A COMPARISON OF THE EFFECTS OF PROPRANOLOL AND OXPRENOLOL ON FOREARM BLOOD FLOW AND SKIN TEMPERATURE

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- 1 The effects of oxprenolol 80 mg and propranolol 80 mg on resting forearm blood flow (RFBF) and skin temperature were compared in seven normotensive subjects, for 4 h after an oral dose.
- 2 There was a significant fall of RFBF after propranolol (mean $\pm$ s.e. mean 0.74 ± 0.24 ml 100 g $^{-1}$ min $^{-1}$) compared to a smaller non-significant reduction after oxprenolol (0.35 ± 0.19 ml 100 g $^{-1}$ min $^{-1}$). Propranolol produced a greater fall in heart rate than oxprenolol at all times except at 2.5 h. Three subjects experienced falls in skin temperature of over 4°C with propranolol. There were no comparable falls after oxprenolol.
- 3 The results suggest that at the same dose oxprenolol has less effect on RFBF and skin temperature than propranolol.

Introduction

Patients taking propranolol not infrequently complain of coldness of the extremities and an exacerbation of Raynaud's phenomenon, one series quoting an incidence of 5.8% (Greenblatt & Koch Weser, 1974). There have also been reports of propranolol causing an exacerbation of intermittent claudication (Rodger, Sheldon, Lerski & Livingstone, 1976; Frohlich, Tarazi & Dunstan, 1969) and of the same problems occurring with the use of other β -adrenoceptor blocking agents (Simpson, 1974) including oxprenolol. It has been suggested that the incidence of these unwanted effects occurs less often with oxprenolol than propranolol (Marshall, Roberts & Barritt, 1976), although the evidence has been criticised (Marsden & Bayliss, 1976). The present study is concerned with a comparison of the effect of oral oxprenolol and propranolol on resting forearm blood flow and skin temperature.

Method

The protocol had the approval of the London Hospital ethics committee. Seven normal volunteers were studied (aged 21–32 years). Contraindications to β -adrenoceptor blockade were excluded by a full history, clinical examination and a standard 12-lead electrocardiogram. Forearm blood flow, arm, leg and

core temperature, arterial blood pressure and heart rate were measured at rest, after 1.5 h acclimatisation in a clinical laboratory temperature-stable room and then at 0.5 hourly intervals for 4 h after an oral dose of either 80 mg of propranolol or oxprenolol, administered according to a randomised observer-blind cross-over trial design. The drugs were dispensed by the clinic nurse and the observer did not know which of the treatments had been taken. There was a period of at least 2 weeks between measurements. The volunteers were non-smokers and were receiving no other drugs. Forearm blood flow was measured using the mercury-in-rubber strain-gauge plethysmograph as described by Whitney (Greenfield, Whitney & Mowbray, 1963) applied to the left forearm with an occlusive cuff at the wrist. It was measured 5 times for each observation time and the mean used for analysis. Skin temperature of the right hand and foot was measured using thermocouples placed on the ball of the thumb and big toe respectively. Blood pressure (x2) was measured using a Roche arteriosonde and the heart rate obtained from an ECG trace by analysis of 5 R-R intervals. The environmental temperature rose slowly by an average of $1.3^{\circ}\text{C} \pm 1.2^{\circ}$ s.d. over the course of the observations. There was no significant difference between the initial and final laboratory temperatures in the propranolol and oxprenolol studies.

Figure 1 Fall in forearm blood flow (mean $\pm$ s.e. mean) after an 80 mg oral dose of either oxprenolol (●) or propranolol (○) ($n = 7$). * $P < 0.05$, ** $P < 0.01$ fall in propranolol flows. † $P < 0.05$, †† $P < 0.01$ significant difference between oxprenolol and propranolol.

Results

Blood flow (Figure 1)

There was a significant fall in the forearm blood flow from $2.24 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1} \pm 0.22$ (s.e. mean) to $1.50 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1} \pm 0.27$ (s.e. mean) ($P < 0.05$) after 80 mg of propranolol, maximal at 2.5 h and a non-significant fall after oxprenolol from $2.25 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1} \pm 0.10$ (s.e. mean) to $1.90 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1} \pm 0.16$ (s.e. mean). The difference between the change in blood flow after oxprenolol and that after propranolol was significant from 1.5 h after dosing to the end of the experiment ($P < 0.05$ or 0.01).

Heart rate (Figure 2)

The heart rate fell significantly after both propranolol and oxprenolol the fall being significantly greater after propranolol than oxprenolol at all times except at 0.5 h and 2.5 h after dosing ($P < 0.05$).

Blood pressure (Figure 3)

There was no change in systolic or diastolic blood

pressure after oxprenolol but a significant rise of diastolic pressure (7.8 mmHg) took place after propranolol ($P = 0.02$) and this was significantly different from the changes after oxprenolol ($P < 0.05$).

Arm and leg temperature (Figure 4)

There was no change in mean arm and leg temperature after oxprenolol and at the time of maximal reduction in blood flow (2.5 h after drug administration) mean $\pm$ s.e. mean arm temperature changed from $31.6^\circ\text{C} \pm 0.7$ to $31.9^\circ\text{C} \pm 0.5$. There was however a non-significant fall in temperature after propranolol, the mean $\pm$ s.e. mean arm temperature falling from $31.3^\circ\text{C} \pm 0.8$ to $29.3^\circ\text{C} \pm 1.3$ and leg temperature $27.6^\circ\text{C} \pm 0.9$ to $26.0^\circ\text{C} \pm 1.5$. This reduction was due to two patients having a fall in arm temperature of 7°C and 9°C after propranolol and three a fall of leg temperature of 9°C , 5°C and 4°C . There were no comparable drops in temperature after oxprenolol. Comparison between the mean temperature changes in the arm and leg after the two drugs revealed no significant difference.

