An assessment of the partial agonist activity of Ro 31–1118, flusoxolol and pindolol in man

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1 The effects of single oral doses of three β -adrenoceptor partial agonists (Ro 31–1118, flusoxolol and pindolol), two β -adrenoceptor antagonists (propranolol and atenolol), two β -adrenoceptor agonists (salbutamol and prenalterol) and placebo on sleeping heart rate, quality of sleep, supine heart rate, exercise heart rate, blood pressure, forearm blood flow and finger tremor were studied in eight healthy male volunteers.

2 Sleeping heart rate was increased by Ro 31–1118, flusoxolol, pindolol, salbutamol and prenalterol and decreased by propranolol and atenolol.

3 None of the drugs studied affected quality of sleep.

4 Supine heart rate was increased by flusoxolol, prenalterol and salbutamol, unaffected by Ro 31–1118 and pindolol and reduced by propranolol and atenolol.

5 Exercise heart rate was reduced by both β -adrenoceptor antagonists and the three partial agonists and unaffected by salbutamol and prenalterol.

6 Systolic blood pressure was increased by Ro 31–1118, flusoxolol, salbutamol and prenalterol, unaffected by pindolol and reduced by propranolol and atenolol. Diastolic blood pressure was reduced by salbutamol and prenalterol.

7 Forearm blood flow was increased by Ro 31–1118, salbutamol and prenalterol, unchanged by pindolol and flusoxolol and decreased by atenolol and propranolol.

8 Finger tremor was increased by Ro 31–1118, flusoxolol, pindolol, salbutamol and prenalterol.

9 β -adrenoceptor partial agonists have different effects on the cardiovascular system and finger tremor to β -adrenoceptor antagonists.

10 While Ro 31–1118 and flusoxolol are antagonists mainly at the β_1 -adrenoceptor they have agonist activity at both β_1 - and β_2 adrenoceptors.

11 While pindolol is a non-selective antagonist its agonist activity is mainly at the β_2 -adrenoceptor.

Keywords partial agonist activity pindolol flusoxolol Ro 31–1118 β -adrenoceptor antagonist

Introduction

β -adrenoceptor antagonists have a number of additional properties including cardioselectivity, lipid solubility, membrane stabilising activity

and partial agonist activity (Fitzgerald, 1984). To demonstrate partial agonist activity β -adrenoceptor antagonists must be shown to cause both

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measurable agonist and antagonist responses. By definition the agonist activity should never cause as great a biological effect as that produced by a full agonist, such as isoprenaline, no matter how high the dose given. The observed effects of β -adrenoceptor agonist and antagonist activity depend on the degree of sympathetic drive. Agonist effects are most easily seen when the level of sympathetic tone is low such as during sleep and antagonist activity predominates when the level of sympathetic tone is high such as during exercise.

The classical studies of partial agonist activity have been performed in experimental animals in which the effects of reflex sympathetic stimulation and endogenous catecholamines have been removed (Barrett & Carter, 1970; Bilski *et al.*, 1979). Demonstration of partial agonist activity in man has been more difficult because reflexes are intact and it is not possible to remove endogenous catecholamines. However a number of studies in man have shown that β -adrenoceptor partial agonists differ from β -adrenoceptor antagonists by causing less reduction in supine heart rate and cardiac output (Svensen *et al.*, 1979; 1981; Taylor *et al.*, 1982) and having flatter dose-response curves for reduction of exercise tachycardia (McDevitt *et al.*, 1977).

Ro 31-1118 (1 - (4 - [2 - (4 - fluorophenethoxy) - ethoxy] phenoxy) - 3 - isopropylamino - 2 - propanol hydrochloride is a long acting cardioselective β -adrenoceptor partial agonist (Blaber *et al.*, 1983; O'Connor *et al.*, 1985) and flusoxolol is its S-enantiomer. Pindolol is a non cardioselective partial agonist though it has been suggested that its agonist activity is mainly at the β_2 -adrenoceptor (Clark, 1984). Atenolol and propranolol are β -adrenoceptor antagonists, with and without cardioselectivity respectively. Salbutamol is a β_2 -adrenoceptor agonist (Hartley *et al.*, 1968) and prenalterol is a predominantly β_1 -adrenoceptor agonist but has been shown to have some activity at the β_2 -adrenoceptor (Mattsson *et al.*, 1982a,b).

