Withdrawal phenomena after atenolol and bopindolol: haemodynamic responses in healthy volunteers

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- 1 The effect of withdrawal of atenolol and bopindolol administration was studied in 12 normal volunteers; six on each drug.
- 2 Following sub-maximal cycle-ergometer exercise training six sets of base-line observations were made of heart-rate (HR) and blood pressure (BP) responses; supine, 60° head-up tilt, during graduated isoprenaline infusion and sub-maximal cycle exercise.
- 3 The results show that withdrawal phenomena occur following both drug treatments. Atenolol produced a hypersensitivity to isoprenaline and a small overshoot of HR in response to physiological manoeuvres. In contrast bopindolol produced a prolonged state of reduced sensitivity to isoprenaline and some evidence of overshoot of HR with physiological manoeuvres. The differences between the responses may be explained by the different properties of the two β -adrenoceptor blocking drugs.
- 4 Some subjects showed clear evidence of overshoot of HR and BP on exercise demonstrating that certain individuals may be more prone to have withdrawal effects than others.
- 5 The length of time during which withdrawal phenomena can occur is probably longer than has previously been realised.
- 6 Hormonal changes were found in the withdrawal period (Walden *et al.*, 1990).

Keywords β -adrenoceptor blocker withdrawal phenomena normal volunteers haemodynamic responses

Introduction

The clinical observation that unpleasant and sometimes dangerous withdrawal phenomena occur on stopping β -adrenoceptor drugs in patients with ischaemic heart disease is well documented. Healthy volunteers' studies have confirmed the existence of withdrawal phenomena and demonstrated a different type of response to isoprenaline infusion after drugs without partial agonist activity (PAA) compared with drugs with PAA. These observations have been consistent with the finding that during treatment with non-PAA β -adrenoceptor-blockers there is an increase in β -adrenoceptor density leading to a greater reactivity on withdrawal of the β -adrenoceptor blocking drug. In contrast, during treatment

with drugs with PAA such as pindolol, there is a down-regulation of β -adrenoceptors leading to a period of decreased sensitivity to isoprenaline on withdrawal of the drug. Most studies agree that there are only very small haemodynamic changes of blood pressure or heart rate responses and, that changes in plasma catecholamine levels, plasma thyroid hormones and plasma renin activity are not important (Prichard *et al.*, 1988).

In the present study we have extended observations of withdrawal phenomena made previously to include more pre-treatment base-line observations and a longer period of observation during the withdrawal phase. In addition, we have measured various hormone levels before and during the withdrawal phase;

this is reported elsewhere (Walden *et al.*, 1990). The two drugs chosen for this study were atenolol, a β_1 -adrenoceptor-selective drug without any PAA and bopindolol, a long acting non-selective drug with moderate PAA. We have previously found consistent evidence of withdrawal post β -adrenoceptor blockade with atenolol (Walden *et al.*, 1982).

Methods

Subjects

Twelve healthy volunteers were recruited, seven female and five male. Details of their sex, age, height and weight are shown in Table 1. They were fully informed of the nature of the study which had been approved by the University College Hospital Ethics Committee and had given their written consent.

Design

The study design was double-blind and between subject with random allocation of treatment. There were four phases.

Phase 1 A training phase during which each subject exercised on a cycle ergometer at two loads (for 2 min each) previously selected as being submaximal (HR above 150 beats min^{-1}). This was repeated at intervals of 2 days until the rise in end exercise heart rate (EEHR) did not vary by more than $\pm 5\%$.

Phase 2 At the end of training, six sets of baseline observations were made at intervals of 2 days. The volunteers were instructed not to smoke or take any caffeine containing drinks for

12 h nor alcohol for 36 h before each study session. A light meal was taken approximately 2 h before each experiment. The following procedures were carried out in a quiet temperature controlled laboratory ($22 \pm 2^\circ \text{C}$). The subjects rested supine for 30 min. They were tilted 60° head up for 5 min and then returned to the supine position. A graded intravenous infusion of isoprenaline was administered through an indwelling cannula inserted into a forearm vein and maintained patent by a continuous saline drip. Dosage increments of isoprenaline (Suscardia) were made on a logarithmic scale starting at $0.25 \mu\text{g min}^{-1}$.

