THE INFLUENCE OF AGE, SMOKING AND HYPERTHYROIDISM ON PLASMA PROPRANOLOL STEADY STATE CONCENTRATION

JOHN FEELY, JAMES CROOKS & I.H. STEVENSON

Department of Pharmacology and Therapeutics,
Ninewells Hospital and Medical School,
Dundee DD1 9SY

- 1 Plasma propranolol steady state concentration (C_{ss}) was determined during chronic dosage (160 mg/day) in 22 hyperthyroid patients (aged 16–75 years, 11 smokers, 11 non-smokers) and again following treatment when euthyroid.
- 2 There was a positive correlation between plasma propranolol C_{ss} and age in patients both when hyperthyroid ($r = 0.74$, $P < 0.01$) and when euthyroid ($r = 0.58$, $P < 0.05$).
- 3 Plasma propranolol C_{ss} in hyperthyroid patients were lower ($P < 0.05$) in smokers than in non-smokers.
- 4 Following correction of hyperthyroidism there was a significant increase ($P < 0.01$) in both the plasma propranolol C_{ss} and degree of plasma protein binding of propranolol.
- 5 Hyperthyroidism and smoking are known to increase the rate of drug metabolism and it is suggested that these variables may give rise to or accentuate an age related reduction in propranolol clearance.

Introduction

The elimination of a number of drugs which are metabolised primarily by hepatic microsomal oxidative steps appears to be impaired in elderly subjects (for review see Crooks, O'Malley & Stevenson, 1976). Data, for the most part, has been obtained from single dose studies but recent evidence suggests that in patients given the same dose of drug chronically, plasma drug steady state concentrations may increase with age e.g. phenytoin (Houghton, Richens & Leighton, 1975), imipramine and amitriptyline (Nies *et al.*, 1977). This effect of age on plasma drug steady state concentration will be most obvious with drugs such as propranolol which are extensively metabolised by the liver and there is evidence (Castleden & George, 1979) that the elimination of propranolol is reduced in elderly subjects.

The hepatic metabolism of some drugs may be increased in hyperthyroidism (Eichelbaum, 1976) and it is also known that smoking, probably through hepatic enzyme induction (Vestel *et al.*, 1975) increases the rate of elimination of certain drugs and may thus be a complicating factor when assessing the influence of age on drug handling. The present study reports on the influence of ageing, smoking and hyperthyroidism on plasma propranolol steady state concentration (C_{ss}) in a group of patients both when hyperthyroid and again following treatment when euthyroid.

Methods

Twenty-two hyperthyroid outpatients (20 female, 2 male, 11 smokers (10 or more cigarettes daily), 11 non-smokers) aged 16–75 years (mean 46) were studied during continuous treatment for more than 1 week with propranolol 160 mg/day when hyperthyroid and again in 18 of these patients when biochemically euthyroid following surgery (12 patients), carbimazole (3 patients) or radioiodine therapy (3 patients) (Table 1). Diagnosis of hyperthyroidism was based on clinical grounds, a hyperthyroid diagnostic index (Crooks, Murray & Wayne, 1959) and standard biochemical tests of thyroid function, the values obtained ($\pm$ s.e. mean, which is used throughout) being serum thyroxine 230.7 ± 18.8 nmol/l (normal range 75–140), free thyroxine index 272.2 ± 23.9 (normal range 70–145), and serum triiodothyronine (T_3) 4.6 ± 0.5 nmol/l (normal range 0.9–2.4). The patients mean body weight was 53.9 ± 1.9 kg when hyperthyroid and 56.1 ± 1.8 kg when euthyroid. Serum creatinine was within the normal range in all patients and glutamate-oxalacetate aminotransferase (γ GTP) was elevated in 14 patients when hyperthyroid, but returned to within the normal range in ten of these patients when euthyroid. Fifteen patients were social drinkers. A 10 day supply of propranolol tablets was issued and those remaining after 1 week were counted. If there was a discrepancy of more than two tablets, or if patients admitted to

Table 1 Clinical details and plasma propranolol C_{ss} and degree of protein binding when hyperthyroid and following treatment when euthyroid

