Br. J. clin. Pharmac. (1984), **17**, 265–271

Changes in blood chemistry in hypertensive patients during propranolol therapy

F. ANDREASEN[1], P. JAKOBSEN[1], H. J. KORNERUP[2], E. B. PEDERSEN[2], O. LEDERBALLE PEDERSEN[4] & J. WEEKE[3]

[1]Division of Clinical Pharmacology, Institute of Pharmacology, University of Aarhus, [2]Medical Department C, Aarhus Kommunehospital, [3]Medical Department M, Aarhus Kommunehospital and [4]Medical Department I, Aarhus Amtssygehus, Denmark

1 Propranolol induced changes in blood plasma chemistry were followed in thirty hypertensive patients (WHO I-II) who were seen each week during 14–15 weeks. The initial 4 weeks were a drug free period and the next 2 weeks were a drug adjustment period. After that the patients were on an unchanged propranolol dose for 8 weeks (40, 80 or 160 mg four times daily).

2 For all observed changes the correlation was studied to (1) dose, (2) free and total simultaneously determined plasma concentration and (3) free and total average plasma concentration of unchanged drug during the preceding 24 h period.

3 Total protein and albumin did not change significantly.

4 After 4 and 8 weeks on the final dose orosomucoid was increased significantly (by 10%) compared with the value from the end of the drug free period.

5 Creatinine rose significantly during the initial 4–6 weeks therapy to remain at the same level during the last 4 weeks. Urate was increased at the two lowest dose levels.

6 Total cholesterol fell significantly (5%) while triglycerides increased significantly (16%).

7 T_4 rose significantly, T_3 fell and r-T_3 rose significantly in a dose dependent way. Interindividually r-T_3 was the only biochemical change showing a significant relationship to the propranolol plasma concentration. The relationship reached the highest level of significance to the average 24 h free concentration.

Keywords propranolol plasma concentration unbound drug metabolic effects thyroid hormones

Introduction

Most studies on the effects of β-adrenoceptor blockade have focused on cardiovascular or renal function, but during recent years several papers have been published on changes in blood lipids and hormones. Conflicting results have been published about renal effects (Weber & Drayer, 1980; O'Connor & Preston, 1982) as well as on blood lipids (Birnbaum *et al.*, 1983) and thyroid hormones (Jones *et al.*, 1981).

In the following we report metabolic effects of propranolol therapy in 30 patients with essential hypertension: (1) the main purpose was to compare the propranolol induced biochemical changes at three different dose levels in men and women with essential hypertension, (2) in addition the relation of the biochemical changes to drug concentrations were studied: (a) to the free and total plasma propranolol determined in the blood sample used for the determination of the biochemical change and (b) to estimated values of the total and free mean propranolol concentrations during the preceding 24 h.

Methods

Patients

Consecutive patients of either sex below 60 years and characterized as suffering from essential hypertension (WHO I-II) were randomly allocated to one of three groups. Each group was to be of 10 persons at the beginning of the period during which the intended final dose was to be given: Group 1 to be treated with 40 mg propranolol four times daily, group 2 with 80 mg four times daily and group 3 with 160 mg four times a day. All patients gave consent to the study after being carefully informed of all relevant aspects of the procedure.

Exclusion criteria: (1) The occurrence of intolerable symptoms during the dose adjustment period, (2) evidence of secondary hypertension, (3) the necessity of or actual administration of diuretics, cardiac glycosides or additional antihypertensive drugs, (4) diseases and medication of other kinds, (5) a lack of compliance which in a few cases was not revealed before the whole study was completed.

Procedure

After 4 weeks without antihypertensive therapy 20 mg propranolol four times daily was given to all the patients. After 3–4 days the dose was increased to 40 mg four times daily and if the patients were to belong to group 2 the dose was doubled again after 3–4 days and for group 3 patients the dose was doubled once more after further 3–4 days. For the individual patient the time 0 was the time when the final dose had been given for 1 week. During the following 8 weeks the patients were seen once a week and 15 ml of heparin blood was taken between 2 and 3 h after the morning dose. The heparinized plasma was kept at −20°C until the study was completed and all samples were analyzed in one sequence. At each visit to the clinic the 24 h urine production from the preceding 24 h was brought. A sample of the 24 h urine was kept deep frozen until analyzed together with the plasma samples. On four occasions fasting blood samples were obtained: *A*: At the end of the drug free period, *B*: At the end of the drug adjustment period, *C*: After 4 weeks on the final dose and *D*: After 8 weeks on the final dose.

