The impairment of lignocaine clearance by propranolol—major contribution from enzyme inhibition

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1 To account for a 40% lowering of the systemic clearance of lignocaine by propranolol treatment it has been proposed that propranolol reduces liver blood flow by 25% and causes a 50% decrease in the intrinsic clearance of lignocaine by enzyme inhibition.

2 In theory, the contribution of direct enzyme inhibition is best evaluated using oral administration of lignocaine when models of hepatic drug clearance predict that propranolol could increase the AUC_{po} of lignocaine by 100–140%.

3 This hypothesis was tested in six healthy men who received 200 mg lignocaine HCl.H₂O orally with and without propranolol pre-treatment (80 mg twice daily for 3 days). Propranolol treatment increased the mean plasma AUC_{po} of lignocaine by 113 ± 58 s.d.% ($P < 0.005$); it increased the peak plasma lignocaine concentration by 79 ± 50 s.d.% ($P < 0.025$) and it prolonged the elimination half-life of lignocaine by 20 ± 13 s.d.% ($P < 0.05$).

4 Propranolol treatment lowered indocyanine green clearance by 11 ± 15 s.d.%, but this change was not significant statistically.

5 These experimental results are in accord with the theoretical predictions suggesting that propranolol lowers the systemic clearance of lignocaine mainly by direct inhibition of its metabolism rather than by a lowering of the hepatic blood flow.

Keywords lignocaine propranolol enzyme inhibition

Introduction

Propranolol treatment lowers the systemic clearance (CL) of lignocaine in man by about 40%. Two mechanisms have been proposed to explain this observation, namely a reduction of liver blood flow and direct inhibition of oxidative drug metabolism by propranolol (Ochs *et al.*, 1980; Conrad *et al.*, 1983; Tucker *et al.*, 1984). The first of these mechanisms is believed to be the result of a combination of blockade of β_1 -receptors in the heart, lowering cardiac output, and of β_2 -receptors in the splanchnic circulation, causing a specific decrease in hepatic portal blood flow (Westaby *et al.*, 1984). Thus, a maximum fall in hepatic blood flow of 20–25% occurs after

therapeutic doses of propranolol. However, the extent of this change is insufficient to explain all of the effect of propranolol on lignocaine clearance and *in vitro* data, from studies with rat and human liver microsomes, indicate an additional inhibitory influence of propranolol on the enzymes which metabolise lignocaine (Deacon *et al.*, 1981; Al-Asady *et al.*, 1982; Bax *et al.*, 1983; Tucker *et al.*, 1984).

Using mathematical models of hepatic drug clearance, Tucker *et al.* (1984) have suggested that if propranolol lowers hepatic blood flow by 25% and also decreases the intrinsic hepatic metabolic clearance of lignocaine by 50%, this

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would account for the observed 40% reduction in the systemic clearance of lignocaine. These calculations were based upon the 'well-stirred' model and the 'parallel-tube model' (Shand, 1978), which define the respective clearance values, CL_I and CL_{II} , by equations (1) and (2):

$$CL_I = Q_H \cdot \frac{f u_B \cdot CL_{u_{int},I}}{Q_H + f u_B \cdot CL_{u_{int},I}} \quad \dots (1)$$

$$CL_{II} = Q_H (1 - e^{-f u_B \cdot CL_{u_{int},II}/Q_H}) \quad \dots (2)$$

(where: Q_H = hepatic blood flow; $f u_B$ = free fraction of drug in blood; $CL_{u_{int}}$ = intrinsic hepatic clearance).

It was assumed that the normal hepatic clearance of lignocaine, which approximates to its total clearance, is $0.95 \text{ L} \cdot \text{min}^{-1}$, that normal hepatic blood flow is $1.5 \text{ L} \cdot \text{min}^{-1}$ and that the free fraction of lignocaine in blood is 0.36 (Tucker *et al.*, 1977; Tucker & Mather, 1979). It has been shown that propranolol does not alter the plasma binding of lignocaine when the drugs are present together in clinically relevant concentrations (McNamara *et al.*, 1981).