Patient	Sex	Age (years)	Smoker	Serum γ GTP (7-42 IU; normal range)	Treatment	Interval between studies (weeks)	Plasma propranolol C _{ss} (ng/ml)		Protein binding (%)	
							Hyperthyroid	Euthyroid	Hyperthyroid	Euthyroid
1	F	16	+	21	C	5	13	38	89.6	90.7
2	F	17	-	25	C	8	34	56	87.5	92.2
3	M	29	-	32	S	6	32	61	90.6	91.7
4	F	30	-	58	S	-	31	-	-	-
5	F	31	+	20	S	6	5	45	87.7	92.7
6	F	33	+	55	S	5	28	62	80.9	88.3
7	F	38	-	22	S	4	29	48	78.3	84.8
8	F	39	+	26	S	5	17	52	-	-
9	F	40	+	54	S	3	20	54	85.5	85.2
10	F	45	+	55	S	5	28	68	-	-
11	F	46	-	15	S	4	26	66	86.1	90.5
12	F	46	+	43	S	-	24	-	-	-
13	F	47	-	54	S	3	69	96	85.1	87.3
14	F	47	-	46	S	8	28	35	86.5	85.2
15	M	48	-	43	C	5	64	115	-	-
16	F	52	+	46	S	3	31	74	81.6	85.5
17	F	56	+	33	S	6	56	43	-	-
18	F	64	-	91	RAI	5	98	251	80.8	83.6
19	F	65	-	89	RAI	10	65	86	93.5	92.5
20	F	66	+	90	RAI	12	51	91	85.4	88.7
21	F	73	-	45	RAI	-	205	-	-	-
22	F	75	+	34	RAI	-	97	-	-	-

C = Carbimazole, S = Surgery, RAI = Radioactive iodine

missing one dose within the preceding 48 h (five propranolol half-lives being taken as sufficient time to regain steady state) then compliance was regarded as inadequate. Furthermore, in 8 of the surgically treated patients including the patient (5) with the lowest level, a second plasma propranolol C_{SS}, which was obtained following at least 24 h supervised propranolol administration in hospital, was within $\pm 20\%$ of the original value. With the exceptions of one patient (no. 8) receiving oral contraceptive steroids, one patient (no. 17) diazepam and the three patients (nos. 1, 2 and 15) receiving carbimazole, there was no concomitant drug therapy. Propranolol was discontinued in four patients (two because of severe lethargy, and two due to non-compliance following thyroidectomy) before a euthyroid state was achieved. Plasma propranolol was measured by a specific gas liquid chromatographic method (Walle, 1974). Samples were taken by direct venepuncture approximately 4 h (3.9 ± 0.1) post-dosage during chronic therapy after at least 1 week of therapy (8.4 ± 0.5 days when hyperthyroid) and 5.6 ± 0.6 weeks when euthyroid. The 4 h post dosage sampling time was chosen because previous studies both in hyperthyroid (Rubinfeld *et al.*, 1979) and in euthyroid (Walle *et al.*, 1978) suggested that it approximated to the mean plasma propranolol level. In addition a series of hourly samples were taken throughout a 6 h dosage interval in five of these patients and the area under the plasma propranolol concentration ν time curve was calculated by the trapezoidal rule. The mean plasma propranolol concentration was calculated by dividing the latter by the dosing interval. The degree of plasma protein binding of propranolol was determined in 14 patients by ultrafiltration (Bloxxham, Curzon & Hutson, 1977) on the samples

taken for plasma propranolol estimation. Patients 8 and 17 were excluded because of concomitant drug therapy although patients 1 and 2 who were receiving carbimazole were included. To duplicate 250 μ l of plasma [¹⁴C]-propranolol (100 ng/ml) was added, mixed and allowed to stand at room temperature for 60 min before centrifugation at 1500 g for 30 min using a PM 10 Amicon membrane in the cell. The percentage protein binding was calculated from

$$\frac{\text{Radioactivity in plasma} - \text{Radioactivity in ultrafiltrate}}{\text{Radioactivity in plasma}} \times 100$$

The addition of unlabelled propranolol in the range encountered in the patients plasma (5–250 ng/ml) did not influence the degree of binding and the mean coefficient of variation of 20 replicate samples was 3.4%. Statistics were performed by Student's paired *t*-test, Wilcoxon's rank sum test and correlation by the method of least squares analysis.

