Br. J. Pharmac. (1982) **77**, 667–677

THE EFFECT OF CHLORPROMAZINE, METYRAPONE, IMIPRAMINE AND SKF 525-A ON THE HEPATIC FIRST PASS ELIMINATION OF PROPRANOLOL IN THE PITHED RAT

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1 The effect of chlorpromazine, metyrapone, imipramine and SKF 525-A on the hepatic first pass elimination of propranolol has been studied in the pithed rat.

2 The effect of chlorpromazine, metyrapone, imipramine and SKF 525-A on the inhibition caused by propranolol of an elicited electrically induced tachycardia has also been studied.

3 The hepatic first pass elimination of propranolol was reduced following pretreatment with chlorpromazine, imipramine and SKF 525-A but was not affected by pretreatment with metyrapone.

4 Chlorpromazine, imipramine and SKF 525-A all resulted in an increased propranolol blood concentration after hepatic portal vein administration which was associated with decreased formation of metabolites and an enhanced inhibition of an electrically induced tachycardia.

Introduction

The β-adrenoceptor blocking agent propranolol undergoes extensive first-pass elimination (FPE) after oral administration. This results in low oral bioavailability and large inter-individual variation in blood concentrations (Shand, Nuckolls & Oates, 1970).

Reduction of the hepatic first pass elimination (HFPE) of propranolol has been investigated in the pithed rat. The effects of chlorpromazine and known inhibitors of hepatic drug metabolizing enzymes, imipramine, metyrapone and SKF 525-A, have been studied using methods which permit the simultaneous measurement of the pharmacokinetics and pharmacological effects of propranolol. Preliminary accounts of this work have been presented to the British Pharmacological Society (Barber, Kitteringham & Petrie, 1980; 1981).

Methods

Experimental procedures

Male Sprague-Dawley rats (200–250 g) were pithed under halothane anaesthesia following tracheal cannulation. They were immediately respired with 100% O_2 by means of a small animal ventilator. The right carotid artery was cannulated and blood pressure was measured (Gould Statham transducer) and displayed on a Grass polygraph. The pressure pulse was used to trigger a heart rate meter. The contralateral carotid artery was cannulated for removal of blood samples. The left external jugular vein was cannulated for intravenous (i.v.) drug administration. Oral administration of drugs was simulated by injection directly into the hepatic portal vein (h.p.v.). This was accomplished by cannulation of the splenic vein such that the tip of the cannula was secured in the anastomosis of the splenic and hepatic portal veins. The rectal temperature of the rat was monitored continuously and maintained at 36.5 ± 0.5°C by external heating.

Experimental details for chlorpromazine on the pharmacokinetics of propranolol in the pithed rat

Chlorpromazine (0.27 mg kg^{-1} min^{-1}; 0.83 μmol kg^{-1} min^{-1}) or saline (0.27 ml kg^{-1} min^{-1}) was infused for 15 min via the hepatic portal vein (h.p.v.). The infusion rate was then reduced to 0.5 ml kg^{-1} min^{-1} (0.5 mg kg^{-1} min^{-1} of chlorpromazine) and was maintained at that rate throughout the remainder of the experiment. [^{3}H]-propranolol (100 μg kg^{-1}; 0.38 μmol kg^{-1}; 200 μCi kg^{-1}) was rapidly injected 45 min after the start of the chlorpromazine infusion, via either the i.v. or the h.p.v. routes. Blood samples (0.24 ml) were removed at specific times and were assayed for propranolol and its metabolites as described below.

0007-1188/82/120667-11 $01.00

Experimental details for imipramine, metyrapone and SKF 525-A on the pharmacokinetics of propranolol in the pithed rat

Equimolar doses (1.56 μmol kg^{-1} min^{-1}) of imipramine (0.53 mg kg^{-1} min^{-1}), metyrapone (0.38 mg kg^{-1} min^{-1}) or SKF 525-A (0.61 mg kg^{-1} min^{-1}) were infused for 15 min via the h.p.v. Saline (0.27 mg kg^{-1} min^{-1}) was infused in control animals. [^{3}H]-propranolol (100 μg kg^{-1}; 0.38 μmol kg^{-1}; 200 μCi kg^{-1}) was injected after the 15 min infusion via the h.p.v. and blood samples were removed for assay at specific times.

Experimental details for chlorpromazine, imipramine, metyrapone and SKF 525-A on the pharmacological effect of propranolol in the pithed rat.

The preganglionic sympathetic nerves to the heart were stimulated between the pithing rod and an indifferent electrode placed subcutaneously dorsal and parallel to the spine (Gillespie, Maclaren & Pollock, 1971).

A discrete tachycardia of 25–30 beats/min above resting values was elicited every minute by short trains of stimuli (0.05 ms, 1 Hz, 30 V, 3–5 s duration). The pharmacological effect of propranolol was quantified in control and drug pretreated animals by the percentage inhibition of the electrically induced tachycardia.