The present studies were undertaken to demonstrate the partial agonist activity of Ro 31-1118, flusoxolol and pindolol in man and to compare their effects on the cardiovascular system and finger tremor to those of propranolol, atenolol, salbutamol, prenalterol and placebo. Fixed oral doses were used and no formal dose-response observations were made because of the number of drugs studied. The doses of those drugs with β -adrenoceptor antagonist activity were those which have been shown to have approximately equal β -adrenoceptor blocking activity.

Methods

Observations were made in 16 healthy male subjects who gave informed consent after the procedures involved had been fully explained to them. The studies were approved by the Research Ethical Committee of the Queen's University of Belfast.

Study 1

Eight healthy male volunteers (mean age 23 ± 4 years, mean weight 77 ± 7 kg) took part in the study. At weekly intervals, double-blind and following a randomised Latin Square design each received on separate occasions, single oral doses of Ro 31-1118 160 mg, flusoxolol 80 mg, pindolol 10 mg, atenolol 50 mg, propranolol 80 mg, salbutamol 8 mg, prenalterol 50 mg and placebo.

In the late afternoon on each study day electrodes were attached to the anterior chest wall of the volunteer in a modified lead II position and to an Oxford Medilog 4-24 miniature tape recorder worn in a leather case at the waist. The drugs were administered orally between 23.00 h and 24.00 h. Volunteers retired to bed within 30 min of drug administration. They were asked to press the event button when they went to bed, when they awoke in the morning and if they awoke during the night. The tape recorder was removed the following morning. The volunteer completed a St Mary's Hospital sleep questionnaire (Ellis *et al.*, 1981) and a visual analogue scale for assessing the quality of sleep. The visual analogue scale was 10 cm long, with 'the best night's sleep ever' written at one end and 'the worst night's sleep ever' written at the other end. The same verbal instructions were given each day: 'Regarding how you slept last night please mark the line between the best night's sleep and the worst night's sleep ever. Your normal night's sleep would be in the middle'. The tape was analysed using the Oxford Instruments ECG Analysis system. Side effects were elicited by the written question 'Did you notice anything unusual?'

Hourly mean heart rates for the 8 h after treatment were compared using the SPSS parametric analysis of variance and Duncan's multiple range test. The results of the sleep questionnaire and visual analogue scale were analysed using Friedman's two way analysis of variance. Statistically significant differences were considered to exist when P was < 0.05 . Results are expressed as the mean $\pm$ the s.d..

Study 2

Eight healthy male volunteers (mean age $22 \pm$

0.5 years, mean weight 74 ± 11 kg) took part in the study. At weekly intervals, double-blind and following a randomised Latin Square design each received on separate occasions, single oral doses of Ro 31-1118 160 mg, flusoxolol 80 mg, pindolol 10 mg, propranolol 80 mg, atenolol 50 mg, salbutamol 8 mg, prenalterol 50 mg and placebo. All studies were carried out in the morning in a temperature controlled room ($24\text{--}25^\circ\text{C}$). On the morning of the study the volunteer had a light breakfast without caffeine. After 30 min of supine rest, heart rate, blood pressure, finger tremor and forearm blood flow were measured. Heart rate was measured from a direct writing electrocardiogram and blood pressure using a Hawksley random zero sphygmomanometer. The Korotkoff fourth sound was used for the diastolic blood pressure. Finger tremor was measured using a piezo electric accelerometer attached to the dorsum of the middle finger of the left hand (Arnold & McDevitt, 1983; Riddell *et al.*, 1986). Forearm blood flow was measured using venous occlusion plethysmography (Riddell *et al.*, 1986). Forearm vascular resistance was calculated by dividing mean arterial blood pressure by forearm blood flow.

The measurements were repeated after a further 15 min. The drugs were then administered orally with 30 ml of water. The above measurements were repeated at 30 min intervals for 3 h. An exercise step test was then performed which involves stepping on and off a box 46 cm high, 32 times min^{-1} for 3 min. Heart rate was measured within 5 s of completing exercise. Spontaneously reported side effects were documented.

The results for supine heart rate, exercise heart rate and percentage change in finger tremor were log transformed. The results for systolic blood pressure and diastolic blood pressure were subjected to a square root transformation. As some of the values for percentage change in finger tremor were negative 100 was added to each. The results were compared using a parametric analysis of variance and Duncan's multiple range test. A *P* value of < 0.05 was considered significant. Percentage change in forearm blood flow was analysed using Friedman's analysis of variance and Wilcoxon's signed rank test because of significant differences in the variances. A *P* value of < 0.02 was considered significant.

