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ROLES OF HEPATIC BLOOD FLOW AND ENZYME ACTIVITY IN THE KINETICS OF PROPRANOLOL AND SOTALOL

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1 The roles of the hepatic blood flow and the drug oxidizing enzyme system in eliminating oral propranolol and sotalol were studied in twelve subjects with biopsy proven liver parenchymal disease.

2 The apparent plasma clearance of propranolol was closely related both to the *in vivo* (antipyrine test) and *in vitro* (cytochrome P-450) indices of the activity of the hepatic mixed function oxidase system.

3 Propranolol clearance had also a clear relationship to the estimated liver blood flow. Altered flow was, however, suggested to be a minor factor when compared with changes in the enzyme system.

4 The elimination rate of sotalol had no correlation to the indices of hepatic drug metabolism or to the estimated liver blood flow.

5 It is concluded that both the deteriorated sinusoidal perfusion and the decreased mass of drug metabolizing enzymes may be responsible for the impaired elimination of oral propranolol in subjects with parenchymal liver disease.

Introduction

Propranolol is one of the oldest β-adrenoreceptor antagonists, having a vast use in the treatment of arterial hypertension, angina pectoris and some cardiac arrhythmias. Its metabolic fate is extensively hepatic oxidation, only negligible amounts being excreted in unchanged form (Bond 1967; Shand, Nuckolls & Oates 1970). Liver blood flow and the activity of the hepatic mixed function oxidase system are main determinants of propranolol elimination, though also the route of drug administration is important (Kornhauser, Wood, Vestal, Wilkinson, Branch & Shand 1978). After intravenous injection, the hepatic clearance of a highly extracted drug, such as propranolol, is greatly dependent on liver blood flow, but after oral administration the apparent clearance is, in theory, not altered by the liver blood flow, provided the hepatic vascular anatomy is normal (Shand, Kornhauser & Wilkinson 1975; Wilkinson & Schenker 1975; Wilkinson & Schenker 1976; Niess, Shand & Wilkinson 1976; Kornhauser *et al.*, 1978). Hence the clearance of oral propranolol is greatly, if not entirely, dependent on the activity of the hepatic drug metabolizing enzymes in subjects with normal liver. However, in subjects with disturbed liver architecture, the roles of liver blood flow and enzyme activity are poorly known.

The aim of the present study was to elucidate the problem by examining the relationship of the elimination of oral propranolol to the estimated liver blood flow and the *in vivo* (antipyrine test) and *in vitro* (cytochrome P-450) assays of the hepatic drug oxidizing enzyme system in subjects with altered liver parenchyma. To clarify the effect of hepatic factors on the kinetics of β-adrenoreceptor antagonists we examined also the plasma clearance of another β-blocking agent, sotalol, known to be eliminated unchanged (Garret & Schnelle 1971; Sundqvist, Anttila & Arstila 1974; Anttila, Arstila, Pfeffer, Tikkanen, Vallinkoski & Sundqvist 1976), and hence independently of the altered liver function.

Methods

Subjects

Twelve subjects (eleven men, one woman) with arterial hypertension or angina pectoris were

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Table 1 Clinical data, estimated liver size and serum biochemistry in propranolol subjects.

Patient	Age (years) and sex	Body weight (kg)	Cardiovascular diagnosis	Liver diagnosis	Liver weight (g)	Serum biochemistry BSP (%)	alb. (g/l)	TT (%)	ALAT (u/l)	A-P (u/l)
	43 M	52	Arterial hypertension	Fatty liver	1640	5.9	37	82	63	138
2	46 M	86	Angina pectoris	Fatty liver	2518	20.4	41	100	113	159
3	27 M	98	Arterial hypertension	Fatty liver	2637	8.9	43	86	83	161
4	38 M	100	Arterial hypertension	Fatty liver +hepatitis	1950	13.0	44	100	40	178
5	20 M	106	Arterial hypertension	Fatty liver +hepatitis	1970	4.3	50	60	34	182
6	52 F	64	Arterial hypertension	Fatty liver +hepatitis	2319	8.5	35	100	132	249
7	56 M	74	Angina pectoris	Cirrhosis	2258	26.0	41	90	114	203

M=male, F=female, BSP=BSP retention/45 min (normal less than 5%), alb.=serum albumin concentration (normal 40–54 g/l), TT=Thrombotest (normal 60–100%), ALAT=alanine aminotransferase (normal less than 40 u/l), A-P=alkaline phosphatase (normal 60–250 u/l).