In experiments in which either chlorpromazine or imipramine was administered, and in the respective control experiments, stimulation of the cardioaccelerator nerves was continuous (0.05 ms, 1 Hz, 20–60 V). Such continuous stimulation in these experiments was necessitated because of the noradrenergic uptake blocking action of chlorpromazine and imipramine (Iversen, 1965). Both drugs potentiated and prolonged the duration of a discrete tachycardia induced as above. Therefore, in pretreated animals the applied voltage was reduced, compared with controls, such that a continuous tachycardia of 100 beats/min above resting values was elicited in both drug pretreated and control animals.

Analysis of blood samples for propranolol and metabolites

Blood concentrations of [^{3}H]-propranolol were quantified by liquid scintillation spectrometry after separation from its metabolites by solvent extraction and high performance liquid chromatography (h.p.l.c.). [^{14}C]-propranolol (0.3 μg, 3.6 nCi) was added to each blood sample before extraction and acted as an internal standard. The assay methods used were those of Pritchard, Schneck & Hayes (1979) adapted to measure [^{3}H]-propranolol in whole blood samples. The elution of propranolol from the h.p.l.c. column (Spherisorb ODS 5 μm packing) was monitored fluorimetrically (Perkin Elmer LC1000 fluorimeter) at excitation and emission wavelengths of 301 nm and 340 nm respectively. The h.p.l.c. solvent (50:50 v/v acetonitrile: phosphoric acid [0.4 M] containing the propranolol was collected and counted in Picofluor (Packard) scintillation fluid (10 ml). Dual isotope quench correction, with external standardization, was used to determine the d/min for [^{14}C]- and [^{3}H]-propranolol. The total propranolol concentration in each blood sample was calculated from the specific activity of the dose. The recovery of [^{3}H]-propranolol after extraction and h.p.l.c. was determined by calculating the [^{14}C]-propranolol recovery and assuming equal recovery of [^{3}H]-propranolol.

Individual metabolites were not quantified but three groups, basic, acidic and highly polar non-extractable metabolites were measured by scintillation counting after differential solvent extraction. The concentration of metabolites in each group was expressed in propranolol equivalent concentrations as authentic samples of all the metabolites were unavailable.

Materials

All drugs were administered in 0.9% w/v NaCl (saline) and concentrations quoted refer to the base. The following drugs were used: propranolol HCl (Sigma), [4-^{3}H]-propranolol HCl (Amersham), [^{14}C]-propranolol (a gift from ICI), chlorpromazine HCl (May and Baker), imipramine HCl (Geigy), SKF 525-A β-diethylaminoethyldiphenylpropyl acetate HCl) (Smith Kline and French) and metyrapone (Sigma). All analytical reagents were analar grade.

Calculation of pharmacokinetic values

Blood concentration-time data from individual animals were analysed by non-linear regression using the computer programme AUTOAN (Sedman & Wagner, 1971) and declined in a bi-exponential manner. The area under the blood concentration-time curve from zero to infinite time (AUC_0^∞) was calculated from computer estimates of A, α, B and β, using the relation

$$AUC_0^\infty = \frac{A}{\alpha} + \frac{B}{\beta}$$

where α and β are both hybrid rate constants and A and B are the extrapolated zero time intercepts of each exponential.

Total body clearance was obtained from

$$\frac{\text{dose}}{AUC_0^{\infty}}$$

the apparent volume of distribution from

$$\frac{\text{dose}}{\beta \; AUC_0^{\infty}}$$

and the extraction ratio (E) after h.p.v. administration from

$$E = 1 - \frac{AUC_0^{\infty}\,(\text{h.p.v.})}{AUC_0^{\infty}\,(\text{i.v.})}.$$

Results

The effects of chlorpromazine, imipramine, metyrapone and SKF 525-A on the blood concentrations of propranolol