Drug assay

Total propranolol concentrations in plasma were determined by gas liquid chromatography and the free concentrations after equilibrium dialysis (Pedersen *et al.*, 1981). The average total and free plasma propranolol concentrations during the preceding 24 h were estimated from the urinary excretion of propranolol after determination of the orosomucoid concentration in plasma and of the endogenous 24 h-creatinine clearance (Andreasen *et al.*, 1983).

Methods for studying blood chemistry

The concentration of albumin and of α_1-acid glycoprotein (orosomucoid) were determined by the rocket method (Laurell, 1966). Concentrations of uric acid, creatinine, triglyceride and cholesterol were determined by standard laboratory procedures (Departments of Clinical Chemistry). Triiodine-thyronine (T_3), thyroxine (T_4) and reverse T_3) (r-T_3) were determined by single-antibody wick chromatographic radioimmunoassays (Weeke & Ørskov, 1978; Laurberg & Weeke, 1977).

Statistical methods

The statistical significance of observed differences was tested by the Wilcoxon test for paired differences or by the Pratts test (Rahe, 1974) which differs from the Wilcoxon test by including differences which are 0. Correlations were tested by linear correlations and *t*-statistics.

Results

Table 1 shows average values of plasma proteins before and during propranolol therapy. The only significant change occurred in α_1-acid glycoprotein which was increased by 10% after 4 and 8 weeks on an unchanged dose. No change was seen in total protein or albumin.

The plasma concentrations of creatinine and uric acid rose as shown in Table 2. The average increase in plasma urate was 15–20% at the two lower levels but less than 2% at the highest dose levels. The increase is significant ($P < 0.05$) for the two lowest dose levels but not for the two highest dose levels. Apparently the increase in creatinine reached the maximum value at C. The increase in plasma creatinine was not sufficient to cause a significant fall in creatinine clearance.

The investigated changes in blood lipids are listed in Table 3. Total cholesterol was significantly decreased already after the drug adjust-

Table 1 Plasma concentrations of proteins in hypertensive patients before and during propranolol therapy (g l ± s.d). Doses were unchanged for 8 weeks after initial adjustment to 160 (group 1), 320 (group 2) or 640 mg/day (group 3). Fasting values were obtained at the end of the initial drug free period (A), at the end of the adjustment period (B), after 4 weeks on the final dose (C) and after 8 weeks on the final dose (D).

		A	*B*	*C***	*D**
Group 1	Total protein	74 ± 4.0	72 ± 2.9	71 ± 1.8	71 ± 3.5
(n = 8)	Albumin	47 ± 3.6	47 ± 1.7	47 ± 5.3	46 ± 4.8
	Orosomucoid	0.88 ± 0.24	0.84 ± 0.29	0.93 ± 0.20	0.98 ± 0.32
Group 2	Total protein	71 ± 5.3	72 ± 6.0	73 ± 5.7	73 ± 6.1
(n = 10)	Albumin	48 ± 3.8	47 ± 4.0	47 ± 3.1	47 ± 3.4
	Orosomucoid	0.87 ± 0.64	0.84 ± 0.29	1.04 ± 0.40	0.88 ± 0.24
Group 3	Total protein	70 ± 2.0	70 ± 2.9	71 ± 3.8	70 ± 2.5
(n = 7)	Albumin	46 ± 2.4	46 ± 3.2	46 ± 2.7	45 ± 2.3
	Orosomucoid	0.88 ± 0.18	0.92 ± 0.14	0.94 ± 0.16	1.05 ± 0.33

Significances of changes during therapy: *orosomucoid group 1+2+3, $P < 0.05$; **orosomucoid group 1+2+3, $P = 0.01$.

Table 2 Average fasting values of plasma concentrations of creatinine (μmol/l) and uric acid (mg 100 ml) before and during propranolol therapy (mean ± s.d.). Groups 1, 2 and 3 and A, B, C, D are defined in Table 1.

