PHARMACEUTICAL EVALUATION OF HOLLOW TYPE SUPPOSITORIES. IV. 1) IMPROVEMENT OF BIOAVAILABILITY OF PROPRANOLOL IN RABBITS AFTER RECTAL ADMINISTRATION

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Three kinds of suppositories were constructed with oleaginous base material (Witepsol H-15): a conventional type suppository containing propranolol (PPL) hydrochloride mixed with a base material (I), a hollow type suppository containing PPL in a form of aqueous solution (PPL was dissolved in isotonic NaCl solution) in its cavity (II), a hollow type suppository containing PPL as powder (hydrochloride salt) in its cavity (III).

Bioavailability was estimated after rectal administration of each suppository in rabbits and compared with oral administration. The peak plasma PPL concentration (Cmax) and the area under the plasma concentration-time curve (AUC) were lower with I than with II or III. The Cmax and the AUC measured after rectal administration of III were significantly higher than those in the case of oral administration. By using III, the highest values of the mean Cmax (795 ± 160 ng/ml) and of the mean AUC (459 ± 21 h·ng/ml) were obtained.

It was found that systemic availability was increased by rectal administration of PPL hollow type suppositories. These data on bioavailability suggested that PPL was absorbed more efficiently with the hollow type suppository than with the conventional one. PPL was released faster from II and III than from I. It was concluded that the hollow type suppository was a suitable device for absorption of PPL into the rectum.

**Keywords** — hollow type suppository; propranolol; rectal administration; rectal absorption; bioavailability parameter; first-pass elimination; plasma propranolol concentration; rabbit

INTRODUCTION

Although propranolol (PPL) is generally administered as an oral pharmaceutical preparation, it is well known that the systemic bioavailability of PPL is low after its oral administration despite complete alimentary absorption. PPL undergoes extensive presystemic (first-pass) elimination before reaching the general circulation since the hepatic clearance of PPL is so high.

In this study, hollow type suppositories containing PPL (HCl salt powder and aqueous solution) in their cavity were administered into the rectum of rabbits and the bioavailability of PPL was estimated. The drug in the hollow type suppository was released faster than that in the conventional type and it may be assumed that PPL was absorbed by the rectum more efficiently.

MATERIALS AND METHODS

**Materials** — PPL hydrochloride (BP) was a gift from I.C.I. Ltd., Macclesfield, Cheshire, U.K. A suppository base, Witepsol H-15 (H-15) (Dynamit Nobel, Witten, F.R.G.) was used. The other reagents were obtained commercially.

**Preparation of Suppositories** — PPL hydrochloride was passed through a No. 200 sieve. A conventional suppository was prepared by a fusion process method. PPL (0.12 g), calculated as the base, was homogenously mixed with 30 g of molten H-15 at 40 °C, and the mixture was poured into a metallic mold. It was allowed to stand for 2 h at room temperature (24–26 °C) to solidify. The conventional suppository weighed about 2.5 g and the PPL amount, calculated as the base, was 10 mg per suppository (9.8 ± 0.2 mg (n = 10)).

A hollow type suppository (Fig. 1) was constructed in the same manner as described in the previous report, i.e., an aliquot amount of H-15 was melted at 45 °C, poured into a metallic mold equipped with an adapter (Fig. 2) for the

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FIG. 1. Schematic Illustration of PPL Hollow Type Suppository

Numbers, 1: oleaginous base material (Witepsol H-15); 2: PPL (powder or aqueous solution); 3: plug (Witepsol H-15); 4: thickness of wall (about 2 mm); 5: inner diameter (about 5 mm); 6: length (30–40 mm).

Weight of hollow type suppository is about 2 g and its inner volume is 0.5 cm³. The dimensions of 4 and 5 and the inner volume can be varied.

preparation of hollow type suppositories at 30 °C and then allowed to solidify at room temperature. A dose of PPL (1, 3 or 10 mg/kg, calculated as the base) was accurately weighed, added to each cavity (Table I) and then the opening at the hind part of the suppository was closed with H-15. The suppositories which had been stored in a refrigerator overnight after preparation were tested.

Release Measurement in Vitro — An instrument (Model TMS-103, Toyama Sangyo Co., Ltd., Osaka, Japan) for measuring PPL release from suppositories was employed according to the method of Muranishi et al. The dissolution medium was 500 ml of isotonic phosphate buffer solution (pH 7.4, PBS). In order to observe the difference of dissolution percentage of PPL from conventional and hollow type suppositories in vitro, each suppository was placed directly on a metallic net of plastic cylindrical cell without a membrane. The plastic cylindrical cell was immersed in the dissolution medium at a constant temperature (37 °C) and the dissolution medium was stirred at 100 rpm with a polytetrafluoroethylene stirring bar placed at the bottom of the sink. An aliquot of 2 ml of dissolution medium was taken and medium was replenished with the same volume of PBS. Dissolved PPL was assayed spectrophotometrically at 290 nm (Model UV-240 spectrophotometer, Shimadzu Seisakusho Ltd., Kyoto, Japan) following dilution with PBS.

