The effect of a week's β -adrenoceptor antagonism on daytime heart-rates, subjective responses to exercise, and physical activity in normal subjects

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1 The effects on heart rate (HR) and physical activity of 1 week's treatment with three different β -adrenoceptor antagonists (20 mg betaxolol (Lorex); 160 mg propranolol LA; or 100 mg atenolol daily) have been compared with placebo in a double-blind study of 12 normal men.

2 On the fifth day of each treatment a body-borne tape-recorder was worn during waking hours for recording of ECG and footfall signals. Each record was calibrated in terms of the subject's response to laboratory ergometer exercise, and a computer analysis provided objective indices of physical activity.

3 While on β -adrenoceptor antagonists the subjects perceived standard exercise as significantly harder than on placebo and reported more side-effects (albeit mild and transient).

4 Ambulatory monitoring of HR showed that subjects spent 13% of their waking day at heart rates below 50 beats min^{-1} while on propranolol, compared with 1% on placebo and 20% on atenolol and betaxolol. On these latter drugs, the group spent as much as 10% of their waking time with HR below 45 beats min^{-1} . The lowest individual heart-rates recorded were below 35 beats min^{-1} .

5 Objective indices of physical activity, such as the duration of periods spent with heart rates above the HR found at 100 W in the ergometer test, showed *no* differences between the treatments. This negative finding was confirmed by pedometer step counts over the whole week.

Keywords β -adrenoceptor antagonists physical activity perceived exertion heart rate side-effects

Introduction

When β -adrenoceptor antagonist drugs are used in the long-term management of active asymptomatic patients (e.g. those with hypertension), they often give rise to complaints of fatigue and leg tiredness (Editorial, 1980; Lewis

et al., 1984). These drugs, which attenuate the rise in cardiac output (Epstein *et al.*, 1965) and reduce muscle blood flow during exercise (Smith & Warren, 1982), are known to reduce maximum working capacity (Twentyman *et al.*,

1981) and to make the performance of standard submaximal work feel harder (Pearson *et al.*, 1979).

These effects may have implications for the pattern of everyday physical activity. Some well-motivated patients will continue to take part in regular sustained exercise such as jogging or even marathon running (Breckenridge, 1982) despite the extra discomfort caused by the drugs, though it is likely that peak competitive performance will be adversely affected (Snow & Summers, 1977). It is possible that others might be dissuaded by symptoms of fatigue from being as active as usual and thus they may reduce their physical condition and put on weight.

The cardiac effects of β -adrenoceptor antagonists are manifested by a reduction in heart rate at rest as well as during exercise. This bradycardia is commonly used as a guide to the safe levels of dosage, and it is recommended that treatment be terminated or the dosage reduced if 'undue bradycardia' is seen (Data Sheet Compendium, 1983). However, no study seems to have been made of the normal extent of this bradycardia, showing the time spent below particular criterion values of heart rate.

Using body-borne cassette tape-recorders (Bassey *et al.*, 1980) we have studied the effect of β -adrenoceptor blockade on the pattern of heart rate during the waking day in normal subjects. This study was part of an investigation of the influence of three different β -adrenoceptor antagonists on finger tremor (Wharrad *et al.*, in preparation). The recorded ECG data provide evidence relating both to daily physical activity and to periods of profound bradycardia.

A preliminary report of this work has been presented (Patrick & Wharrad, 1984).

Methods

Subjects

Twelve healthy adult male volunteers, university personnel, participated in the study after giving informed consent in writing. The approval of the Medical School Ethical Committee had been given. The subjects' age range was 20–51 years (mean 28.3 years), their body weights were between 62 and 83 kg (mean 72.4 kg), and their forced expiratory volumes in 1 s (FEV₁) were between 71 and 95% (mean 85%) of their forced vital capacities (FVC). They were judged healthy after a routine clinical history and examination, and were taking no current medication. Before the start of the

experiment all the procedures were explained and practised.

