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THE ASSESSMENT OF β-ADRENOCEPTOR BLOCKING DRUGS IN HYPERTHYROIDISM

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1 Intravenous propranolol and practolol both reduced resting supine heart rate in patients with hyperthyroidism. Propranolol produced a significantly greater reduction than practolol, which did not have a dose-dependent effect.

2 The effect of these drugs on resting heart rate was much less than their effect on the tachycardias produced both by severe exercise and by standing upright in hyperthyroid patients. Propranolol again produced a significantly greater reduction than practolol in each situation, but practolol did have a dose dependent effect on exercise heart rate.

3 The percentage reduction of standing tachycardia produced by the two drugs appeared to parallel closely the reduction in exercise tachycardia.

4 It is concluded that a simple and convenient way of assessing the activity of β-adrenoceptor blocking drugs in hyperthyroid patients would be to measure their effect on the tachycardia induced by standing. Their effect on resting heart rate should not be used.

5 Practolol may be useful in the management of hyperthyroidism in patients in whom propranolol and similar non-selective β-adrenoceptor blocking drugs are contraindicated.

Introduction

Propranolol has been shown to lower the resting heart rate significantly in patients with hyperthyroidism (McDevitt, Shanks, Hadden, Montgomery & Weaver, 1968). In addition, it controls the peripheral symptoms and signs of hyperthyroidism (Shanks, Hadden, Lowe, McDevitt & Montgomery, 1969). Thus β-adrenoceptor blockade by this drug has attained a place in various aspects of the management of hyperthyroidism (Bayliss, 1971).

The effectiveness and usefulness of other β-adrenoceptor blocking drug with intrinsic sympa- would appear that drugs possessing intrinsic sympathomimetic activity, such as alprenolol, oxprenolol, practolol and pindolol, fail to produce a dose-dependent slowing of hyperthyroid tachycardia (Turner & Hill, 1968; Turner, 1970; Arbab & Turner, 1971), in contrast to drugs lacking intrinsic activity (propranolol, sotalol and Ro 3-3528) (Kofi Ekue, Lowe & Shanks, 1970; Phillips, Turner, Houghton & Ferriman, 1973). The difference in response between the two types of compound has been attributed to increased responsiveness to agonist activity in the hyperthyroid state (Turner & Hill, 1968). For this reason, drugs with intrinsic sympathomimetic activity have also been said to have dysrhythmic properties in hyperthyroidism (Turner & Hill, 1968).

The accepted methods for demonstrating the effectiveness of β-adrenoceptor blocking drugs in man have been their effect on the tachycardia induced either by isoprenaline infusion (Brick, Hutchison, McDevitt, Roddie & Shanks, 1968; Dollery, Paterson & Conolly, 1969), by severe exercise (Brick *et al.*, 1968; Coltart & Shand, 1970), or by the sublingual administration of glyceryl trinitrate (Fitzgerald, 1970; Kofi Ekue, Shanks & Walsh, 1974). So far none of these methods have been applied to the assessment of β-adrenoceptor blocking drugs in hyperthyroid patients; their effect on resting heart rate alone has been reported.

The present study was designed to compare the effects of propranolol and practolol on resting heart rate, and on the increases in heart rate induced by standing and by exercise in patients with hyperthyroidism.

Methods

Observations were made on 15 patients with hyperthyroidism. The sex and range of values for

age, serum protein bound iodine (P.B.I.), serum thyroxine (Thyopac-4) and free-thyroxine index (F.T.I.) are shown in Table 1. All subjects were in sinus rhythm and did not suffer from cardiac disease or bronchial asthma.

Study 1

Ten patients were investigated after overnight bed rest in hospital and a light breakfast. With the patient resting in the supine position, heart rate was recorded using an electrocardiograph (lead 1), by determining the time taken for five complete cardiac cycles. When the heart rate was constant, either propranolol, 0.2 mg/kg, or practolol, 0.2 or 0.4 mg/kg, was administered intravenously over a 3 min period on three consecutive days. All patients received all treatments, the order of which was randomized. Heart rate was recorded at 1 min intervals for the 5 min following injection of the drug and at less frequent intervals for a further 55 minutes.

