Br. J. clin. Pharmac. (1979), **8**, 163–167

PLASMA CONCENTRATIONS OF PROPRANOLOL AND 4-HYDROXYPROPRANOLOL DURING CHRONIC ORAL PROPRANOLOL THERAPY

LORETTA WONG

Department of Pharmacy Practice, College of Pharmacy

ROGER L. NATION & WIN L. CHIOU

Clinical Pharmacokinetics Laboratory, Department of Pharmacy

P.K. MEHTA

Section of Nephrology, University of Illinois at the Medical Center, Chicago, Illinois 60612, USA

1 The plasma levels of propranolol and 4-hydroxypropranolol have been measured in 17 hypertensive patients receiving chronic oral therapy with propranolol.

2 The range of plasma propranolol concentrations was from 5.3 to 300 ng/ml, and that of 4-hydroxypropranolol was from 2.1 to 36.0 ng/ml.

3 The mean (± s.d.) plasma concentration ratio of 4-hydroxypropranolol to propranolol was 0.130 (±0.055); however, a very wide range was observed with individual values ranging from 0.057 to 0.241.

4 A statistically significant correlation was observed between the plasma concentration of 4-hydroxypropranolol and that of propranolol.

5 Propranolol and 4-hydroxypropranolol plasma concentrations were each significantly, but poorly, correlated with daily propranolol dose.

6 The clinical significance of the results has been discussed.

Introduction

Propranolol, a β-adrenergic receptor blocking drug, has found wide application in the control of disease states such as hypertension, angina pectoris and cardiac arrhythmias, but its use has also been suggested in other conditions. Since the discovery that propranolol forms at least one pharmacologically active metabolite (Fitzgerald & O'Donnell, 1971), 4-hydroxypropranolol, speculation has ensued about its therapeutic role. Fitzgerald & O'Donnell (1971) reported that propranolol and its 4-hydroxy metabolite were of similar potency, based on dosage, when tested for β-adrenoceptor blocking activity in animal models. Using ^{14}C-labelled propranolol Paterson, Conolly, Dollery, Hayes & Cooper (1970) were able to detect 4-hydroxypropranolol in the blood of patients who received single doses of the parent drug orally, but not following intravenous administration. A similar observation has been made using radio-labelled material in the dog and monkey (Hayes & Cooper, 1971). In addition, in the dog, levels of 4-hydroxypropranolol comparable with those attained following oral administration of propranolol were observed after administration of the drug into the hepatic portal vein. Several theories have been tendered in an attempt to explain these findings (Paterson *et al.*, 1970; Fitzgerald & O'Donnell, 1971; Hayes & Cooper, 1971). Further, it has been suggested, without corroborative plasma level data, that 4-hydroxypropranolol is present in plasma soon after a single oral dose of propranolol, but virtually absent during chronic oral therapy (Cleaveland & Shand, 1972). There is a paucity of information in the literature relating to the plasma concentration of 4-hydroxypropranolol achieved in patients who are receiving chronic oral therapy with propranolol. The considerable difficulties encountered in developing a chemical assay for this metabolite probably account in large measure for this situation. Only three brief reports appear to have been published on the topic (Walle, Morrison, Walle & Conradi, 1975a; Walle, Morrison, Walle & Conradi, 1975b; Walle, Conradi, Walle, Fagan & Gaffney, 1977). It is the purpose of the present paper to report the plasma concentrations of propranolol

0306–5251/79/080163–05 $01.00

and 4-hydroxypropranolol in a group of hypertensive patients who were receiving chronic oral propranolol therapy.

Methods

The patient population was comprised of 17 (10 female, 7 male) ambulant hypertensive adults (Table 1). All patients had apparent normal hepatic function and 14 had no overt clinical signs of renal disease at the time of study; the remainder (patients 1, 3, and 17) either had clinical or laboratory indications of renal disease. The age range of the patients was 33–75 years and body weight range was 62–107 kg. Patients were prescribed propranolol at a dose recommended by their physician. Pregnant women, patients allergic to propranolol, patients with bronchial asthma, and patients with congestive heart failure not due to a tachyarrhythmia treatable with propranolol were excluded from the study. Length of oral therapy with propranolol ranged from 3 weeks to 3 years, and all patients had been on their present dosage regimen for at least 1 week (Table 1). Most patients were currently taking other drugs, including antihypertensives.