The dose was increased at intervals of 4 min until either the heart rate had risen by 30 beats min^{-1} or a rate of 95 beats min^{-1} was reached. The subjects exercised on a cycle ergometer as described above.

At 1 min intervals during each of the four manoeuvres, heart rate and BP were recorded, from an ECG monitor and a LSHTM sphygmomanometer calibrated to 111 mm Hg. All BP measurements were made by the same observer. Samples of venous blood were taken at intervals for the measurement of plasma cortisol, prolactin, insulin, glucose, potassium, noradrenaline, adrenaline. The details of this are described elsewhere (Walden *et al.*, 1990).

Phase III In the dose titration phase that followed, either bopindolol or atenolol were given double-blind and in random order. The starting dose for bopindolol was 0.5 mg and for atenolol 50 mg. The dose was increased sequentially to 1, 2 and 4 mg of bopindolol and 100, 200 and 400 mg atenolol once daily at intervals of 48 h. All doses were given once daily, usually at lunch time and the study observations were carried out 24 h later. If no further reduction in EEHR was observed with a dose increment, the previous lower dose level was given for the final dosage phase. The final dose was maintained to make a total of 16 days drug administration. A full set of observations, as in phase II, was made near the end of the period of drug administration.

Phase IV The final part of the study was the withdrawal phase. Complete sets of observations were made as described above on days 1, 3, 5, 7, 9, 11, 13, 17 and 21 from the end of atenolol or bopindolol administration.

Statistical analysis

The group mean values and individual subject's values were analysed by calculating confidence

Table 1 Subject details and final doses of atenolol and bopindolol. Figures given as mean with range in brackets

	Bopindolol	Atenolol
Number of subjects (sex)	6 (2 male)	6 (3 male)
Age (years)	23 (21–25)	22 (18–25)
Weight (kg)	66.7 (53–92)	70.8 (61–79)
Height (cm)	175.2 (163–192)	173.8 (163–187)
Final dosage (mg day^{-1})	2.0 $n = 1$ 4.0 $n = 5$	200 $n = 1$ 400 $n = 5$

levels for the six pre-treatment observations; values outside these limits during the withdrawal phase are reported as significant.

Results

Table 1 shows details of subjects and drug dosage. Subjective side effects were limited to the expected increased fatigue on exercise with both drugs and one complaint of anxiety when a subject was receiving bopindolol. This volunteer was newly engaged in a high stress occupation which may have accounted for his symptoms.

Heart rate and blood pressure responses

There was a small elevation of heart rate in the withdrawal period at times following atenolol (Figures 1, 2, 3 and 4): supine 3 min (max 72 beats min^{-1} on day 9 compared with baseline

level of 65 with a 70 beats min^{-1} – 95% CI), on tilt 1 min (90 beats min^{-1} compared with baseline level of 79 with an 84 beats min^{-1} – 95% CI) and 5 min (95 beats min^{-1} compared with baseline level of 82 with a 93 beats min^{-1} – 95% CI) and at 1 min pre-exercise but not at 2 or 3 min (max 89 beats min^{-1} compared with baseline of 78 with an 82 beats min^{-1} – 95% CI). Following bopindolol: pre-exercise at 3 min only (max 94 beats min^{-1} compared with baseline of 83 with a 90 beats min^{-1} – 95% CI).

There was no increase in heart rate response to exercise following drug withdrawal in either group (Figure 4). Individual subjects did show overshoot of EEHR however, notably; No 5 on seven occasions on withdrawal of atenolol (max 163 beats min^{-1} on day 3 compared with baseline of 155 with a 162 beats min^{-1} – 99% CI) and No 8 on four occasions on withdrawal of bopindolol (max 173 beats min^{-1} on day 7 compared with baseline of 158 with a 169 beats min^{-1} – 99% CI).