Results

Study 1

Hourly mean heart rates for the 8 h post dosing for each treatment are shown in Table 1. Hourly

Table 1 Hourly mean heart rate in beats min^{-1} ($\pm$ s.d.) before and hourly for 8 h after each treatment

Drugs	0	1	2	3	4	5	6	7	8
Placebo	80 $\pm$ 14	77 $\pm$ 10	70 $\pm$ 11 $\dagger$	63 $\pm$ 11 $\dagger$	60 $\pm$ 10 $\dagger$	60 $\pm$ 10 $\dagger$	59 $\pm$ 10 $\dagger$	58 $\pm$ 9 $\dagger$	59 $\pm$ 10 $\dagger$
Propranolol	77 $\pm$ 12	72 $\pm$ 14 $\dagger$	59 $\pm$ 10 $\dagger$	57 $\pm$ 10 $\dagger$	55 $\pm$ 8 $\dagger$	55 $\pm$ 10 $\dagger$	54 $\pm$ 9 $\dagger$	54 $\pm$ 8 $\dagger$	54 $\pm$ 8 $\dagger$
Atenolol	76 $\pm$ 13	78 $\pm$ 12	61 $\pm$ 11 $\dagger$	57 $\pm$ 10 $\dagger$	56 $\pm$ 10 $\dagger$	55 $\pm$ 8 $\dagger$	54 $\pm$ 9 $\dagger$	56 $\pm$ 9 $\dagger$	56 $\pm$ 8 $\dagger$
Pindolol	81 $\pm$ 8	74 $\pm$ 11 $\dagger$	66 $\pm$ 10 $\dagger$	64 $\pm$ 9 $\dagger$	63 $\pm$ 9 $\dagger$	62 $\pm$ 8 $\dagger$	61 $\pm$ 7 $\dagger$	62 $\pm$ 9 $\dagger$	63 $\pm$ 8 $\dagger$
Ro 31-1118	77 $\pm$ 12	76 $\pm$ 13	67 $\pm$ 13 $\dagger$	65 $\pm$ 9 $\dagger$	64 $\pm$ 12 $\dagger$	64 $\pm$ 7 $\dagger$	63 $\pm$ 9 $\dagger$	64 $\pm$ 9 $\dagger$	63 $\pm$ 8 $\dagger$
Flusoxolol	81 $\pm$ 10	78 $\pm$ 14	74 $\pm$ 14 $\dagger$	69 $\pm$ 9 $\dagger$	67 $\pm$ 9 $\dagger$	66 $\pm$ 11 $\dagger$	65 $\pm$ 11 $\dagger$	67 $\pm$ 11 $\dagger$	67 $\pm$ 10 $\dagger$
Salbutamol	75 $\pm$ 12	74 $\pm$ 11	72 $\pm$ 10	71 $\pm$ 10 $\dagger$	66 $\pm$ 9 $\dagger$	64 $\pm$ 7 $\dagger$	64 $\pm$ 10 $\dagger$	63 $\pm$ 7 $\dagger$	63 $\pm$ 7 $\dagger$
Prenalterol	78 $\pm$ 10	79 $\pm$ 12	82 $\pm$ 11 $\dagger$	83 $\pm$ 12 $\dagger$	75 $\pm$ 8 $\dagger$	76 $\pm$ 12 $\dagger$	77 $\pm$ 8 $\dagger$	74 $\pm$ 10 $\dagger$	74 $\pm$ 13 $\dagger$

* $P < 0.05$ vs placebo, ** $P < 0.01$ vs placebo, $\dagger P < 0.05$ vs baseline, $\ddagger P < 0.01$ vs baseline.

mean heart rate at baseline was not significantly different from placebo for any of the treatments. When the effects of the different treatments were compared with placebo, propranolol and atenolol reduced hourly mean heart rate. Pindolol reduced mean hourly heart rate in the early part of the night but caused a rise in heart rate in the latter half of the night. There was an increase in hourly mean heart rate after Ro 31-1118, flusoxolol, salbutamol and prenalterol.