FIG. 2. A Cross-Sectional Diagram of the Mold for Preparing Hollow Type Suppositories

Apparatus consists of (1) adapter (A, B, C) and (2) mold (F). Keys: (A), stainless steel pipe (after solidification of base material, this pipe is withdrawn by thermal treatment); (B), rubber O ring; (C), mounting plate; (D), piercing pipe hole; (E), mounting plate holder; (F), suppository mold (metallic etc.); (G), hollow place for construction of suppository (shapes: torpedo, cylindrical etc.).

TABLE I. PPL Suppository Preparations

<table>
<thead>
<tr>
<th>Suppository*</th>
<th>Form of PPL added</th>
<th>Dose** (mg/kg)</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>—</td>
<td>3</td>
<td>I</td>
</tr>
<tr>
<td>Hollow</td>
<td>Solution³</td>
<td>3</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Fine powder⁴</td>
<td>1</td>
<td>III-a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>III-b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>III-c</td>
</tr>
</tbody>
</table>

a) Base: Witepsol H-15.  b) PPL dose was calculated as the base.  c) PPL content as the base was 4 mg/g, and 0.75 g of suppository per kg of body weight was administered.  d) PPL HCl was dissolved in isotonic (0.9%) NaCl solution (20 mg as the base/mL), and then 150 μL of this solution per kg of body weight was added to each cavity.  e) PPL HCl was passed through No. 200 sieve.
Animal Experiments — Male albino rabbits weighing 2.9 ± 0.1 kg were used. The animals were fasted for one night preceding each experiment, but they were allowed free access to water. The rabbits were restrained with light-fitting neck stocks that allow them to assume a natural resting (crouching) posture, and a suppository (Table I) was inserted into the rectum. The anus was then closed with a plastic clip to prevent leakage during the experimental period of 6 h.

For oral administrations, PPL HCl was dissolved in isotonic (0.9%) NaCl solution and then each dose of PPL, calculated as the base, was administered orally by gastric intubation. The animals were rested for 10 d before their use for the next experiment.

After administration, blood samples were taken from the auricular vein at predetermined intervals and centrifuged at 3000 rpm for 15 min. The plasma layer was transferred to stoppered polyethylene tubes and kept at −20 °C until assays were performed.

PPL in plasma was assayed by a high performance liquid chromatographic (HPLC) method of Drummer et al., using an LC-3A system (Shimadzu Seisakusho Ltd., Kyoto, Japan) and a Zorbax ODS column (Du Pont, Wilmington, DE, USA).

Pharmacokinetic Analysis — Bioavailability Parameters — the peak plasma PPL concentration (Cmax), the peak concentration time (tmax), the area under the plasma concentration-time curve (AUC) and the AUC-dose ratio (AUC/dose) — were obtained from the plasma PPL concentration-time curves measured after administration.

The elimination rate constant (ke) was calculated from the terminal phase of the curve obtained by means of linear regression analysis. AUC0−∞ was estimated according to the trapezoidal rule, while the extrapolation to infinity was carried out by dividing the last measured plasma concentration by ke. The mean residence time (MRT) of the drug in the body was determined by the method of Yamaoka et al.,

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

RESULTS AND DISCUSSION

Release of PPL from Suppositories in Vitro

Figure 3 illustrates the relationship between the dissolution percentage of PPL from suppository (Table I) and time. It was clear that PPL was released more rapidly from the hollow types.
TABLE II.  Bioavailability Parameters of PPL in Rabbits after Rectal Administration of Suppositories

<table>
<thead>
<tr>
<th>Suppositorya</th>
<th>C_max (ng/ml)</th>
<th>t_max (min)</th>
<th>k_el (h⁻¹)</th>
<th>AUC₀⁻→∞ (h·ng/ml)</th>
<th>MRT (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>139±21</td>
<td>18±3</td>
<td>0.27±0.02</td>
<td>273±54</td>
<td>3.13±0.26</td>
</tr>
<tr>
<td>II</td>
<td>585±73b</td>
<td>7±0c</td>
<td>0.38±0.03</td>
<td>367±41</td>
<td>1.83±0.10c</td>
</tr>
<tr>
<td>III-b</td>
<td>795±160e</td>
<td>9±2e</td>
<td>0.37±0.03</td>
<td>459±21d</td>
<td>1.85±0.11e</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.E. of five rabbits. a) Suppository, see Table I. PPL dose: 3 mg/kg. Statistically significant differences: b) p < 0.05, c) p < 0.01 in II vs. I; d) p < 0.05, e) p < 0.01 in III-b vs. I.

(II) and (III-b) than from the conventional type (I). In II and III-b, PPL was released almost completely within 10–15 min after melting of the exterior oleaginous base material, but in I, the dissolution percentage increased slowly and reached less than 80% in 90 min.