Results

There was a wide inter-individual variation in the plasma propranolol C_{SS} in the patients studied both when hyperthyroid (range from 5 to 205 ng/ml) and following treatment when euthyroid (range 35 to 251 ng/ml). As is evident from Figure 1 there was a positive correlation ($r = 0.74$, $P < 0.01$) between the logarithm of plasma propranolol C_{SS} and age in hyperthyroid patients. No correlation existed between the logarithm of plasma propranolol C_{SS} and either serum thyroxine, serum T₃, free thyroxine index, or body weight, nor was there any correlation between age and the biochemical indices of hyperthyroidism. There was a positive correlation between γ GTP and both age ($r = 0.52$, $P < 0.05$) and plasma propranolol C_{SS} ($r = 0.46$, $P < 0.05$). The plasma propranolol C_{SS} rose significantly in the 18 patients maintained on propranolol (for 5.6 ± 0.6 weeks) until euthyroid, the mean plasma propranolol C_{SS} being higher ($P < 0.01$, $n = 18$) in the euthyroid (74.5 ± 11.5 ng/ml) than in the hyperthyroid state (38.6 ± 5.6 ng/ml). In the euthyroid state there was again a positive correlation ($r = 0.58$, $P < 0.05$) with age which was less marked than in the hyperthyroid state (Figure 1).

In the hyperthyroid state plasma propranolol C_{SS} were lower ($P < 0.05$) in smokers (age 45 ± 5 years) than in non-smokers (46 ± 5 years) the mean levels being 33.6 ± 7.8 and 61.9 ± 15.9 ng/ml respectively. There was a significant relationship between age and plasma propranolol C_{SS} for both smokers ($r = 0.82$, $P < 0.01$) and non-smokers ($r = 0.78$, $P < 0.01$), which is shown in Figure 2. When euthyroid following treatment of hyperthyroidism there was again a significant correlation ($r = 0.74$, $P < 0.05$, $n = 8$) between plasma propranolol C_{SS} and age in smokers only but

Figure 1 The relationship between plasma propranolol steady state concentration (C_{SS}) and age in patients when hyperthyroid (Δ , $r = 0.74$, $n = 22$ and $P < 0.001$) and again when euthyroid ($\blacktriangle$, $r = 0.58$, $n = 18$ and $P < 0.05$).

Figure 2 The influence of age and smoking habits (▲ smokers, △ non smokers) on plasma propranolol steady state concentration (C_{ss}) in hyperthyroid patients. Smokers ($r = 0.82$, $P < 0.01$, $n = 11$), non-smokers ($r = 0.78$, $P < 0.01$, $n = 11$).

not in non-smokers ($r = 0.56$, NS). The mean plasma propranolol C_{ss} when euthyroid was higher in non-smokers (87.4 ± 19.6 ng/ml) than in smokers (58.1 ± 6.4 ng/ml) but did not reach statistical significance. However it should be noted that the number of patients in each group was reduced, three smokers being excluded following thyroidectomy (two due to inadequate compliance and a third patient stopped smoking).

That steady state had been achieved during chronic treatment was supported by the finding that the plasma propranolol concentration at the beginning (mean 22.3 ± 2.6 and 38.8 ± 12.7 ng/ml) and at the end (20.8 ± 2.9 and 37.1 ± 9.9 ng/ml) of the dosage interval were similar both when hyperthyroid and euthyroid. There was also in these patients a positive correlation in both the hyperthyroid ($r = 0.89$, $P < 0.05$) and euthyroid ($r = 0.9$, $P < 0.05$) state between the plasma propranolol concentration 4 h following dosage (42.4 ± 7.2 and 67.0 ± 14.1 ng/ml respectively) and the mean plasma propranolol concentration during the dosage interval (45.2 ± 9.8 and 64.2 ± 17.3 ng/ml respectively). This suggests that the plasma propranolol C_{ss} (4 h post dosage) represents the mean propranolol concentration during a 6 h dosage interval. The degree of plasma protein binding of propranolol increased from $85.7 \pm 1.2\%$ to $88.5 \pm 0.86\%$ ($P < 0.01$) following treatment of hyperthyroidism and the omission of the two patients receiving carbimazole from the analysis did not materially affect the results ($85.2 \pm 1.2\%$ and $88.0 \pm 0.9\%$, $P < 0.01$). The degree of protein binding did not however correlate with the patients' age.