If propranolol has no effect on the intrinsic clearance of lignocaine then the contribution of a 25% decrease in hepatic blood flow would predict a 17% lowering of CL based on equation (1) and a 13% lowering based on equation (2).

Corresponding equations for the AUC of a drug after oral dosage (D_{po}) given by the two models are (Pang & Rowland, 1977):

$$AUC_{po,I} = \frac{D_{po}}{f u_B \cdot CL_{u_{int},I}} \quad \dots (3)$$

and

$$AUC_{po,II} = \frac{D_{po} (e^{-f u_B \cdot CL_{u_{int},II}/Q_H})}{Q_H (1 - e^{-f u_B \cdot CL_{u_{int},II}/Q_H})} \quad \dots (4)$$

Substitution into these equations predicts that a 25% lowering of hepatic blood flow together with a 50% decrease in the intrinsic clearance of lignocaine would increase AUC_{po} by 100% and 142%, respectively. A 25% decrease in hepatic blood flow alone predicts no change in AUC_{po} according to model I and a decrease of 18% according to model II.

The present study, involving the oral administration of lignocaine with and without propranolol pre-treatment, was performed to test these predictions. The effect of propranolol on indocyanine green (ICG) clearance was also measured. This compound has a similar hepatic extraction ratio (about 0.7) to that of lignocaine (Caesar *et al.*, 1961; Leevy *et al.*, 1962; Grainger *et al.*, 1983) and, provided that propranolol does not inhibit its intrinsic clearance, changes in its systemic clearance should reflect the effect of

propranolol on hepatic blood flow. Thus, if propranolol lowers hepatic blood flow by 25% then ICG clearance should decrease by 13–17%, as predicted by equations (1) and (2).

Methods

Subjects

Six healthy male volunteers (aged 26–34 years, weight 63–75 kg) from the staff of this Department took part in the study. All were non-smokers and none were taking other drugs. Written informed consent was obtained from each subject and the study was approved by the Royal Hallamshire Hospital Ethics Committee.

Study design

Each subject received an oral dose of lignocaine hydrochloride monohydrate on two occasions separated by 2–3 weeks. One dose served as a control, the other being preceded by oral treatment with propranolol hydrochloride. During both phases of the study each subject received an intravenous dose of indocyanine green. The order of the two treatment phases was randomised.

Drug dosage

1. **Lignocaine** After an overnight fast 200 mg of lignocaine HCl.H₂O was given orally in 100 ml water at 09.00 h. The subjects were supine for 15 min before dosing and remained so for a further 3.5 h.

2. **Propranolol** Propranolol HCl, 80 mg, was given orally every 12 h for 3 days prior to lignocaine dosing. The final dose was taken with 20 ml water at 08.30 h on the day of lignocaine dosing.

3. **Indocyanine green** ICG, 0.5 mg kg⁻¹, was injected into an antecubital vein over 10 s at 11.30 h on the day of lignocaine dosing.

Blood sampling

Venous blood samples for the measurement of plasma lignocaine were taken at 10, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 240, 300, 360, 420 and 480 min after lignocaine dosing. After injection of ICG venous blood samples were taken for measurement of plasma concentrations of the dye at 2 min intervals for 20 min. All blood samples taken up to 240 min after lignocaine dosing were collected through an indwelling intravenous cannula sited in the arm opposite to

that used for ICG injection. The cannula was kept patent by a slow infusion of 0.9% w/v sodium chloride at a rate of 10 ml h⁻¹. Blood samples taken after 240 min were obtained by venepuncture. All samples were collected into lithium heparin tubes and the plasma was separated immediately. ICG concentrations were measured immediately and the plasma for lignocaine measurement was stored at -20°C until assayed.

Lignocaine assay

Plasma lignocaine was measured by g.l.c. (Bax *et al.*, 1980). The lower limit of the assay was 10 ng ml⁻¹ and at this concentration the coefficient of variation was 5.5%.

