Enhancing Effect of Viscous Sodium Hyaluronate Solution on the Rectal Absorption of Morphine\(^1\)

Yoshiaki Matsumoto,* Ikuo Yamamoto, Yoshiteru Watanabe, and Mitsuo Matsumoto

Department of Pharmaceutics, Showa College of Pharmaceutical Sciences, 3156 Higashi-Tanagavagakuen 3-chome, Machida, Tokyo 194, Japan. Received April 18, 1995; accepted September 5, 1995

The effect of the viscosity of sodium hyaluronate solution on the rectal absorption of morphine was determined in rabbits. Hollow-type suppositories containing 10 mg morphine in viscous sodium hyaluronate solution of various mean molecular weights (MWs) were prepared. Rectal absorption of morphine in the sodium hyaluronate solution (MW \(2.1 \times 10^5\) daltons) was dependent on sodium hyaluronate concentrations in the range of 0.1 to 3% (w/v). Bioavailability after rectal administration of morphine in 0.1% sodium hyaluronate solution is consistent with that of morphine solution in the absence of sodium hyaluronate and the sustained-release plasma profile was observed for morphine in 3% sodium hyaluronate solution. Administration of hollow-type suppositories containing 10 mg morphine in 1% sodium hyaluronate solution resulted in the highest bioavailability of approximately 2-fold that after administration of morphine in physiological saline solution.

Five kinds of sodium hyaluronate solution with MWs of \(2.4 \times 10^5\), \(1.0 \times 10^6\), \(1.2 \times 10^6\), \(1.8 \times 10^6\) and \(2.1 \times 10^6\) daltons and respective viscosities of 70, 3.3 \(\times 10^3\), 3.2 \(\times 10^5\), 5.1 \(\times 10^5\) and 5.7 \(\times 10^5\) cp (20°C) were examined. Optimal viscosity of the sodium hyaluronate solution was found to enhance rectal morphine absorption. These results indicate that the selection of relevant viscosity of the sodium hyaluronate solution may contribute to the improvement of bioavailability of morphine on rectal administration.

Key words sodium hyaluronate; morphine; rectal absorption; viscosity; rabbit

A dosage form for sedatives which can be administered with ease to patients suffering from a terminal disease is highly desired. Morphine has been used for the treatment of severe chronic pain associated with malignant cancer.\(^2\) Oral morphine treatment frequently encounters the difficulty of continues administration with side effects such as vomiting, and continuous intramuscular injection is not desirable. The rectal administration of morphine is recognized to be an attractive alternative to these treatments. Rectal administration of aqueous morphine solution\(^3\) and morphine suppository\(^4,5\) was investigated. The factors influencing rectal absorption of a drug such as the absorption site\(^6\) where first-pass elimination occurs, formulation variability by viscosity\(^7\) and pH\(^8\) were reported. The hollow-type suppository is a useful vehicle\(^9,10\) because its cavity can be filled with a solution, a semisolid or a solid.

Various polymers for use as controlled-release drug delivery systems are currently being investigated. A natural polymer, hyaluronate, is a glycosaminoglycan with an unbranched chain of repeating disaccharide units of N-acetylgalactosamine and glucuronic acid.\(^11\) We previously reported that bioavailability of vancomycin in sodium hyaluronate solution was improved compared with that in the absence of sodium hyaluronate.\(^11\) Morimoto et al.\(^12\) found an enhancing effect of sodium hyaluronate on nasal absorption of vasopressin. Igaru et al.\(^13\) showed that sodium hyaluronate enabled sustained release of erythropoietin following subcutaneous administration. The objective of this study was to evaluate the enhancing effect of sodium hyaluronate solution in terms of the viscosity and the mean molecular weight (MW) using the hollow-type suppository on the rectal morphine absorption in rabbits.

\* To whom correspondence should be addressed.