Figure 1 Mean supine HR and BP.

Supine HR was reduced by atenolol (●, ■) but not bopindolol (■, □). There was a small rebound overshoot of HR after atenolol. - - - atenolol 95% CI, - - - bopindolol 95% CI

Figure 2 Mean tilt HR and BP.

Tilt HR was reduced by atenolol (●, ■) but not bopindolol (■, ■). There was a small rebound overshoot of HR after atenolol. - - - atenolol 95% CI, — bopindolol 95% CI

In neither drug group was there evidence of any rebound overshoot of blood pressure above baseline levels in the withdrawal period either supine (Figure 1), on tilt (Figure 2), pre-exercise (Figure 3), or during exercise (Figure 4). Some individuals did show increases of systolic BP in the withdrawal phase, notably at end exercise; no 1 (atenolol) on three occasions (max 169 mm Hg compared with a baseline of 148 with a 161 – 95% CI) and no 2 (bopindolol) on three occasions (max 197 mm Hg compared with a baseline of 183 with a 194 – 95% CI).

Isoprenaline results

Bopindolol blocked the heart rate response to isoprenaline to a far greater extent than atenolol

(Figure 5). The dose of isoprenaline for D25 was $3.5 \mu\text{g min}^{-1}$ and $112.1 \mu\text{g min}^{-1}$, compared with baseline values of 1.9 and 2.1 for atenolol and bopindolol respectively. In the withdrawal phase the dose of isoprenaline required to increase heart rate by $25 \text{ beats min}^{-1}$ was significantly less compared with the baseline on five occasions in the atenolol group, days 3, 5, 7, 13 and 17 (minimum dose $1.2 \mu\text{g min}^{-1}$ compared with baseline values of 1.9 pre-treatment with 95% CI – $1.6 \mu\text{g min}^{-1}$). Following bopindolol there was an increased resistance to isoprenaline which, although declining, had not returned to baseline levels by the end of 21 days of observation ($3.5 \mu\text{g min}^{-1}$ compared with baseline of 2.1 with 95% CI – 1.6).

Figure 3 Mean pre exercise HR and BP.

There was an overshoot of HR after bopindolol (●, ■) but not atenolol (■, □) - - - atenolol 95% CI, -- bopindolol 95% CI

Discussion

Supine heart rate and blood pressure

In a previous study of normal volunteers (Walden *et al.*, 1982) we found no overshoot of supine HR in the 14 days of observation after withdrawal of propranolol (mean daily dosage 614 mg) or atenolol (mean daily dosage 634 mg) whereas, after stopping pindolol (mean daily dosage 18 mg), which did not reduce supine HR during its administration, the HR was elevated above control levels. The duration of treatment was approximately 21 days. In the present study a small overshoot of supine HR occurred after atenolol withdrawal on day 9 and 21 but no significant overshoot was seen after bopindolol.

Rangno *et al.* (1982a) reported findings similar to our earlier observations with pin-

dolol; 10 hypertensive patients taking pindolol (10 mg twice daily for at least 4 weeks) showed an elevation in resting HR of 6 to 22 beats min^{-1} on days 2 to 6 after treatment withdrawal, compared with subsequent stable values, at 14 days post drug. Szecsi *et al.* (1982) also found an overshoot in resting HR in healthy subjects ($n = 12$) given pindolol 10 mg three times daily for 4 weeks (an increase from a mean pre-treatment HR of 70 beats min^{-1} to 80 beats min^{-1} , $P = 0.04$) 5 days after withdrawal. These two groups also found an overshoot of supine HR after metoprolol. Rangno *et al.* (1982a) noted rebound from the second day, peaking at 8 days following metoprolol 100 mg three times daily given to hypertensive males ($n = 8$) for at least 6 weeks. The median supine HR was 86 beats min^{-1} compared to a stable level of 75 beats min^{-1} obtained at 10–14 days after withdrawal.