A single 5 ml venous blood sample was collected from each subject during a regular clinic visit, at least one hour after the time of the patient's previous propranolol dose (Table 1). Each blood sample was collected into a syringe by venipuncture, deposited in a glass tube containing 50 IU of heparin sodium, and sealed with a Teflon-lined screw cap. This procedure was used in order to avoid spurious assay results (Cotham & Shand, 1975). Blood samples were centrifuged, and plasma was harvested and stored in a frozen state until the time of analysis. The majority of the samples were analyzed within 2–14 days after collection, and the remainder within 1 month. The metabolite, 4-hydroxypropranolol, is stable under such conditions of storage (Garceau, Davis & Hasegawa, 1978). Each plasma sample was analyzed for propranolol and 4-hydroxypropranolol content in two replicates by a high pressure liquid chromatographic procedure (Nation, Peng & Chiou, 1978), and only the mean values are reported here.

Results

The plasma concentrations of propranolol and 4-hydroxypropranolol in the hypertensive patients are summarized in Table 2. The range of plasma propranolol concentrations was from 5.3 to 300 ng/ml, and that of 4-hydroxypropranolol was from 2.1 to 36.0 ng/ml. In one subject (patient 10) measurable levels of the metabolite were not observed, and the concentration of propranolol was very low. The individual values of the ratio of the plasma concentration of the metabolite to that of the

Table 1 Details of the patients and their propranolol therapy.

Patient	Sex	Age (years)	Weight (kg)	Duration of propranolol therapy (years)	Time on present propranolol dose (weeks)	Propranolol daily dose (mg)	Propranolol dose (mg kg^{-1} day^{-1})	Time blood drawn after previous propranolol dose (h)
1	M	*	*	1.5	78	320	*	1.75
2	F	55	107	2.0	2	160	1.49	3.17
3	F	75	62	2.5	3	320	5.15	3.00
4	F	63	88	1.5	20	40	0.46	3.83
5	F	50	57	1.5	65	80	1.40	1.25
6	F	49	69	2.5	8	120	1.74	1.67
7	F	55	88	*	4	320	3.63	2.25
8	M	69	100	0.75	39	60	0.60	3.17
9	F	64	70	0.5	2	120	1.71	2.75
10	F	57	73	1.5	78	40	0.55	6.58
11	M	51	*	*	2	80	*	2.75
12	F	51	77	1.75	78	80	1.04	2.50
13	M	63	102	3.0	2	120	1.18	5.67
14	M	33	77	0.25	2	320	4.14	1.83
15	F	45	106	0.083	1	40	0.38	5.00
16	M	52	73	0.058	1	160	2.20	1.33
17	M	37	77	1.75	20	160	2.07	3.17

* Unable to obtain information.

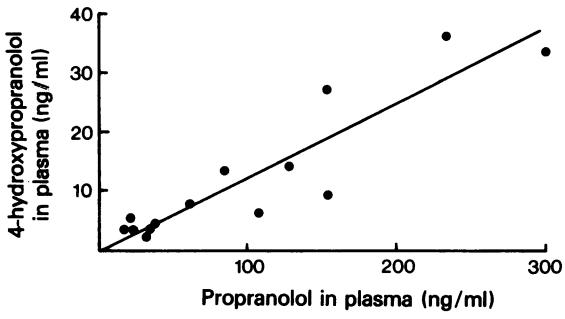

Figure 1 Relationship between plasma concentration of 4-hydroxypropranolol and that of propranolol in hypertensive patients receiving chronic oral propranolol therapy. ($y = -0.0322 + 0.122x$; $r = 0.911$; $P < 0.005$).