Drugs and general procedures

The drugs used were propranolol in a sustained release formulation (160 mg LA), atenolol (100 mg), and betaxolol (20 mg; Lorex) given once daily in the morning. The formulations, and a lactose placebo, were identical in appearance and enclosed within hard opaque gelatin capsules. The doses were chosen after a perusal of the relevant literature (Leahey *et al.*, 1980a, b; Balnave *et al.*, 1981) and a pilot study on three subjects, in the anticipation that equivalent β_1 -adrenoceptor antagonist activity would be achieved after several days. Betaxolol is a highly cardioselective drug devoid of membrane stabilising properties or intrinsic sympathomimetic activity, and with a half-life of the order of 20 h (Guidicelli *et al.*, 1980). The capsules were administered in a double-blind crossover manner in an order which was randomized between individuals to reduce bias due to any habituation effect of the tests. All subjects underwent a week's treatment with every formulation in turn. A washout period of at least 7 days elapsed between each treatment. Subjects swallowed their first capsule on Day 1 of the 7-day treatment period immediately after the baseline tests had been completed. Thereafter they were instructed to take one capsule at the same time each morning (with a light breakfast) for the following 6 days (days 2 to 7).

Exercise test and ventilatory capacity measurement

On Day 1 of each treatment period before the first capsule was taken, subjects performed a continuous progressive test on a Lode cycle ergometer. After a preliminary adaptation period of at least 2 min at 15 W, the work-rate was raised sharply to 100 W and held for 5 min. Thereafter, it was raised by 25 W every 2 min until the test was terminated at the work-rate which elicited a heart rate of at least 150 beats min⁻¹. The ECG was continuously recorded using precordial electrodes, a Diascope monitor, and a Grass polygraph. The R-waves were counted over the final minute at each work-rate. During the last half-minute at 100 W and again during the final half-minute of the exercise test, the subject was asked for his rating of the perceived intensity of exertion (RPE) on a 15-point (6–20) integer scale (Borg, 1970) whose odd numbers are verbally labelled, e.g. 09 = very light, 17 = very hard. The same ergometer

test was repeated with the same terminal work-rate on Day 7 of the treatment period 3 h after the last capsule had been taken.

Between 3 and 5 min after each exercise test, the FEV₁ as a percentage of the FVC (FEV%) was measured from the best of three forced expirations using a Vitalograph dry spirometer.

Subjective impressions and side effects relating to exercise tolerance

On Day 7 subjects were prompted with a checklist of 14 symptoms and asked if any had occurred during the week of treatment. Six of the listed symptoms related to reduction of exercise tolerance and inadequate circulatory responses: 'fatigue', 'tiredness/lack of energy', 'weakness', 'limitation of strenuous activities', 'dizziness/faintness' and 'cramps/aching limbs'.

Measurements of physical activity

(a) *Body-borne tape-recorders* On Day 5 of each week, the subject wore a body-borne cassette tape-recorder (Oxford 'Medilog') from about 09.00 h until bedtime. This weighs 400 g and does not interfere with normal activity (Bassey *et al.*, 1980). One channel recorded the ECG from precordial electrodes and the second recorded a footfall signal from a carbon pad under the heel. Off-line processing of the cassette data using a play-back monitor running at 25 times real time, an analogue-to-digital converter, and a main-frame computer provided an analysis of the heart rate (HR) and stepping patterns during the day. Interference due to noise on the ECG channel was filtered by software, and a 21-beat running average was used to smooth the HR pattern and to bridge any short gaps in the record.

Maximum and minimum heart rates and averages over each 0.5 h by the clock were calculated. In addition, particular attention was directed to the extremes of the distribution of instantaneous heart rates in order (a) to examine the incidence of sinus bradycardia below specified HR limits, and (b) to quantify periods of physical activity as represented by elevations of HR above the level associated with exercise at a standard work-rate (100 W on the cycle ergometer; i.e. the reference HR). This bio-calibration allowed for the overall reduction in HR caused by the β -adrenoceptor antagonist drugs.

Three indices were selected to represent the day's physical activity (Bassey *et al.*, 1983). 'Walking time' is the total duration of all the walking periods recorded by the footfall transducer: isolated steps are discounted. The second

index ('walking tachycardia') was the total duration of heart rate elevations above the reference HR while the footfall transducer was indicating that the subject was walking. The third index was the total duration of heart rate elevations over the reference HR that lasted for at least 2 min on each occasion: no footfall criterion was applied. This index ('sustained tachycardia') was designed to include non-walking activity of at least moderate intensity and duration (Bassey *et al.*, 1983).