MATERIALS AND METHODS

Materials Morphine hydrochloride was purchased from Takeda Chemical Industries Ltd. (Osaka, Japan). Sodium hyaluronates, HAHO, FCH, ASAHI, HAQ and L1530, were supplied by Hoya Corporation (Saitama, Japan), Kibun Food Chemifa Co., Ltd. (Tokyo, Japan), Asahi Chemical Industry Co., Ltd. (Aichi, Japan), and QP Corporation (Tokyo, Japan), respectively. Nalorphine hydrochloride was supplied by Dainippon Pharmaceutical Co., Ltd. (Osaka, Japan). Witepsol H-15 (H-15, Hüls AG, Germany) was used as the base. All other chemicals were of analytical grade.

Preparation of Suppositories The hollow-type suppository was chosen for use in terms of proper preparation for clinical dosage form and less interaction between a sodium hyaluronate solution and a suppository base. The hollow-type suppository was constructed by the fusion method\(^14\) using H-15. Morphine (10 mg) was dissolved in physiological saline solution (0.15 m NaCl, pH 4.7) to which sodium hyaluronate was added afterward. The solution of viscous sodium hyaluronate (pH 5.1—5.9) containing 10 mg morphine hydrochloride was placed in the cavity of the hollow-type suppository.

Release Test from Suppository Percentage release was measured using an instrument (model TMS-103, Toyama Sangyo Co., Ltd., Osaka, Japan) as previously reported.\(^15\) Isotonic phosphate buffer solution (500 ml) was used as the dissolution medium.

Determination of Viscosity There is a correlation between the intrinsic viscosity and MW.\(^16,17\) The intrinsic viscosity of various sodium hyaluronate solutions (0.02—0.05%) was measured using an Ubbelohde viscometer (JIS, 1A, according to JP XII). MW was calculated using the equation of Laurent et al.\(^18\) The viscosity of a gel that exhibits non-Newtonian flow is usually measured

© 1995 Pharmaceutical Society of Japan
using a cone-and-plate viscometer. Thus, we determined the apparent viscosity of sodium hyaluronate solution (0.1—8.5%) using a cone-and-plate viscometer (Visconic, Tokimec Co., Ltd., Tokyo, Japan). Based on the previous report that the viscosity of sodium hyaluronate solution depended on shear rates, and because of the wide viscosity range and instrument limitation, we used two instruments, RE-500 L: 7.7 and 9.7 mm radius cone plate (radian; 3°, shear rate; 101/s), 24 mm radius cone plate (radian; 1.34°, shear rate; 9.6 l/s), EMD: 7.7 mm radius cone plate (radian; 3°, shear rate; 10 and 11/s) for measurements conducted at 20±0.5°C.

**Animal Experiments** Male albino rabbits (2.8—3.3 kg) were subjected to an overnight fast prior to the experiment, but water was given freely. The hollow-type suppository was administered into the rectum and the anus was closed with a plastic clip to prevent leakage. Animals were secured in a crouching posture. In a comparative study, 10 mg morphine (dissolved in 1 ml physiological saline solution) was infused for 60 min into the rectum using a microinjection pump (CMA/100, CMA, Stockholm, Sweden) by inserting a 2.5 cm polyethylene tube (i.d. 0.58 mm) into the anus. In a previous study, we measured the position of a hollow-type suppository after rectal administration, and found that the middle of the suppository was located 2.5 cm from the anus. After drug 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.