The blood concentrations of propranolol following

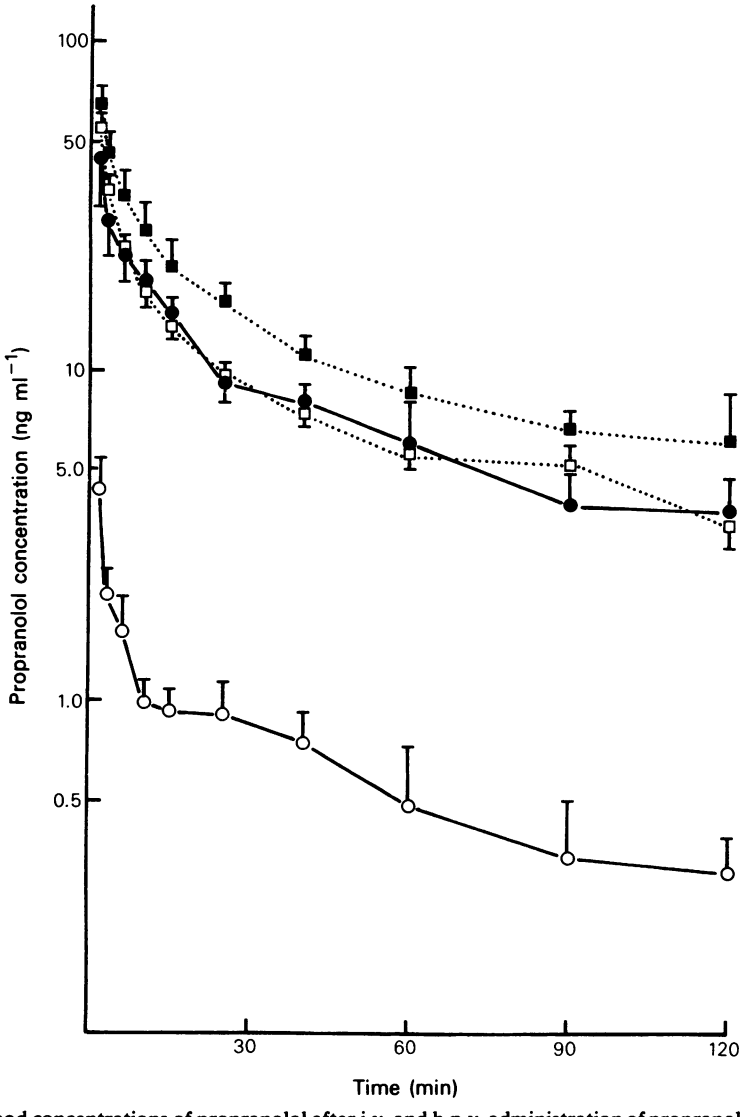

Figure 1 The blood concentrations of propranolol after i.v. and h.p.v. administration of propranolol (100 μg kg^{-1}) in control and chlorpromazine (Cpz) pretreated pithed rats: propranolol i.v. (□); propranolol h.p.v. (○); pretreatment Cpz + propranolol i.v. (■); pretreatment Cpz + propranolol h.p.v. (●).

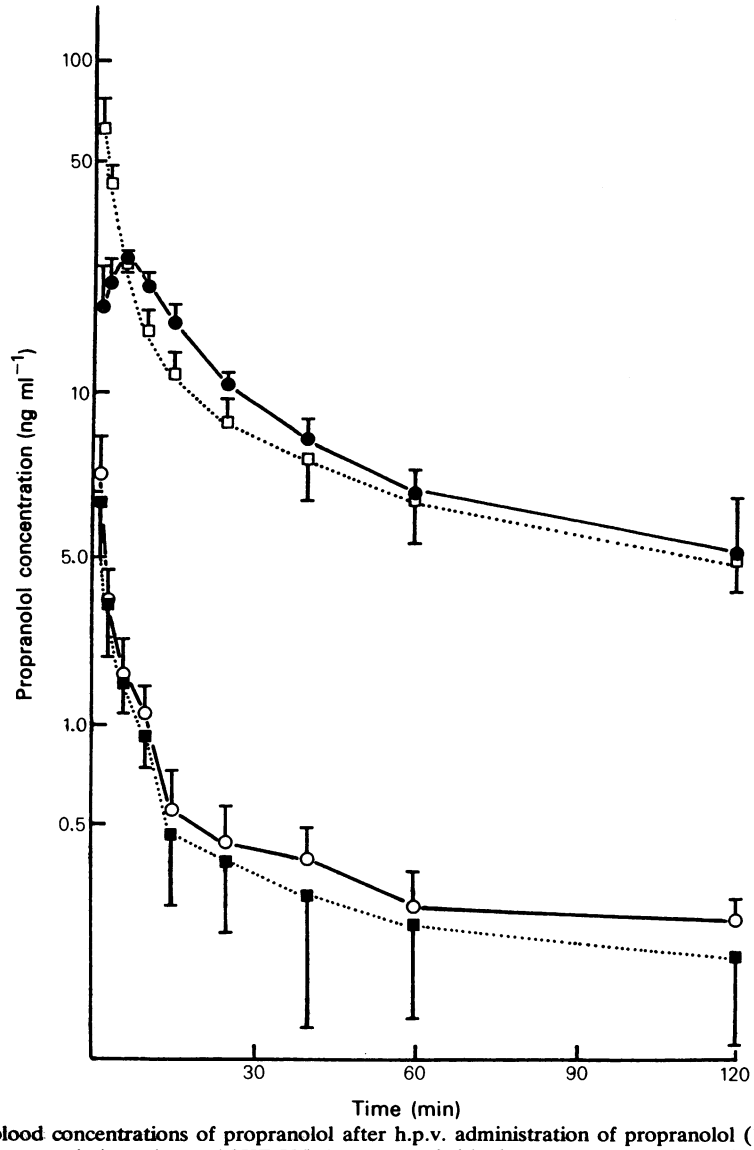

Figure 2 The blood concentrations of propranolol after h.p.v. administration of propranolol (100 μg kg^{-1}) in control and metyrapone, imipramine and SKF 525-A pretreated pithed rats: propranolol h.p.v. (○); pretreatment metyrapone + propranolol h.p.v. (■); pretreatment imipramine + propranolol h.p.v. (□); pretreatment SKF 525-A + propranolol h.p.v. (●).

i.v. and h.p.v. administration in control and chlorpromazine pretreated animals are shown in Figure 1. Chlorpromazine had only a small effect on the concentration of i.v. propranolol. In contrast, chlorpromazine markedly increased the blood concentrations following h.p.v. propranolol resulting in approximately 10 fold higher blood concentrations at all sampling times.