		A	*B*	*C*	*D*
Group 1	Creatinine	77 ± 7	88 ± 12*	89 ± 9*	91 ± 16*
(n = 8)	Uric acid	4.1 ± 1.4			4.9 ± 1.4
Group 2	Creatinine	87 ± 13	93 ± 13**	97 ± 13**	95 ± 14**
(n = 10)	Uric acid	5.7 ± 1.2			6.5 ± 1.9*
Group 3	Creatinine	88 ± 17	95 ± 14**	105 ± 17**	103 ± 11*
(n = 7)	Uric acid	5.2 ± 1.5			5.3 ± 1.3

Significance of change: *$P < 0.05$, **$P < 0.01$.

Table 3 The fasting plasma concentrations of cholesterol (Ch) and triglyceride (Tr) (mg/100 ml) in hypertensive patients before and during treatment with propranolol (mean ± s.d.). The meaning of groups 1, 2 and 3 and of A, B, C and D are explained in Table 1.

Patients		*A*	*B*	*C*	*D*
Group 1	Ch	254 ± 39	244 ± 39*	233 ± 46	235 ± 35*
(n = 8)	Tr	117 ± 42	114 ± 44	117 ± 38	111 ± 38
Group 2	Ch	258 ± 54	247 ± 50	245 ± 51	252 ± 46
(n = 10)	Tr	104 ± 40	142 ± 91*	134 ± 97	141 ± 81
Group 3	Ch	238 ± 28	232 ± 38	235 ± 22	227 ± 29
(n = 7)	Tr	92 ± 45	101 ± 28	110 ± 32	114 ± 44
All patients	Ch	251 ± 43	238 ± 42**	239 ± 41**	239 ± 38*
(n = 25)	Tr	105 ± 41	122 ± 66*	122 ± 67*	124 ± 60
All men	Ch	246 ± 42	232 ± 44*	246 ± 37	238 ± 44
(n = 13)	Tr	115 ± 48	132 ± 84	142 ± 83	140 ± 71
All women	Ch	248 ± 50	247 ± 42	231 ± 46*	233 ± 43
(n = 12)	Tr	95 ± 31	111 ± 37	101 ± 37*	106 ± 42

Significance of changes: *$P < 0.05$, **$P < 0.01$.

Table 4 Plasma concentrations of thyroid parameters in hypertensive patients before and during propranolol therapy. Means and ranges (nmol l^{-1}) of T_4, T_3 and r-T_3. The definitions of groups 1, 2 and 3, and of times A, B, C and D are given in Table 1. The numbers listed at C and D are means of the value obtained at C or D and the values from the preceding three visits.

		A	*B*	*C*	*D*
Group 1	T_4	129	136	131	139*
		66–205	98–180	104–200	88–218
(n = 8)	T_3	2.00	1.75	1.69**	1.72*
		1.44–2.35	1.43–2.27	1.38–2.21	1.21–2.26
	r-T_3	0.249	0.346*	0.366*	0.422*
		0.080–0.422	0.169–0.771	0.198–0.687	0.230–0.955
Group 2	T_4	127	134*	136*	142
		82–209	81–161	82–209	103–206
(n = 10)	T_3	2.03	1.66**	1.60**	1.63**
		1.74–2.43	1.26–1.89	1.24–1.89	1.23–2.27
	r-T_3	0.287	0.462*	0.464**	0.473**
		0.180–0.401	0.198–0.863	0.321–0.693	0.330–0.713
Group 3	T_4	143	139	149	156
		112–178	88–193	106–169	120–191
(n = 7)	T_3	1.84	1.48*	1.43**	1.40**
		1.67–2.29	1.29–1.72	1.24–1.61	1.20–1.52
	r-T_3	0.333	0.682**	0.756**	0.736**
		0.223–0.469	0.485–1.101	0.581–1.083	0.637–0.802
Groups	T_4	133	136	139*	145**
1+2+3	T_3	1.97	1.61**	1.55**	1.58**
	r-T_3	0.283	0.492**	0.515**	0.533**

Significance of change: *$P < 0.05$, **$P < 0.01$.

ment period and simultaneously the plasma concentration of triglycerides was increased. The increase in plasma triglyceride levels in the males did not reach significance at any time in contrast to what was found in the females. The reductions in cholesterol were significant in both sexes.

Table 4 shows that highly significant changes occurred in the thyroid parameters studied. An average decrease in T_3 of about 20% and a corresponding 10% increase in T_4 were observed. The most striking finding, however, was a 90% increase in r-T_3.