Hourly mean heart rates after pindolol, Ro 31-1118 and flusoxolol were significantly higher than those after propranolol and atenolol over the majority of hourly intervals. Hourly mean heart rate after prenalterol was significantly higher than after all other drugs over most hourly intervals.

Quality of sleep Quality of sleep as assessed by St Mary's Hospital Sleep Questionnaire was unaffected by any of the drugs. There was no difference between drugs and placebo in the number of awakenings recorded on the tape.

The mean distance in mm ($\pm$ s.d.) from 'the best night's sleep ever', on the visual analogue scale was 40 ± 18 after placebo, 44 ± 18 after

pindolol, 49 ± 19 after prenalterol, 48 ± 18 after salbutamol, 48 ± 17 after flusoxolol, 49 ± 14 after Ro 31-1118, 44 ± 17 after propranolol and 40 ± 16 after atenolol. These results did not differ significantly.

Study 2

Supine heart rate Supine heart rate for each treatment over the 3 h period is shown in Table 2. Baseline heart rate was not significantly different for any drug. When the different treatments were compared to placebo, Ro 31-1118 and pindolol caused no change, atenolol and propranolol reduced heart rate and flusoxolol, salbutamol and prenalterol increased heart rate.

When different treatments were compared to each other prenalterol produced a significantly greater increase in heart rate than all other treatments over the 3 h period. Heart rate after Ro 31-1118, flusoxolol and pindolol was significantly higher than that after atenolol and propranolol.

Systolic blood pressure Mean systolic blood pressure for each treatment over the 3 h period is shown in Table 3. Baseline systolic blood pressure

Table 2 Mean heart rate in beats min^{-1} ($\pm$ s.d.) before and at 0.5 h intervals for 3 h after each treatment

Drugs	Time (h)						
	0	0.5	1	1.5	2	2.5	3
Placebo	60 $\pm$ 6	59 $\pm$ 6	60 $\pm$ 7	61 $\pm$ 7	62 $\pm$ 8	60 $\pm$ 8	60 $\pm$ 9
Propranolol	60 $\pm$ 8	58 $\pm$ 8	57 $\pm$ 10	56 $\pm$ 11*	53 $\pm$ 9 $\ddagger$ **	53 $\pm$ 7 $\ddagger$ **	53 $\pm$ 9 $\ddagger$ **
Atenolol	59 $\pm$ 7	57 $\pm$ 7	55 $\pm$ 10 $\ddagger$ *	53 $\pm$ 9 $\ddagger$ **	54 $\pm$ 8 $\ddagger$ **	53 $\pm$ 7 $\ddagger$ **	53 $\pm$ 9 $\ddagger$ **
Pindolol	62 $\pm$ 9	62 $\pm$ 10	61 $\pm$ 10	61 $\pm$ 9	60 $\pm$ 8	60 $\pm$ 7	61 $\pm$ 8
Ro 31-1118	58 $\pm$ 6	58 $\pm$ 7	58 $\pm$ 7	59 $\pm$ 6	60 $\pm$ 7	60 $\pm$ 8	63 $\pm$ 8
Flusoxolol	62 $\pm$ 9	61 $\pm$ 10	61 $\pm$ 10	64 $\pm$ 12	64 $\pm$ 11	65 $\pm$ 10	67 $\pm$ 11*
Salbutamol	61 $\pm$ 6	60 $\pm$ 3	66 $\pm$ 11*	71 $\pm$ 14 $\ddagger$ **	74 $\pm$ 10 $\ddagger$ **	75 $\pm$ 17 $\ddagger$ **	74 $\pm$ 10 $\ddagger$ **
Prenalterol	62 $\pm$ 8	68 $\pm$ 11 $\ddagger$ **	81 $\pm$ 17 $\ddagger$ **	89 $\pm$ 17 $\ddagger$ **	86 $\pm$ 17 $\ddagger$ **	90 $\pm$ 23 $\ddagger$ **	89 $\pm$ 21 $\ddagger$ **

* $P < 0.05$ vs placebo, ** $P < 0.01$ vs placebo, $\ddagger$ $P < 0.05$ vs baseline, $\ddagger$ $P < 0.01$ vs baseline.