ICG assay

Plasma ICG was measured spectrophotometrically at 805 nm (Caesar *et al.*, 1961). Calibration curves were prepared using blank plasma from each subject. The lower limit of the assay was 0.25 µg ml⁻¹ at which concentration the coefficient of variation was 4.9%.

Pharmacokinetic analysis

The area under the plasma lignocaine concentration-time curve (AUC_{po}) was measured using the linear trapezoidal rule with extrapolation to infinity of the terminal slope. The terminal elimination half-life (*t*_{1/2,z}) of lignocaine was calculated from the terminal elimination rate constant (λ_z) obtained by least squares regression analysis of log plasma drug concentrations beyond 75–120 min.

The plasma clearance of ICG was calculated by dividing the dose by the area under the plasma dye concentration-time curve extrapolated to infinity.

Assessment of β -adrenoceptor blockade

The percentage decrease in exercise heart rate following a stepped exercise test on a bicycle ergometer was used to assess the degree of β -adrenoceptor blockade. Exercise tests were performed before and on the third day of treatment with propranolol 3–4 h after the morning dose. In the control periods the exercise heart rates were greater than 150 beats min⁻¹.

Statistical analysis

Comparisons between control data and data obtained after propranolol treatment were made using Student's *t*-test. A value of $P \leq 0.05$ was taken to indicate statistical significance.

Results

Plasma lignocaine concentration-time curves for each subject are shown in Figure 1.

Treatment with propranolol increased the mean AUC_{po} of lignocaine by 113 ± 58 s.d.% ($P < 0.005$); it increased the peak plasma concentration of lignocaine by 79 ± 50 s.d.% ($P < 0.025$) and it prolonged the *t*_{1/2,z} of lignocaine by 20 ± 13 s.d.% ($P < 0.05$). The time of the peak plasma concentration of lignocaine (20–50 min) was not affected by propranolol (Table 1).

Propranolol decreased ICG clearance by 11 ± 15 s.d.% but this change was not significant statistically (Table 1). The mean percentage decrease in exercise heart rate produced by propranolol was 31 ± 9 s.d.%.

Discussion

The experimental findings were in good agreement with the theoretical expectations. Thus, the observed 113% increase in the AUC_{po} of lignocaine compares with values of 100% and 142% predicted by the 'well-stirred' and 'parallel-tube' models, respectively.

The possibility that the experimental data might be explained by increased absorption of lignocaine across the gut wall in the presence of propranolol can be dismissed since lignocaine is completely absorbed (Keenaghan & Boyes, 1972; Bennett *et al.*, 1982). Furthermore, the comparison of observed and predicted changes is not complicated by any non-linearity in the kinetics of lignocaine since dose-independency over the range of plasma drug concentrations encountered has been established for both i.v. and oral administration (Bennett *et al.*, 1982; Ochs *et al.*, 1983a).

Although not significant statistically, the observed 11% decrease in ICG clearance during propranolol treatment is compatible with the 13–17% change predicted by the models and based upon a 25% lowering of liver blood flow. Thus, the overall findings support the conclusion that enzyme inhibition by propranolol, rather than its influence on hepatic perfusion, makes the major contribution to the observed 40% lowering of the systemic clearance of lignocaine produced by propranolol in man (Ochs *et al.*, 1980; Conrad *et al.*, 1983).

The results suggest that average therapeutic doses of propranolol may inhibit the intrinsic clearance of lignocaine by about 50%. Direct evidence for inhibition of lignocaine metabolism by propranolol has been obtained using rat and human liver microsomes (Deacon *et al.*, 1981; Al-Asady *et al.*, 1982; Bax *et al.*, 1983; Tucker *et al.*, 1984). These *in vitro* studies also showed that

Figure 1 Plasma lignocaine concentrations after oral administration of 200 mg lignocaine HCl.H₂O in six subjects: ○, control; ●, during propranolol treatment.