**Analytical Method** Plasma morphine concentration was determined by the method of Svensson with a slight modification. Plasma (0.5 ml) was added to a test tube containing 50 µl of nalorphine hydrochloride solution (50 µg/ml) as internal standard. The mixture was passed through a solid-phase (Sep-Pak® tC18, Waters, Massachusetts, U.S.A.) and washed with 2 ml of distilled water, followed by 3 ml of 5% acetone. Morphine was eluted with 4 ml of 70% methanol. The eluate was evaporated to dryness at 60°C under a stream of nitrogen gas. Then, the residue was dissolved with 200 µl of the mobile phase, and 50 µl of the solution was injected into the HPLC system. HPLC was performed using the following set up: LC-6A constant-flow pump (Shimadzu, Kyoto, Japan), SIL-9A sample injector (Shimadzu, Kyoto), TSK-gel ODS-120T column (15 cm x 4.6 mm i.d.; Tosoh, Tokyo, Japan), and L-ECD-6A electrochemical detector (0.8 V; Shimadzu, Kyoto). The mobile phase was 10 mM sodium dihydrogen phosphate buffer at pH 2.1 (pH was adjusted with phosphoric acid) containing 1 mM sodium dodecyl sulfate—acetonitrile (75:25). The flow rate was 1 ml/min. Even with the use of 1.0 ml plasma, this method can detect morphine concentrations as low as 0.5 ng/ml.

**Pharmacokinetic Analysis** The peak plasma concentration (Cmax), the peak plasma concentration time (tmax), and the area under the plasma concentration—time curve (AUC) were obtained from each plasma concentration—time data. AUC0−∞ was calculated using the trapezoidal rule, while the extrapolation to infinity was carried out by dividing the last measured plasma concentration value by the value of the slope. The mean residence time (MRT) of the drug was calculated according to the method of Yamaoka et al. To investigate the release rate of morphine as a function of dose administered with time, this equation was used with a slight modification:

\[
\frac{M}{M_w} = k(t-t')^n
\]  

(1)

Phenomenologically, it is possible to express the fraction released, \(\frac{M}{M_w}\), as a power function of time, \(t, t'\) is lag time, \(k\) is a constant of the system and \(n\) is an exponent characteristic of the mode of transport. To estimate the pharmacokinetic parameters of morphine after rectal administration, 1 ml of morphine (10 mg) in physiological saline solution was administered by constant rate infusion with the rate of 10 mg/h for 1 h. This infusion time was determined based on a finding that almost all morphine in 1% HAHO solution was released within 1 h. The plasma morphine concentration—time data were simulated according to a three-compartment model with first-order absorption by use of the ADAPT II program as follows:

\[
\begin{align*}
\frac{dx_1}{dt} &= -k_1x_1 \\
\frac{dx_2}{dt} &= k_1x_1 - (k_{21} + k_{23} + k_{32})x_2 + k_{33}x_3 + k_{42}x_4 \\
\frac{dx_3}{dt} &= k_{23}x_2 - k_{33}x_3 \\
\frac{dx_4}{dt} &= k_{24}x_2 - k_{42}x_4 \\
C &= x_3/V_d
\end{align*}
\]

where \(x_1\) is the amount at absorption site, \(x_2\) is amount at central compartment, \(x_3\) and \(x_4\) are peripheral compartments, and \(k_i\) is absorption rate constant. The rate constant \(k_{20}\) is associated with the loss of drug from the central compartment. The rate constants \(k_{23}, k_{32}, k_{34}\) and \(k_{42}\) are characterized by the transfer rate constants. \(C\) is the drug concentration and \(V_d\) is the apparent volume distribution in the serum compartment. Using the function of dose administered with time calculated by fitting equation (1) and these pharmacokinetic parameters, the plasma profile after administration of the hollow-type suppository containing morphine in 1% HAHO solution was evaluated.

Statistical analysis was performed using the one-way ANOVA and Dunnett’s tests, and the differences were considered to be significant when \(p<0.05\).

**RESULTS AND DISCUSSION**

**MW and Viscosity of Sodium Hyaluronate Solution** The release of the drug depends on the MW of the viscous polymer. The MW is determined by the calculation of intrinsic viscosity using Laurent’s equation. The calculated results of the intrinsic viscosity and MW of various sodium hyaluronates are shown in Table 1. The rheological characteristics of sodium hyaluronate solutions were measured by a cone-and-plate viscometer. The viscometer is often used in these solutions that are
Table 1. Viscosity and Mean Molecular Weight (MW) of Sodium Hyaluronic Acid Solution