Table 2 Clinical data, estimated liver size and serum biochemistry in sotalol subjects.

Patient	Age (years and sex	Body weight (kg)	Cardiovascular diagnosis	Liver diagnosis	Liver weight (g)	Serum biochemistry BSP (%)	alb. (g/l)	TT (%)	ALAT (u/l)	A-P u/l
1	43 M	52	Arterial hypertension	Fatty liver	1640	5.9	37	82	63	138
2	34 M	66	Arterial hypertension	Fatty liver	1425	—	41	100	65	128
3	55 M	83	Arterial hypertension	Fatty liver	2541	21.6	47	100	94	146
4	50 M	69	Arterial hypertension	Hepatitis	1796	9.3	44	100	45	290
5	50 M	104	Arterial hypertension	Liver cirrhosis	2097	13.0	43	100	38	214
6	42 M	91	Arterial hypertension	Liver cirrhosis	2558	—	44	65	122	134

investigated (Tables 1 and 2). One subject (No 1) was tested in crossover fashion with propranolol and sotalol and the others by only one of these drugs. Subject No 1 was an epileptic undergoing long-term phenytoin treatment, predicting induction of the hepatic drug metabolizing enzymes. Each patient had clinical or laboratory evidence of liver disease indicating diagnostic liver biopsy. None of the subjects had manifest heart failure, and their renal function, as judged by creatinine clearance, was normal. Informed consent was obtained before the antipyrine test.

Protocol

All subjects underwent a careful clinical and laboratory evaluation, including physical examination, hematologic studies, analysis of serum electrolytes, tests of liver and kidney function, electrocardiography and X-ray studies. The blood samples were taken after an overnight fast.

An oral antipyrine test (20 mg/kg body weight in 100 ml fruit juice) was performed to each subject after a night's fast. Venous blood samples for plasma antipyrine concentrations were drawn before and at 1, 3, 6, 9, 12, 24 and 48 h after the administration.

On the morning after the antipyrine test propranolol (dose 2×40 mg tablets) was administered to seven patients and sotalol (dose 2×80 mg tablets) to six patients after a 12 h fast. Plasma propranolol levels were determined from venous blood samples taken before and 1, 2, 4, 8 and 12 h after the administration, and plasma sotalol concentrations from specimens drawn before administration and 1, 2, 4, 8, 12, 24, 28, 30 and 32 h after it.

The simultaneous estimation of the size and blood flow of the liver with dynamic ^{99m}-Tc-sulphur colloid scan was performed before the antipyrine test. A liver biopsy with a ThruCut needle was taken after the scanning. All the samples were used for histologic studies and part of each specimen for determination of cytochrome P-450 contents. The patients were classified according to the histologic findings into the groups of fatty liver, hepatitis and cirrhosis.

Drug metabolism analyses

Plasma propanolol was assayed by the fluorometric technique of Shand *et al.*, (1970), and plasma sotalol by the method of Garret & Schnelle (1971) as modified by Sundqvist *et al.* (1974). Cytochrome P-450 was determined from the total homogenate of the biopsy material by the method of Greim, Schenkman, Klotzbucher & Remmer (1970). Plasma antipyrine concentrations were measured by a gas-liquid chromatographic method with phenacetin as an internal standard (Prescott, Adjepon-Yamoah & Roberts 1973).

Estimation of liver blood flow

Liver blood flow was measured by dynamic ^{99m}Tc-sulphur colloid scans as described earlier (Pirttiaho & Pitkänen 1977). Liver size was measured simultaneously by the method of Rollo & Deland (1968), and the relative blood flow per unit weight of the liver was obtained by dividing the total flow by liver weight.

Serum biochemistry

The determinations of serum alanine aminotransferase and alkaline phosphatase activities and serum albumin concentration were performed with standard automatized laboratory methods, according to the Scandinavian recommendation (SMAC Auto-Analyzer, Technicon). Thrombotest was determined by an automatic instrument (Thrombolab 702, Stockholm, Sweden). The 45-min retention of bromsulphtalein test was performed according to the standard method (Sherlock 1975).

