LETTERS

Avoidance of First-Pass Metabolism of Propranolol after Rectal Administration as a Function of the Absorption Site

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The route of administration markedly affects the bioavailability of drugs that are rapidly and extensively metabolized in the gut and the liver. The "first-pass effect" after oral drug administration has been reviewed for β-adrenoreceptor blockers, analgesics, opiate antagonists, antiarrhythmics, calcium antagonists, vasoactive or psychotherapeutic drugs (1). Bypassing the liver as well as the gut wall by nonportal routes could result in a substantial increase in drug bioavailability.

It has been proposed that, after rectal administration, a large part of the absorbed drug enters the systemic circulation without first passing through the liver (2), because at least the lower hemorrhoidal veins are not connected to the portal system but directly to the inferior vena cava (3). Partial to complete avoidance of the first-pass metabolism after rectal administration has first been reported for lidocaine in man (4) and in rats (5). The rectal route in rats was also found to be almost entirely systemic for propranolol (6), while in humans it is only partially systemic, and the extent to which first-pass metabolism is avoided is probably dependent on the drug, dosage form, site of absorption (application) in the rectum and species (7). However, Kamiya et al. (8) have demonstrated that the extent of avoidance first-pass metabolism after rectal administration of nitroglycerin in rats is dependent on the rectal length of drug exposure.

To further test the importance of rectal exposure length, the apparent systemic availability of propranolol was investigated after oral and rectal administration (2.5 mg/kg) to rats, the rectal exposure length of which was either unrestricted or restricted to 2.5 cm from the anus.

Materials and Methods

Animal Experiments

Male Wistar rats, 204–240 g (7 weeks old), were cannulated in the right jugular vein with silicone polymer tubing (i.d. 1.0 mm; o.d. 1.5 mm, Dow Corning, Tokyo). Animal care was as reported previously (9, 10) except that the fasting interval was 16 h and heparinized saline was not utilized. All experiments with bolus i.v., p.o. and rectal administration were performed within 15 h after the cannulation surgery to avoid severe coagulation inside the cannula. Each of three or five unanesthetized rats was given 2.5 mg/kg of propranolol (as propranolol hydrochloride donated by Sumitomo Chemical Ind. Co., Osaka) via the cannula (i.v.), by gastric intubation (p.o.) or with a syringe through a septum plug (S-54, 5 mm diameter and 4.5 mm depth, Gaschro-Kogyo Co., Nagoya) at the anus (rectal). For unrestricted dosing, a septum plug (S-54) was affixed to the anus with Aron Alpha glue (Toa-Gousei Co., Nagoya). For restricted rectal dosing, a device similar to that reported by Kamiya et al. (8) was constructed to give a fixed distance of 2.5 cm available for intraluminal exposure to drug solution. The upper septum plug (S-75, 7 mm diameter and 5 mm depth) was used to prevent upward spreading of drug solution, while the lower one (S-54) was glued to the anus. Insertion of a plug or the device with two plugs and injection of drugs solution (4 ml/kg) were carried out under slight ether anesthesia. Sequential blood samples (~0.25 ml) were immediately heparinized in chilled centrifuge tubes before obtaining the plasma samples upon centrifugation at 3000 rpm for 15 min.

Analytical Procedures

Unchanged propanolol in plasma was determined by slightly modifying the spectrofluorometric method of Vervloet et al. (11). This assay method includes separation of the metabolites by duplicate extractions and was proved to be specific for propranolol in rat plasma. The plasma sample (0.1 ml) was transferred to a centrifuge tube containing 4N NaOH (0.1 ml) and this mixture was extracted with 6 ml *n*-heptane containing 1.5 % isoamyl alcohol by vigorous shaking for 20 min. After centrifugation, 5.0 ml of the organic layer was reextracted with 4.0 ml 0.1 N HCl. The fluorescence of this aqueous phase was measured at an excitation wavelength of 288 nm and an emission wavelength of 351 nm with a Shimadzu RF-510 spectrofluorometer (Shimadzu Seisakusho Co., Kyoto). The glue and septum plugs used in the rectal experiments did not absorb propranolol nor interfered in the assay.

Calculation and Statistics

The area under the plasma concentration-time curves (AUC) was calculated by the trapezoidal rule for the observed values ($t = 0 \sim t$) and then extrapolated to time infinity ($t = t \sim \infty$). The apparent systemic availability after oral or rectal dosing was estimated by the method of comparing each $AUC_{0-\infty}$ to that obtained after an equivalent intravenous dosing. All data were tested for statistically significant differences using Student's t-test.