Table 1 The effect of propranolol on lignocaine and indocyanine green kinetics

Subject	AUC_{po} ($\mu\text{g ml}^{-1} \text{min}$)		Lignocaine				t_{max} (min)		Indocyanine green plasma clearance ($\text{ml min}^{-1} \text{kg}^{-1}$)	
			$t_{1/2,z}$ (min)		C_{max} (ng ml^{-1})					
	C	Pr	C	Pr	C	Pr	C	Pr	C	Pr
1	64	98	80	94	445	709	50	40	11.3	8.1
2	51	145	103	133	611	1179	30	50	7.9	7.8
3	36	102	100	112	473	1175	20	30	9.8	9.7
4	51	107	103	108	319	692	40	40	10.7	11.5
5	93	162	126	178	614	879	30	40	10.8	7.8
6	51	87	108	122	552	614	30	30	9.8	8.2
Mean	58	117	103	125	502	875	33	38	10.1	8.9
s.d.	19	30	15	29	114	250	10	8	1.2	1.5
P	< 0.005		< 0.05		< 0.025		NS		NS	

C, control phase; Pr, propranolol treatment phase

other β -adrenoceptor antagonists inhibited lignocaine metabolism in relation to their lipid-solubility. On this basis, Tucker *et al.* (1984) predicted possible effects of a series of β -adrenoceptor antagonists on lignocaine clearance in man. The prediction for propranolol is supported by the present data, but those for the other agents need some revision in the light of more recent experimental findings (Table 2).

Evidence is now available in man showing that cardioselective β -adrenoceptor antagonists may not lower total hepatic blood flow significantly (Westaby *et al.*, 1984). This is rationalised as follows. Blockade of cardiac β_1 -adrenoceptors causes a decrease in hepatic arterial blood flow through lowering of cardiac output. However, a compensatory reflex increase in hepatic portal blood flow occurs such that total flow is unaltered. In contrast, intra-hepatic β_2 -adrenoceptor blockade by non-selective β -adrenoceptor antagonists augments the effect of the fall in cardiac output such that total hepatic blood flow is decreased. Agents with intrinsic sympathomimetic activity (ISA) do not lower cardiac output (Svendsen *et al.*, 1982) and intra-hepatic regulation of arterial and portal flows may maintain normal total hepatic blood flow. Thus, significant changes in hepatic blood flow might be anticipated only with non-selective β -adrenoceptor antagonists without ISA. Ahmad *et al.* (1984) have shown that the extraction ratio of lignocaine in the perfused rat liver is greater when input is through the portal vein compared to the hepatic artery. However, any such difference is likely to be of much less significance in man where the value of the extraction ratio is considerably less (0.7 vs > 0.9).

Whereas Conrad *et al.* (1983) showed that metoprolol lowered the clearance of lignocaine significantly by about 25%, more recent studies found no significant effects (Jordo *et al.*, 1984; Miners *et al.*, 1984). However, it is possible that

the power of these studies was not sufficient to detect the predicted small decrease in the clearance of lignocaine due to enzyme inhibition. Others have shown that metoprolol causes small but statistically significant decreases in the clearance of antipyrine (Bax *et al.*, 1981) and theophylline (Conrad & Nyman, 1980). Penbutolol, which is more lipid-soluble than propranolol and might therefore be expected to show greater inhibition of lignocaine metabolism, was shown to be without effect on lignocaine clearance (Ochs *et al.*, 1983t). As discussed by Bax *et al.* (1985), who showed that penbutolol, unlike propranolol, does not inhibit antipyrine clearance in man, these findings may reflect differences in the doses of the β -adrenoceptor antagonists, differences in their concentrations at the enzyme site *in vivo* and *in vitro* and the possibility that propranolol may have a unique inhibitory effect mediated by the formation of a covalently-bound metabolic intermediate.

The balance of the evidence indicates that any inhibitory effects of β -adrenoceptor antagonists on the metabolic clearance of other drugs is likely to be clinically significant only in the case of propranolol. Lignocaine is not used orally but the present findings suggest that possible effects of propranolol on the 'first-pass' metabolism of other high clearance drugs, such as tricyclic antidepressants, analgesics, phenothiazines and calcium-channel blockers, should be investigated. Propranolol is already known to double the plasma concentrations of chlorpromazine and this may account for its therapeutic effect in schizophrenic patients treated with the combination of these drugs (Peet *et al.*, 1980).