Table 3 Mean systolic blood pressure in mm Hg ($\pm$ s.d.) before and at 0.5 h intervals for 3 h, after each treatment

Drugs	Time (h)						
	0	0.5	1	1.5	2	2.5	3
Placebo	100 $\pm$ 10	100 $\pm$ 12	99 $\pm$ 11	100 $\pm$ 12	101 $\pm$ 9	101 $\pm$ 11	101 $\pm$ 11
Propranolol	101 $\pm$ 6	98 $\pm$ 6	95 $\pm$ 5 $\ddagger$	94 $\pm$ 7 $\ddagger$ *	94 $\pm$ 4 $\ddagger$ **	95 $\pm$ 7 $\ddagger$ **	93 $\pm$ 8 $\ddagger$ **
Atenolol	101 $\pm$ 8	98 $\pm$ 8	94 $\pm$ 10 $\ddagger$ *	94 $\pm$ 9 $\ddagger$ *	92 $\pm$ 8 $\ddagger$ **	92 $\pm$ 8 $\ddagger$ **	93 $\pm$ 10 $\ddagger$ **
Pindolol	102 $\pm$ 8	101 $\pm$ 8	99 $\pm$ 6	99 $\pm$ 9	100 $\pm$ 9	99 $\pm$ 8	101 $\pm$ 12
Ro 31-1118	99 $\pm$ 6	98 $\pm$ 5	101 $\pm$ 4	101 $\pm$ 7	104 $\pm$ 8 $\ddagger$	104 $\pm$ 6 $\ddagger$	104 $\pm$ 8 $\ddagger$
Flusoxolol	103 $\pm$ 8	102 $\pm$ 8	102 $\pm$ 11	105 $\pm$ 10**	106 $\pm$ 9**	108 $\pm$ 10 $\ddagger$ **	107 $\pm$ 10**
Salbutamol	100 $\pm$ 10	101 $\pm$ 12	104 $\pm$ 12*	110 $\pm$ 11 $\ddagger$ **	108 $\pm$ 12 $\ddagger$ **	108 $\pm$ 11 $\ddagger$ **	109 $\pm$ 14 $\ddagger$ **
Prenalterol	99 $\pm$ 12	114 $\pm$ 24 $\ddagger$ **	122 $\pm$ 17 $\ddagger$ **	122 $\pm$ 11 $\ddagger$ **	121 $\pm$ 15 $\ddagger$ **	121 $\pm$ 16 $\ddagger$ **	119 $\pm$ 15 $\ddagger$ **

* $P < 0.05$ vs placebo, ** $P < 0.01$ vs placebo, $\ddagger$ $P < 0.05$ vs baseline, $\ddagger$ $P < 0.01$ vs baseline

was not different for any drug. When the different treatments were compared with placebo, Ro 31-1118 and pindolol caused no change. Systolic blood pressure was reduced by propranolol and atenolol to minimum values of 93 ± 8 mm Hg and 92 ± 8 mm Hg respectively. Compared with placebo (101 ± 11 mm Hg), flusoxolol increased systolic blood pressure to a maximum of 108 ± 10 mm Hg and after salbutamol systolic blood pressure rose to a maximum of 109 ± 14 mm Hg. Prenalterol caused a significant increase in systolic blood pressure compared to placebo (100 ± 12 mm Hg) to a maximum of 122 ± 11 mm Hg. When the different treatments were compared, systolic blood pressure was higher after prenalterol than after all other treatments.

Forearm blood flow There were small but significant differences in baseline forearm blood flow values; therefore percentage change was calculated. Percentage change in forearm blood flow for all treatments over the 3 h period is shown in Figure 1. Compared with placebo, pindolol and flusoxolol tended to increase forearm blood flow but the increase was not significant. The percentage reductions in forearm blood flow after propranolol ($-16 \pm 13\%$) and atenolol ($-10 \pm 9\%$) were significant at 2 h. Ro 31-1118 caused a significant increase at 3 h ($28 \pm 20\%$). Salbutamol produced an increase at 1.5 and 3 h to a maximum of $30 \pm 25\%$. Prenalterol produced

a percentage increase at 2.5 and 3 h to a maximum of $74 \pm 70\%$.

When the different treatments were compared, the percentage increases in forearm blood flow after Ro 31-1118 and pindolol were significantly greater than after atenolol and propranolol.