parent drug ranged from 0.057 to 0.241 (mean ± s.d.: 0.130 ± 0.055; CV: 42.3%). A statistically significant correlation was observed between plasma concentration of the metabolite and plasma concentration of propranolol (Figure 1) ($r = 0.911$, $P < 0.005$). On the other hand, no relationship existed between the ratio of plasma concentrations (4-hydroxypropranolol/propranolol) and propranolol daily dose (absolute or adjusted on a body weight basis), ratio and propranolol plasma concentration, ratio and time the blood sample was drawn after the previous dose, ratio and the length of time the patient had been receiving propranolol, and, finally, ratio and patient age (in all cases $P > 0.3$). However, propranolol plasma concentration and daily propranolol dose were significantly related, both when absolute dose ($r = 0.739$, $P < 0.005$) and dose adjusted on a body weight basis ($r = 0.655$, $P < 0.05$) were used. In a similar manner 4-hydroxypropranolol plasma concentration and daily propranolol dose were significantly correlated (absolute daily dose, $r = 0.710$, $P < 0.005$; daily dose adjusted according to body weight, $r = 0.689$, $P < 0.05$).

Discussion

It is appropriate at this point to comment on a number of factors which should be kept in mind when one is interpreting the results of a study such as this, particularly when examining the outcome of attempts at correlation between variables. Firstly, the patients represent a diverse group with regard to sex, age, and pathophysiological condition. Of particular importance for propranolol (which has a high hepatic extraction ratio) would be inter-patient variability in the intrinsic clearance of the liver as it relates to the

Table 2 Plasma concentrations of propranolol and 4-hydroxypropranolol in hypertensive patients receiving chronic oral therapy with propranolol

Patient	*Propranolol concentration in plasma (ng/ml)*	*4-Hydroxypropranolol concentration in plasma (ng/ml)*	*Ratio of 4-Hydroxypropranolol to propranolol concentration*
1	300	33.7	0.112
2	154	9.3	0.060
3	236	36.0	0.153
4	36.6	3.6	0.098
5	84.6	13.6	0.161
6	38.9	4.4	0.113
7	224†	18.6†	0.083†
8	33.9	2.1	0.062
9	23.1	3.4	0.147
10	5.3	‡	*
11	22.4	5.4	0.241
12	108	6.2	0.057
13	17.8	3.7	0.208
14	61.3	7.9	0.129
15	23.0	§	*
16	128	14.0	0.109
17	156	27.5	0.176

* Unable to calculate.
† Haemolysis of blood sample. Data not used in final analysis.
‡ No measurable peak.
§ Interference in chromatogram.

systemic availability of a drug following oral administration. Secondly, the blood samples were collected at variable times during a dosage interval; however, 11 of the 17 samples collected were obtained between 1.5 and 3.5 h after the previous dose. Thirdly, difference may exist among patients in biopharmaceutical problems associated with release of the drug from the dosage form and absorption into the hepatic portal vein. Last, but by no means least, is the consideration which must be given to the question of compliance in such a group of outpatients. The influence of the above factors would be most likely to jeopardize the making of valid conclusions in the cases where a measured variable is correlated with prescribed propranolol dose.

In the absence of a suitable chemical assay for 4-hydroxypropranolol in plasma, Cleaveland & Shand (1972) used a bioassay technique in an attempt to gain an insight into the time course of that active metabolite in plasma. Two hours after oral administration of a single dose of propranolol, the degree of β-adrenoceptor blockade associated with a given plasma propranolol concentration was greater than that seen with the same concentration achieved by intravenous administration (when it was assumed that 4-hydroxypropranolol was not formed). After 6 h, this disparity was no longer apparent. During long-term 6-h administration, the effect of the twenty-first dose both 2 and 6 h after administration was the same as that resulting from similar plasma levels achieved by intravenous administration. That is, at the end of a 6 h dosage interval and after chronic oral administration the effects of propranolol seemed to be due entirely to circulating levels of the parent drug.

The results from the present investigation in 17 hypertensive patients indicate that plasma concentrations of 4-hydroxypropranolol do exist during chronic oral therapy with propranolol, even after 2–3 years of treatment. On the average the plasma concentration of the metabolite was 13% that of the parent drug; the individual values ranged from 5.7 to 24.1%. There was no statistically significant relationship between the magnitude of the ratio of plasma concentrations and the length of time the patient had been receiving propranolol.

