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Dose-dependent presystemic elimination of propranolol due to hepatic first-pass metabolism in rats

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Gastrointestinal first-pass elimination of propranolol and the effect of dose (1·0, 2·5, 5·0 and 10·0 mg kg^{-1}) on its systemic availability were studied in male Wistar rats which received the drug intravenously, orally or intraportally. The plasma elimination half-life was not altered either by the route of administration or the dose. There was no gastrointestinal first-pass metabolism of propranolol, since the same systemic availability was obtained after oral and intraportal administration. Hepatic clearance was estimated to be constant at any dose. In contrast, the hepatic intrinsic clearance was found to be largely dependent on the portal dose.

Propranolol has been used by Shand et al (1975) to validate the 'venous equilibration' (or 'well-stirred') model of hepatic clearance described by Rowland et al (1973). The model requires that the drug be absorbed completely and eliminated exclusively by the liver. Oral propranolol is almost completely absorbed from the gastrointestinal tract, but undergoes substantial presystemic metabolism before reaching the general circulation (Paterson et al 1970; Shand et al 1970; Lo et al 1982). Its renal clearance has been reported to be insignificant in normal rats older than 7 weeks (Iwamoto et al 1985). It has been suggested that, in dogs, 26 and 9% of the total body clearance of (+)- and (−)-propranolol, respectively, may be due to extrahepatic elimination (George et al 1976). These authors suggested the gastrointestinal tract as a possible site of extrahepatic metabolism, since the possibility for the drug's pulmonary metabolism was ruled out by them using a canine isolated lung preparation. There have been other papers suggesting that the gastrointestinal metabolism is insignificant in man and dogs (Shand et al 1971, 1972; Lo et al 1982).

The gastrointestinal first-pass metabolism of propranolol and the effect of oral dosing on it have never been studied in rats, despite extensive work on non-linearity in its hepatic first-pass metabolism in man, dogs and rats (Shand & Rangno 1972; Shand et al 1972; Suzuki et al 1974). The present investigation was designed, therefore, to examine gastrointestinal first-pass elimination of propranolol and the effect of dose on its systemic availability and/or clearance in rats, by analysing the plasma level data after i.v., oral and intraportal administration.

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Methods

Male Wistar rats (7-weeks old, 205–235 g), which were chronically cannulated into the right jugular vein with silicone polymer tubing (i.d. 1·0 mm; o.d. 1·5 mm) one day before the experiments as described by Iwamoto et al (1982), and fasted overnight (for 16 h), were divided into twelve groups (n = 4). Each of the unanaesthetized rats in eight groups was given a bolus dose of 1·0, 2·5, 5·0 or 10·0 mg kg^{-1} propranolol intravenously via the cannula or orally by gastric intubation. Each rat in four other groups was given one of the above doses by a constant rate intraportal infusion over 20 min as described by Iwamoto et al (1982, 1983). Heparinized saline was not used for flushing the cannula (Iwamoto & Watanabe 1985).

Blood samples (0·25 ml) were withdrawn at timed intervals and plasma propranolol determined by a slightly modified method of Vervleot et al (1977) (see Iwamoto & Watanabe 1985). Plasma concentration (C)-time curves obtained after i.v. dosing were analysed according to a least-squares regression analysis program MULTI (Yamaoka et al 1981) for bi-exponential decline ($C = Ae^{-\alpha t} + Be^{-\beta t}$). The area under the plasma concentration-time curve after oral (AUC_o) or intraportal (AUC_p) dosing was estimated by the trapezoidal rule for the observed data and then by extrapolation to time infinity, whereas $AUC_{i.v.}$ was estimated by the equation, $AUC_{i.v.} = A/\alpha + B/\beta$. The total body clearance (CL_{tot}) of propranolol was estimated by the equation, $CL_{tot} = Dose/AUC_{i.v.}$, whereas the intrinsic clearance (CL_{int}) was estimated by the equation (Wilkinson & Shand 1975; Gibaldi & Perrier 1982), $CL_{int} = Dose\ (AUC_p \cdot f)$, where f is a free fraction of plasma total propranolol which has been reported previously (Iwamoto et al 1985). Systemic availability (F) was estimated by the equation, $F = AUC_o/AUC_{i.v.}$ or $AUC_p/AUC_{i.v.}$.