Discussion

A wide inter-individual variation in plasma propranolol concentration has been found after the same dose both in euthyroid (Shand, 1974) and in hyperthyroid patients (Feely *et al.*, 1977). The inter-individual variation in the plasma propranolol C_{ss} fell considerably following correction of hyperthyroidism. Of interest, and in contrast to these findings and those of Shand (1974), is the small degree of inter-individual variability noted by Walle *et al.* (1978) in patients hospitalized with hypertension and coronary artery disease. The degree of variability in the latter study also decreased with dosage of greater than 160 mg/day. Saturation of the variable first-pass effect at higher dosage levels and a more rigid control of diet and compliance in hospitalized patients may in part explain the apparent discrepancies.

The influence of ageing on the handling of propranolol in euthyroid subjects has recently been studied by a number of groups. Castleden & George (1979) found higher plasma propranolol levels in the elderly following acute oral dosage and the elimination half-life following intravenous dosage was prolonged in the elderly. They suggested that in addition to a diminution in intrinsic clearance of propranolol by metabolism there was also a slowing in the distribution of propranolol to the tissues. Their findings are consistent with the known effect of age on both hepatic drug metabolism (Crooks *et al.*, 1976) and liver blood flow (Sherlock *et al.*, 1950). However, Schneider *et al.* (1980) following single oral doses of 40 and 80 mg of propranolol did not find an age related reduction in the clearance of propranolol in non-smoking healthy subjects. They suggested that the use of sick elderly subjects in the former study may explain the different findings. The influence of age on the disposition of propranolol during chronic dosing was also studied by Vestal *et al.* (1979). The systemic clearance of propranolol decreased, which was attributed to a parallel reduction in apparent liver blood flow, with age. The intrinsic (oral) clearance of propranolol, which is determined by the activity of hepatic drug metabolising enzymes (Routledge & Shand, 1979), decreased with age only in smokers. The overall mean propranolol blood levels were twice as high in non-smokers as in smokers. They concluded that there was a decreased induction of drug-metabolising enzymes in the elderly thus the higher levels in the elderly smokers may incorrectly be attributed to an age related reduction in propranolol's intrinsic clearance. Our findings are in agreement with the latter study and suggest that an age related reduction in intrinsic clearance is seen only in the presence of hepatic enzyme inducing agents (smoking) or disease (hyperthyroidism). Hepatic dysfunction occurs commonly in hyperthyroidism (Kimberg, 1971) as indicated by elevation of

γ GTP. A greater degree of hepatic dysfunction in the elderly, as evidenced by the higher γ GTP levels, may in this study have resulted in a reduction in propranolol clearance. Furthermore hyperthyroidism may have a profound effect on drug metabolising enzyme systems (Eichelbaum, 1976) and as suggested by Vestal *et al.*, (1979) decreased induction of drug metabolising enzyme may occur with ageing which would result in markedly lower levels in the enzyme induced younger but not older hyperthyroid patient.

Many environmental factors may contribute to the variability in plasma drug concentration. Caffeine and ethanol use had no apparent effect on antipyrine clearance (Vestal *et al.*, 1975). Smoking habits are also however, a major determinant of antipyrine clearance (Vestal *et al.*, 1975; Wood *et al.*, 1979). This may be an age related effect of sufficient magnitude to give significance to a correlation between age and antipyrine clearance in a population despite the fact that there is no change in clearance in the non-smoking section of the group (Wood *et al.*, 1979).