(b) *Mechanical pedometers* On each of the 6 full days while taking each drug (days 2–7) the subject wore a mechanical pedometer ('Digiped'; Yamasa) on the hip. The digital reading was noted by the subject each night and the pedometer then reset ready for the next day. The pedometers were calibrated both before and after the week's recordings using a turntable to simulate the accelerations which occur during walking (Irving & Patrick, 1982). The calibration constant thus obtained was used to convert the reading to thousand steps per day. The average daily count over the week was used as an index of walking activity.

Statistical analysis

Standard SPSS routines (Nie *et al.*, 1975) have been used to compare Day 1 and Day 7 values from the ergometer test (treatment *vs* control) for each treatment (paired *t*-test), and to compare indices of activity between treatments (analysis of variance with *a posteriori* contrasts). Symptom incidence has been analyzed with a χ^2 -test of association.

Results

Response to standard exercise

There were no systematic differences between the four Day 1 baseline values for any variable in the ergometer test, indicating that the subjects were stable throughout the testing period.

Table 1a shows the indices obtained from the cycle ergometer and the ventilatory function tests on Day 1 and Day 7 of each treatment period. Table 1b shows the *differences* between Day 1 and Day 7 for each index, indicating the change due to each treatment. When the subjects were on placebo, none of the variables changed significantly between Day 1 and Day 7 (paired *t*-test), except the slope of the heart rate *vs* work relation which fell by 10%. This fall

Table 1a Mean values $\pm$ s.e. mean for ergometer test variables in 12 subjects before (Day 1) and after (Day 7) each of four treatments

	Placebo		Betaxolol		Atenolol		Propranolol	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
Heart rate at 100 W (beats min ⁻¹)	115.3 3.5	117.1 3.4	116.6 3.5	90.6 2.7	114.3 3.4	90.4 1.8	115.8 3.5	96.9 3.7
Heart rate at end of test (beats min ⁻¹)	150 0	150 2	150 0	112 2	150 0	114 2	150 0	123 2
Slope of HR/work relation (beats min ⁻¹ W ⁻¹)	0.54 0.05	0.49 0.04	0.53 0.04	0.33 0.02	0.54 0.03	0.34 0.03	0.55 0.04	0.40 0.03
Intercept of HR/work relation (beats min ⁻¹)	61.1 5.7	68.1 5.3	63.7 4.6	57.9 2.5	59.6 3.1	56.8 2.8	61.2 5.3	56.8 4.7
FEV ₁ $\times$ 100/FVC (%)	85.2 2.4	83.4 1.7	85.2 1.9	84.0 1.9	84.8 2.1	82.8 2.5	84.4 1.7	82.3 2.0
RPE at 100 W (units)	10.8 0.5	10.7 0.5	10.5 0.5	11.2 0.3	10.6 0.5	11.2 0.5	10.4 0.5	10.5 0.4
RPE at end of test (units)	14.3 0.5	14.2 0.3	14.2 0.4	15.1 0.5	14.2 0.5	15.1 0.6	14.3 0.5	14.6 0.4

Table 1b Baseline measurements (mean $\pm$ s.e. mean) and changes in ergometer test variables between Day 1 and Day 7 (mean differences $\pm$ s.e. mean) in 12 subjects on each of four treatments. Significance levels for the differences are indicated as: *, $P < 0.05$; **, $P < 0.01$

	Average of all Day 1 measurements (n = 48)	Changes while taking			
		Placebo	Betaxolol	Atenolol	Propranolol
Heart rate at 100 W (beats min ⁻¹)	115.5 1.7	1.8 2.3	-26.0** 1.9	-23.8** 2.4	-18.8** 1.8
Heart rate at end (beats min ⁻¹)	150 0	-0.5 1.7	-38.5** 1.8	-36.0** 2.1	-27.2** 2.1
Slope of HR/work relation (beats min ⁻¹ W ⁻¹)	0.54 0.02	-0.055* 0.022	-0.204** 0.029	-0.204** 0.033	-0.142** 0.018
Intercept of HR/work relation (beats min ⁻¹)	61.4 2.3	7.0 3.8	-5.7 3.7	-2.7 3.3	-4.4 2.6
FEV ₁ $\times$ 100/FVC (%)	84.9 1.0	-1.9 1.6	-1.2 0.7	-2.1 1.1	-2.1 1.1
RPE at 100 W (units)	10.6 0.2	-0.08 0.26	0.67* 0.27	0.58* 0.26	0.08 0.33
RPE at end of test (units)	14.2 0.2	-0.17 0.27	0.91* 0.23	0.91* 0.31	0.33 0.31

was associated with a non-significant rise in the intercept, but no change in the heart rate at 100 W.