The effects of pretreatment with imipramine, metyrapone and SKF 525-A on the blood concentration of h.p.v. propranolol are shown in Figure 2. Imipramine and SKF 525-A, but not metyrapone, increased propranolol concentrations to an extent similar to that seen after chlorpromazine pretreatment. After pretreatment with SKF 525-A the mean peak concentration of propranolol was not achieved until after 10 min.

Average values of the pharmacokinetic parameters of propranolol from control and drug pretreated rats are shown in Table 1. After i.v. administration there was no statistically significant difference between any of the calculated parameters in control and

Table 1 Pharmacokinetic parameter estimates for propranolol in the pithed rat

	I.v. administration		*H.p.v. administration*				
	Control (5)	+ Cpz (3) pretreatment	Control (9)	+ Cpz (5) pretreatment	+ Imipramine (4) pretreatment	+ SKF 525-A (4) pretreatment	Metyrapone (4) pretreatment
AUC_0^∞ (ng min ml^{-1})	1543 ± 358	2224 ± 452	114 ± 23	1214 ± 240***	1256 ± 287***	1298nn ± 250***	51 ± 8
Total body clearance (ml min^{-1} kg^{-1})	88 ± 26	47 ± 5	1587 ± 494	97 ± 20**	93 ± 20*	84* ± 11	2117 ± 281
$T_{\frac{1}{2}}$ (β) (min)	81 ± 32	69 ± 11	65 ± 15	56 ± 11	96 ± 65	74 ± 30	29 ± 7
Apparent volume of distribution (l kg^{-1})	6.3 ± 1.5	4.5 ± 0.5					
Extraction ratio, (E)			0.93	0.45			

The number of experiments in each group are shown by the figures in parentheses. Cpz = chlorpromazine.
Statistical treatment of data employed Student's *t* test. Differences between control and drug pretreated animals, after administration of propranolol by the same route, are indicated: *$P<0.05$; **$P<0.01$; ***$P<0.001$.

Table 2 Propranolol metabolites in blood after i.v. and h.p.v. administration of propranolol (100 μg kg^{-1}) to pithed rats

	AUC_0^{25} (ng min ml^{-1})			AUC_0^{60} (ng min ml^{-1})			AUC_0^{120} (ng min ml^{-1})		
	Basic	*Acidic*	*Total*	*Basic*	*Acidic*	*Total*	*Basic*	*Acidic*	*Total*
I.v. administration									
Control (4)	50 ± 9	33 ± 5	391 ± 20	95 ± 15	87 ± 26	1151 ± 146**	143 ± 31	206 ± 63	2859 ± 340*
H.p.v. administration									
Control (8)	46 ± 4	42 ± 5	880 ± 65	81 ± 11	95 ± 10	2248 ± 189	115 ± 22	148 ± 54	4721 ± 392
+ Chlorpromazine (5)	76 ± 13*	25 ± 1*	621 ± 28**	148 ± 41	64 ± 3*	1814 ± 82	273 ± 61*	134 ± 6	3942 ± 213
+ Imipramine (4)	59 ± 5	36 ± 7	618 ± 47*	197 ± 9***	72 ± 9	1625 ± 61*	297 ± 22***	154 ± 21	3265 ± 97*
+ SKF 525-A (4)	89 ± 7***	28 ± 3	499 ± 62***	170 ± 16***	87 ± 14	1509 ± 165*	269 ± 34**	178 ± 38	3229 ± 418*
+ Metyrapone (4)	111 ± 5***	27 ± 4	1058 ± 151	98 ± 9	78 ± 15	2724 ± 461	147 ± 25	159 ± 33	5977 ± 908

Areas under the blood metabolite concentration (in propranolol equivalent concentrations) versus time curves were computed, using the trapezoidal rule, from 0 to 25 min (AUC_0^{25}), 0 to 60 min (AUC_0^{60}) and 0 to 120 min (AUC_0^{120}). Statistical analysis between h.p.v. controls and i.v. control animals and between h.p.v. control and drug pretreated animals employed non-paired Student's *t* tests: *$P<0.05$; **$P<0.01$; ***$P<0.001$.

chlorpromazine pretreated animals. Nevertheless, the values of apparent volume of distribution and elimination half life were lower in the chlorpromazine pretreated animals and the area under the blood concentration time curve (AUC_0^∞) was 44% greater than in control animals.

The kinetics of propranolol after h.p.v. administration were markedly altered by chlorpromazine pretreatment. The AUC_0^∞ was increased by 8 fold after chlorpromazine pretreatment reflecting a 50% decrease in the extraction ratio of propranolol during HFPE. The total body clearance was decreased by chlorpromazine to a value similar to that seen in control rats after i.v. administration.

Imipramine and SKF 525-A both altered the AUC_0^∞ and the total body clearance of propranolol following h.p.v. administration by amounts similar to that seen after chlorpromazine. Metyrapone had little effect on propranolol kinetics. No statistically significant changes in these parameters were observed. The values of clearance and half life suggest if anything, an enhanced rate of drug elimination.

None of the drug pretreatments resulted in a statistically significant change in drug half life.