Forearm vascular resistance Percentage change in forearm vascular resistance was calculated because of small differences in baseline forearm blood flow. Compared with placebo, pindolol and flusoxolol caused no change in forearm vascular resistance. Propranolol ($11 \pm 24\%$) and atenolol ($5 \pm 14\%$) caused a significant increase in forearm vascular resistance at 2 h compared with placebo ($-1 \pm 10\%$). Forearm vascular resistance fell after Ro 31-1118 ($-18 \pm 13\%$) at 3 h. Salbutamol caused a fall at 1.5 and 3 h to a minimum of $-22 \pm 6\%$ and prenalterol caused falls at 2.5 and 3 h to a minimum of $-27 \pm 28\%$ compared with placebo ($-2 \pm 9\%$).

Finger tremor There was significant baseline variation, therefore percentage change in finger tremor was calculated. Percentage change in finger tremor over the 3 h period is shown in Figure 2. Placebo was associated with a small but significant increase in finger tremor to a maximum of $77 \pm 96\%$. Compared with placebo, propranolol produced a reduction at 3 h ($0.5 \pm 60\%$). Similarly atenolol reduced finger tremor compared to placebo at 3 h ($-9 \pm 68\%$). Pindolol

Figure 1 Mean percentage change in forearm blood flow at each time measured for the 3 h after each treatment. ○ placebo, ◇ salbutamol 8 mg, □ prenalterol 50 mg, ● Ro 31-1118 160 mg, ▼ atenolol 50 mg, ▽ propranolol 80 mg, ▲ pindolol 10 mg and ◆ flusoxolol. * $P < 0.02$ vs placebo

Figure 2 Mean percentage change in finger tremor at each time measured for the 3 h after each treatment. ○ placebo, ◇ salbutamol 8 mg, □ prenalterol 50 mg, ● Ro 31-1118 160 mg, ▼ atenolol 50 mg, ▽ propranolol 80 mg, ▲ pindolol 10 mg and ◆ flusoxolol. * $P < 0.05$ vs placebo, ** $P < 0.01$ vs placebo

increased finger tremor to a maximum of $709 \pm 1252\%$. Ro 31-1118 and flusoxolol increased finger tremor to maximum values of $358 \pm 137\%$ and $297 \pm 169\%$ respectively. Finger tremor rose to a maximum of $876 \pm 1335\%$ after salbutamol and to a maximum of $283 \pm 220\%$ after prenalterol.

The percentage increase in finger tremor after salbutamol was significantly greater than that after prenalterol, propranolol and atenolol. It was also higher after salbutamol than after Ro 31-1118 and flusoxolol at 1, 1.5 and 2 h and after pindolol at 2 h.

Exercise heart rate Exercise heart rate was significantly lower after propranolol (127 ± 14 beats min^{-1}), atenolol (130 ± 11 beats min^{-1}), pindolol (123 ± 8 beats min^{-1}), Ro 31-1118 (126 ± 8 beats min^{-1}) and flusoxolol (132 ± 10 beats min^{-1}) than after placebo (166 ± 12 beats min^{-1}) and was unchanged by salbutamol (169 ± 14 beats min^{-1}) and prenalterol (169 ± 13 beats min^{-1}). Exercise heart rate after pindolol was significantly less than after atenolol and flusoxolol. Salbutamol and prenalterol caused no change in exercise heart rate compared with placebo.

Discussion

To fulfill the criteria for partial agonist activity, Ro 31-1118, flusoxolol and pindolol should have

agonist effects less than that of full agonists and demonstrable antagonist effects. Because of the number of drugs involved in this study, fixed oral doses were used and no formal dose-response observations were made. However, in the second study, as observations were made before and at half hourly intervals after dosing, some estimate of the dose-response relationship may be inferred. In particular the time effect curves plateau at about 2 h and there is no indication of a decrease in agonist effect at 3 h when plasma concentrations would be expected to be beginning to fall. This suggests that near maximal agonist effects are being observed. Also, as maximal partial agonism is usually seen at doses lower than those causing antagonism (Bowman & Rand, 1980; Bilski *et al.*, 1979) we are likely to be seeing an effect approaching maximal. The drugs with antagonist activity caused similar reductions in exercise heart rate and as they are primarily adrenoceptor antagonists it seemed reasonable to compare them at these doses. During sleep, heart rate normally falls to reach its lowest level after 6 h (Kleitman, 1963). This fall is thought to be due to predominance of parasympathetic and withdrawal of sympathetic tone during sleep (Baust & Bohnert, 1969). This reduced sympathetic activity provides ideal conditions for demonstrating β -adrenoceptor partial agonism by an increase in heart rate. Sympathetic tone is also low in the resting supine position (Aellig, 1977)

allowing a similar opportunity to assess partial agonist activity.