<table>
<thead>
<tr>
<th>Hyaluronate</th>
<th>Intrinsic viscosity (dL/g)</th>
<th>MW ($\times 10^6$)</th>
<th>Concentration (% w/v)</th>
<th>Viscosity (cP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAHO</td>
<td>30.8</td>
<td>2.1</td>
<td>0.1</td>
<td>140$^{a}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
<td>1600$^{a}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>5700$^{a}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>4500000$^{a}$</td>
</tr>
<tr>
<td>FCH</td>
<td>26.8</td>
<td>1.8</td>
<td>1</td>
<td>5100$^{a}$</td>
</tr>
<tr>
<td>ASAHI</td>
<td>19.6</td>
<td>1.2</td>
<td>1</td>
<td>3200$^{a}$</td>
</tr>
<tr>
<td>HAQ</td>
<td>17.4</td>
<td>1.0</td>
<td>1</td>
<td>3300$^{a}$</td>
</tr>
<tr>
<td>L1530</td>
<td>5.8</td>
<td>0.24</td>
<td>1</td>
<td>70$^{o}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8.5</td>
<td>40000$^{o}$</td>
</tr>
</tbody>
</table>

$^{a}$ RE-500-L; 24 mm cone plate (1.34°), shear rate, 9.6 s$^{-1}$.  
$^{b}$ RE-500-L; 9.7 mm cone plate (3°), shear rate, 10 s$^{-1}$.  
$^{c}$ RE-500-L; 7.7 mm cone plate (3°), shear rate, 10 s$^{-1}$.  
$^{d}$ EMD; 7.7 mm cone plate (3°), shear rate, 1 s$^{-1}$.  
$^{e}$ EMD; 7.7 mm cone plate (3°), shear rate, 10 s$^{-1}$.  
Each value represents mean of three experiments.

![Graph](image)

**Fig. 1.** Release Behavior of Morphine from Suppositories Containing Morphine in HAHO Solution

- 0% HAHO, ▲ 0.5% HAHO, ● 1% HAHO, ○ 3% HAHO. Each point represents the mean ± S.E. of three experiments.

classified as non-Newtonian liquids. A substantial increase in viscosity of 1% sodium hyaluronic acid solutions was observed with increasing MW (Table 1).

**Release of Morphine in HAHO Solution from Hollow-Type Suppository**  
The influence of the concentration of HAHO solution (0, 0.5, 1 and 3% w/v) on the release of morphine was determined and results are shown in Fig. 1. The release profiles of morphine in the absence of HAHO and in 0.1% HAHO solution (data not shown) were identical. Morphine in 0.5% HAHO solution was almost completely released from the hollow-type suppository within 45 min. In 3% HAHO solution, a slow release profile indicating the zero-order release of morphine was obtained. The viscosity of the polymer is reported to be related to release of the drug. [2,2] Our data suggest that the release of morphine can be controlled by adjusting the viscosity of the HAHO solution.

**Difference in Morphine Absorption Following Rectal Administration of Suppositories Containing Different HAHO Concentrations**  
The effect of HAHO concentration on the rectal absorption of morphine in rabbits was determined. Figure 2 presents the mean morphine plasma levels after administration of a suppository containing morphine in 0, 0.1, 0.5, 1 or 3% (w/v) HAHO solution. The corresponding pharmacokinetic parameters are summarized in Table 2.

![Graph](image)

**Fig. 2.** Mean Plasma Concentration–Time Curves of Morphine Following Rectal Administration of Suppositories Containing Morphine Hydrochloride in HAHO Solution to Rabbits

- 0% HAHO, ▲ 0.1% HAHO, ● 0.5% HAHO, ○ 1% HAHO, ○ 3% HAHO. Each point represents the mean ± S.E. of four rabbits.