Results

Fig. 1 shows the plasma propranolol-time curves after i.v., oral and intraportal administrations at 1·0, 2·5, 5·0 or 10·0 mg kg^{-1}. The plasma concentration after intraportal infusion was much lower than that after i.v. administration and was not significantly different from that obtained after oral administration, at all time points

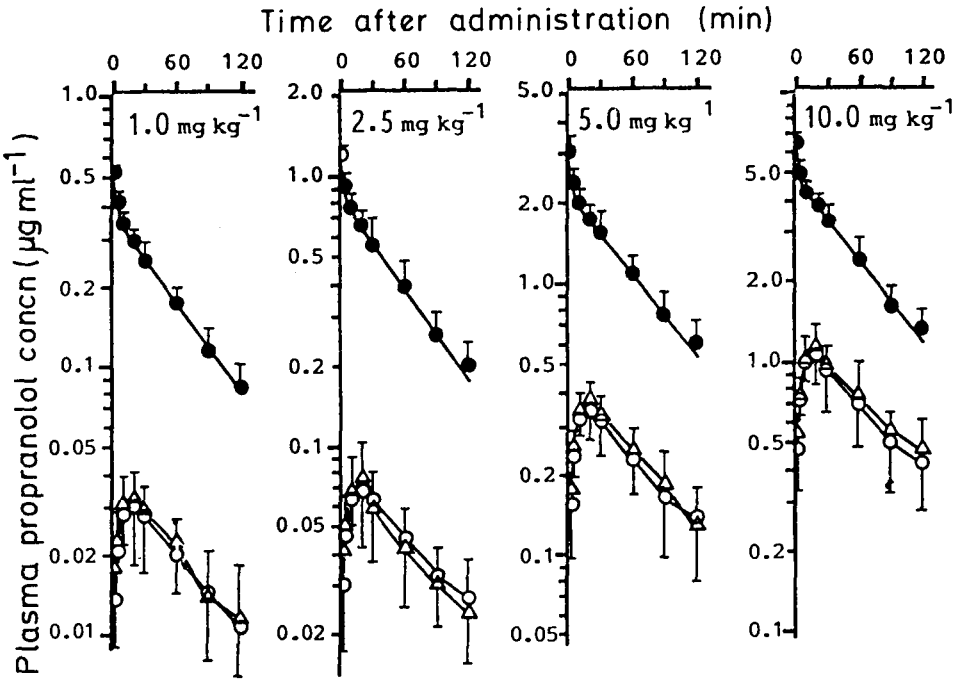

FIG. 1. Plasma propranolol concentration-time curves after intravenous (●), intraportal (△) or oral (○) administration of 1·0, 2·5, 5·0 and 10·0 mg kg^{-1} to four rats which were 7 weeks old. Each point represents the mean data point with s.d. Solid line for intravenous administration represents best computer-fitted bi-exponential curve weighted with reciprocal of square of the concentration.

after all doses. The plasma elimination half-life was not altered either by the route of administration or the dose, ranging from approximately 45 to 55 min. AUC value increased proportionately ($AUC_{i.v.}$, 17·5–171 μg min ml^{-1} as the mean value) with the i.v. dose ($Dose_{i.v.}$, 1·0–10·0 mg kg^{-1}), while those after oral ($AUC_{p.o.}$) and intraportal (AUC_p) dosage were found to be non-linear, yielding 1·31, 3·56, 12·2 and 43·2 μg min ml^{-1} for AUC_o and 1·35, 3·28, 13·7 and 45·1 μg min^{-1} for AUC_p at 1·0, 2·5, 5·0 and 10·0 mg kg^{-1}, respectively.

Table 1 summarizes the effect of propranolol dose on the average systemic availability (F), total body clearance (CL_{tot}) and intrinsic hepatic clearance (CL_{int}). The average systemic availability was essentially the same for both routes of administration but increased with the dose higher than 2·5 mg kg^{-1}. There was no dose-dependence in the total body clearance as expected from the linearity obtained in the AUC values after i.v. dosing. On the other hand, the hepatic intrinsic clearance was significantly reduced with the dose higher than 2·5 mg kg^{-1}.

Table 1. Effect of dose on the average systemic availability (F), total body clearance (CL_{tot}) and intrinsic clearance (CL_{int}) of propranolol in rats.

