROP rabbits, the increase in first-pass metabolism due to excision of the upper rectum might be offset by the decrease in P-glycoprotein expression in the colon, and thus the bioavailability of morphine does not change. However, a more detailed study is needed to clarify this.

In the report of Højsted et al., the comparative bioavailability of morphine suppositories in human ranged from 0.1 to 127% (mean 43%) comparing to the case of i.r. administration (Højsted et al., 1990). They explained this low bioavailability might be due to loose morphine into the outside of body and to adsorption to feces. In general, in well-controlled human colostoma, most of the patients have normal water content feces. On the other hand, all of the SOP rabbits used in this study had diarrhea-like loose stools. So, we thought that the difference in bioavailability of morphine between the patients and SOP rabbits was due, at least in part, to the different water content of feces. Therefore, it is noted that the condition of feces, water content, might be one of the important factors for determining the bioavailability of morphine suppositories.

The i.s. administration of morphine suppositories to SOP rabbits increased the plasma concentrations of morphine and its two metabolites in comparison with normal rabbits. This increase of morphine and M6G levels is expected to result in potentiation of analgesic effect and high expression rate of adverse effects, such as mental derangement and impediment of gastrointestinal tract, although we did not evaluate them in this study. Therefore, we considered that when a morphine suppository was intracolostomally administered to the colostoma-constructed patients, a careful monitoring for the efficacy and adverse effect of morphine should be paid.

On the basis of the results obtained here, it is suggested that because of the similarity of the pharmacokinetics in rabbit and human, when administering morphine suppositories intracolostomally to colostoma-constructed patients, but not intrarectally to rectal-resected ones, the dosage should be controlled, and careful therapeutic drug monitoring including observation of the feces status is needed to avoid adverse effects due to the unexpected elevation of the morphine and M6G concentrations.

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