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Enhanced bioavailability of morphine after rectal administration in rats

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Abstract—Plasma morphine levels and the area under the plasma concentration-time curve (AUC) after i.v. (10 mg kg^{-1}), p.o. (100 mg kg^{-1}) and rectal (unrestricted or restricted to 1·5 cm from the anus, 10 mg kg^{-1}) administration of morphine hydrochloride were determined in 10 or 11-week-old male Wistar rats to compare bioavailability of morphine after the rectal dosage with that after oral administration. The AUC value after oral administration (15 μg min mL^{-1}), which was normalized by the dose, was only one-tenth of that after i.v. dosing (151 μg min mL^{-1}). In contrast, the AUC after rectal administration (unrestricted, 133 μg min mL^{-1}; restricted, 142 μg min mL^{-1}) was almost comparable with that after i.v. administration. From the comparison of these AUC values, the extent of systemic availability of morphine after rectal (unrestricted or restricted) and p.o. administration was estimated to be approximately 90 and 10%, respectively.

The clinical efficacy of orally administered morphine to control chronic pain is affected by its extensive presystemic metabolism in the gut and the liver (Brunk & Delle 1974; Säwe et al 1981). Furthermore, patients with cancer of the digestive system and with intractable nausea or vomiting cannot easily receive oral medication.

Because at least the lower haemorrhoidal veins are connected directly to the inferior vena cava, the rectal route has been advocated as a means of avoiding liver metabolism of the drug. Rectal premedication with morphine in either solution or hydrogel to patients undergoing surgery has demonstrated a relatively large variability in systemic availability of the drug (Lindahl et al 1981; Westerling et al 1982; Westerling & Andersson 1984). Higher plasma levels for morphine were achieved with the rectal suppository than with the oral solution in patients with cancer pain (Ellison & Lewis 1984). However, as the kinetics and extent of systemic availability of morphine after oral and rectal admininstration have not been compared in man or animals, no definite evaluation has been made of the usefulness of rectal delivery with morphine.

In the present study, plasma levels and the area under the plasma concentration-time curve for morphine after intravenous (i.v., 10 mg kg^{-1}), oral (p.o., 100 mg kg^{-1}) and rectal (10 mg kg^{-1}) administration have been determined in male Wistar rats to compare pharmacokinetics and the extent of bioavailability of morphine after rectal administration with that after oral dosage.

Materials and methods

Materials. Morphine hydrochloride (JP X grade) purchased from Shionogi & Co., Ltd. (Osaka, Japan) was used after recrystallization from ethanol. Orcinol was purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). All other chemicals used were of analytical grade.

Animal experiments. Male Wistar rats (220–260 g, 10 to 11 weeks), were chronically cannulated into the right jugular vein as reported by Upton (1975), and fasted overnight (about 20 h) before the experiment.

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Morphine hydrochloride prepared in normal saline solution was given to the rat via the cannula (i.v.) at 10 mg kg^{-1}, by gastric intubation (p.o.) at 100 mg kg^{-1} or with a syringe through a septum plug (S-75, 7 mm diameter and 5 mm depth, Gaskuro Kogyo Inc., Tokyo, Japan) at the anus (rectal) at 10 mg kg^{-1}. For unrestricted dosing, a septum plug (S-75) was affixed to the anus with Aron Alpha glue (Toa-Gousei Co., Tokyo, Japan). For restricted rectal dosing, a device similar to that reported by Kamiya et al (1982) and Iwamoto & Watanabe (1985) was constructed to give a fixed distance of 1·5 cm available for intraluminal exposure to drug solution. The upper septum plug (S-75) was used to prevent upward spreading of drug solution, while the lower one (S-75) was glued to the anus. Insertion of a plug or the device with two plugs were carried out under slight ether anaesthesia, while the injection of drug solution (1 mL kg^{-1}) was done without anaesthesia. Blood samples (0·13 or 0·25 mL) were collected periodically from the jugular vein cannula. The plasma was obtained by centrifugation of the heparinized blood at 3000 rev min^{-1} for 10 min.

Analytical procedures. To a plasma sample (0·05 or 0·1 mL) was added methanol (0·25 or 0·5 mL) containing orcinol (30 or 300 ng mL^{-1}) as an internal standard. The mixture was vortexted and centrifuged at 15000 rev min^{-1} for 5 min to obtain the supernatant. An aliquot (10 μL) of the supernatant was then injected into a HPLC column to analyse unchanged morphine in plasma. The separation was achieved by using a 150 mm × 4·6 mm (i.d.) column packed with reverse-phase Nucleosil C_{18} (particle size 5 μm, Macherey-Nagel, West Germany) at 40°C. The mobile phase, 0·1 M KH_2PO_4-CH_3OH (93:7, pH 4·0), was degassed and its flow rate was set at 1·3 mL min^{-1}. The HPLC system was combined with an electrochemical detector (L-ECD-6A, Shimadzu Corporation, Kyoto, Japan), equipped with a glassy carbon electrode. The potential was set at +0·8V versus a reference electrode (Ag-AgCl). The detector was connected with CHROMATOPAC C-R2AX data module (Shimadzu Corporation). One assay for analysing intact morphine by this HPLC method was completed within 15 min. Linearity of calibration curves for morphine in plasma was obtained with concentrations up to 8·0 μg mL^{-1}. The quantitation was based on the peak area ratio of morphine to internal standard.