Associated with β -adrenoceptor blockade there were highly significant reductions in the HR at 100 W and at the end of the test. The

slope of the relation between heart rate and work was substantially and significantly reduced, but the small fall in the intercept was not significant. The higher the work-rate, the more apparent was the attenuation of the exercise tachycardia. The effect of propranolol at the

dose used was significantly less (by about 30%) than the effects of betaxolol and atenolol which were the same.

There were no significant changes in the post-exercise FEV% associated with any of the treatments.

Both betaxolol and atenolol significantly raised the Borg rating of perceived exertion (RPE) at the end of the exercise test by about 1 unit. Smaller increases were found at the intermediate 100 W stage. Propranolol again had less effect.

Subjective impressions concerning tolerance of everyday physical activity

Eight of the twelve subjects reported the occurrence of at least one of the symptoms related to reduced exercise tolerance and inadequate circulation while on 1 week's treatment with a β -adrenoceptor antagonist, but two others reported a single symptom while on placebo. Thirteen episodes were reported on atenolol, 10 on betaxolol and five on propranolol. None were more than brief and minor. A χ^2 -test showed that the incidence of these symptoms differed significantly between the four treatments.

Day-long tape-recordings

Four of the 48 tape-recordings were lost for technical reasons: two from the atenolol group, one propranolol and one placebo, all from different subjects. The average record length was 12.2 h and the average total time rejected from the analysis because of noise was 57 min.

(a) *Daytime heart rates* The half-hourly average heart rates while on the four treatments are shown in Figure 1. Table 2 shows the average values for minimum, maximum, mean and 'walking' heart rates on each treatment. β -adrenoceptor blockade reduced the heart rate by about 20 beats min^{-1} throughout the day and propranolol again had the least effect at the dose used. Figure 2 shows the proportions of the waking day spent with heart rates below various values. On betaxolol, for example, subjects had heart rates below 45 beats min^{-1} for 9% of the time (range 0–52%; about 65 min), and below 40 beats min^{-1} for about 3% of the time (range 0–28%; about 22 min). Similar values were obtained for subjects on atenolol and propranolol (Table 2). On placebo the heart rate never fell to these levels.

(b) *Activity indices* There were no significant differences between treatments for any of the activity indices derived from the ambulatory tape-recording (Table 2). For the two indices based on the ECG record many subjects had zero values showing that their heart rate never reached the reference HR under the specified conditions during the day on which they wore the tape-recorder.

Pedometer step-counts

The pedometer count of steps taken shows no significant difference between the treatments, although the step-count was on average about 10% less while the subjects were taking the β -adrenoceptor antagonists (Table 2).

Figure 1 Half-hourly averages of heart rate in 12 normal subjects on the fifth day of treatment with (●) placebo, (■) propranolol, (▼) atenolol and (▲) betaxolol.

Table 2 Indices of heart rate and physical activity measured on Day 5 with a body-borne tape-recorder, and step counts on Days 2–7 with a mechanical pedometer. The mean, s.e. mean and range (in brackets) for each variable in 10–12 subjects on each drug are given

	<i>Placebo</i>	<i>Betaxolol</i>	<i>Atenolol</i>	<i>Propranolol</i>
Minimum heart rate (beats min ⁻¹)	56 3 (40–78)	42 2 (33–50)	44 2 (32–55)	45 2 (34–56)
Maximum heart rate (beats min ⁻¹)	142 6 (109–191)	103 6 (79–149)	117 5 (82–157)	112 7 (96–151)
Mean heart rate (beats min ⁻¹)	79 4 (62–105)	60 3 (47–77)	61 3 (43–78)	63 3 (47–84)
Mean heart rate while walking (beats min ⁻¹)	93 5 (74–129)	70 3 (54–91)	71 4 (52–99)	74 3 (55–94)
Time spent below 45 beats min ⁻¹ (% of day)	0.1 0.0 (0–1)	9.3 5.1 (0–52)	9.3 5.3 (0–65)	5.8 4.2 (0–46)
Walking time (min)	68 9 (31–132)	50 6 (20–78)	60 9 (9–88)	60 8 (11–97)
Walking tachycardia (min)	3 1 (0–14)	1 1 (0–6)	4 2 (0–23)	2 1 (0–6)
Sustained tachycardia (min)	8 3 (0–34)	7 3 (0–22)	15 8 (0–80)	6 2 (0–18)
Pedometer step count (thousand/day)	11.8 1.8 (5.1–25.4)	10.7 1.2 (6.6–20.3)	10.8 1.7 (4.4–25.5)	10.4 1.0 (7.0–18.1)