Table 5 summarizes the observed biochemical changes. A large number of the laboratory tests were significantly altered but few were related to the drug dose given and even fewer were related to plasma concentrations of propranolol.

The correlations between individual plasma concentrations and individually observed effects on thyroid parameters were studied after 4 weeks on an unchanged dose. There were significant relationships between the available 19 individual values of increases in plasma concentrations of r-T_3 and plasma propranolol. The r-value was 0.4333 for directly measured propranolol (NS), for directly determined free propranolol it was 0.4664 ($P < 0.05$), for the average total 24 h-plasma propranolol it was 0.4848 ($P < 0.05$), and for the average free 24 h-plasma propranolol it was 0.7266 ($P < 0.001$). The relationships to increases in T_4 and to decreases in T_3 were not significant.

Discussion

Significant reductions in blood pressure and heart rate were achieved by giving propranolol to the hypertensive patients in the present study. These effects and the effects on electrolytes have been reported elsewhere (Pedersen *et al.*, 1981). The purpose of the present investigation was to study the influence of time, dose and propranolol concentrations on changes in blood chemistry. No relationship between propranolol dose or concentration and effect could be anticipated if: (1) the maximal effect of the drug had been achieved already at a dose level lower than the lowest used here or (2) too many modifying steps were involved between the initial event-starting binding of propranolol to a protein (receptor) and the observation of the effect. In an attempt to elucidate the first of these possibilities we always studied the interindividual concentration/effect relationships in patients treated with the lowest dose—they did show a range in plasma concentrations from zero and up to the average of the concentrations determined during

Table 5 Summary of propranolol induced biochemical changes in hypertensive patients. The three patient groups (1, 2 and 3) and the times A, B, C and D are characterized in Table 1.

P = plasma	*Initial changes A→B*	*Later changes*	*Apparent connection between dose and magnitude of changes*	*Correlation between change and drug concentration*
Total P-protein	No	No	No	No
P-albumin	No	No	No	No
P-α_1 acid-glycoprotein	No	↑ $P < 0.05$ at C and D	No	No
P-creatinine	↑ $P < 0.05$	↑ B→C (NS)	No	No
P-uric acid	Not measured at B	↑ $P < 0.05$ for A *vs* D	Only groups 1 and 2 show increase	No
U-creatinine	No	↑ NS	No	No
P-cholesterol	↓ $P < 0.01$	No	No	No
P-triglycerid	↑ $P < 0.05$	No	Decrease in group 1	No
P-T_4	↑ $P < 0.01$	No	No	
P-T_3	↓ $P < 0.01$	↓ NS	Stronger effect with increasing dose	*
P-rT_3	↑ $P < 0.01$	↑ NS	Stronger effect with increasing dose	**

P Plasma
* Yes (Between means)
** Yes (Between means and between individual values)

therapy with the middle dose. The second of the above mentioned possibilities must be discussed in the light of knowledge of mechanisms of action. In the following discussion we therefore attempt to distinguish between propranolol induced changes which are secondary to β-adrenoceptor blockade and changes which are elicited by a different mechanism.

Anticipated effects secondary to β-adrenoceptor blockade

The glomerular filtration rate (GFR) as well as the renal plasma flow (RPF) can be reduced by propranolol (O'Connor & Preston, 1982; Leeuw & Birkenhäger, 1982). At rest, however, these changes are small and insignificant (Pedersen, 1979). Changes in plasma concentrations of creatinine are often taken as indications of changes in the GFR. If a reduction in the GFR were the sole explanation of the significant elevation in plasma creatinine in our ambulatory patients it should be reflected in the urinary excretion of creatinine. We found no evidence of a reduced renal excretion of creatinine. The explanation of the changes in plasma creatinine may be a combination of an increased endogenous production and a 24 h-GFR which possibly is only temporarily decreased. There seem to be three possible explanations for the increased plasma urate observed after 8 weeks propranolol therapy: (a) a decreased tubular secretion secondary to a reduced RPF, (b) an increased endogenous production of uric acid, (c) an increased endogenous production of a uric acid 'analogue' reabsorbed in competition with uric acid would explain that plasma urate was increased at the two lower dose levels only. A similar dose relation was reported during timolol therapy (Pedersen & Mikkelsen, 1979).