Figure 2 Fall in heart rate (mean $\pm$ s.e.mean) after an oral dose of 80 mg oxprenolol (●) or propranolol (○) ($n = 7$). * $P < 0.01$, ** $P < 0.001$ significant fall in heart rate with oxprenolol or propranolol. † $P < 0.05$ significant difference between oxprenolol and propranolol.

Figure 3 The change in systolic and diastolic blood pressures (mean $\pm$ s.e.mean) after an 80 mg oral dose oxprenolol (●) or propranolol (○) ($n = 7$). * $P < 0.05$ significant rise in BP after propranolol, † $P < 0.05$ significant difference between oxprenolol and propranolol.

Figure 4 Changes (mean $\pm$ s.e. mean) in a) leg and b) arm skin temperature 2.5 h and 4 h after 80 mg of either oxprenolol or propranolol in seven subjects and the mean $\pm$ s.e. mean.

Core temperature

There were no changes in core temperature on either propranolol (mean $\pm$ s.e. mean $36.6^{\circ}\text{C} \pm 0.06$ to $36.5^{\circ}\text{C} \pm 0.08$) or oxprenolol ($36.5^{\circ}\text{C} \pm 0.08$ to $36.4^{\circ}\text{C} \pm 0.11$).

Discussion

Propranolol has been shown to significantly reduce blood flow to almost all tissues except brain after

acute administration to animals (Nies, Evans & Shand, 1973). In man, intravenous administration has been shown to cause a fall in forearm blood flow (Robinson & Wilson, 1968). However, when administered intra-arterially it caused little change (Brick, Glover, Hutchinson & Roddie, 1966). Oral propranolol administered to normal subjects and hypertensive patients reduced calf blood flow and post-exercise hyperaemia (McSorley & Warren, 1978). Our observations with propranolol are consistent with the above reports and we have furthermore shown there to be a significant difference in the change of forearm blood flow after oral oxprenolol as compared to propranolol.

McSorley & Warren (1978) showed similar differences between propranolol and metoprolol and suggested that this was due to the cardioselectivity of metoprolol, a property which would selectively avoid blockade of the vasodilator β -adrenoceptors, which mediate dilation in muscle blood vessels. It seems probable that the findings in the present study are due to other differences in the pharmacological properties of propranolol and oxprenolol. Oxprenolol, in contrast to propranolol has intrinsic sympathomimetic activity (ISA) and weak prejunctional α -adrenoceptor blocking activity (Rand, Law, Story & McCulloch, 1976) both of which may result in β -adrenoceptor-mediated vasodilation. The acute rise in blood pressure after propranolol is likely to be due to a reduction in cardiac output which could lead to baroreceptor mediated peripheral vasoconstriction (Struyker-Boudier, Smits & Van Essen, 1979). This might have been exacerbated by increased catecholamines in anxious subjects. The fact that it did not occur after oxprenolol may be due to a lesser reduction in cardiac output (Wilson, Watson, Peel, Langley & Tarren, 1968).

The skin temperature changes are in agreement with the observation of Roberts, Marshall & Barritt (1977). Slight rises in skin temperature observed in a few patients on both drugs may be attributable to the slight rises of environmental temperature which were the same for both drugs as mentioned earlier. Three subjects became peripherally cyanosed after propranolol and showed a large drop in skin temperature. No patients showed this response after oxprenolol. The difference in changes of hand and foot temperature is probably due to increased sympathetic activity secondary to the larger fall in cardiac output on propranolol and not due to the ISA of oxprenolol.

The study was restricted to the use of a single dose of each drug and the differences found could be attributed to a difference in relative effectiveness of two drugs as regards their β -adrenoceptor blocking activity. The same dose of each drug was administered because the drugs have been shown equipotent by weight in the suppression of the

heart rate response to exercise (Taylor, Thadani, Davidson, Singleton & Myint, 1975) and in the treatment of angina (Thadani, Sharma, Meeran, Majid, Whitaker and Taylor, 1973; Sowton, Das Crupta & Baker, 1975) and hypertension (Davidson, Thadani, Singleton & Taylor, 1976; Waal-Manning & Hendrita, 1970). Our observations that the resting heart rate was higher after oxprenolol than propranolol is in agreement with others (Thadani *et al.*, 1973) and may be due to intrinsic sympathomimetic activity. For these reasons we consider that equivalent dosages were used. However, we did not estimate the degree of β -adrenoceptor blockade.

The clinical implications of our results must be interpreted with caution. This was an acute study on normal subjects, not a long term study on patients. There is a well documented incidence of cold limbs in patients treated with propranolol, but the evidence that this drug increases the symptom of claudication has been either anecdotal (Rodger *et al.*, 1976; Frohlich *et al.*, 1969) or retrospective (Zachariasis, Cowen, Prestt, Vickers & Wall, 1970). A prospective

study in which patients suffering from intermittent claudication were treated with propranolol (Reichert, Shibolet, Adar & Gatni, 1975) did not reveal exacerbation of this symptom and, indeed, propranolol was initially used for the treatment of intermittent claudication in other countries (Skawinski, Wojcikiewicz & Peiker, 1971).

However, the findings indicate that at a given dosage the effect on forearm blood flow of oxprenolol is less marked than propranolol and that if a patient is symptomatic on propranolol it may be worth changing to oxprenolol, if the same dosage is used.

We also feel that propranolol should be used with extreme caution in patients in whom a reduction of muscle blood flow may be dangerous.

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