Results and Discussion

Figs. 1 a, b and c show plasma concentration-time curves for propranolol after bolus i.v., p.o. and rectal administration (2.5 mg/kg) to rats, respectively. There was no significant difference in the terminal elimination half-life ($t_{1/2\alpha}$, min) of

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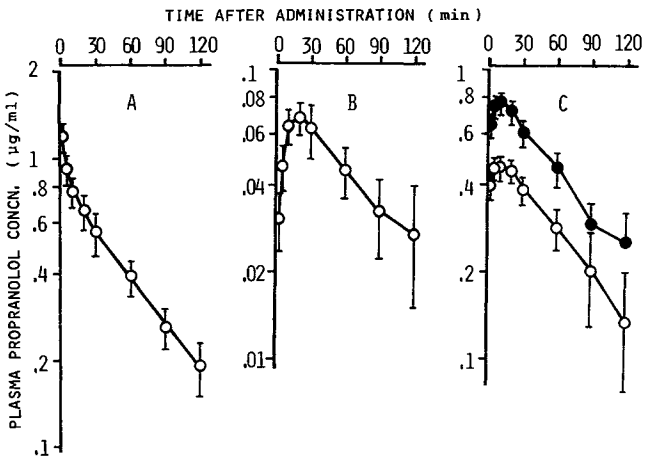

Fig. 1 Plasma concentration-time curves for unchanged propranolol following intravenous [A, n = 5], oral [B, n = 5] and rectal [C, nonrestricted (○, n = 5); restricted (●, n = 3)] administration (2.5 mg/kg) to rats. Each point with vertical bar represents the mean data point with standard deviation.

propranolol after i.v. (35.7±1.24), p.o. (39.2±4.60) and rectal (nonrestricted: 33.7±5.86, restricted: 37.4±3.88) administration.

Oral bioavailability of propranolol (2.5 mg/kg) was shown to be poor (8 %), while the rectal systemic bioavailability was considerably greater (55 %) (Fig. 1, Table I). When the rectal exposure to drug solution was restricted to a 2.5 cm length from the anus, the mean apparent availability further increased to 87 %. These results and those of a previous study with apparently nonrestricted dosing (6) suggest almost complete rectal absorption of propranolol, as was found for the oral absorption of this drug (12, 13).

De Boer et al. have reported an almost complete bypass of the liver after unrestricted rectal administration of propranolol (6) and lidocaine (5) in rats. However, the present results that show maximal bypass only for restricted rectal dosings agree with those obtained for nitroglycerin (8). This discrepancy may be accounted for by the larger dose (8 to 10 mg/kg) used by De Boer et al. (6), which could saturate the gastrointestinal and hepatic first-pass metabolism (10, 14, 15). Furthermore, a relatively small volume (0.5 ml) of drug solution was used previously (6), while a volume of 0.8 to 1.0 ml was employed in this study. The effect of the instillation volume on the avoidance of the hepatic first-pass metabolism has been discussed for nitroglycerin by Kamiya et al. (8). The smaller volume used in the previous study (6) might permit less upward spreading of the dose, thus allowing more complete avoidance of first-pass metabolism even after nonrestricted rectal dosing.

Table I. AUC and Apparent Systemic Availability of Propranolol Following Oral and Rectal Administration (2.5 mg/kg) to Rats

Route of administration	AUC[a] (µg·min/ml) mean ± S.D.	Apparent systemic availability[b] (%)
Intravenous	44.7 ± 2.32	100
Oral	3.56 ± 1.26[c]	8.0
Rectal (nonrestricted)	24.5 ± 4.97[d]	54.8
Rectal (restricted)	39.0 ± 5.83	87.2

[a]Calculated by the trapezoidal rule and extrapolation to time infinity except for the intravenous data which were estimated by the equation, $A/\alpha + B/\beta$.
[b]Expressed as the percentage of the mean AUC value following i.v. dosing.
[c]Significantly different from all other AUC values ($p<0.001$).
[d]Significantly different from the AUC values following i.v. ($p<0.01$) and restricted rectal ($p<0.05$) dosing.

In conclusion, the rectal administration of propranolol at a relatively low dose (2.5 mg/kg) leads to substantial avoidance of the first-pass metabolism of this drug. Consistent with anatomical predictions, the extent of this avoidance decreases when the rectal dose is exposed to the upper rectal areas where the drug can be absorbed through the upper rectal veins and transported via the portal vein to the liver. Subsequent to the completion of this study, De Leede et al. (16) have also found that the systemic availability of propranolol after rectal administration is highly dependent upon the site of rectal absorption.

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