The inhibition of the catecholamine stimulated triglyceride lipase caused the expected rise in the fasting plasma triglyceride level, which also has been demonstrated by other investigators (Day *et al.*, 1979; Leren *et al.*, 1980; Gemma *et al.*, 1982) while Birnbaum *et al.* (1983) found no significant triglyceride increase after 240 mg propranolol daily for 6 weeks.

Propranolol effects not related to β-adrenoceptor blockade

Propranolol is bound to α_1-acid glycoprotein (Piafsky *et al.*, 1978; Scott *et al.*, 1979) but other plasma constituents influence the binding as well (Sager *et al.*, 1979). *In vivo* the concentration of α_1-acid glycoprotein, however, is a major determinant for the plasma binding of the drug (Andreasen *et al.*, 1983). Therefore the demonstration of significant (10%) increases in the concentration of orosomucoid after 4 as well as after 8 weeks of propranolol therapy is of considerable interest. The mechanism for this rise in concentration is unknown. A decreased breakdown (propranolol protection) or an increased synthesis (negative feedback) are possible explanations. At a total propranolol concentration of 100 ng/ml in plasma only one propranolol molecule is found per 250 orosomucoid molecules. The distribution of propranolol is inhomogenous, however, (V_d = 4–5 l/kg) and it is quite possible that the concentration of propranolol-orosomucoid complexes may be much higher in areas where the regulation of orosomucoid synthesis takes place.

In general β-adrenoceptor blockade is effective in the management of hyperthyroidism (McDevitt, 1976). The effects of propranolol on the plasma levels of the thyroid hormones and of r-T_3, however, are not found for other β-adrenoceptor blocking agents (Heyma *et al.*, 1980). A direct effect of propranolol on a plasma hormone regulating mechanism is suggested by the significant relationships we have demonstrated here between propranolol concentration and observed effect. A likely explanation seems to be an inhibition of the transformation of T_4 to T_3 as well as of the breakdown of r-T_3 (cf. Wenzel, 1981).

The significant fall in plasma cholesterol demonstrated in the present study is in agreement with the recent results of Birnbaum *et al.* (1983), but others have not been able to demonstrate any change in plasma cholesterol during propranolol therapy (Day *et al.*, 1979; Scheuer *et al.*, 1980; Leren *et al.*, 1980; Gemma *et al.*, 1982). It is impossible to state whether this change is related to the β-adrenoceptor blockade as the picture obviously is very complex. Thus Gemma *et al.* (1982) in hypertensive patients found a reduction in total cholesterol during treatment with prazosin if propranolol had been given prior to prazosin, while no significant cholesterol change was found if prazosin was given first and then followed by propranolol.

In view of changes in the secretion pattern of anterior pituitary hormones induced by propranolol therapy (Dart *et al.*, 1981) it was justified to look for a sex-influence in changes in biochemistry caused by propranolol. Furthermore, almost all the studies mentioned above on blood lipids were done in men while most studies on thyroid hormones were performed in women. In the present study we have found no evidence of sex related differences in the effect of propranolol on blood chemistry.

The study was supported by the Danish Heart Association.

References

Andreasen, F., Jakobsen, P., Kornerup, H. J., Pedersen, E. B. & Pedersen, O. L. (1983). Urine and plasma propranolol. *Clin. Pharmac. Ther.*, **33**, 10–18.

Birnbaum, J., DiBianco, R., Becker, K. L., Muesing, R., Costello, R. B., Singh, S. N., Gottdiener, J. S. & Fletcher, R. D. (1983). Glucose and lipid metabolism during acebutol and propranolol therapy of angina in nondiabetic patients. *Clin. Pharmac. Ther.*, **33**, 294–300.

Dart, A. M., Lewis, M. J., Groom, G. V., Meek, E. M. & Henderson, A. H. (1981). The effect of chronic propranolol treatment on overnight plasma levels of anterior pituitary and related hormones. *Br. J. clin. Pharmac.*, **12**, 849–853.

Day, J. L., Simpson, N., Metcalfe, J. & Page, R. L. (1979). Metabolic consequences of atenolol and propranolol in treatment of essential hypertension. *Br. med. J.*, **1**, 77–80.