Study 2

Five patients with hyperthyroidism were studied as outpatients, each for four consecutive mornings at 09.00 h after a light breakfast. Each patient rested supine for 20 min, with heart rate recorded as previously described, when an intravenous injection was given over a 3 min period, and the heart rate was recorded at 1 min intervals for 5 minutes. The subject then stood upright and heart rate was again recorded immediately and at 1 min intervals for 3 minutes. Finally, each subject performed a period of standardized exercise which consisted of stepping on and off a box at a fixed speed. The height of the step, rate and duration of the exercise period were individually determined for each patient to make the exercise as severe as possible. Each patient received saline, propranolol, 0.2 mg/kg, and practolol 0.2 and 0.4 mg/kg. The order of the first two treatments was randomized but the practolol was always given on the third and fourth days, with the lesser dose first, because of the possibility of the prolonged pharmacological action of practolol (Carruthers, Kelly, McDevitt & Shanks, 1973).

Results

Study 1

The effect of the intravenous injection of propranolol, 0.2 mg/kg, and of two doses of practolol, 0.2 and 0.4 mg/kg, on heart rate in 10 hyperthyroid subjects is shown in Table 2. Each of the drugs produced a significant fall in resting heart rate after 5 min and this effect persisted for at least 60 minutes. The effect of propranolol was significantly greater than that of either dose of practolol at 5, 30 and 60 minutes. No dose-response relationship was observed with the increasing doses of practolol, indeed the effect of the lower dose appeared to be marginally better. The reduction of resting heart rate in the hyperthyroid subjects induced by propranolol was between 18-21%, whereas that induced by practolol was between 8-11.5% during the first 60 min after injection. No patient developed dysrhythmia or any increase in cardiac extrasystoles.

Study 2

The effect of the intravenous injection of saline, propranolol, 0.2 mg/kg, and practolol, 0.2 and 0.4 mg/kg, on the resting heart rate 5 min after the

Table 1 Sex distribution and range of values for age, serum protein bound iodine (P.B.I.), serum thyroxine and free thyroxine index (F.T.I.) in the two series of investigations.

Patients	*Sex*	*Age (years)*	*P.B.I.* (μg/100 ml)*	*Serum** thyroxine (Thyopac-4) (μg/100 ml)*	*F.T.I.†*
Study 1					
Resting heart rate	6F, 4M	25-70	9.5-15.0	13.4-19.6	15.1-24.6
Study 2					
Standing and exercise heart rate	5F	30-58	11.7-15.0	12.4-23.9	15.5-33.0

* Normal range 3.7-7.4 μg/100 ml.
** Normal range 4.3-12.1 μg/100 ml.
† Normal range 4.0-11.2 (Free Thyroxine index = $\frac{\text{'Thyopac-4'}}{\text{'Thyopac-3'}}$)

Table 2 Effect of propranolol, 0.2 mg/kg, and practolol, 0.2 and 0.4 mg/kg, on resting heart rate in 10 patients with hyperthyroidism (mean of observations ±S.E.M.)

	Resting heart rate							
	Drug administered	5 min after injection		30 min after injection		60 min after injection	
		Beats/min	% reduction†	Beats/min	% reduction†	Beats/min	% reduction†
Propranolol, 0.2 mg/kg	97.3 ± 1.5	79.4 ± 1.3*	18.0	76.1 ± 1.3*	21.8	76.9 ± 1.4*	21.0
Practolol, 0.2 mg/kg	97.0 ± 1.1	88.1 ± 1.2*	9.2	85.9 ± 1.5*	11.4	85.8 ± 1.5*	11.5
Practolol, 0.4 mg/kg	94.2 ± 1.5	86.7 ± 1.4*	8.0	85.2 ± 1.5*	9.6	83.4 ± 1.6*	11.5

† '% reduction' is the percentage reduction in resting heart rate compared with the value before injection.
* = $P < 0.05$. Values of P relate to significant differences compared with values of resting heart rate before injection.

injection, on the heart rate after standing upright for 3 min and after a 1.5-2.0 min period of severe exercise in five hyperthyroid patients is shown in Table 3. There was no significant difference between the resting heart rates before injection in any of the four groups.

The injection of saline was associated with a slight fall in resting heart rate but this was not significant. Propranolol, 0.2 mg/kg, reduced resting heart rate to a mean of 93.6 beats/min which is significantly less than that obtained after saline ($P < 0.01$). Both doses of practolol reduced resting heart rate but with neither dose was the reduction significantly greater than that occurring after saline. The effect after the larger dose of practolol was similar to that of the smaller dose.