Discussion

β-adrenoceptor blockade and the responses to ergometer exercise

The effects of the β -adrenoceptor antagonists on the heart rate response to progressive ergometer exercise are entirely consistent with previous studies (Anderson *et al.*, 1979; Pearson *et al.*, 1979; Wilcox *et al.*, 1984). Provided that any concomitant intrinsic sympathomimetic activity or α -adrenoceptor antagonist is allowed for, this procedure provides a useful test of the β_1 -adrenoceptor antagonist effect produced by different doses and by different treatment regimes. Our results demonstrate that after 7 days' treatment the daily dose of 160 mg propranolol LA was less potent in attenuating exercise tachycardia than 20 mg betaxolol and 100 mg atenolol. This is in agreement with the finding of McAinsh *et al.* (1978) that sustained release formulations of propranolol produce lower peak plasma concentrations of the drug

and longer times to peak than conventional propranolol. Serlin *et al.* (1983) also found that after 1 month's treatment LA propranolol showed slower absorption and the area under the curve of plasma concentration *vs* time was significantly lower than after conventional propranolol.

As expected, no effect on the post-exercise FEV₁% was seen in these normal subjects who had no history of asthma or atopy.

Subjective responses relating to exercise

After 1 week's treatment with β -adrenoceptor antagonists, these healthy subjects perceived the exertion of a standard ergometer test to be harder, and reported mild and transient symptoms suggesting impaired tolerance of everyday exercise. These findings are consistent with previous reports of these and similar drugs given either acutely (Anderson *et al.*, 1979;

Figure 2 The tail of the cumulative frequency distribution of time spent at different heart rates by 12 normal subjects during the fifth day of treatment with (●) placebo, (■) propranolol, (▼) atenolol and (▲) betaxolol.

Davies & Sargeant, 1979; Pearson *et al.*, 1979; Wilcox *et al.*, 1984) or chronically (Zacharias, 1976; Simpson, 1977; Stone, 1979; Lewis *et al.*, 1984; Wilcox *et al.*, 1984). The relative magnitudes of the subjective effects of the three drugs used here run parallel with the relative effects on exercise tachycardia: 160 mg LA propranolol lowered the exercise heart rate less and produced fewer symptoms and less elevation of the Borg rating. This observation adds weight to the supposition that the subjective effects are a consequence of the reduced cardiac output. The data from the studies cited suggest that the Borg rating rises by half a unit for every 20 beats min⁻¹ reduction in heart rate: the relation is roughly the same for different dosage regimes of both cardio-selective and non-selective antagonists.

Daily physical activity

These changes in the subjective response to exercise might have been expected to have

caused a reduction in the subjects' daily physical activity, but *no* change was seen with either cardio-selective or non-selective β -adrenoceptor antagonists. The group was small and only a single day's tape-recording was made, and it is possible that a small change in activity might have been missed. The pedometer data, obtained over 6 days, showed a 10% reduction in step-count which was, however, not statistically significant. It is also possible that 1 week was too short a time for the subjects to respond to the symptoms, or that these were not severe enough to have caused any alteration in physical activity. Lewis *et al.* (1984) reported that despite marked leg tiredness in hypertensive patients under treatment with β -adrenoceptor antagonist drugs, there was no alteration in general well-being. They also comment that 'symptoms which are undoubtedly present need not necessarily interfere with the quality of life'.