Walle *et al.* (1975a, 1975b, 1977) were also able to demonstrate the existence of plasma levels of 4-hydroxypropranolol under steady-state conditions. The plasma concentration ratio (4-hydroxypropranolol/propranolol) 2 h after an oral dose was reported by Walle *et al.* (1975a) to average 0.23 for four patients who were each receiving 160 mg propranolol per day. The individual values of the ratio in that study fell within a relatively narrow range from 0.20–0.26. In another report Walle *et al.* (1977) suggested that the plasma concentration ratio might be dose dependent. They found that the ratio was greater than 1 at propranolol doses less than 80 mg per day but decreased to about 0.1 at doses greater than 320 mg per day. Seven patients (patients 4, 5, 8, 10, 11, 12, and 15) in the present study were receiving daily propranolol doses of 80 mg or less. However, the mean concentration ratio for five of these patients (Table 2) was 0.124. This value was not significantly different ($P = 0.05$, t-test) from the mean concentration ratio of 0.134 found for the remaining patients who were receiving higher propranolol doses. Furthermore, there was not a significant correlation between the magnitude of the ratio and propranolol daily dose (absolute or body weight adjusted). The explanation for the discrepancy in the magnitude of the ratio between the present study and that of Walle *et al.* (1977) is not clear. It is interesting to note that Paterson *et al.* (1970) suggested that a larger proportion of an oral dose of propranolol may be metabolized to 4-hydroxypropranolol as the size of the dose is increased. This tissue would probably be best examined in the same subject receiving various propranolol doses on different occasions.

The plasma concentration of propranolol and 4-hydroxypropranolol were each significantly correlated with propranolol daily dose. However, as has been commented upon for similar correlations with propranolol plasma levels only, it is doubtful that such relationships would prove to be clinically useful as a guide to dosage requirements in patients because of the wide scatter of plasma levels at any given daily dose (Chidsey, Morselli, Bianchetti, Morganti, Leonetti & Zanchetti, 1975).

The inter-patient variability in the magnitude of the plasma concentration ratio (Table 2) probably represents actual differences in the disposition of propranolol among the patients. This, in turn, may arise from differences in pathophysiology. Patient age does not appear to be an important determinant of the ratio although this would need to be positively established under more controlled conditions. It is doubtful that the inter-patient variability in the magnitude of the ratio arises in large measure from the differences in the time period between administration of the previous dose and collection of the blood sample. There was no correlation between the ratio and that time period. In addition, Walle *et al.* (1975b, 1977) reported that peak concentrations of propranolol and 4-hydroxypropranolol occur at 2–2.1 h after each propranolol dose, and that thereafter plasma concentrations of the two species decline in parallel.

There is considerable interindividual variation in the plasma level of propranolol required to produce a given effect, and it has been suggested that interindividual variation in the extent of 4-hydroxylation of propranolol may account, at least in part, for this phenomenon (Zacest & Koch-Weser, 1972; Nies & Shand, 1975; Johnsson & Regardh, 1976).

This would not appear to be an important consideration in view of the low levels of the metabolite, relative to the parent drug, observed in all the patients of this study. That conclusion is based on the premise that 4-hydroxypropranolol does not have much greater potency than propranolol as a β-adrenoceptor blocker, when the comparison is based on plasma levels. Probably more important considerations are interindividual variation in the extent of plasma binding of propranolol and true receptor sensitivity (McDevitt, Frisk-Holmberg, Hollifield & Shand, 1976).