<table>
<thead>
<tr>
<th>Hyaluronate concn. (% w/v)</th>
<th>C$_{\text{max}}$ (ng/ml)</th>
<th>t$_{\text{max}}$ (min)</th>
<th>AUC$_{0-\infty}$ (h ng/ml)</th>
<th>MRT (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>369 ± 106</td>
<td>19 ± 4</td>
<td>321 ± 71</td>
<td>1.23 ± 0.20</td>
</tr>
<tr>
<td>0.1</td>
<td>465 ± 103$^{a}$</td>
<td>19 ± 4</td>
<td>365 ± 82</td>
<td>1.64 ± 0.44</td>
</tr>
<tr>
<td>0.5</td>
<td>471 ± 80$^{a}$</td>
<td>23 ± 4</td>
<td>486 ± 148</td>
<td>1.78 ± 0.86</td>
</tr>
<tr>
<td>1</td>
<td>411 ± 47$^{a}$</td>
<td>49 ± 17</td>
<td>684 ± 68$^{a}$</td>
<td>2.05 ± 0.57</td>
</tr>
<tr>
<td>3</td>
<td>104 ± 29</td>
<td>56 ± 22</td>
<td>312 ± 47</td>
<td>2.91 ± 0.61</td>
</tr>
</tbody>
</table>

$^{a}$ Statistically significant difference, p < 0.05 in 0.1, 0.5 and 1% vs. 3%.

After rectal administration of the hollow-type suppository containing morphine in 0.1% HAHO solution, the plasma morphine concentration was rapidly increased, and the $C_{\text{max}}$ (465 ± 103 ng/ml) was obtained at 19 ± 4 min. This profile was identical to a previously reported profile obtained after rectal administration of the hollow-type suppository containing morphine in physiological saline solution. [3] These results indicate that morphine in 0.1% HAHO solution was rapidly released into the rectal lumen after melting of the suppository made of H-15, and then immediately absorbed. The bioavailability of morphine in 1% HAHO solution was increased more than two times compared with that of morphine solution in the absence of HAHO. [4] Bioavailability of morphine in HAHO solution up to 1% concentration was increased in proportion to the viscosity. However, when 3% HAHO solution was used, $C_{\text{max}}$ was lower and t$_{\text{max}}$ and MRT were longer than when 0.1, 0.5 and 1% HAHO solutions were used. The bioavailability after administration of morphine in 3% HAHO solution was one-half that of 1% HAHO solution. These results suggest that the absorbed morphine using 3% HAHO solution would be eliminated by the hepatic metabolism of the systemic circulation, because morphine
is a high clearance drug and was released slowly due to the high viscosity of 3% HAHO solution.

**Plasma Concentration of Morphine Following Administration of Suppositories Containing Morphine in Various Sodium Hyaluronate Solutions** One percent sodium hyaluronate has also found clinical use. The bioavailability of morphine in various 1% (w/v) sodium hyaluronate solutions was determined. In Fig. 3 are shown the plasma morphine concentration levels after administration of a suppository containing morphine in various 1% sodium hyaluronate solutions. The pharmacokinetic parameters are listed in Table 3.

The bioavailability of morphine after administration of suppository containing morphine in 1% L1530 solution was significantly lower than that after administration of a suppository containing morphine in 1% HAHO solution. It can be assumed that part of the morphine solution with 1% L1530, which viscosity is low compared with 1% HAHO solution, spread to the upper part of the rectum that undergoes first pass elimination. Yanaki and Yamaguchi reported that the molecular mechanism of flow of 1% sodium hyaluronate solutions was classified with respect to molecular weight. The sodium hyaluronate (MW < 3.5 x 10^6) is dispersed molecularly in solution and this is applicable to 1% L1530 solution. The network of sodium hyaluronate (MW < 160 x 10^6) is saturated dynamically and 1% HAHO solution is thought to show this network. The network formation of sodium hyaluronate solution may be attributed to the release of drug and the viscosity. Bioavailabilities are listed in order of MW (daltons): 2.1 x 10^6 > 1.8 x 10^6 > 1.0 x 10^6 > 1.2 x 10^6 > 2.4 x 10^5 daltons. The rank order of the viscosity may be consistent with the rank order of the bioavailability. We found that $AUC_{0-\infty}$ of morphine in various 1% (w/v) sodium hyaluronate solutions showed a viscosity-dependent increase. A good correlation (correlation coefficient $r = 0.88$) was obtained between the viscosity of 1% hyaluronate solution and the $AUC_{0-\infty}$ of morphine (Fig. 4). The enhancing effects of sodium hyaluronate solution on the rectal absorption of morphine might be dependent on its concentration and the viscosity that relates to mucoadhesive properties. Morimoto et al. reported that the mucoadhesive strength of 1.5% sodium hyaluronate solution was 1.5-fold larger than that of 0.5% solution. Therefore, viscosity of sodium hyaluronate solution, which is thought to be strongly related to mucoadhesive strength, is a very important factor contributing to a successful formulation.