Daytime bradycardia

The standard ergometer test showed that β -adrenoceptor antagonism caused a reduction in heart rate of approximately 25% across a wide range of work-rates, and the day-long tape-recording showed a substantial depression of HR by comparison with placebo. Using body-borne tape-recorders several authors have shown the effect of β -adrenoceptor blockade on heart rate during the day or over 24 h (Carrageta *et al.*, 1982; Floras *et al.*, 1982; Rowlands *et al.*, 1982). Their data have been presented as averages over consecutive periods of 1 h or 0.5 h. This technique gives a useful overall impression of the reduction in heart rate (Figure 1) but conceals periods of profound bradycardia as well as the periods of exercise tachycardia considered above. The tail of the distribution of time spent at different heart rates gave a clear indication of the extent of the bradycardia in normal subjects on β -adrenoceptor antagonist drugs (Figure 2): minimum heart rates below 35 beats min⁻¹ were recorded in some subjects (Table 2). Hypertensive patients on these drugs probably have a similar heart rate distribution.

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References

- Anderson, S. D., Bye, P. T. P., Perry, C. P., Hamor, G. P., Theobald, G. & Nyberg, G. (1979). Limitation of work performance in normal adult males in the presence of beta-adrenergic blockade. *Austr. N.Z. J. Med.*, **9**, 515–520.
- Balnave, K., Neill, J. D., Russell, C. J., Harron, D. W. G., Leahey, W. J., Wilson, R. & Shanks, R. G. (1981). Observations on the efficacy and pharmacokinetics of betaxolol (SL75212), a cardioselective β -adrenoceptor blocking drug. *Br. J. clin. Pharmacol.*, **11**, 171–180.
- Bassey, E. J., Bryant, J. C., Fentem, P. H., Macdonald, I. A. & Patrick, J. M. (1980). Customary physical activity in elderly men and women using long-term ambulatory monitoring of ECG and footfall. In *Proceedings of the 3rd International Symposium on Ambulatory Monitoring, 1979*, edited by Stott, F. D., pp. 425–432. London: Academic Press.
- Bassey, E. J., Patrick, J. M., Irving, J. M., Blecher, A. B. & Fentem, P. H. (1983). An unsupervised 'aerobics' physical training programme in middle-aged factory workers: feasibility, validation and response. *Eur. J. appl. Physiol.*, **52**, 120–125.
- Borg, G. (1970). Perceived exertion as an indicator of somatic stress. *Scand. J. rehabilitation Med.*, **2**, 92–98.
- Breckenridge, A. (1982). Jogger's blockade. *Br. med. J.*, **284**, 532–533.
- Cadigan, P. J., London, D. R., Pentecost, B. L., Bianchetti, G., Gomeni, R., Kilborn, J. R. & Morselli, P. L. (1980). Cardiovascular effects of single oral doses of the new β -adrenoceptor blocking agent betaxolol (SL 75212) in healthy volunteers. *Br. J. clin. Pharmacol.*, **9**, 569–575.
- Carrageta, M., Soares, R. & Martins, A. (1982). Treatment of essential hypertension with single dose beta-blockers: analysis by ambulatory monitoring of arterial pressure. In *Proceedings of the 4th International Symposium on Ambulatory Monitoring, 1981*, eds Stott, F. D. et al., pp. 559–562. London: Academic Press.
- Davies, C. T. M. & Sargeant, A. J. (1979). The effects of atropine and practolol on the perception of exertion during treadmill exercise. *Ergonomics*, **22**, 1141–1146.
- Data Sheet Compendium (1983–4). Datapharm Publications Ltd: London.
- Editorial (1980). Fatigue as an unwanted effect of drugs. *Lancet*, **i**, 1285–1286.
- Epstein, S. E., Robinson, B. F., Kahler, R. L. & Braunwald, E. (1965). Effects of beta-adrenergic blockade on the cardiac output response to maximal and submaximal exercise in man. *J. clin. Invest.*, **44**, 1745–1753.
- Floras, J. S., Jones, J. V., Hassan, M. O., Osikowska, B. A., Sever, P. S. & Sleight, P. (1982). Differences between cuff and direct ambulatory blood pressures in patients with essential hypertension. In *Proceedings of the 4th International Symposium on Ambulatory Monitoring, 1981*, eds Stott, F. D. et al., pp 515–521. London: Academic Press.