Figure 4 Mean end exercise HR and BP.

There was no overshoot of HR or BP after bopindolol (■, □) or atenolol (●, ☒). - - - atenolol 95% CI, -- bopindolol 95% CI

Szecsí *et al.* (1982) found a slight increase in supine HR ($68\text{--}73\text{ beats min}^{-1}$, $P = 0.04$) 5 days after stopping metoprolol 100 mg three times daily given for 4 weeks to healthy subjects ($n = 12$). In a study of propranolol withdrawal in hypertensives ($n=9$), Nattel *et al.* (1979) showed an early peak in resting HR at 2 days but this was not different from stable values recorded after 14 days. Four patients showed a rebound increase of about 6 beats min^{-1} between days 2 to 8 after stopping propranolol (median daily dose 240 mg for at least 3 months).

A number of studies have not demonstrated any overshoot of supine HR after stopping β -adrenoceptor blockers including Lindenfeld *et al.* (1980) who studied 10 normal subjects and 10 angina patients 2 and 4 days after stopping 12–16 days of propranolol 160 mg day^{-1} ; Goldstein *et al.* (1981) who studied 14 normal subjects on

days 1, 2 and 7 after stopping propranolol $80\text{--}240\text{ mg day}^{-1}$ given for 24 to 79 days and Pedersen *et al.* (1979) studied hypertensives 1 and 2 days after cessation of metoprolol $150\text{--}300\text{ mg day}^{-1}$ ($n = 5$) and propranolol 160 mg day^{-1} ($n = 1$) given for 2 to 10 months. Baseline levels were taken as those recorded at 7 days post treatment. Ross *et al.* (1981) found no evidence of overshoot of supine HR in normal subjects during 6 days after stopping propranolol 160 mg day^{-1} given for 4 days ($n = 6$), 1 week ($n = 6$) and 6 weeks ($n = 5$), nor in angina patients treated for at least 3 months ($n = 5$), or in hyperthyroid patients treated for 6 weeks ($n = 5$). They also studied the effect of stopping atenolol 200 mg day^{-1} (6 weeks, $n = 6$), oxprenolol 160 mg day^{-1} (1 week, $n = 6$) and acebutolol 400 mg day^{-1} (1 week, $n = 6$) in normal subjects. Ross *et al.* (1981) took control

Figure 5 Mean $\pm$ s.e. mean Δ 25 HR response to isoprenaline infusion normalised to mean pretreatment values.

After atenolol there was a significant increase in sensitivity to isoprenaline but after bopindolol reduced sensitivity to isoprenaline persisted.

values at day 6 after stopping therapy (10 days in the case of atenolol) as their preliminary studies had shown HR responses to return to normal after this interval. There was no evidence of overshoot. However, other groups have found that baseline levels are not attained for 10–14 days depending upon the parameter being observed and the drug involved. An overshoot could have been missed by making observations too early or assuming a baseline had been reached at a time when rebound was still possible. Variations in dosage used and length of drug administration may also be important.

It can be concluded therefore, that although there is some evidence of overshoot of supine heart rate after stopping β -adrenoceptor blockers, the findings are not entirely consistent, and the changes are small.

In a previous study (Walden *et al.*, 1982) we showed a peak increase in supine systolic BP on day 10 post atenolol and values on days 8, 11, 12 and 13 were also greater than pre-treatment baseline. The propranolol and pindolol groups showed a tendency for supine systolic BP to rise towards the end of the withdrawal phase but, this did not reach significance. Supine diastolic BP showed no clear overshoot in any group. In

the study reported here, there was no significant rise in BP on withdrawal of atenolol or bopindolol in the supine position. Lindenfield *et al.* (1980) and Goldstein *et al.* (1981) were also unable to find any overshoot of resting BP in normal subjects after propranolol but, Nattel *et al.* (1979) reported a rebound in systolic and diastolic BP in six of nine hypertensives around day 6 after stopping propranolol.