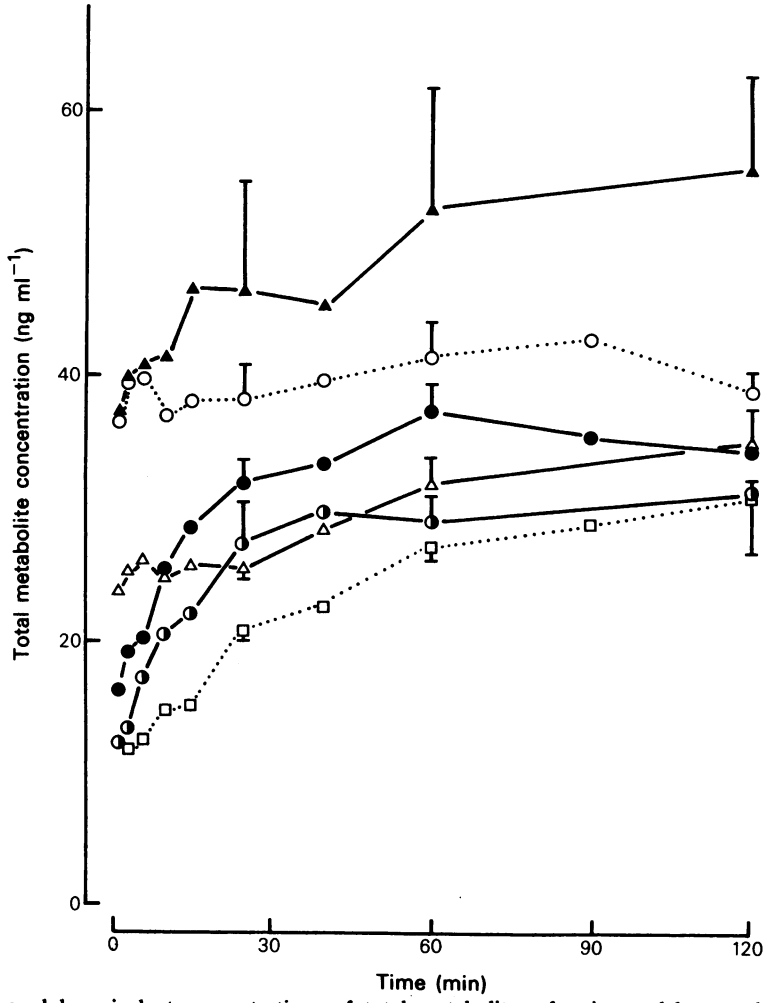

Figure 3 Propranolol equivalent concentrations of total metabolites after i.v. and h.p.v. administration of propranolol (100 μg kg^{-1}) in control and chlorpromazine (Cpz), metyrapone, imipramine and SKF 525-A pretreated pithed rats. For clarity, standard error bars are included at certain times only. Propranolol i.v. (□); propranolol h.p.v. (○); pretreatment metyrapone + propranolol h.p.v. (▲); pretreatment Cpz + propranolol h.p.v. (●); pretreatment imipramine + propranolol h.p.v. (△); pretreatment SKF 525-A + propranolol h.p.v. (◑).

The effect of chlorpromazine, imipramine, SKF 525-A and metyrapone on the formation of propranolol metabolites

The mean concentrations, in propranolol equivalents, of total metabolites in blood following i.v. administration of propranolol in control animals, and after h.p.v. administration of propranolol in control and drug pretreated animals are shown in Figure 3.

Initially, the concentration of metabolites was at least 3 fold greater after h.p.v. compared with i.v. administration of propranolol to control animals. Chlorpromazine, imipramine and SKF 525-A all decreased the metabolite concentrations after h.p.v. administration of propranolol during the early blood samples. However, metyrapone did not affect the concentrations in the initial samples but increased the concentrations subsequently such that, after 2 h the metabolite concentration was significantly greater than in h.p.v. controls.

The areas under the blood metabolite concentration-time curves were calculated using the trapezoidal rule, from 0 to 25 min, 0 to 60 min and 0 to 120 min and the mean values are displayed in Table 2. The contributions to the total metabolite AUC of metabolites extractable from basic and acidic media are also given in Table 2 for the same time periods; the remainder of the total AUC being attributable to non-extractable, highly polar metabolites. Under the assay conditions employed, the basic and acidic metabolites extracting from the aqueous medium include 4-hydroxypropranolol, naphthoxylactic acid, N-desisopropyl propranolol, propranolol glycol and α-napththol (Pritchard, Schneck & Hayes, 1979). In no case could more than 25% (mean 13 ± 2%) of the AUC for total metabolites be accounted for by these known metabolites; the remainder resisted attempts to isolate them from aqueous solution.

Comparison of metabolite profiles in control animals after h.p.v. and i.v. administration of propranolol shows that the AUC of total metabolites is significantly less, after i.v. dosing for at least 2 h. At all times the concentrations of acidic and basic metabolites were very similar.

