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The effect of Miglyol 812 oil on the oral absorption of propranolol in the rat

S. G. WOOLFREY*, K. J. PALIN, S. S. DAVIS, *Department of Pharmacy, University of Nottingham, Nottingham NG7 2RD, UK*

Abstract—This work has examined the effect of Miglyol 812 oil and its composite fatty acids on the oral absorption of propranolol with reference to its intravenous (i.v.) pharmacokinetics. Propranolol hydrochloride, spiked with 4-^{3}H labelled compound, was administered i.v. or orally to male Wistar rats and blood concentrations of parent material determined by liquid scintillation counting after extraction into toluene. An i.v. dose-linearity study indicated dose-independent pharmacokinetics for propranolol at 1–2 mg kg^{-1}, with a mean Cl_s, V_{ss}, $MRT_{i.v.}$ and $t_{0.5\beta}$ of 0·076 L min^{-1} kg^{-1}, 4·74 L kg^{-1}, 57·81 min and 47·10 min, respectively. At 5 mg kg^{-1}, there was evidence of non-linearity with $MRT_{i.v.}$ increased by about 250%, V_{ss} by 170% and $t_{0.5\beta}$ by 230% compared with the lower doses. After oral administration of propranolol (10 mg kg^{-1}) in aqueous solution, with or without Tween 80 (6%), the mean absorption time (MAT) and terminal half-life were approximately 55 min and 86 min, respectively. The MAT for propranolol administered in a 50% octanoic and lauric acid (1:1 by weight) oil-in-water emulsion, stabilized with 6% Tween 80 (129·90 min), was significantly longer compared with that for a 50% Miglyol 812 oil-in-water emulsion containing the same surfactant (16·55 min). The terminal half-life of propranolol administered in the fatty acid formulation (128·96 min), unlike that for the Miglyol emulsion (54·37 min), was significantly longer compared with that observed after i.v. administration ($t_{0.5\beta}$ = 47 min). The fraction available for propranolol was independent of formulation with mean values between about 16 and 24%. These results show that the absorption of propranolol in the fatty acid formulation was decreased possibly due to a reduced rate of gastric emptying.

The oral bioavailability of a drug can be altered by administration in a lipid vehicle. Triglycerides and their composite fatty acids have been reported to alter the absorption of compounds by modifying physiological parameters such as gastric emptying rate (Bates & Sequira 1975), lymphatic absorption (Sieber et al 1974; Palin & Wilson 1984), bile salt solubilization (Miyazaki et al 1980) and membrane permeability (Inui et al 1974). The effect of a lipid vehicle depends on both the composition of the oil and the physicochemical characteristics of the drug. Many reported studies have used lipophilic molecules although some effects have been observed with more hydrophilic compounds (Palin et al 1986). In the present study the effect of Miglyol 812 oil (fractionated coconut oil) on the pharmacokinetics of propranolol hydrochloride, a relatively hydrophilic molecule subject to a high first-pass metabolism, was investigated using the rat. The rate and extent of propranolol absorption was characterised using the mean absorption time (MAT) (Yamaoka et al 1978) and the fraction available (F) (Gibaldi & Perrier 1982), respectively. These parameters require that the intravenous disposition of the drug is linear over the blood concentrations observed following oral administration. An intravenous dose-linearity study was therefore performed to determine the blood concentrations of propranolol where dose-independent pharmacokinetics prevailed.

Materials and methods

The aqueous and Tween 80 propranolol formulations for oral administration were prepared from aqueous solutions of propranolol hydrochloride (4 mg mL^{-1}) (Sigma, St. Louis, USA) spiked with [4-^{3}H] propranolol (specific activity 67 mCi mg^{-1}, Amersham International, Amersham, UK) with or without Tween 80 (6%). For the emulsion systems, an equal volume of Miglyol 812 oil or a 1:1 mixture (by weight) of octanoic (BDH, Poole, UK) and lauric acids (Sigma, St. Louis, USA) was added to surfactant solution (12%) containing radiolabelled spiked propranolol (8 mg mL^{-1}) and emulsified using a Silverson blender. Formulations for i.v. administration consisted of a radiolabelled solution of propranolol in isotonic phosphate-buffered saline (pH 7·4).