Tilt heart rate and blood pressure

We previously found that with 60° tilt a significant increase of HR occurred on day 3 of the withdrawal phase after pindolol but not propranolol or atenolol, compared with baseline (Walden *et al.*, 1982). This coincided with the start of overshoot of supine HR. In the present study we found a small overshoot of HR on days 9 and 21 after atenolol, but no significant increase after bopindolol.

Other published studies have reported an increase of erect HR on drug withdrawal more often than of supine HR. In their study of propranolol withdrawal in normal subjects ($n = 14$) Goldstein *et al.* (1981) found an increase of HR on tilting (mean 27 beats min^{-1} on each of days 1, 2 and 7) after stopping propranolol compared to 21 beats min^{-1} pretreatment but there was only one pretreatment observation.

Pedersen *et al.* (1979) found the standing HR to be raised on days 1 and 2 (mean 91 and 95 respectively) after metoprolol ($n = 5$) and also on propranolol withdrawal ($n = 1$) with a value of 89 beats min^{-1} on day 7. There was no associated postural fall in BP in these six hypertensive patients but, a gradual rise in standing systolic and diastolic BP to pre-treatment levels. Ross *et al.* (1981) found an increase of standing HR in normal subjects 3 days after stopping propranolol given for 6 weeks but not after 1 week or with only 4 days treatment. They also found a significant peak of standing HR in normal subjects 3 days after stopping acebutolol but not after oxprenolol or atenolol.

In our previous study we found a significant increase in tilt systolic BP on days 11 and 13 after propranolol but not pindolol or atenolol (Walden *et al.*, 1982). We have now found that tilt systolic blood pressure is unchanged after atenolol and bopindolol withdrawal. There were no significant changes in diastolic BP.

To summarise, small but statistically significant increases of tilt HR can occur on withdrawal of β -adrenoceptor blockers with and without PAA. Changes in systolic blood pressure responses are less clear and appear to

be minimal or absent. The average changes of HR reported are unlikely to be of clinical significance, however, it is possible that important changes occur to some individuals.

Pre-exercise heart rate and blood pressure

Examination of pre-exercise HR seated on cycle (Walden *et al.*, 1982) showed significant rises after pindolol but not propranolol or atenolol withdrawal. In the present study we found a rise in HR after atenolol and to a lesser extent bopindolol but, the changes were small. It is difficult to explain why these changes should occur in one study and not the other when the methods used were so similar. Presumably variation between subjects is a more important factor than variation between treatments.

End exercise heart rate and blood pressure

We were unable to demonstrate any significant overshoot of EEHR, systolic or diastolic blood pressure in any treatment group in the previous (Walden *et al.*, 1982) or present investigations.

Jackson *et al.* (1979) using just one baseline reading, found an overshoot of blood pressure response to exercise at 42 and 54 h after the last dose of propranolol 80 mg four times daily given to normal subjects for 1 week ($n = 5$) and at 66 h after atenolol, 100 mg daily for 1 week ($n = 5$). The fixed doses of propranolol and atenolol used were considerably smaller than the doses we used in our study and would only have produced a small degree of β -adrenoceptor blockade. There was no withdrawal overshoot of EEHR.

Rangno *et al.* (1982b) studying 10 hypertensives reported a rebound in EEHR (treadmill exercise) on days 2 and 4 after stopping pindolol 10 mg twice daily given for 4 weeks or more in a study of 10 hypertensive subjects. Exercise systolic blood pressure did not overshoot. Supine heart rate was elevated at day 2 in this study. Rangno *et al.* (1982a) commenced exercise tests 12 h after the last drug dose and then on alternate days so that the apparent rise in EEHR on day 2 could have been a training effect. The subjects in our study were trained and showed a reduction in EEHR to a stable level after three or four exercise training sessions, baseline observations were then made. Increases in EEHR or blood pressure were not reported by Rangno *et al.* (1982a) or Nattel *et al.* (1979) after propranolol or metoprolol withdrawal.