Chlorpromazine, imipramine and SKF 525-A, but not metyrapone, all reduced the AUC for total metabolites after h.p.v. propranolol during the first 25 min (the period most likely to reflect reduced HFPE). The decreased formation of acidic metabolites observed after all pretreatments was only statistically significant after chlorpromazine whereas chlorpromazine, metyrapone and SKF 525-A all significantly increased the concentrations of basic metabolites compared with h.p.v. controls. The trends observed during the first 25 min were reflected in the values of AUC up to 2 h.

The AUC for total circulating radiolabelled compounds, i.e. the sum of the AUC for propranolol and total metabolites, up to 25, 60 and 120 min after propranolol administration is shown in Table 3. There are no statistically significant differences between any of these values.

The effect of chlorpromazine, imipramine, SKF 525-A and metyrapone on the pharmacological effect of propranolol

The average percentage inhibition of the induced tachycardia caused by propranolol after i.v. and h.p.v. administration in control and drug pretreated rats is displayed in Figure 4. The area under the percentage inhibition-time curve was calculated, from 0 to 20 min, for individual experiments and the mean values are given in Table 4. Calculation of the AUC for pharmacological effect allowed direct comparison of the results irrespective of the method used to induce the initial tachycardia (i.e. continuous or

Table 3 Total radiolabelled compounds in blood after i.v. and h.p.v. administration of [^{3}H]-propranolol to pithed rats

	AUC_0^{25} (ng min ml^{-1})	AUC_0^{60} (ng min ml^{-1})	AUC_0^{120} (ng min ml^{-1})
I.v. administration			
Control (4)	912 ± 67	1891 ± 104	3804 ± 274
H.p.v. administration			
Control (8)	914 ± 69	2305 ± 190	4816 ± 403
+ Chlorpromazine (5)	1137 ± 88	2618 ± 231	4974 ± 400
+ Imipramine (4)	1216 ± 134	2467 ± 196	4669 ± 355
+ SKF 525-A (4)	956 ± 81	2207 ± 181	4219 ± 339
+ Metyrapone (4)	1088 ± 150	2756 ± 462	6026 ± 910

Areas under the radiolabelled compounds concentration (in propranolol equivalent concentration) versus time curves were computed, using the trapezoidal rule, from 0 to 25 (AUC_0^{25}), 0 to 60 (AUC_0^{60}) and 0 to 120 min (AUC_0^{120}).

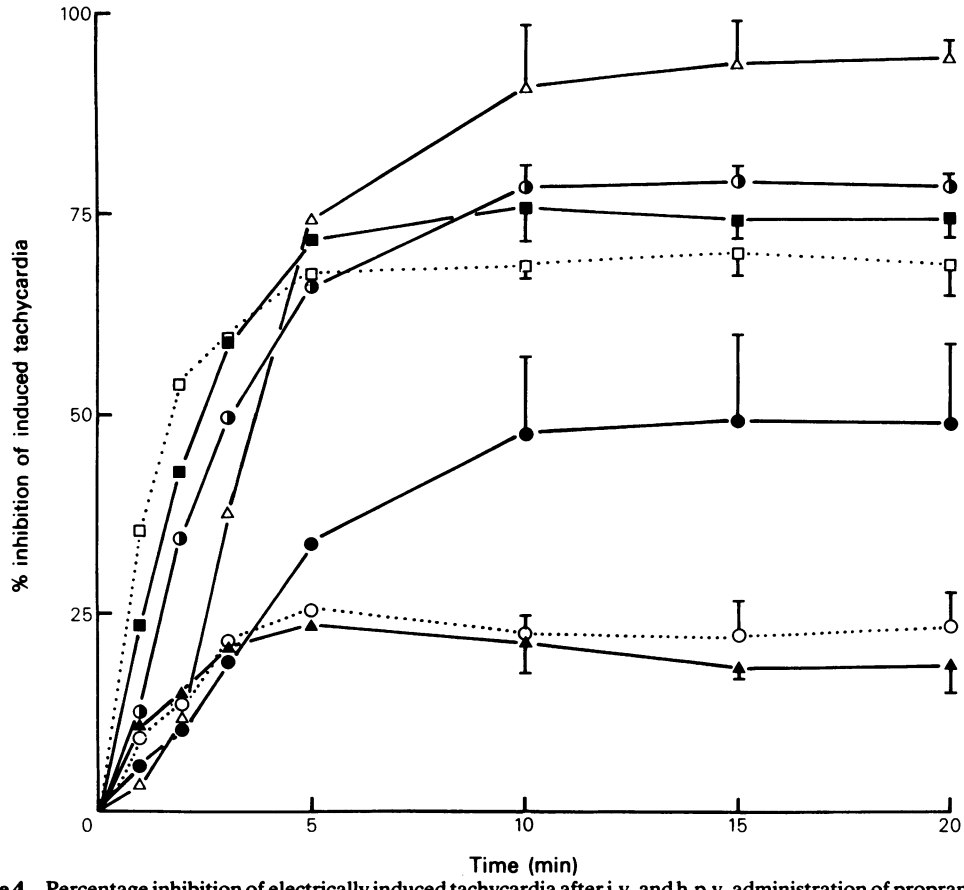

Figure 4 Percentage inhibition of electrically induced tachycardia after i.v. and h.p.v. administration of propranolol ($100\,\mu g\,kg^{-1}$) in control, and chlorpromazine (Cpz), metyrapone, imipramine and SKF 525-A pretreated pithed rats: propranolol i.v. (□); pretreatment Cpz + propranolol i.v. (■); propranolol h.p.v. (○); pretreatment Cpz + propranolol h.p.v. (●); pretreatment metyrapone + propranolol h.p.v. (▲); pretreatment imipramine + propranolol h.p.v. (△); pretreatment SKF 525-A + propranolol h.p.v. (◑).