Prenalterol and salbutamol increased both sleeping and supine heart rate. Salbutamol has been shown to increase supine heart rate in previous studies (Leitch *et al.*, 1976; Philips *et al.*, 1980; Kennedy & Simpson, 1969) and the specific β_2 -adrenoceptor antagonist, ICI 118,551 (Bilski *et al.*, 1983) has been shown to abolish this increase in heart rate (McCaffrey *et al.*, 1986) indicating that it is mediated by the β_2 -adrenoceptor. However the mechanism of the rise in heart rate is unclear and may be partly reflex, secondary to peripheral vasodilation or due to direct stimulation of β_2 -adrenoceptors in the heart (Stiles *et al.*, 1983) or stimulation of presynaptic β_2 -adrenoceptors facilitating norepinephrine release at the sympathetic nerve endings (Stjarne & Brundin, 1976).

The two β -adrenoceptor antagonists, propranolol and atenolol reduced sleeping and supine heart rate. Ro 31-1118, and pindolol caused a smaller reduction in sleeping heart rate and no change in supine heart rate, while flusoxolol caused a smaller reduction in sleeping heart rate and an increase in supine heart rate. These results would be in keeping with partial agonist activity at either the β_1 - or β_2 -adrenoceptor.

Disturbed sleep may increase heart rate but we were unable to detect an effect of the drugs on the quality of sleep. Previous studies using subjective methods for assessing the effects of β -adrenoceptor antagonists on sleep have revealed conflicting results, with some groups reporting adverse effects (Weiner & Rossner, 1983; Betts & Alford, 1985) and others no effect (Bengtsson *et al.*, 1980). Most studies using EEG monitoring, have found that at the doses used in clinical practice β -adrenoceptor antagonists do not affect quality of sleep (Dunleavy *et al.*, 1971; Bender *et al.*, 1979). However, a recently reported study using objective measurements of the quality of sleep has shown that pindolol, propranolol and metoprolol adversely affect sleep (Kostis & Rosen, 1987). Our study may have failed to detect an effect because our volunteers were young males, who sleep so well that they are not easy to disturb (Oswald, 1980). The fact that changes were observed in sleeping heart rate but not in supine heart rate for some of the drugs may be due to a lower sympathetic tone during sleep than when supine.

Prenalterol caused a rise in systolic blood pressure as previously noted (Svensen *et al.*, 1980). The increase in systolic blood pressure produced by salbutamol has been reported previously (Corea *et al.*, 1984) although other authors have

shown a fall (Mc Devitt *et al.*, 1975) or no change (Walker *et al.*, 1972; Watson & Richens, 1974). Salbutamol has been shown to improve indices of myocardial contractility (Sharma & Goodwin, 1978; Bourdillon *et al.*, 1980) although it is not clear if this is due to a positive inotropic effects or a reduction in afterload caused by vasodilation. The rise in systolic blood pressure may have been partly due to stimulation of β_2 -adrenoceptors on the myocardial cells (Stiles *et al.*, 1983) causing a significant increase in heart rate and this could produce a rise in systolic blood pressure. However in a study comparing the effects of atropine and salbutamol it was noted that with comparable increases in heart rate salbutamol increased cardiac output while atropine did not (Gibson & Coltart, 1970). Again, stimulation of presynaptic β_2 -adrenoceptors has been shown to release catecholamines from human vasoconstrictor nerves (Stjarne & Brundin, 1976) and this may have contributed to the rise in systolic blood pressure.

Propranolol and atenolol both reduced systolic blood pressure. Flusoxolol increased systolic blood pressure compared with placebo and Ro 31-1118 caused an increase compared with baseline but not compared to placebo. In agreement with these results a previous study showed that Ro 31-1118 had no effect on supine systolic blood pressure in mild hypertension (Jamieson *et al.*, 1985). The apparent difference between the two enantiomers may be due to the fact that the baseline value was higher, although not significantly so, before flusoxolol than before both placebo and Ro 31-1118. The most likely cause of the rise in systolic blood pressure is agonist activity at the β_1 -adrenoceptor in the heart and this is consistent with the much greater rise in systolic blood pressure caused by the predominantly β_1 -adrenoceptor agonist, prenalterol.