Calculations

The plasma half-life ($T_{\frac{1}{2}}$) was read from the linear part of the time-concentration curve on a semilog graph. The apparent clearance (CL) was calculated from the equation $CL = D/AUC$, where D is the oral dose and AUC the area under the plasma concentration curve. AUC was obtained by the trapezoidal rule and the area to infinite time added by integration (C_t/k), where C_t is the last drug concentration value and k the elimination rate constant calculated from the equation $k = 0.693/T_{\frac{1}{2}}$. The apparent volume of distribution (aV_d) was calculated from the equation $aV_d = D/AUC \times k$. Statistical treatment of the data employed Student's *t*-test and regression analysis.

Results

Liver blood flow, hepatic enzyme activity and propranolol elimination

Tables 1 and 2 give the clinical data, liver size and serum biochemistry, and Tables 3 and 4 the results of drug metabolism and liver blood flow studies. The clearance rate of propranolol was significantly related to the plasma clearance of antipyrine and to the hepatic cytochrome P-450 content, whereas the correlation of propranolol half-life values to these parameters was not so good, as shown in Table 5. Fig. 1 shows the clear relationship of plasma propranolol clearance to antipyrine clearance and liver blood flow per unit weight of the liver. Though the correlations were somewhat poorer when the

Table 3 Estimated liver blood flow, indices of drug metabolism and kinetics of propranolol

	Liver blood flow			*Antipyrine Clearance*			*Cytochrome P-450*		*Propranolol*	
Patient	*Absolute* (*ml/min*)	*Relative* (*ml min^{-1} 1000 g^{-1}*)	$T_{\frac{1}{2}}$ (*h*)	*Absolute* (*ml/min*)	*Relative* (*ml min^{-1} 1000 g^{-1}*)	aV_d (*l/kg*)	*Content* (*nmol/g*)	*Total* (*μmol*)	$T_{\frac{1}{2}}$ (*h*)	*Clearance* (*ml/min*) × 10^3
1	2049	1250	3.7	124.5	75.9	0.78	17.14	28.11	4.6	10.40
2	1504	600	10.8	42.2	16.8	0.45	1.70	4.28	3.4	2.20
3	1848	700	12.0	32.5	12.3	0.34	2.70	7.12	5.1	0.95
4	1978	1010	6.2	56.8	29.1	0.31	12.75	24.86	2.9	4.90
5	1739	880	10.1	56.6	28.7	0.46	14.07	27.72	4.3	3.30
6	1426	610	10.2	26.2	11.3	0.36	4.80	11.13	4.6	1.29
7	1675	740	23.2	20.8	9.2	0.64	5.28	11.92	4.9	1.90

$T_{\frac{1}{2}}$ = half-life, aV_d = apparent volume of distribution

Table 4 Estimated liver blood flow, indices of drug metabolism and kinetics of sotalol

	Liver blood flow			*Antipyrine Clearance*			*Cytochrome P-450*		*Sotalol*	
Patient	*Absolute* (*ml/min*)	*Relative* (*ml min^{-1} 1000 g^{-1}*)	$T_{\frac{1}{2}}$ (*h*)	*Absolute* (*ml/min*)	*Relative* (*ml min^{-1} 1000 g^{-1}*)	aV_d (*l/kg*)	*Content* (*nmol/g*)	*Total* (*μmol*)	$T_{\frac{1}{2}}$ (*h*)	*Clearance* (*ml/min*)
1	2049	1250	3.7	124.5	75.9	0.78	17.14	28.11	8.0	114.9
2	1087	760	14.0	21.4	15.0	0.39	10.30	14.68	7.5	190.5
3	1567	620	14.2	28.6	11.3	0.42	4.50	11.43	8.7	128.2
4	1246	690	9.2	39.1	21.8	0.45	2.20	3.95	15.0	90.4
5	1269	610	13.2	58.2	27.8	0.64	3.10	6.50	10.5	242.4
6	1152	450	33.8	17.2	6.7	0.58	5.98	15.30	8.5	126.4