The rectal absorption of morphine is thought to be affected by the pH of morphine solution and the pH has been reported to be an absorption-enhancing mechanism. In this regard, morphine absorption is believed to be independent of pH based on the results of this study, because the pH of the various sodium hyaluronate

---

**Fig. 4. Relationship between AUC Following Rectal Administration of Suppositories Containing Morphine Hydrochloride in Various Kinds of Sodium Hyaluronate Solutions to Rabbits and Viscosity of Sodium Hyaluronate Solutions**

Each point represents the mean of at least three experiments.

**Table 3. Pharmacokinetic Parameters of Morphine after Rectal Administration of Suppositories Containing Morphine Hydrochloride in Various Kinds of Sodium Hyaluronate Solution to Rabbits**

<table>
<thead>
<tr>
<th>Hyaluronate</th>
<th>Conc. (%)</th>
<th>$C_{max}$ (ng/ml)</th>
<th>$t_{max}$ (min)</th>
<th>$AUC_{0-\infty}$ (h·ng/ml)</th>
<th>MRT (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAHO</td>
<td>1</td>
<td>411 ± 47</td>
<td>49 ± 17</td>
<td>684 ± 684</td>
<td>2.05 ± 0.57</td>
</tr>
<tr>
<td>FCH</td>
<td>1</td>
<td>495 ± 121</td>
<td>23 ± 4</td>
<td>542 ± 59</td>
<td>1.72 ± 0.54</td>
</tr>
<tr>
<td>ASAHI</td>
<td>1</td>
<td>303 ± 59</td>
<td>19 ± 4</td>
<td>415 ± 67</td>
<td>1.71 ± 0.51</td>
</tr>
<tr>
<td>HAQ</td>
<td>1</td>
<td>348 ± 63</td>
<td>30 ± 6</td>
<td>529 ± 60</td>
<td>1.75 ± 0.18</td>
</tr>
<tr>
<td>L1530</td>
<td>1</td>
<td>439 ± 75</td>
<td>19 ± 4</td>
<td>375 ± 46</td>
<td>1.31 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>8.5</td>
<td>387 ± 30</td>
<td>30 ± 11</td>
<td>683 ± 69</td>
<td>2.15 ± 0.03</td>
</tr>
</tbody>
</table>

a) Statistically significant difference, $p<0.05$ in 1% HAHO and 8.5% L1530 vs. 1% L1530. Each value represents the mean ± S.E. of four rabbits.
solutions is approximately 5.

Evaluation of Increased Absorption  The rate of morphine release from suppository and absorption rate of morphine are important factors contributing to its high clearance. To evaluate a plasma morphine concentration after administration of suppository containing morphine in 1% HAHO solution, first, the percentage release profile was simulated as a function of dose administered with time (Fig. 5). The percentage release profile could be fitted by equation (1) \( n=0.34, k=89, t'=6 \text{ min}, \text{ correlation coefficient } r=0.98 \). Using this fitting equation, the dose of morphine administered after rectal administration and which altered with time was calculated. Second, to obtain the pharmacokinetic parameters of morphine after rectal administration, 10 mg morphine in 1 ml physiological saline solution was infused for 60 min because the release of morphine in a 1% HAHO suppository was thought to be complete after 1 h (Fig. 1).