Goldstein *et al.* (1981) found an increased HR response to upright bicycle exercise 6–9 days after stopping propranolol in normal subjects. The peak effect occurred on day 2 (mean increase EEHR of 12 beats min^{-1}) compared with pretreatment baseline levels. The baseline values in this study were obtained before treatment but, on only one occasion. There was no reference to previous training and this may have affected the results.

Lindenfeld *et al.*'s study (1980) produced results similar to our own with no overshoot of EEHR or exercise systolic BP in a group of 10 normal subjects and 10 angina patients 2 and 4 days after stopping propranolol. The patients were admitted to hospital but, only during the withdrawal phase so, positive or negative training effects should have been minimal.

The absence of withdrawal rebound increases in EEHR in any treatment group in our studies masked an overshoot of EEHR in certain individual subjects. It is therefore important when assessing the significance of the negative findings we report, to remember that individual patients may have increased HR responses to exercise after stopping β -adrenoceptor blockers.

Overall, there was some overshoot of heart rate and blood pressure responses in the withdrawal phase after β -adrenoceptor blockade but, in normal subjects the rises were small.

Isoprenaline responses

In our previous study of atenolol withdrawal, which is β_1 -selective and without PAA, a state of hypersensitivity to isoprenaline was produced (Walden *et al.*, 1982, 1990). This was also true in the present study. In complete contrast, bopindolol, which like pindolol has moderate PAA, produced a prolonged state of reduced sensitivity to isoprenaline which persisted, although declining, up to the last day of observation (day 21 of withdrawal). A rebound increase in isoprenaline sensitivity could have occurred after this time but, this is unlikely. The results suggest that the duration of the state of hyposensitivity lasts more than 21 days after bopindolol withdrawal. The difference in HR responses to isoprenaline challenge on withdrawal of atenolol and bopindolol may reflect the β_2 -adrenoceptor agonist action of bopindolol, which results in a down-regulation of β_2 -adrenoceptors offsetting any up-regulation of β_1 -adrenoceptors. This subject has been fully reviewed (Prichard *et al.*, 1988).

General discussion

A paper particularly relevant to the present investigation is that of Olsson *et al.* (1984). One hundred and fifteen patients from a 3 year, double-blind, post-infarction study were divided as follows; 58 were taking metoprolol 100–200 mg daily and 57 placebo. Study medication was withdrawn under blind conditions by reducing the doses in stages during 7 days. The patients were investigated on days, 0, 7, 14, 28, 90 and 180 of withdrawal. There was a greater incidence of mental discomfort and angina up to day 30 in the metoprolol group compared with the placebo group. Disabling mental and cardiac symptoms occurred requiring reinstitution of treatment in 14 of 58 in the metoprolol group vs 4 of 57 in the placebo group. A significant rebound increase in supine heart rate and of the heart rate response to standing occurred during the 3 weeks after withdrawal of metoprolol compared with

values obtained at 6 months. The authors were surprised at the late appearances of symptoms after withdrawal of metoprolol and speculate on the cause; changes in beta-adrenoceptor function, adaptation to treatment or slow disappearance of the drug from tissues after long term administration were suggested explanations.

If the findings of Olsson *et al.* (1984) and our own are meaningful, they suggest that the period of risk for exacerbation of symptoms in patients with ischaemic heart disease on withdrawal of β -adrenoceptor blockade, could be longer than previously recognised. Furthermore, it seems that the factors provoking symptoms of ischaemia under these conditions are not necessarily limited to exercise. These observations may apply to all classes of β -adrenoceptor blocker. Additional controlled studies with longer periods of observation would help to clarify these findings.

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