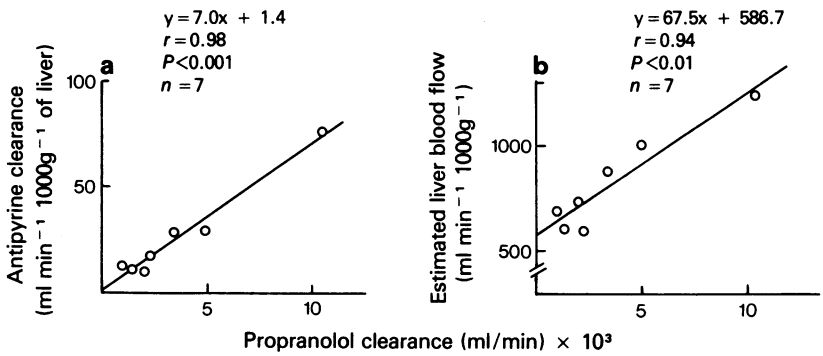

Figure 1 Relationship of propranolol clearance to a) antipyrine clearance and b) estimated liver blood flow.

absolute values were used, the differences between the respective correlation coefficients were not statistically significant. The kinetics of sotalol was not related to the indices of hepatic drug metabolism or to liver blood flow.

Comparison of factors affecting propranolol elimination

The results of liver blood flow in subjects tested with propranolol varied from 1504 to 2049 ml/min and from 600 to 1250 ml/min/1000 g indicating not more than two-fold differences. The variations in the indices of hepatic drug metabolism were considerably greater. The ranges of cytochrome P-450 concentration were from 1.70 to 17.14 nmol/g, a 10-fold difference, and the ranges of antipyrine clearance per unit weight of the liver were from 9.2 to 75.9 ml min^{-1} 1000 g^{-1}, an eight-fold variation. The difference between the lowest (0.95 (ml/min) $\times 10^3$) and the highest (10.40 (ml/min) $\times 10^3$) propranolol clearance was over ten-fold.

Discussion

The main determinants of propranolol pharmacokinetics are the protein binding of the drug, the blood flow of the liver and the anatomical arrangement of hepatic vasculature, and the activity of hepatic drug metabolizing enzyme system (Branch & Shand 1976). In chronic liver disease all these factors may be affected, circulatory and enzymatic alterations being the most important. Decrease in the activity and amount of drug metabolizing enzymes has been reported in liver disease (Schoene, Fleischman, Remmer & v. Oldershausen 1972; Sotaniemi, Ahlqvist, Pelkonen, Pirttiaho & Luoma 1977; Pirttiaho, Sotaniemi, Ahlqvist, Pitkänen & Pelkonen 1978, Pirttiaho 1979), and specially in cirrhosis, hepatic blood flow and its intrahepatic distribution are deteriorated (Popper, Elias & Petty 1952; Groszmann, Kotelanski, Cohn & Khatri 1972; Groszmann, Kravetz & Parysov, 1977).

There are only few studies focussed to analyze the relative role of the various factors influencing the elimination of propranolol in subjects with liver disease. Wood, Kornhauser, Wilkinson, Shand & Branch (1978) showed high steady state propranolol concentrations in cirrhotic subjects, caused evidently by a reduced intrinsic clearance and/or mesenteric shunting. In the work of Pessayre, Lebrec, Descatoire, Peignoux & Benhamon (1978) the hepatic clearance of intravenous propranolol was impaired, resulting mainly from the decreased intrinsic clearance and, in a minor degree, from reduced liver blood flow. Consistent with these studies, the present data revealed a significant relationship of propranolol clearance to antipyrine clearance and cytochrome P-450 concentration, the reflectors of the activity of hepatic drug metabolizing enzyme system. Propranolol clearance was also related to the liver blood flow. This indicated that liver enzyme activity and hepatic blood flow both contribute the reduced propranolol plasma clearance in liver disease. The difference in the indices of enzyme activity was eight to ten-fold as compared to the only two-fold variation in the liver blood flow. Hence it is reasonable to presume that the hepatic enzyme activity plays a dominant role in propranolol elimination by the diseased liver.