In conclusion, relatively low plasma levels of 4-hydroxypropranolol have been detected in hypertensive patients receiving chronic oral therapy with propranolol. The low ratio of plasma level of the metabolite to that of the parent drug probably accounts for the fact that Cleaveland & Shand (1972) could not detect the effects of 4-hydroxypropranolol during chronic oral administration. The contribution of 4-hydroxypropranolol to the pharmacologic effect of propranolol during chronic oral therapy may be of minor importance. However, a number of facets of the clinical pharmacokinetics and clinical pharmacology of propranolol require further elucidation. The time course of plasma level of 4-hydroxypropranolol during the first oral dose and through chronic therapy warrants investigation. Also included would be a re-evaluation of the relative potency of propranolol and 4-hydroxypropranolol based on plasma concentration data.

We wish to thank Dr E. Gurwich of the Department of Pharmacy Practice for his assistance. Reprint requests should be addressed to W.L.C.

References

CHIDSEY, C.A., MORSELLI, P., BIANCHETTI, G., MORGANTI, A., LEONETTI, G. & ZANCHETTI, A. (1975). Studies of the absorption and removal of propranolol in hypertensive patients during therapy. *Circulation*, **52**, 313–318.

CLEAVELAND, C.R. & SHAND, D.G. (1972). Effect of route of administration on the relationship between β-adrenergic blockade and plasma propranolol level. *Clin. Pharmac. Ther.*, **13**, 181–185.

COTHAM, R.H. & SHAND, D. (1975). Spuriously low plasma propranolol concentrations resulting from blood collection methods. *Clin. Pharmac. Ther.*, **18**, 535–538.

FITZGERALD, J.D. & O'DONNELL, S.R. (1971). Pharmacology of 4-hydroxypropranolol, a metabolite of propranolol. *Br. J. Pharmac.*, **43**, 222–235.

GARCEAU, Y., DAVIS, I. & HASEGAWA, J. (1978). Fluorometric TLC determination of free and conjugated propranolol, napthoxylactic acid, and p-hydroxypropranolol in human plasma and urine. *J. pharm. Sci.*, **67**, 826–831.

HAYES, A. & COOPER, R.G. (1971). Studies on the absorption, distribution and excretion of propranolol in rat, dog, and monkey. *J. Pharmac. exp. Ther.*, **176**, 302–311.

JOHNSSON, G. & REGARDH, C.G. (1976). Clinical pharmacokinetics of β-adrenoreceptor blocking drugs. *Clin. Pharmacokin.*, **1**, 233–263.

McDEVITT, D.G., FRISK-HOLMBERG, M., HOLLIFIELD, J.W. & SHAND, D.G. (1976). Plasma binding and the affinity of propranolol for a receptor in man. *Clin. Pharmac. Ther.*, **20**, 152–157.

NATION, R.L., PENG, G.W. & CHIOU, W.L. (1978). High pressure liquid chromatographic method for the simultaneous quantitative analysis of propranolol and 4-hydroxypropranolol in plasma. *J. Chromatog.*, **145**, 429–436.

NIES, A.S. & SHAND, D.G. (1975). Clinical pharmacology of propranolol. *Circulation*, **52**, 6–15.

PATERSON, J.W., CONOLLY, M.E., DOLLERY, C.T., HAYES, A. & COOPER, R.G. (1970). The pharmacodynamics and metabolism of propranolol in man. *Pharmacologia Clinica*, **2**, 127–133.

WALLE, T., CONRADI, E., WALLE, K., FAGAN, T. & GAFFNEY, T.E. (1977). Steady-state kinetics of the active propranolol metabolite 4-hydroxypropranolol and its glucuronic acjd conjugate in patients with hypertension and coronary artery disease. *Clin. Res.*, **25**, 10A.

WALLE, T., MORRISON, J., WALLE, K. & CONRADI, E. (1975a). Simultaneous determination of propranolol and 4-hydroxypropranolol in plasma by mass fragmentography. *J. Chromatog.*, **114**, 351–359.

WALLE, T., MORRISON, J., WALLE, K. & CONRADI, E. (1975b). Simultaneous determination of propranolol and its active metabolite 4-hydroxypropranolol in plasma. *Pharmacologist*, **17**, 268.

ZACEST, R. & KOCH-WESER, J. (1972). Relation of propranolol plasma level to β-blockade during oral therapy. *Pharmacology*, **7**, 178–184.

(Received September 19, 1978)