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Table 2 Predicted and observed changes in lignocaine clearance after various changes in hepatic blood flow and intrinsic clearance produced by β -adrenoceptor antagonists

β -adrenoceptor antagonist	K_p	ISA	Cardio-selective	Perturbation? [*]		Predicted ^{**}		% change in lignocaine clearance		P value	Reference
				Q_H	CL_{int}	WSM	PTM	Mean (range) ^{***}	Observed n		
Atenolol	0.013	-	+	$\longleftrightarrow$	$\longleftrightarrow$	0	0	$\downarrow 0.8 (+30, -32)$	7	NS	1
Pindolol	0.70	+	-	$\longleftrightarrow$	$\downarrow 25\%$	$\downarrow 11$	$\downarrow 17$	$\downarrow 7$	8	NS	2
Metoprolol	0.89	-	+	$\longleftrightarrow$	$\downarrow 25\%$	$\downarrow 11$	$\downarrow 17$	$\downarrow 25 (+7, -60)$ $\downarrow 11 (+29, -44)$ $\downarrow 6$	6 7 6	<0.01 NS NS	3 1 4
Propranolol	22.4	-	-	$\downarrow 25\%$	$\downarrow 50\%$	$\downarrow 37$	$\downarrow 42$	$\downarrow 35 (-9, -69)$ $\downarrow 23 (-10, -37)$ $\downarrow 43 (-23, -68)$ $\downarrow 19$	7 7 6 8	<0.05 <0.02 <0.001 <0.02	5a 5b 3 2
Penbutolol	179	+	-	$\longleftrightarrow$	$\downarrow > 50\%$	$\downarrow > 37$	$\downarrow > 42$	$\uparrow 19$	7	NS	6

K_p , n octanol/buffer pH 7.4, 37°C partition coefficient (Bax *et al.*, 1983); ISA, intrinsic sympathomimetic activity; Q_H , hepatic blood flow; CL_{int} , intrinsic clearance.

^{*}Based upon the assumptions that only non-selective agents without ISA lower hepatic blood flow (by a maximum of 25%—see text) and that agents with low, intermediate and high lipid solubility decrease the intrinsic clearance of lignocaine by 0, 25 and 50% respectively (Tucker *et al.*, 1984).

^{**}Predicted changes calculated assuming the 'well-stirred' model (WSM) and 'parallel tube' model (PTM) of hepatic drug clearance.

^{***}Where ranges are quoted, the mean value has been calculated from data from each subject.

References and drug dosages (as salts where appropriate).

1. Miners *et al.* (1984): metoprolol, 100 mg p.o. twice daily for 7 days; atenolol 50 mg p.o. once daily for 7 days; lignocaine 75–100 mg i.v. over 2 min
2. Svendsen *et al.* (1982): pindolol, 0.023 mg kg⁻¹ i.v. single dose; propranolol, 0.18 mg kg⁻¹ i.v. single dose; lignocaine 2 mg min⁻¹ i.v. for 6 h
3. Conrad *et al.* (1983): metoprolol, 50 mg p.o. every 6 h for 1 day; propranolol, 40 mg p.o. every 6 h for 1 day; lignocaine 2.5–3 mg.min⁻¹ i.v. over 10 min
4. Jordo *et al.* (1984): metoprolol, 100 mg p.o. twice daily for 2 days; lignocaine 100 mg i.v. over 12 min
- 5a. Ochs *et al.* (1980): propranolol, 80 mg p.o. every 8 h for 3 days; lignocaine 150–300 mg i.v. over 4 min
- 5b. Ochs *et al.* (1980): propranolol, 80 mg every 8 h 3 days; lignocaine 100 mg i.v. over 3 min then 2 mg min⁻¹ for 36 h
6. Ochs *et al.* (1983b): penbutolol, 60 mg p.o. once daily for 3 days; lignocaine 100 mg i.v. over 3 min

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