Dose (mg kg^{-1})	F[a]		CL_{tot}[b] (ml min^{-1} kg^{-1})	CL_{int}[c] (ml min^{-1} kg^{-1})
	Oral	Intraportal		
1·0	0·075	0·077	57·1 ± 4·1[d]	3820 ± 310
2·5	0·079	0·073	55·4 ± 3·9	3790 ± 420
5·0	0·141	0·158	57·8 ± 4·7	1870 ± 250
10·0	0·253	0·264	58·5 ± 5·6	1150 ± 190

[a] Estimated by the equation, $F = AUC_o/AUC_{i.v.}$ or $AUC_p/AUC_{i.v.}$.
[b] Estimated by the equation, $CL_{tot} = Dose/AUC_{i.v.}$.
[c] Estimated by the equation, $CL_{int} = Dose/(AUC_p \cdot f)$.
[d] S.d.

Discussion

With bolus i.v. dosing at 5·0 mg kg^{-1}, the pharmacokinetics of propranolol in the present study were fairly consistent with other data reported for male, Wistar rats of the same age (Bianchetti et al 1980). However, the elimination half-life (approximately 40 min) and the distribution volume (2·7 litre kg^{-1}) after the i.v. dosing at 2·5 mg kg^{-1} were substantially different from their results (63 min and 8·5 litre kg^{-1}, respectively) obtained in male, Sprague-Dawley rats given 2·0 mg kg^{-1}. Some inter-strain differences therefore, may be suggested in the disposition kinetics of propranolol in rats.

The present results observed in AUC and F (Table 1) values after oral and intraportal dosings suggest that there is no gastrointestinal first-pass metabolism of propranolol in rats as has also been demonstrated in man (Shand et al 1971; Shand & Rangno 1972) and in dogs (Lo et al 1982). Furthermore, the presystemic elimination (hepatic metabolism) of propranolol after oral and intraportal administration was found to be

dependent on the dose higher than 2·5 mg kg^{-1}. The relatively small systemic availability of propranolol after oral or portal administration thus increased with the dose, ranging from approximately 8–25% on average.

Provided that there is no pulmonary clearance, the total body clearance could be essentially assigned to the hepatic clearance, since renal clearance of this drug was insignificant in the rats older than 7 weeks (Iwamoto et al 1985). Estimated hepatic clearance of propranolol was constant at any present dose ranging from 1·0 to 10·0 mg kg^{-1}. In contrast, the hepatic intrinsic clearance was found to be largely dependent on the portal dose, suggesting evidence for the saturation kinetics in hepatic first-pass metabolism of propranolol.

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Modification of the inotropic effect of digoxin by diazepam in rat left atria

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There is a pharmacokinetic interaction between digoxin and diazepam that increases the elimination half-life of digoxin. It may be due to a reduction of digoxin tissue concentrations and to an enhanced effect of diazepam on digoxin binding to plasma albumin. Diazepam (10^{-5} M) also induces a positive inotropic effect in guinea-pig isolated atria. In a study of a possible pharmacodynamic interaction between both drugs, the inotropic response to digoxin has been examined in rat isolated atria in the presence of diazepam. The atria were kept in Tyrode at 37 °C, bubbled with 95% O_2 and 5% CO_2 and electrically stimulated at twice the threshold voltage. The results indicate that diazepam induces an inotropic effect at 10^{-5} M ($P < 0.05$) and reduces ($P < 0.05$) at 10^{-9}, 10^{-7} and 10^{-5} M the inotropic response to digoxin (10^{-5} M).

It has been shown in rats, dogs and healthy humans that, in the presence of diazepam, digoxin reaches higher plasma concentrations, its elimination half-life increases, its urinary excretion decreases and its tissue levels at several sites also decrease (Castillo-Ferrando et al 1980; Castillo-Ferrando & Carmona 1981). An enhanced effect exerted by diazepam and other benzodiazepines on digoxin binding to protein might account for the pharmacokinetic changes described above (Castillo-Ferrando 1983).

We have examined a possible pharmacodynamic interaction between diazepam and digoxin in the isolated rat atria.

Material and methods

Albino, Wistar rats of either sex, 200–300 g, were used (n = 26). Rats were killed and the left atria excised and tied by one end to a force-displacement transducer (Ugo-Basile) connected to a polygraph; the other end was attached to an electrode connected to a stimulator (SRI). The atria were stimulated at twice the threshold voltage at 1 Hz rate. The Tyrode bathing solution was at

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