Both salbutamol and prenalterol increased forearm blood flow and reduced forearm vascular resistance. Prenalterol has previously been shown to increase forearm blood flow and decrease forearm vascular resistance (Fitzpatrick *et al.*, 1983) and these effects have been interpreted as being indicative of agonist activity at both the β_1 - and β_2 -adrenoceptor. Propranolol and atenolol reduced forearm blood flow while Ro 31-1118 caused an increase and flusoxolol and pindolol no change. The effects of the β -adrenoceptor partial agonists (Ro 31-1118, flusoxolol and pindolol) on forearm blood flow lay between those of the full agonists, salbutamol and prenalterol and the β -adrenoceptor antagonists atenolol and propranolol. This is in keeping with partial agonist activity at the β_2 -adrenoceptor.

There was a small but significant increase in finger tremor after placebo. This increase may have been due to the fact that all these studies were carried out in the morning following a light breakfast. It has previously been noted that omission of breakfast caused an increase in tremor by late morning (Tuttle *et al.*, 1949) and, in another study, fasting tended to increase finger tremor, although the increase did not reach statistical significance (Wharrad *et al.*, 1985).

Stimulation of the β_2 -adrenoceptor has been shown to augment physiological finger tremor (Larsson & Svedmyr, 1977) and β_2 -adrenoceptor agonists would be expected to increase finger tremor. In this study tremor was increased by salbutamol and to a lesser but significant degree by prenalterol. The increase in finger tremor produced by prenalterol would be consistent with agonist activity at the β_2 -adrenoceptor, which has been shown in previous animal (Mattsson *et al.*, 1982b) and human studies (Fitzpatrick *et al.*, 1983). Some contribution from the ballistocardiographic effect cannot be ruled out as prenalterol caused a marked increase in heart rate and is known to have positive inotropic effects (Rasmussen *et al.*, 1984). However, previous studies have shown that the contribution of the ballistocardiographic effect accounts for less than 10% of overall tremor (Marsden *et al.*, 1969) and the increase in tremor is probably due to β -adrenoceptor stimulation.

Atenolol and propranolol caused no change in finger tremor over the 3 h period. After propranolol and atenolol the percentage change in finger tremor was significantly less than after placebo at 3 h. This is consistent with previous studies which have shown that both atenolol and propranolol reduce physiological finger tremor (Birmingham *et al.*, 1981; Abila *et al.*, 1985).

Pindolol has been shown to have significant agonist activity at the β_2 -adrenoceptor in animal studies (Clark, 1984). The marked increase in finger tremor caused by pindolol in this study would indicate significant agonist activity at the β_2 -adrenoceptor in man. Tremor has been reported as a side effect of pindolol (Hod *et al.*, 1980; Rosenthal *et al.*, 1979) and using objective

measures Reid *et al.* (1986) showed that pindolol caused an increase in finger tremor in diabetic patients with autonomic neuropathy.

Ro 31-1118 and flusoxolol increased finger tremor and tremor has also been reported as a side effect of Ro 31-1118 (O'Connor *et al.*, 1985). The antagonist activity of these drugs has been shown to be β_1 -selective (Blaber *et al.*, 1983; O'Connor *et al.*, 1985) but agonist activity at both adrenoceptors can be demonstrated in man, in agreement with animal studies (Blaber *et al.*, 1983). The increase in finger tremor after Ro 31-1118, flusoxolol and pindolol was much less than after the full agonist, salbutamol, fulfilling the criterion for partial agonist activity.

The selectivity of the agonist activity may differ from the selectivity of the antagonist activity. For example, Ro 31-1118 and flusoxolol which are antagonists mainly at the β_1 -adrenoceptor demonstrate agonist activity at both receptors and pindolol which is an antagonist at both receptors but an agonist mainly at the β_2 -adrenoceptor. Full dose-response curves for both the agonist and antagonist activity of these drugs would be required to confirm these findings.

In conclusion, Ro 31-1118, flusoxolol and pindolol fulfilled the criteria for the demonstration of partial agonist activity. A measurable agonist response was demonstrated by increases in sleeping heart rate, finger tremor and systolic blood pressure which were less than the increase produced by the full agonist. In contrast the two β -adrenoceptor antagonists reduced these parameters. A measurable antagonist response was illustrated by the reduction in exercise heart rate which was comparable with that produced by the β -adrenoceptor antagonists, while the full agonists caused no change.

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