Table 4 The pharmacological effect of propranolol after i.v. and h.p.v. administration in pithed rats

Treatment	AUC_0^{20} (% inhibition min)
I.v. administration	
Control (5)	1268 ± 25**
+ Chlorpromazine (3)	1339 ± 71**
H.p.v. administration	
Control (8)	413 ± 34
+ Chlorpromazine (5)	783 ± 138*
+ Imipramine (4)	1537 ± 94**
+ SKF 525-A (4)	1364 ± 96**
+ Metyrapone (4)	379 ± 71

The area under the percent inhibition versus time curve was computed, using the trapezoidal rule, up to 20 min following propranolol ($100\,\mu g\,kg^{-1}$) administration. Statistical analysis between h.p.v. control and all other treatments was by non-paired Student's *t* test: $^*P<0.01$; $^{**}P<0.001$. Number of experiments is given in parentheses.

short train stimulation) since h.p.v. administration of propranolol to control animals resulted in virtually identical values of AUC_0^{20} for both types of stimulation.

Intravenous and h.p.v. administration of equal doses of propranolol produced very different effects upon heart rate consistent with the difference in blood propranolol concentrations. Pretreatment with chlorpromazine, imipramine and SKF 525-A potentiated the percentage inhibition of electrically induced tachycardia from h.p.v. propranolol, whereas, after metyrapone, the response to propranolol was virtually identical to that of control animals. A correlation between the pharmacological effect and blood concentration of propranolol was attempted by plotting the AUC_0^{20} for percentage inhibition against the logarithm of AUC_0^{20} of propranolol concentration (Figure 5). Responses in control animals after h.p.v. and i.v. administration are joined by the broken line.

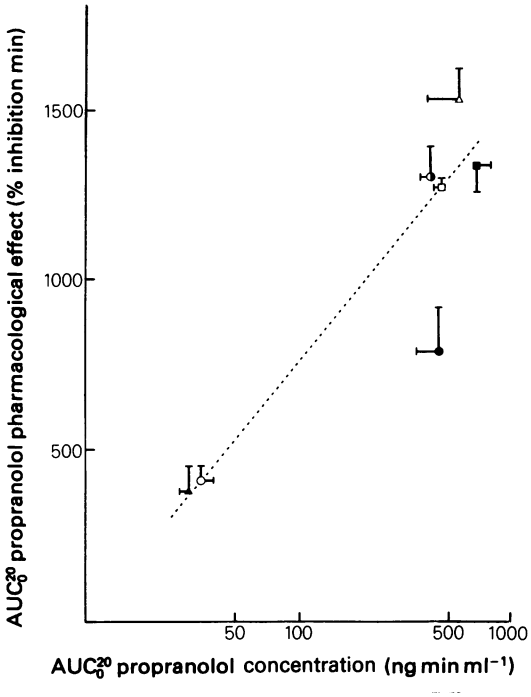

Figure 5 The mean pharmacological effect plotted against the blood concentrations of propranolol after i.v. and h.p.v. administrations of propranolol after i.v. and h.p.v. administration of propranolol ($100\,\mu g\,kg^{-1}$) in control and chlorpromazine (Cpz), metyrapone, imipramine and SKF 525-A pretreated pithed rats: propranolol i.v. (□); pretreatment Cpz + propranolol i.v. (■); propranolol h.p.v. (○); pretreatment Cpz + propranolol h.p.v. (●); pretreatment metyrapone + propranolol h.p.v. (▲); pretreatment imipramine + propranolol h.p.v. (△); pretreatment SKF 525-A + propranolol h.p.v. (◑).

The responses after chlorpromazine treatment were lower than would be predicted from the propranolol concentrations after both i.v. and, particularly, h.p.v. administration. This suggests that a pharmacodynamic interaction may occur between chlorpromazine and propranolol.

Discussion

This study shows that the hepatic first pass elimination (HFPE) of propranolol in the pithed rat is reduced following pretreatment with chlorpromazine, imipramine and SKF 525-A, but is not affected by pretreatment with metyrapone. Chlorpromazine, imipramine and SKF 525-A all resulted in an increased propranolol blood concentration after hepatic portal vein (h.p.v.) administration which was associated with decreased formation of metabolites and enhanced β-adrenoceptor blockade.

Chlorpromazine, imipramine and SKF 525-A all increased the AUC_0^{∞} of h.p.v. propranolol to such an extent that the bioavailability approached that obtained after i.v. administration. Although the AUC_0^{∞} of h.p.v. propranolol was altered similarly by chlorpromazine, imipramine and SKF 525-A, an interesting difference in the blood concentration profile was observed following SKF 525-A. SKF 525-A appeared to delay the passage of propranolol into the systemic circulation, an effect which may be due to altered hepatic blood flow. Reduced blood flow after SKF 525-A has been reported in the rat (Marchand & Brodeur, 1970) although other studies have shown no change (Nies, Wilkinson, Rush, Strother & McDevitt, 1976).