Male Wistar rats, 180–220 g, fasted for 18 h with water freely available, were used. For intravenous delivery, the animals were anaesthetized with pentobarbitone (intraperitoneally, 90 mg kg^{-1}) and a midline ventral incision made in the neck. A jugular vein was cannulated with polythene tubing (Portex, Hythe, UK; 0·58 mm i.d., 0·96 mm o.d.) which was exteriorized via the dorsal surface of the neck. Following recovery from the anaesthetic, 100 μL of the i.v. dose containing propranolol hydrochloride (1, 2 or 5 mg kg^{-1}, 50 μCi kg^{-1}) was injected via the cannula. Before oral delivery of the propranolol formulations (10 mg kg^{-1}, 100 μCi kg^{-1}) by gastric intubation (2·5 mL kg^{-1}), animals underwent a similar surgical procedure but with ligation, rather than cannulation of the jugular vein. Blood samples were collected from the tail into heparinized tubes at time intervals after oral and i.v. administration.

An aliquot (100 μL) of each blood sample was mixed with 50 μL 0·1 M sodium hydroxide and propranolol extracted into 1 mL toluene. Following centrifugation, 0·7 mL of the organic layer was transferred to 5 mL Cocktail-T scintillation fluid (BDH, Poole, UK) and the level of radioactivity determined by liquid scintillation counting. The blood concentrations of propranolol were calculated with reference to the measured specific activity of the original dose and a determined extraction efficiency of 90·8%.

Individual blood concentration-time profiles after i.v. administration showed a biexponential decline and were analysed according to a two compartment open model using the non-linear extended-least squares regression program, MKMODEL II plus (Holford 1983). From this analysis a number of model-dependent pharmacokinetic parameters were calculated including the initial half-life ($t_{0.5\alpha}$), the terminal half-life ($t_{0.5\beta}$) and the apparent volume of distribution of the central compartment (V_c). The model-independent parameters used were volume of distribution at steady state (V_{ss}), total body clearance (Cl_s) and mean residence time ($MRT_{i.v.}$) (Gibaldi & Perrier 1982). The rate and extent of propranolol absorption was characterized from the individual blood concentration-time profiles by MAT and F, respectively (Yamaoka et al 1978; Gibaldi & Perrier 1982). Areas under the curve and the first moments curve to infinity were calculated using the linear trapezoidal rule with the extrapolated portion estimated from the last data point and the terminal half-life. For the oral data, the terminal half-life was determined from at least 3 data points and possessed a correlation coefficient of $\geq$0·9. All statistical tests were performed assuming a 5% significance level.

* Present address and correspondence to: S. G. Woolfrey, Sterling Research Group Europe, Sterling-Winthrop Research Centre, Willowburn Avenue, Alnwick, Northumberland NE66 2JN, UK.

Results

Blood concentrations of propranolol declined in a biexponential manner following i.v. bolus doses of 1, 2 and 5 mg kg^{-1} (Fig. 1).

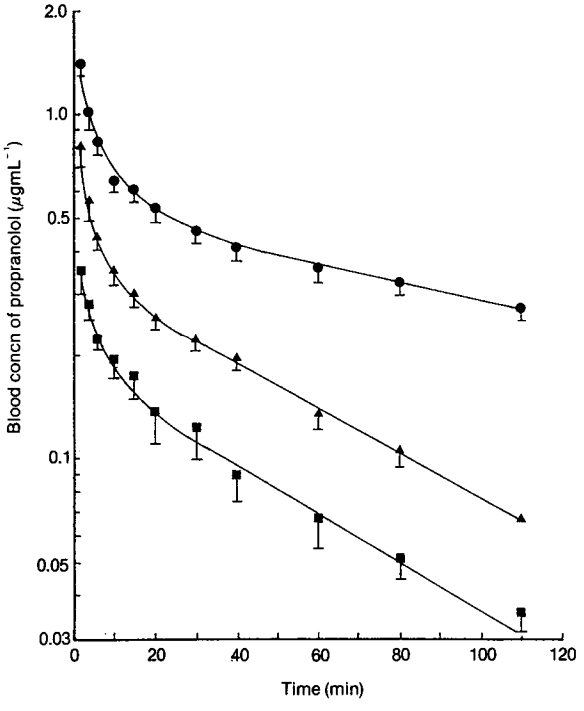

FIG. 1. Blood concentration-time profiles for propranolol after i.v. administration to rats at various doses. (mean ± s.e.m; n = 5). ● 5; ▲ 2; ■ 1 mg kg^{-1}.

Table 1. Pharmacokinetic parameters for propranolol after i.v. administration to rats.