Five minutes after the injection of saline, the mean heart rate increased to 131.9 beats/min on standing upright for 3 minutes. This was a significant increase. Propranolol and the two doses of practolol all caused a significant reduction in this standing tachycardia ($P < 0.01$). There was again no significant difference between the effects of the two doses of practolol. Propranolol, 0.2 mg/kg, resulted in a significantly greater reduction of standing tachycardia than did practolol, 0.4 mg/kg ($P < 0.05$).

Following the injection of saline, the mean heart rate was 179.0 beats/min after a period of strenuous exercise. The greatest reduction in exercise tachycardia occurred after propranolol but both doses of practolol also produced significant reductions in exercise tachycardia ($P < 0.01$). The mean exercise heart rate after practolol, 0.2 mg/kg, was 153.8 beats/min and after practolol, 0.4 mg/kg, was 146.6 beats/minute. There is a significant difference between these values ($P < 0.02$). Propranolol, 0.2 mg/kg, produced a significantly greater reduction in exercise tachycardia than practolol, 0.4 mg/kg ($P < 0.05$).

Discussion

Although the administration of the two doses of practolol, 0.2 and 0.4 mg/kg, reduced resting heart rate in the patients who were in hospital during the night preceding the study, the effect was not dose dependent. In contrast, propranolol and sotalol have been shown to produce a dose-dependent reduction in heart rate in such patients (Kofi Ekue *et al.*, 1970). The reason for the absence of a dose-response effect with practolol is not clear. In the patients with hyperthyroidism who attended hospital daily, practolol, 0.2 and 0.4 mg/kg, had no effect on resting heart rate while propranolol reduced it. A similar effect was described by Turner & Hill (1968). There is no

obvious explanation for the difference in the effects of practolol in the two groups of patients. Although resting heart rate was higher in the second group of patients, this did not appear to result from an increase in sympathetic activity, as practolol did not reduce heart rate and the effect of propranolol was less. The higher heart rate in these patients may have resulted from reduced parasympathetic activity or from the direct effects of increased amounts of thyroid hormones.

The reduction in heart rate produced by propranolol results from inhibition of cardiac sympathetic drive (Black, Duncan & Shanks, 1965). The intrinsic sympathomimetic activity, which is present in practolol but not propranolol, may counteract the effect of practolol in reducing cardiac sympathetic drive, so that little change in heart rate is produced (Dunlop & Shanks, 1968). Thus the effect of practolol on resting heart rate depends on the balance between intrinsic activity and the amount of cardiac sympathetic activity (Kofi Ekue & Shanks, 1974), and may not be a reliable index of the β-adrenoceptor blocking activity of practolol. In normal subjects, Schneck, Aoki, Kroetz & Wilson (1972) showed that a series of doses of practolol, 1.5, 3.0 and 12.0 mg/kg orally, did not affect supine resting heart rate, whilst several studies have shown that propranolol does reduce resting supine heart rate (Robinson, Epstein, Beiser & Braunwald, 1966; Svedmyr, Jakobsson & Malmberg, 1969). However, there is evidence that the tachycardia of hyperthyroidism is not due to increased sympathetic activity, for not only is the intrinsic heart rate in patients with this disease above normal, but propranolol induces a similar mean percentage reduction in heart rate in patients with both hyperthyroidism and hypothyroidism (McDevitt *et al.*, 1968). It, therefore, seems unlikely that the assessment of β-adrenoceptor blocking drugs in hyperthyroidism by their effect on resting heart rate will demonstrate their true activity.

This is confirmed by the present study in which β-adrenoceptor blocking activity was assessed by the effect of the drugs on the increases in heart rate on standing and on severe exercise, both of which result from increased sympathetic drive (Robinson *et al.*, 1966). Practolol, 0.2 mg/kg, reduced standing and exercise heart rate by 17.8% and 14.1% respectively, and practolol, 0.4 mg/kg, by 19.9% and 18.1% respectively. Propranolol reduced both tachycardias by 25.1% (Table 4). These contrast with the reduction of resting heart rate by practolol, 0.2 mg/kg, practolol, 0.4 mg/kg and propranolol of 5.0, 7.2 and 14.4% respectively and appear to be similar to the effects of the two drugs in normal subjects (Brick *et al.*, 1968), in whom practolol is less effective than propranolol in reducing an exercise tachycardia. In the present study, practolol did have a dose-dependent effect on exercise heart rate in hyperthyroid patients.