Calculation of pharmacokinetic parameters. Plasma concentration (C)-time data after the i.v. administration were analysed according to least-squares regression analysis program MULTI (Yamaoka et al 1981) for the bi-exponential decline ($C = Ae^{-\alpha t} + Be^{-\beta t}$), where A, B, α and β are hybrid parameters. The area under the plasma concentration-time curve (AUC) value after i.v. administration was calculated from computer-estimated parameters by the equation, $AUC = A/\alpha + B/\beta$. The AUC after p.o. and rectal administration was calculated by the trapezoidal rule for the observed value and then by extrapolation to time infinity. The AUC value after p.o. administration was corrected by the dose for the direct comparison of that with those estimated after other routes. The apparent extent of systemic availability after oral or rectal dosing was estimated by comparing each AUC with that obtained after an equivalent intravenous dosage. Significant differences were quantified by Student's *t*-test.

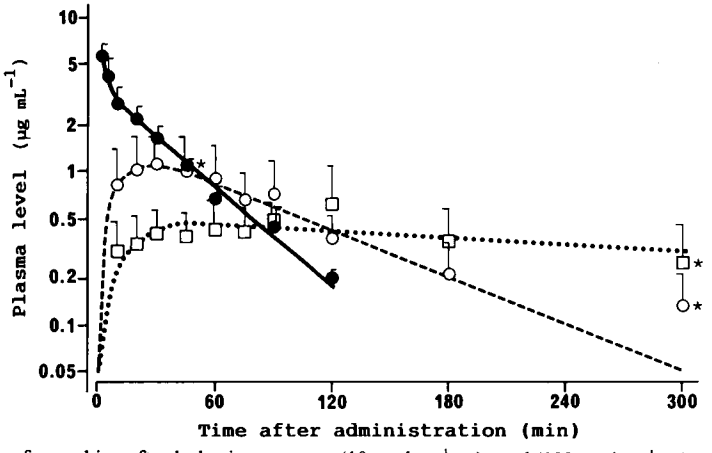

FIG. 1. Plasma levels of morphine after bolus intravenous (10 mg kg^{-1}, ●), oral (100 mg kg^{-1}, □) and restricted rectal (10 mg kg^{-1}, ○) administration of morphine hydrochloride in 10- to 11-week-old male Wistar rats. Each point and verticle bar indicate the mean and s.d. of eight (i.v. and rectal) or seven (oral) male Wistar rats (* for four rats). The solid line shows the computer-fitted bi-exponential curve for the mean i.v. data according to program MULTI [Weight(i) = 1/Ci, where C is the morphine level]. The dotted line shows the computer-fitted curve for the mean oral data by MULTI [Weight(i) = 1]. The broken line shows the computer-fitted curve for the mean data obtained after rectal administration restricted to 1·5 cm from the anus [Weight(i) = 1].

Results

Plasma levels of morphine after intravenous, oral and rectal administration. Plasma concentration-time curves for morphine after bolus i.v. (10 mg kg^{-1}), oral (100 mg kg^{-1}) and restricted rectal (10 mg kg^{-1}) administrations of morphine hydrochloride are shown in Fig. 1. Each line represents best computer-fitted curve for the mean data by weighting with the reciprocal of the concentration (i.v.) based on a two-compartment model or with unity (oral and rectal) based on a one-compartment model with first-order absorption (program MULTI). The plasma morphine concentration after i.v. administration was found to decline bi-exponentially with time, showing relatively rapid distribution into the peripheral compartment. Estimated pharmacokinetic parameters for morphine after the i.v. administration were as follows: $A = 6{\cdot}42 \pm 4{\cdot}23$ μg mL^{-1}; $B = 3{\cdot}09 \pm 0{\cdot}57$ μg mL^{-1}; $\alpha = 0{\cdot}385 \pm 0{\cdot}260$ min^{-1}; $\beta = 0{\cdot}0241 \pm 0{\cdot}0042$ min^{-1}; $t_{\frac{1}{2}\beta} = 29{\cdot}4 \pm 5{\cdot}9$ min.