Parameter (mean ± s.e.m.)	Dose of propranolol (mg kg^{-1}) 1·0	2·0	5·0
V_c (L kg^{-1})	2·16 ± 0·48	1·69 ± 0·22	2·78* ± 0·50
V_{ss} (L kg^{-1})	5·18 ± 0·93	4·30 ± 0·62	7·85** ± 1·08
$t_{0.5\alpha}$ (min)	3·61 ± 1·78	2·11 ± 0·38	3·26* ± 1·85
$t_{0.5\beta}$ (min)	48·37 ± 10·36	45·83 ± 6·30	109·21** ± 28·22
Cl_s (L min^{-1} kg^{-1})	0·077 ± 0·007	0·074 ± 0·006	0·056* ± 0·006
$MRT_{i.v.}$ (min)	57·46 ± 11·73	58·16 ± 7·18	150·25** ± 35·87

Results were compared using a Student-Newman-Keuls Multiple comparison test.
*No differences between doses.
**No differences between the 1 and 2 mg kg^{-1} propranolol doses but differences between the 5 and 1, and 5 and 2 mg kg^{-1} levels.
n = 5.

At a dose of 5 mg kg^{-1}, $MRT_{i.v.}$, $t_{0.5\beta}$ and V_{ss} were significantly greater compared with the values obtained at the 1 and 2 mg kg^{-1} doses (between 150 and 200%), whilst V_c, $t_{0.5\alpha}$ and Cl_s were independent of dose level. There was, therefore, no evidence of dose-dependency in any of the parameters following i.v. bolus doses of $\leqslant$2 mg kg^{-1} (Table 1).

After oral administration, propranolol in the Tween 80 system gave a mean C_{max} which was between 350 and 140% greater compared with the other formulations (Fig. 2, Table 2). The values for t_{max} were similar for the aqueous, Tween 80 and Miglyol 812 formulations (4·0, 3·83 and 4·50 min, respectively) while that for the fatty acid emulsion was considerably longer, being approximately 23 min (Table 2).

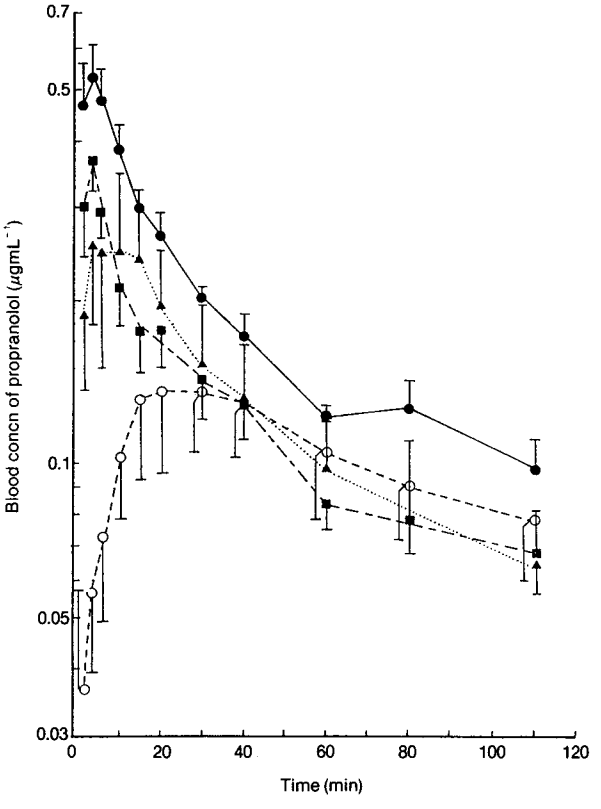

FIG. 2. Blood concentration-time profiles for propranolol after oral administration to rats (10 mg kg^{-1}) in various formulations (mean ± s.e.m.). ■ Aqueous (n = 5); ● 6% Tween 80 (n = 6); ▲ 50% Miglyol 812 Oil emulsion (n = 4); ○ 50% Fatty acid emulsion (n = 5).

Table 2. Pharmacokinetic parameters for propranolol after oral administration to rats (10 mg kg^{-1}) in various formulations.