The present observations show that in hyperthyroid patients, β-adrenoceptor blocking drugs reduce the tachycardia produced by standing. It is of note that the percentage reduction of standing tachycardia produced by the two drugs appeared to parallel closely the reduction in exercise tachycardia. This would suggest that a simple and convenient way of assessing the activity of β-adrenoceptor blocking drugs in hyperthyroid patients would be to measure their effect on the tachycardia induced by standing upright. This test could be performed easily and, if necessary, frequently, and would avoid the difficulties of carrying out strenuous exercise in the presence of either thyrotoxic myopathy or cardiovascular disease. Further support for the use of such a test to evaluate β-adrenoceptor blocking agents in

Table 3 Effect of saline, propranolol, 0.2 mg/kg, and practolol, 0.2 and 0.4 mg/kg, on resting, standing and exercise heart rate in five patients with hyperthyroidism (mean of observations ±S.E.M.)

	Pre-injection (beats/min)	*Post-injection (beats/min)*		
	Resting (20 min)	*Resting (5 min)*	*Standing (3 min)*	*Exercise (1.5 or 2 min)*
Saline (control)	119.4 ± 8.0	112.0 ± 6.8	131.9 ± 6.1	179.0 ± 6.9
Propranolol, 0.2 mg/kg	116.7 ± 6.7	93.6 ± 6.8*	98.8 ± 5.9*	134.0 ± 4.3*
Practolol, 0.2 mg/kg	111.2 ± 6.4	106.4 ± 6.5	108.4 ± 3.7*	153.8 ± 6.4*
Practolol, 0.4 mg/kg	115.2 ± 7.8	104.0 ± 5.9	105.6 ± 4.5*	146.6 ± 6.4*

* = $P < 0.05$. Values of P relate to significant differences compared with the values obtained during the saline control.

Table 4 Effect of propranolol, 0.2 mg/kg, and practolol, 0.2 and 0.4 mg/kg, on heart rate in five hyperthyroid patients. Effect is expressed as % reduction of mean heart rate after resting for 5 min after injection, standing for 3 min or exercise when compared with mean heart rate after saline control.

	% reduction in heart rate after injection		
Injection	*Resting (5 min)*	*Standing (3 min)*	*Exercise*
Propranolol, 0.2 mg/kg	14.4	25.1	25.1
Practolol, 0.2 mg/kg	5.0	17.8	14.1
Practolol, 0.4 mg/kg	7.2	19.9	18.1

patients has recently come from Kofi Ekue *et al.* (1974) who found that practolol reduced standing tachycardia and the tachycardia induced by glyceryl trinitrate to the same extent in patients with ischaemic heart disease.

Practolol, and other β-adrenoceptor blocking drugs with intrinsic sympathomimetic activity, have been labelled as inferior to propranolol and other drugs without intrinsic activity in the treatment of hyperthyroidism but only on the basis of their effect on resting heart rate (Turner & Hill, 1968; Turner, 1970; Arbab & Turner, 1971; Phillips *et al.*, 1973). These present observations would suggest that reduction in resting heart rate is not representative of the β-blocking activity of these drugs and that, whilst propranolol is obviously more effective than practolol in hyperthyroid patients, this merely reflects the comparable activity of these two drugs in normal subjects, and cannot be held to support the idea that patients with hyperthyroidism are unduly sensitive to the effects of catecholamines.

In addition, it must be stressed that a cardiac dysrhythmia has been reported in only one hyperthyroid patient after the administration of a β-adrenoceptor blocking drugs is less certain. It thomimetic activity (in that case, oxprenolol) (Turner & Hill, 1968), so that it seems unreasonable to make this a contraindication for prescribing these drugs in hyperthyroidism.

Although propranolol remains the drug of choice in the control of the peripheral manifestations of hyperthyroidism, these observations suggest that practolol does work in this disease and may be valuable in the management of cases where, because of obstructive airways disease, congestive heart failure or drug intolerance, the use of propranolol may be precluded. There is already evidence of the effectiveness of practolol in the management of hyperthyroid heart failure (Epstein & Pimstone, 1971).

References

ARBAB, A.G. & TURNER, P. (1971). Comparison of propranolol and LB 46 (prinodolol) on hyperthyroid tachycardia. *Postgrad. Med. J.*, **47**, 329-331.