An age related reduction in the plasma protein binding has been shown for warfarin (Hayes, Langman & Short, 1975a) and phenytoin (Hayes, Langman & Short, 1975b) and correlates with the fall in the plasma albumin concentration which occurs with ageing. In this study the degree of plasma protein binding of propranolol did not decrease with age. There was, however, a significant increase in the degree of protein binding following correction of the hyperthyroidism. A similar but non-significant increase in propranolol binding following treatment in six hyperthyroid patients was recently reported by

Kelly & McDevitt (1978). The significant increase in plasma propranolol C_{ss} following treatment of hyperthyroidism is in agreement with our previous findings of an increased oral clearance of propranolol during chronic dosing in hyperthyroidism (Feely, Crooks & Stevenson, 1979).

Plasma propranolol concentrations are positively related to the degree of β -adrenoceptor blockade in both euthyroid (Shand, 1974) and hyperthyroid subjects (Feely *et al.*, 1980). These results suggest that the younger hyperthyroid patient who smokes may achieve only a minor degree of β -adrenoceptor blockade on conventional dosage of propranolol. The findings of higher concentrations of propranolol has lead Castleden & George (1979) to suggest that propranolol dosage should be reduced in the elderly. We feel however, that this may not be necessary. Although adverse reactions to propranolol as reported by the Boston Collaborative Drug Surveillance Program were more common in elderly patients (Greenblatt & Koch-Weser, 1973) than in younger patients the difference was not significant and, in addition adverse reactions to oral propranolol are not dose related (Greenblatt & Koch-Weser, 1974). Furthermore, there is good evidence (Vestal, Wood & Shand, 1979) that the elderly are less sensitive to a given free concentration of propranolol which suggests that a reduction in β -receptor sensitivity may occur with ageing. Further combined pharmacokinetic and dynamic studies are required to determine whether an alteration in propranolol dosage is necessary in the elderly.

References

- BLOXHAM, D.L., CURZON, G. & HUTSON, P.H. (1977). A simple small volume ultrafiltration apparatus applicable to protein binding studies. *Br. J. clin. Pharmac.*, **4**, 405 P.
- CASTLEDEN, C.M. & GEORGE, C.F. (1979). The effect of ageing on the hepatic clearance of propranolol. *Br. J. clin. Pharmac.*, **7**, 49–54.
- CROOKS, J., MURRAY, I.P.C. & WAYNE, E.J. (1959). Statistical methods applied to the clinical diagnosis of thyrotoxicosis. *Quart. J. Med.*, **28**, 211–234.
- CROOKS, J., O'MALLEY, K. & STEVENSON, I.H. (1976). Pharmacokinetics in the elderly. *Clin. Pharmacokin.*, **1**, 280–296.
- EICHELBAUM, M. (1976). Drug metabolism in thyroid disease. *Clin. Pharmacokin.*, **1**, 339–350.
- FEELY, J., FORREST, A.L., GUNN, A., HAMILTON, W.F., STEVENSON, I.H. & CROOKS, J. (1977). Beta-blocking drugs and thyroid function. *Br. med. J.*, **2**, 1352.
- FEELY, J., CROOKS, J. & STEVENSON, I.H. (1979). Altered pharmacokinetics of propranolol in hyperthyroidism. *Br. J. clin. Pharmac.*, **8**, 379 P.
- FEELY, J., FORREST, A., GUNN, A., HAMILTON, W., STEVENSON, I. & CROOKS, J. (1980). Propranolol dosage in thyrotoxicosis. *J. clin. Endocrinol. Metab.*, **51**, 658–661.
- GREENBLATT, D.J. & KOCH-WESER, J. (1973). Adverse reactions to propranolol in hospitalized medical patients: A report from the Boston Collaborative Drug Surveillance Program. *Am. Heart J.*, **86**, 478–484.
- GREENBLATT, D.J. & KOCH-WESER, J. (1974). Adverse reactions to β -adrenergic receptor blocking drugs: A report from the Boston Collaborative Drug Surveillance Program. *Drugs*, **1**, 118–129.
- HAYES, M.J., LANGMAN, M.J.S. & SHORT, A.H. (1975a). Changes in drug metabolism with increasing age: 1. Warfarin binding and plasma proteins. *Br. J. clin. Pharmac.*, **2**, 69–72.
- HAYES, M.J., LANGMAN, M.J.S. & SHORT, A.H. (1975b). Changes in drug metabolism with increasing age: 2. Phenytoin clearance and protein binding. *Br. J. clin. Pharmac.*, **2**, 73–79.
- HOUGHTON, C.W., RICHENS, A. & LEIGHTON, M. (1975).