Propranolol formulation	Parameter (mean ± s.e.m.) MAT (min)	$t_{0.5t}$ (min)	F (%)	C_{max} (μg mL^{-1})	t_{max} (min)
Aqueous (n = 5)	58·43 ± 15·8	88·94 ± 13·59	15·90 ± 1·79	0·38 ± 0·06	4·00 ± 0·00
Tween 80 (n = 6)	50·77 ± 9·73	83·30 ± 7·64	24·13 ± 3·20	0·55 ± 0·09	3·83 ± 1·60
Miglyol 812 emulsion (n = 4)	16·55 ± 1·91	54·37 ± 1·54	12·89 ± 3·40	0·28 ± 0·09	4·50 ± 1·00
Fatty Acid emulsion (n = 5)	129·9 ± 11·82	128·96 ± 10·35	18·93 ± 4·69	0·16 ± 0·06	23·00 ± 12·04
	*	*	**	—	—

MAT, $t_{0.5t}$ and F were compared using a Student-Newman-Keuls Multiple Comparison test.
*Differences between all formulations except the aqueous and Tween 80 formulations.
**No differences between formulations.
$t_{0.5t}$ = Terminal Half-Life.

The fraction of propranolol available was not significantly different for any of the formulations, although other parameters did vary (Table 2). Whilst the MAT for the aqueous and Tween 80 solutions were statistically equivalent, both values were shorter than for the fatty acid emulsion (> 50%) and longer compared with the Miglyol 812 oil formulation (> 350%).

The longest terminal half-life of propranolol was observed for the fatty acid emulsion which was 140–250% greater than that for the other formulations. With the exception of the Miglyol

812 oil emulsion, the terminal half-life was significantly longer ($P < 0.001$, Student's t-test) than $t_{0.5\beta}$ obtained following i.v. administration at 1 and 2 mg kg^{-1} (Tables 1, 2).

Discussion

Although there was no difference in the fraction available for propranolol in the various oral formulations, MAT and t_{max} indicated that the fatty acid emulsion decreased its rate of absorption compared to the other systems. Fatty acids inhibit gastric emptying with the maximal inhibition occurring at about C_{14}, myristic acid (Hunt & Knox 1968). Triglycerides also inhibit gastric emptying but the effect is less potent (Long & Weiss 1974). The slower uptake of propranolol from the fatty acid emulsion may therefore have been a result of reduced gastric emptying prolonging the absorption phase. This is supported by the terminal half-life of propranolol in the fatty acid emulsion which was significantly longer (140–250%) than that observed for the other oral formulations.

Studies in the rat, using both ^{3}H- and ^{14}C-labelled compound, have suggested that the metabolism of propranolol is saturable (Ong et al 1981) owing to the limited capacity of biotransformation (Ong et al 1981; Barger et al 1983). The slow absorption rate of propranolol in the fatty acid emulsion may therefore have resulted in a different metabolic profile compared with that for the other oral formulations, where the drug was more rapidly presented to the liver.

The terminal half-life for propranolol following administration in the Miglyol 812 oil emulsion was statistically equivalent to that observed after i.v. dosing (1–2 mg kg^{-1}, $t_{0.5\beta} = 47.10 \pm 5.41$ min). However, for the Tween 80 and aqueous propranolol formulations, the terminal half-life was significantly longer than $t_{0.5\beta}$ after i.v. administration, suggesting the presence of absorption rate-limited pharmacokinetics. The explanation of these differences is unclear but may be associated with Miglyol 812 oil-induced changes in the metabolism of propranolol.

Previous reports have indicated that non-ionic surfactants, such as Tween 80, can modify gastrointestinal absorption by changing the mucosal barrier and by partitioning of the administered drug into micelles (Dermer 1967; Niazi 1979). In the present study, the addition of 6% Tween 80 had no statistically significant effect on propranolol absorption although the plasma concentrations were increased compared with those from an aqueous solution.

The blood concentrations of propranolol after i.v. administration possessed a $t_{0.5\beta}$ of 47.10 ± 5.41 min (mean $\pm$ s.e.m.) with linear pharmacokinetics at $\leqslant 2$ mg kg^{-1}. Iwamoto & Watanabe (1985) obtained a comparable $t_{0.5\beta}$ for propranolol ($t_{0.5\beta} = 45$–55 min) but observed linear pharmacokinetics up to 10 mg kg^{-1}. Such a discrepancy supports the likelihood of inter-strain differences in the pharmacokinetics of this drug.

In conclusion, this work has determined that the oral absorption of propranolol in an octanoic and lauric fatty acid emulsion reduced the rate of propranolol uptake compared with the Miglyol 812 oil emulsion without any effect on the fraction available.

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