In spite of the relativity high oral dose, the plasma level of morphine was so low that only about 0·5 μg mL^{-1} was found in the first 1 or 2 h. Plasma morphine concentration then declined slowly. After the restricted rectal administration of morphine hydrochloride, the plasma level rose to about 1·2 μg mL^{-1} at 20 min and then declined rapidly compared with that in the elimination phase after oral administration. After the unrestricted rectal administration at 10 μg mL^{-1}, the time course for the mean plasma level of morphine was almost comparable with that after the restricted rectal dosing, but it failed to be fitted by any least-squares regression analysis for a one-compartment model with first-order absorption because of the relatively large interindividual variation.

AUC and systemic availability of morphine after oral and rectal administration. The AUC value and extent of bioavailability of morphine after various routes of administration are summarized in Table 1. The values after i.v., oral restricted and unrestricted rectal administration were 151, 15, 142 and 133 μg mL^{-1}, respectively. The AUC value after p.o. administration was significantly less than those after other routes ($P < 0{\cdot}001$). The extent of oral bioavailability of morphine was calculated to be only 10% based on the comparison of AUC values after p.o. and i.v. dosing. In contrast, the extent of bioavailability after restricted and unrestricted rectal administration was 94 and 88%, respectively.

Table 1. AUC and apparent systemic availability of morphine following intravenous (10 mg kg^{-1}), oral (100 mg kg^{-1}) and rectal (10 mg kg^{-1}) administration to male Wistar rats.

Route of administration	n	AUC[a] (μg min mL^{-1})	Apparent systemic availability[b] (%)
Intravenous	8	150·5 ± 25·2	100
Oral	7	15·3 ± 8·8[c]	10·2
Rectal			
restricted	8	141·6 ± 58·4	94·1
unrestricted	7	132·5 ± 36·1	88·0

[a] Calculated by the trapezoidal rule and extrapolation to time infinity except for the intravenous data which were estimated by the equation, $AUC = A/\alpha + B/\beta$.
[b] Expressed as the percentage of the mean AUC value after i.v.dosing.
[c] Significantly different from all other AUC values ($P < 0{\cdot}001$).

Discussion

The markedly reduced analgesic effects of morphine caused by its lower plasma concentration when it is administered orally have been attributed to the first-pass metabolism by the gut and the liver (Brunk & Delle 1974; Iwamoto & Klaassen 1977; Dahlström & Paalzow 1978).

In the present study, plasma levels and the AUC values for morphine after i.v. (10 mg kg^{-1}), p.o. (100 mg kg^{-1}) and rectal (10 mg kg^{-1}) administration were determined in male Wistar rats to compare the extent of bioavailability of morphine after rectal administration with that after oral dosage. Plasma morphine concentration after i.v. administration was found to decline bi-exponentially with time, whereas those after p.o. and restricted rectal administration could be fitted for one-compartment model with first-order absorption followed by relatively slow elimination. These kinetic inconsistencies might be predominantly attributed to relatively prolonged or delayed absorption of the drug after rectal or p.o. administration. In addition, the slowest terminal phase of plasma morphine concentrations after p.o. dosing might be partially due to the contribution of the enterohepatic circulation of its major metabolite (Walsh & Levine 1975; Iwamoto & Klaassen 1977; Dahlström & Paalzow 1978). The unexpectedly low peak plasma concentration (i.e. only about 0·5 μg mL^{-1}) of morphine even

after the high oral dosage of 100 mg kg^{-1} might be largely the result of the extensive first-pass metabolism (conjugation) in the gut and liver, since saturation of the gastrointestinal absorption of the drug, if any, would produce rather higher plasma levels of morphine. In contrast, much higher peak plasma concentrations were achieved after the rectal administration (10 mg kg^{-1}) of morphine hydrochloride.

The extent of bioavailability of morphine after oral and rectal administration was estimated by comparing each AUC value with that obtained after i.v. administration based on an equivalent dose (Table 1). The oral bioavailability of morphine was only 10%, while systemic availability after the rectal dosage was about 90% irrespective of the length of the lumen exposed to drug solution. Although previous studies with nitroglycerin (Kamiya et al 1982) and propranolol (Iwamoto & Watanabe 1985) have shown that the apparent bioavailability of those drugs, when restricted to the lower region of the rectum as the absorption site, was greater than that when unrestricted, the present study with morphine showed almost the same extent of bioavailability after restricted and unrestricted rectal administration. The complete bioavailability of morphine after unrestricted rectal administration might be owing to the application of a relatively small volume (1 mL kg^{-1}) of drug solution, which may have been prevented from spreading over the upper region. Similar results have been obtained with other high-clearance drugs, e.g. propranolol (De Boer et al 1981) and lignocaine (De Boer et al 1980; De Leede et al 1983) in rats.

The present findings confirm that the systemic availability of morphine is almost complete after rectal dosage compared with poor oral bioavailability.

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