- Guidicelli, J. F., Chauvin, M., Thuillez, C., Richer, C., Bianchetti, G., Gomeni, R. & Morselli, P. L. (1980). β -adrenoceptor blocking effects and pharmacokinetics of betaxolol (SL 75212) in man. *Br. J. clin. Pharmacol.*, **10**, 41–49.
- Irving, J. M. & Patrick, J. M. (1982). The use of mechanical pedometers in the measurement of physical activity. In *Proceedings of the 4th International Symposium on Ambulatory Monitoring, 1981*, eds Stott, F. D. et al., pp. 369–376. London: Academic Press.
- Leahey, W. J., Neill, J. D., Varma, M. P. S. & Shanks, R. G. (1980a). Comparison of the efficacy and pharmacokinetics of conventional propranolol and a long-acting preparation of propranolol. *Br. J. clin. Pharmacol.*, **9**, 33–40.
- Leahey, W. J., Neill, J. D., Varma, M. P. S. & Shanks, R. G. (1980b). Comparison of the activity and plasma levels of oxprenolol, slow release oxprenolol, long acting propranolol and sotalol. *Eur. J. clin. Pharmacol.*, **17**, 419–424.
- Lewis, R. V., Jackson, P. R. & Ramsay, L. E. (1984). Quantification of side-effects of β -adrenoceptor blockers using visual analogue scales. *Br. J. clin. Pharmacol.*, **18**, 325–330.
- McAinsh, J., Barber, N. S., Smith, R. & Young, J. (1978). Pharmacokinetic and pharmacodynamic studies with LA propranolol. *Br. J. clin. Pharmacol.*, **6**, 115–121.
- Nie, N. H., Hull, C. H., Jenkins, J. G., Steinbrenner, K. & Bent, D. H. (1975). *Statistical Package for the Social Sciences*. New York: McGraw Hill.
- Patrick, J. M. & Wharrad, H. J. (1984). The effect of betaxolol, atenolol and propranolol on heart rate and activity in ambulant subjects. *Proceedings of the 8th International Symposium on Biotelemetry* (Dubrovnik, May 1984). (in press).
- Pearson, S. B., Banks, D. C. & Patrick, J. M. (1979). The effect of beta-adrenergic blockade on factors affecting exercise tolerance in normal man. *Br. J. clin. Pharmacol.*, **8**, 143–148.
- Rowlands, D. B., Glover, D. R., Ireland, M. A., Stallard, T. J. & Littler, W. A. (1982). Control of blood pressure with once-daily timolol. In *Proceedings of the 4th International Symposium on Ambulatory Monitoring, 1981*, eds Stott, F. D. et al., pp. 551–558. London: Academic Press.
- Serlin, M. J., L'Orme, M., McIver, M., Green, G. J., Sibeon, R. G. & Breckenridge, A. M. (1983). The pharmacodynamics and pharmacokinetics of conventional and LA propranolol in patients with moderate hypertension. *Br. J. clin. Pharmacol.*, **15**, 519–527.
- Simpson, W. T. (1977). Nature and incidence of unwanted effects with atenolol. *Postgrad. med. J.*, **53** (Suppl 3), 162–167.
- Smith, R. S. & Warren, D. J. (1982). Effect of acute oral beta-adrenergic blockade on muscle blood flow in man. *Cardiovascular Res.*, **16**, 205–208.
- Snow, D. H. & Summers, R. J. (1977). The actions of beta-adrenoceptor blocking agents propranolol and metoprolol in the maximally exercised horse. *J. Physiol.*, **271**, 39–40P.

- Stone, R. (1975). Proximal myopathy during beta-blockade. *Br. med. J.*, **2**, 1583.
- Twentyman, O. P., Disley, A., Gribben, H. R., Alberti, K. G. M. M. & Tattersfield, A. E. (1981). Effect of beta-adrenergic blockade on respiratory and metabolic response to exercise. *J. appl. Physiol.*, **51**, 788–793.
- Wharrad, H. J., Patrick, J. M., Birmingham, A. T. & Wilson, C. G. (1984). Reduction of finger tremor by betaxolol, propranolol and atenolol in normal subjects. (In preparation).
- Wilcox, R. G., Bennett, T., Macdonald, I. A., Herbert, M. & Skene, A. M. (1984). The effects of acute or chronic ingestion of propranolol or metoprolol on the physiological responses to prolonged, submaximal exercise in hypertensive men. *Br. J. clin. Pharmac.*, **17**, 273–281.
- Zacharias, F. J. (1976). Patient acceptability of propranolol and occurrence of side-effects. *Postgrad. med. J.*, **52**, (Suppl 4) 87–89.

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