No difference in dissolution profile was found between II and III-b. The reason for this was presumed to be due to the high solubility of the PPL HCl. These results were similar to the case of the hollow type suppository containing water-soluble dye.5

Bioavailability of Conventional and Hollow Type Suppositories

The mean semi-log plasma concentration-time curves after rectal administrations of the three types of PPL suppositories with the same dose of PPL (3 mg/kg) are given in Fig. 4 and their bioavailability parameters are shown in Table II. The mean plasma concentration-time curve profiles of hollow types (II, PPL aqueous solution) and (III-b, PPL HCl powder) were different from that of the conventional type (I). The plasma concentration of PPL was rapidly increased after the administration of II and III-b, but it was significantly low (p<0.05) at 7 to 60 min after the administration of I. Each bioavailability parameter of II and III-b was statistically (p<0.01, p<0.05) different from that of I (Table II). The mean C_max of I (139±21 ng/ml) was one-sixth of that of III-b (795±160 ng/ml). The mean AUC₀⁻→∞ of I (273±54 h·ng/ml) was about one-half of that of III-b (459±21 h·ng/ml). The release of PPL from I was slower than that from II and III-b and thus, this may be one of the reasons why the systemic availability was low. It is probable that significant difference of MRT between the hollow types (II, III-b) and the conventional type (I) is related to the fact that PPL was slowly released from I.

Recently, De Leede et al.10 and Iwamoto and Watanabe11 demonstrated that the avoidance of PPL pre-systemic elimination was reduced when PPL was absorbed by the upper site of the rectum of rats. Furthermore, the spreading behavior of suppositories to the upper part of the rectum in rats10 and men11,13,14 after administration were reported. A similar phenomenon may occur in rabbits. One of the reasons why large AUC₀⁻→∞ values were obtained with III-b and II may be due to the lesser amounts of PPL.

FIG. 5. Semi Logarithmic Plots of Plasma Concentrations of PPL against Time in Rabbits after Rectal or Oral Administration

Each point represents the mean ± S.E. (vertical bar) of five rabbits.

Suppository (see Table I): III-a (PPL dose, 1 mg/kg) (--•--), III-b (3 mg/kg) (-----), III-c (10 mg/kg) (-----), p.o. (10 mg/kg) (-----).
that spread to the upper site of the rectum since PPL release is faster from III-b and II than from I.

In comparing III-b with II, there was no statistically significant difference between their means of bioavailability parameters. These data suggest that the powder of PPL HCl in a hollow type suppository was quickly dissolved into the rectal fluid after administration and the PPL was rapidly absorbed by the rectum of rabbits. These results in vivo are different from those of the hollow type suppositories containing indomethacin in the form of fine powder or solution with macrogol 300.1,15) In this case, the indomethacin powder released from the hollow type suppository did not become wet easily and dissolution in rectal fluid in rabbits was difficult. Consequently, the $C_{\text{max}}$ was lower and $t_{\text{max}}$ was reached later, but when hollow suppositories containing indomethacin in macrogol 300 were used, the $C_{\text{max}}$ was significantly increased and the $t_{\text{max}}$ was shortened since solubility was improved.

**Bioavailability of Hollow Type Suppository and Oral Administration**

Figure 5 shows the mean semi-log plasma concentration–time curves after the administration of PPL, rectally and orally into rabbits. In order to compare the $AUC/$dose parameter, three doses of PPL were administered. These bioavailability parameters are summarized in Table III.

After the rectal administration of hollow type suppositories III-a, III-b and III-c (Table I), each mean of plasma PPL concentration rapidly increased ($t_{\text{max}}$: 9–15 min). The means of $C_{\text{max}}$ and $AUC_{0-\infty}$ of III-b and III-c were statistically (p<0.01) higher than those of the oral administration with the same doses of PPL (3 and 10 mg/kg) ($AUC$ ratio (rectal/oral): 3 mg/kg, 57; 10 mg/kg, 33). When the dose of PPL was increased from 1 to 10 mg/kg in the hollow types, the $AUC$/dose was not statistically significant. After the oral administration of a dose of 1 mg/kg, PPL in plasma could not be determined since it was lower than the limit of detectable concentration. These data on bioavailability clearly show that the rectal administration of PPL hollow type suppository considerably increases systemic availability in rabbits, compared with the oral administration. De Boer et al.16) suggested that the rectal route could be used for PPL to prevent the hepatic first-pass metabolism in rats.

From these experimental data, it can be concluded that the rectal administration of a PPL hollow type suppository in rabbits attained higher bioavailability compared to the use of a conventional type made of the same kind of oleaginous base material (H-15) and it is confirmed that the rectal administration of PPL is superior to the oral administered PPL.

Therefore, it may be possible to avoid the presystemic first-pass elimination when the PPL hollow type suppository is used.

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