Gemma, G., Montanari, G., Suppa, G., Paralovo, A., Franceschini, G., Mantero, O. & Sirtori, C. R. (1982). Plasma lipid and lipoprotein changes in hypertensive patients treated with propranolol and prazosin. *J. cardiovasc. Pharmac.*, **4**, S233–S237.

Heyma, P., Larkins, R. G. & Campbell, D. G. (1981). Inhibition by propranolol of 3,5,3′-triidothyronine formation from thyroxine in isolated rat renal tubules: An effect independent of β-adrenergic blockade. *Endocrinology*, **106**, 1437–1441.

Jones, G. R., Lazarus, J. H., Wynford-Thomas, D. (1981). A study of long acting propranolol in the early management of hyperthyroidism. *Br. J. clin. Pharmac.*, **12**, 825–828.

Laurberg, P. & Weeke, J. (1977). Radioimmunological determination of reverse triiodothyronine in unextracted serum and serum dialysates. *Scand. J. clin. Lab. Invest.* **37**, 735–739.

Laurell, C. B. (1966). Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. *Analyt. Biochem.*, **15**, 42–52.

Leeuw, de P. W. & Birkenhäger, W. H. (1982). Renal response to propranolol treatment in hypertensive humans. *Hypertension*, **4**, 125–131.

Leren, P., Helgeland, A., Holme, I., Foss, P. O., Hjermann, I. & Lund-Larsen, P. G. (1980). Effect of propranolol and prazosin on blood lipids. *Lancet*, **i**, 4–6.

McDevitt, D. G. (1976). Propranolol in the treatment of thyrotoxicosis: a review. *Postgrad. med. J.*, **52**, suppl. 4, 157–161.

O'Connor, D. & Preston, R. A. (1982). Urinary kallikrein activity, renal hemodynamics, and electrolyte handling during chronic beta blockade with propranolol in hypertension. *Hypertension*, **4**, 742–749.

Pedersen, E. B. (1979). Some aspects of kidney function, the renin-aldosterone system and sympathetic activity in essential hypertension. *Acta med. Scand.* suppl. 636, 11–66.

Pedersen, O. L. & Mikkelsen, E. (1979). Serum potassium and uric acid changes during treatment with timolol alone and in combination with a diuretic. *Clin. Pharmac. Ther.*, **26**, 339–343.

Pedersen, E. B., Kornerup, H. J., Pedersen, O. L., Andreasen, F. & Bjerregaard, P. (1981). Correlation between propranolol in plasma and urine, renin-aldosterone system and blood pressure in essential hypertension. *Eur. J. clin. Pharmac.*, **20**, 251–258.

Piafsky, K. M., Borgå, O., Odar-Cederlöf, I., Johansson, C. & Sjöqvist, F. (1978). Increased plasma protein binding of propranolol and chlorpromazine mediated by disease-induced elevations of plasma α_1-acid glycoprotein. *New Engl. J. Med.*, **299**, 1435–1439.

Rahe, A. J. (1974). Tables of critical values for the Pratt Matched pair signed rank statistic. *J. Am. stat. Ass.*, **69**, 368–373.

Sager, G., Nilsen, O. G. & Jacobsen, S. (1979). Variable binding of propranolol in human serum. *Histochem. Pharmac.*, **28**, 905–911.

Scheuer, I., Schauer, U., Rühling, K. & Thielmann, K. (1980). The effect of propranolol treatment on total cholesterol, HDL cholesterol, triglycerides, postheparin lipolytic activity and lecithin: Cholesterol acyltransferase in hypertensive individuals. *Artery*, **8**, 146–150.

Scott, B. J., Bradwell, A. R., Schneider, R. E. & Bishop, H. (1979). Propranolol binding to serum orosomucoid. *Lancet*, **i**, 930.

Weber, M. A. & Drayer, J. I. M. (1980). Renal effects of beta-adrenoceptor blockade. *Kidney Int.*, **18**, 686–699.

Weeke, J. & Ørskov, H. (1978). Evaluation of thyroid function. In *Recent Advances in Clinical Biochemistry*, ed. Alberti, K. G. M. M., pp. 111–128.

Wenzel, K. W. (1981). Pharmacological interference with *in vitro* tests of thyroid function. *Metabolism*, **30**, 717–732.

(Received July 4, 1983, accepted November 11, 1983)