Table 5 Relationship of propranolol kinetics to antipyrine kinetics, cytochrome P-450 and estimated liver blood flow

	Propranolol	
	Clearance	$T_{\frac{1}{2}}$
Antipyrine clearance	0.972**	−0.108
Antipyrine $T_{\frac{1}{2}}$	−0.631	0.419
Cytochrome P-450 concentration	0.833*	−0.166
Total cytochrome P-450	0.740	−0.225
Total estimated liver blood flow	0.718	−0.065

Values of correlation coefficient (r) are given. Significance of correlation coefficient: $^{**}P < 0.001$, $^{*}P < 0.05$

The present study suggests that the hepatic clearance of a highly extracted drug, propranolol, is related to liver blood flow even after oral administration. The finding is somewhat discordant with the previous reports showing this kind relationship only after intravenous injection (Shand *et al.*, 1975; Kornhauser *et al.*, 1976; Weiss, Safar, Lehner, Levenson, Simon & Alexander, 1978). Previous investigations, based on studies with animals or healthy volunteers, are probably not directly applicable to patients with liver disease, who have an altered enzyme system and vascular bed. Haemodynamic disturbances in cirrhosis, such as intra-and extrahepatic shunts, diminish the effective sinusoidal blood flow (Popper *et al.*, 1952, Groszmann *et al.*, 1972; Groszmann *et al.*, 1977). It is also evident that in parenchymal liver diseases, such as fatty liver or alcoholic hepatitis, the architectural distortion secondary to infiltration of fat and inflammatory cells, ballooning of the hepatocytes, liver cell hyperplasia, tissue necrosis and active regeneration, may interfere with the sinusoidal perfusion (Leevy, ten Hove, Opper & Popovic 1970, Preisig, Bircher & Paumgartner, 1972). When part of the hepatocytic mass, otherwise with normal or slightly decreased function, is shut off from the effective hepatic perfusion, the reasonable consequence is diminished drug clearance.

Our previous investigations have shown a clear correlation between the capacity of the hepatic drug oxidizing enzyme system *in vitro,* measured by cytochrome P-450, and drug metabolism *in vivo* Sotaniemi *et al.*, 1977; Sotaniemi, Pelkonen, Ahokas, Pirttiaho & Ahlqvist, 1977; Pirttiaho, Sotaniemi, Ahokas & Pitkänen, 1978; Pirttiaho, Sotaniemi, Pelkonen & Pitkänen, 1978). This was also true in the present study, cytochrome P-450 concentration correlating with propranolol plasma clearance. The use of propranolol half-life as the only parameter of its elimination appeared to be unreliable, the half-life revealing also a poor correlation to the drug metabolizing capacity *in vitro*. The same kinds of results were obtained when relating elimination rates of propranolol and antipyrine, the correlation between clearance rates being considerably better than that between the half-life values. Consistently with the previous data (Halliwell, Homeida & Roberts, 1977), antipyrine clearance per unit weight of the liver appeared to be a sensitive index of drug metabolizing capacity.

The clearance rate of sotalol showed a relationship neither with *in vivo* or *in vitro* indices of hepatic drug metabolism nor with liver blood flow. This finding was consistent with the reports on factors influencing sotalol elimination (Garret & Schnelle 1971; Sundqvist *et al.*, 1974; Anttila *et al.*, 1976), and, indirectly, also confirmed the results of propranolol studies.

Liver blood flow in the present work was measured by dynamic ^{99m}Tc-sulphur colloid scans, a method based on the principles of Dobson & Jones (1952) who showed that the rate of accumulation of particulate matter to liver reticoloendothelial cells is a measure of hepatic blood flow. Since the reticoloendothelial or Kuppfer cells of the liver are situated only in the hepatic sinusoids, the method measures the effective sinusoidal flow perfusing the hepatocytes, leaving the flow through intra- and extrahepatic shunts without notice. Our previous works with normal subjects have shown a good reproduceability of this method (Pirttiaho & Pitkänen, 1978) as well as a close correlation between its results and those obtained by indocyanine green (Pirttiaho, Rajasalmi, Pitkänen & Ahonen, 1980), indicating that the present technique is well comparable with the earlier methods of measuring liver blood flow.

It is concluded that in subjects with liver disease the elimination rate of propranolol may be decreased by the combined effect of deterioration in the function of mixed function oxidase enzyme system and in the hepatic blood flow. The results are consistent with the intact cell hypothesis (Branch & Shand, 1976) suggesting that the elimination of oral propranolol by the damaged liver is related to the reduced mass of cells with normal function and/or effective perfusion, the reduction of the mass of drug metabolizing enzymes being predominant and the decreased sinusoidal flow a minor factor.

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