The dose of propranolol used in these experiments was low in order to minimize the non-linear kinetics known to occur in rats after larger oral doses (Shand, Rango & Evans, 1972). The doses of chlorpromazine, imipramine and SKF 525-A used were large relative to the dose of propranolol, but were calculated, in the cases of chlorpromazine and imipramine, to produce blood concentrations equivalent to those achieved in clinical practice.

The low dose of propranolol made quantification of individual metabolites difficult but the use of radiolabelled propranolol had the advantage that total metabolite concentrations could be accurately determined. After i.v. or h.p.v. administration at no time could more than 25% of all metabolites be accounted for by basic and acidic metabolites. Thus, the more commonly measured propranolol metabolites, such as 4-hydroxypropranolol and naphthoxylactic acid represented only a small fraction of the total metabolites in this study.

The reduction in total metabolite concentrations caused by chlorpromazine, imipramine and SKF

525-A could not be attributed to decreased basic or acidic metabolite concentrations. On the contrary, concentrations of basic metabolites were generally increased by these three drugs. These results are consistent with the inhibition of a secondary metabolic pathway for the basic metabolites, e.g. glucuronide formation. 4-Hydroxypropranolol glucuronide has been shown to be a major urinary metabolite in man (Walle, Conradi, Walle, Fagan & Gaffney, 1980) and inhibition of glucuronyl transferase would lead to increased circulating 4-hydroxypropranolol concentrations. An alternative explanation may be that other, as yet unidentified, phase I metabolic pathways exist which produce highly polar metabolites, and that inhibition of the enzymes involved would provide more substrate for alternative pathways; thus increased basic metabolite formation would result. The fact that chlorpromazine (Dybing, 1972), imipramine (Dybing, 1973) and SKF 525-A (Cooper, Axelrod & Brodie, 1954) have all been shown to inhibit the glucuronidation of certain drugs suggests that inhibition of phase II metabolism may represent the main mechanism of the reduced HFPE seen in this study.

The lack of effect of metyrapone upon total metabolite formation is also of interest as it has been shown to inhibit the *in vitro* metabolism of the structurally related β-adrenoceptor blocking agent, alprenolol (Grundin, Moldeus, Orrenius, Borg, Skanberg & von Bahr, 1974). Metyrapone differs from SKF 525-A, imipramine and propranolol in that it binds to cytochrome P-450 to produce a type II spectral change (Hildebrandt, 1972). Moreover, it has been shown to increase the metabolism of some compounds, such as acetanilide (Liebman, 1969), as well as inhibiting the metabolism of others. Enhanced hydroxylation of propranolol could account for the transient increase in basic metabolite concentrations which was used in this study.

From the results obtained it is concluded that the HFPE of propranolol was reduced by chlorpromazine, imipramine and SKF 525-A as a result of inhibited metabolism. The possible influence of altered liver blood flow may be unimportant since, theoretically, the clearance of propranolol after oral or h.p.v. administration is dependent solely upon hepatic enzyme activity (Nies *et al.*, 1976). In addition, the pharmacological effects of chlorpromazine and imipramine would be expected to result in opposite changes in liver blood flow, although the prediction of any change is complicated in a pithed animal. Also in addition, an altered volume of distribution is unlikely as a possible explanation for the increased propranolol concentrations since the sum of the concentrations of propranolol and its metabolites were similar after all treatments. The small effect that chlorpromazine had upon disposition of propranolol confirmed that volume of distribution changes could not account for the reduced HFPE.

The clinical implications of these results are of considerable interest and may influence the prescriber to use non-metabolizable, water soluble drugs such as atenolol, nadolol or sotalol rather than extensively metabolizable lipid soluble drugs. Indeed, an interaction between chlorpromazine and propranolol, similar to that demonstrated in the present study, has been observed in man (Vestal, Kornhauser, Hollifield & Shand, 1979).

Established problems with drugs such as propranolol which undergo extensive FPE, include large inter-individual variations in blood concentrations and low oral bioavailability. Two further prescribing problems are indicated by this study. First, there may be a requirement to modify doses when concurrent drugs affecting metabolism are prescribed. Secondly, the effects of variable and sometimes large blood concentrations of circulating metabolites require evaluation. Recently, the effect of propranolol upon chlorpromazine bioavailability has been investigated in man and an increase in the bioavailability of chlorpromazine was reported (Peet, Middlemiss & Yates, 1980); the authors suggested that the antischizophrenic properties of propranolol could be attributed entirely to this pharmacokinetic interaction. The effect of highly metabolized drugs such as propranolol upon the bioavailability of other drugs undergoing extensive FPE is an area of study that also requires further study.

This work was supported by I.C.I. Ltd. We thank Dr J. Cruickshank for his interest in this project.

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(Received March 25, 1982.
Revised July 12, 1982.)