BAYLISS, R.I.S. (1971). Propranolol in the treatment of Graves' Disease. In: *Progress in Clinical Medicine*, ed. I.R. Daley & H. Miller, 6th edition, pp. 217-219, Edinburgh and London: Churchill Livingstone.

BLACK, J.W., DUNCAN, W.A.M. & SHANKS, R.G. (1965). Comparison of some properties of pronethalol and propranolol. *Br. J. Pharmac.*, **25**, 577-591.

BRICK, I., HUTCHISON, K.J., McDEVITT, D.G., RODDIE, I.C. & SHANKS, R.G. (1968). Comparison of the effects of I.C.I. 50172 and propranolol on the cardiovascular responses to adrenaline, isoprenaline and exercise. *Br. J. Pharmac.*, **34**, 127-140.

CARRUTHERS, S.G., KELLY, J.G., McDEVITT, D.G. & SHANKS, R.G. (1973). Duration of action of beta-blocking drugs. *Br. med. J.*, **2**, 177.

COLTART, D.J. & SHAND, D.G. (1970). Plasma propranolol levels in the quantitative assessment of β-adrenergic blockade in man. *Br. med. J.*, **3**, 731-734.

DOLLERY, C.T., PATERSON, J.W. & CONOLLY, M. (1969). Clinical pharmacology of β-receptor-blocking drugs. *Clin. Pharmac. Ther.*, **10**, 765-799.

DUNLOP, D. & SHANKS, R.G. (1968). Selective blockade of adrenoceptive β-receptors in the heart. *Br. J. Pharmac.*, **32**, 201-218.

EPSTEIN, S. & PIMSTONE, B. (1971). Practolol in hyperthyroid cardiac failure. *S.A. med. J.*, **45**, 812-814.

FITZGERALD, J.D. (1970). A new test of the degree of adrenergic β-receptor blockade. *Int. J. Clin. Pharmac.*, **4**, 125-130.

KOFI EKUE, J.M., LOWE, D.C. & SHANKS, R.G. (1970). Comparison of the effects of propranolol and MJ 1999 on cardiac β-adrenoceptors in man. *Br. J. Pharmac.*, **38**, 546-553.

KOFI EKUE, J.M. & SHANKS, R.G. (1974). Some effects of Kö 1313 in animals and man. *Br. J. clin. Pharmac.*, **1**, 27-35.

KOFI EKUE, J.M., SHANKS, R.G. & WALSH, M.J. (1974). Observations on the effect of beta adrenoceptor blocking drugs on a glyceryl trinitrate tachycardia. *Br. J. clin. Pharmac.*, **1**, 19-26.

McDEVITT, D.G., SHANKS, R.G., HADDEN, D.R., MONTGOMERY, D.A.D. & WEAVER, J.A. (1968). The role of the thyroid in the control of heart rate. *Lancet*, **i**, 998-1000.

PHILLIPS, E.M., TURNER, P., HOUGHTON, J. & FERRIMAN, D.G. (1973). Comparison of propranolol

and Ro 3-3528 in hyperthyroid tachycardia and dysrhythmias. *Postgrad. Med. J.*, **49**, 18-23.

ROBINSON, B.F., EPSTEIN, S.E., BEISER, D. & BRAUNWALD, E. (1966). Control of the heart rate by the autonomic nervous system. Studies in man on the inter-relation between baroreceptor mechanisms and exercise. *Circulation Res.*, **19**, 400-411.

SCHNECK, D.W., AOKI, V.S., KROETZ, F.W. & WILSON, W.R. (1972). Correlation of β-blockade with serum practolol levels after oral administration. *Clin. Pharmac. Ther.*, **13**, 685-693.

SHANKS, R.G., HADDEN, D.R., LOWE, D.C., McDEVITT, D.G. & MONTGOMERY, D.A.D. (1969). Controlled trial of propranolol in thyrotoxicosis. *Lancet*, **i**, 993-994.

SVEDMYR, N., JAKOBSSON, B. & MALMBERG, R. (1969). Effects of sotalol and propranolol administered orally in man. *Eur. J. Pharmac.*, **8**, 79-82.

TURNER, P. (1970). Alprenolol and propranolol in hyperthyroid tachycardia. *Br. J. Pharmac.*, **40**, 146-147P.

TURNER, P. & HILL, R.C. (1968). A comparison of three β-adrenergic receptor-blocking drugs in thyrotoxic tachycardia. *J. Clin. Pharmac.*, **8**, 268-271.

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