- Effect of age, height, weight and sex on serum phenytoin concentration in epileptic patients. *Br. J. clin. Pharmac.*, **2**, 251–256.
- KELLY, J.G. & McDEVITT, D.G. (1978). Plasma protein binding of propranolol and isoprenaline in hyperthyroidism and hypothyroidism. *Br. J. clin. Pharmac.*, **6**, 123–127.
- KIMBERG, D.V. (1971). Hyperthyroidism: Liver. In *Thyroid*, eds. Werner, S.C. & Ingbar, S., pp. 569–573. New York: Harper and Row.
- NIES, A., ROBINSON, D.S., FRIEDMAN, M.J., GREEN, R., COOPER, T.B., RAVARIS, C.L. & IVES, J.D. (1977). Relationship between age and tricyclic anti-depressant levels. *Am. J. Psychiat.*, **134**, 790–793.
- ROUTLEDGE, P.A. & SHAND, D.G. (1979). Clinical pharmacokinetics of propranolol. *Clin. Pharmacokin.*, **4**, 73–90.
- RUBENFELD, S., SILVERMAN, V.E., WELCH, K.M.A., MALLETTE, L.E. & KOHLER, P.O. (1979). Variable plasma propranolol levels in thyrotoxicosis. *New Engl. J. Med.*, **300**, 353–354.
- SCHNEIDER, R.E., BISHOP, H., YATES, R.A., QUARTERMAN, C.P. & KENDALL, M.J. (1980). Effect of age on plasma propranolol levels. *Br. J. clin. Pharmac.*, **10**, 169–171.
- SHAND, D.G. (1974). Individualisation of propranolol therapy. *Med. Clin. N. Am.*, **58**, 1063–1069.
- SHERLOCK, S., BEARN, A.G., BILLING, B.H. & PATERSON, J.C.S. (1950). Splanchnic blood flow in man by the bromosulfalein method: the relation of peripheral plasma level to the calculated flow. *J. lab. clin. Med.*, **35**, 923–932.
- VESTAL, R.E., NORRIS, A.H., TOBIN, J.D., COHEN, B.H., SHOCK, N.W. & ANCHES, R. (1975). Antipyrine metabolism in man: influence of age, alcohol, caffeine and smoking. *Clin. Pharmac. Ther.*, **18**, 425–432.
- VESTAL, R.E., WOOD, A.J.J., BRANCH, R.A., SHAND, D.G. & WILKINSON, G.R. (1979). Effect of age and cigarette smoking on propranolol disposition. *Clin. Pharmac. Ther.*, **26**, 8–15.
- VESTAL, R.E., WOOD, A.J.J. & SHAND, D.G. (1979). reduced β -adrenoreceptor sensitivity in the elderly. *Clin. Pharmac. Ther.*, **26**, 181–186.
- WALLE, T. (1974). GLC determination of propranolol, other β -blocking drugs and metabolites in biological fluids and tissues. *J. pharm. Sci.*, **63**, 1885–1891.
- WALLE, T., CONRADI, E.C., WALLE, K., FAGAN, T.C. & GAFFNEY, T.E. (1978). The predictable relationship between plasma levels and dose during chronic propranolol therapy. *Clin. Pharmac. Ther.*, **24**, 668–677.
- WOOD, A.J.J., VESTAL, R.E., WILKINSON, G.R., BRANCH, R.A. & SHAND, D.G. (1979). Effect of age and cigarette smoking on antipyrine and indocyanine green elimination. *Clin. Pharmac. Ther.*, **26**, 16–20.

(Received November 20, 1980)