The plasma morphine concentration and the simulation profile after rectal administration of 10 mg morphine in 1 ml physiological saline solution by infusion for 60 min is shown in Fig. 6. The mean pharmacokinetic parameters were calculated using a three-compartment model with first-order absorption. These parameters are as follows: \( k_2 = 0.85 \text{ h}^{-1}, k_20 = 1.92 \text{ h}^{-1}, k_{23} = 47.9 \text{ h}^{-1}, k_{23} = 0.018 \text{ h}^{-1}, k_{24} = 2.72 \text{ h}^{-1}, k_{42} = 0.070 \text{ h}^{-1}, V_d = 0.584 \text{ l} \). Finally, the simulation profile of morphine after administration of suppository containing morphine in the absence of HAHO solution is given in Fig. 7 (solid line) using these pharmacokinetic parameters and the dose administered with time that was calculated by the in vitro release simulation profile described in Fig. 5. This simulation profile was obviously lower than the plasma morphine concentration (Fig. 7, solid circles) after experimental rectal administration of hollow-type suppository containing 10 mg morphine in 1% HAHO solution to rabbits. The bioavailability after administration of hollow-type suppositories containing morphine in 1% HAHO was approximately 1.5-fold higher than that after 60-min rectal infusion of 10 mg morphine in physiological saline solution. These data indicate that 1% HAHO solution enhances the rectal absorption of morphine.

A markedly low bioavailability after morphine administration in 1% L1530 solution was obtained (Table 3). Therefore, the suppository containing 10 mg morphine in 8.5% L1530 (viscosity, 40000 cP) solution was administered to rabbits. The plasma morphine concentration after administration of the suppository is given in Fig. 3, and the bioavailability parameters are shown in Table 3. The bioavailability of morphine in 8.5% L1530 solution was two times larger than that of morphine in 1% L1530 solution. After performing experiments using sodium hyaluronate solutions of various concentrations and MWs, it is clear that an optimal viscosity might be necessary to improve morphine bioavailability in rectum.

The mechanisms of absorption-enhancing effect of a high-molecular-weight adjuvant for improved bioavailability of drugs were reported. A water-soluble high-molecular weight adjuvant such as polyacrylic acid is thought to decrease surface tension of the mucosal surface and to increase the area of contact. Since the
amount of morphine reaching the systemic circulation after oral administration is decreased due to first-pass elimination via the gut wall and liver,\(^2\) the mucoadhesive properties of these hyaluronate solutions might restrict the spread of morphine to the upper part of the rectum where first-pass elimination occurs. Thus, morphine administered rectally could partly bypass the liver and would be subject in part to hepatic first-pass metabolism when a sodium hyaluronate solution of an appropriate viscosity is incorporated in the formulation. Further studies are necessary to determine the optimal concentration of sodium hyaluronate solutions that leads to the highest morphine bioavailability.

In conclusion, viscous hyaluronate solutions show a moderate enhancing effect on rectal absorption of morphine, and the hollow-type suppository containing morphine in this solution is useful as a vehicle for rectal delivery of the drug. Viscosity of the hyaluronate solution is thought to provide information on the improvement of morphine bioavailability.

Acknowledgment The authors are grateful to Dr. William F. Ebling, State University of New York at Buffalo, for the advice on simulation, and to Tokimec Co., Ltd. for viscosity measurements. They also thank Dai nippon Pharmaceutical Co., Ltd. (Osaka, Japan) and Mitsuba Trading Co., Ltd. (Tokyo, Japan), Hoya Corporation (Saitama, Japan), Kibun Food Chemifa Co., Ltd. (Tokyo, Japan), Asahi Chemical Industry Co., Ltd. (Aichi, Japan), and QP Corporation (Tokyo, Japan) for generously supplying nalorephine hydrochloride, Wit epsol H-15 and sodium hyaluronate, respectively.

REFERENCES


