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COMPARISON OF WITHDRAWAL PHENOMENA AFTER PROPRANOLOL, METOPROLOL AND PINDOLOL

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1 After abrupt propranolol withdrawal a rebound increase in cardiac sensitivity to isoprenaline occurred in 9/9 patients and persisted up to 14 days. A mild brief rebound in resting heart rate occurred in 4/9 patients and a rebound in blood pressure occurred in 6/9 patients. These withdrawal phenomena were prevented by gradual withdrawal on a prolonged small dose of propranolol.

2 After abrupt metoprolol withdrawal a rebound increase in cardiac sensitivity to isoprenaline occurred in 8/8 patients but had resolved by 8 days. A marked persistant rebound in resting heart rate occurred in 8/8 patients while a small brief rebound in blood pressure occurred in only one patient. These withdrawal phenomena were largely prevented by gradual withdrawal on a prolonged small dose of metoprolol.

3 After abrupt pindolol withdrawal there was no rebound in isoprenaline sensitivity but a mild brief rebound in resting heart rate occurred in 9/10 patients. There was no rebound in blood pressure.

4 The type, magnitude and frequency of withdrawal phenomena after various β-adrenergic receptor blockers probably reflects substantial differences in their basic pharmacological characteristics.

5 Caution must be exercised when withdrawing any patient from any β-adrenoceptor blocker since an adverse cardiac event is unpredictable.

Introduction

A withdrawal syndrome after abrupt cessation of the β-adrenoceptor blocker, propranolol, is gaining progressive recognition (Gerber & Nies, 1979; Shand & Wood, 1978). It has been observed mainly in patients with coronary artery disease, manifesting as worsening of angina, myocardial infarction, atrioventricular arrhythmias and sudden death (Mizgala & Counsell, 1976; Nattel *et al.*, 1978; Miller *et al.*, 1975). In hypertensive patients, abrupt withdrawal of β-adrenoceptor blocking drugs has resulted in symptoms of malaise, headache, tremor, sweating, anxiety and palpitations (Lederballe Pedersen, 1976; O'Brien & MacKinnon, 1972). These initial reports led to several prospective studies which attempted to determine the incidence, time course and mechanism of the phenomena. The most viable theory, tested by our group and others (Nattel *et al.*, 1979; Boudoulas *et al.*, 1977) is an adaptive increase in cardiac β-adrenergic receptor sensitivity perhaps as a result of increased receptor number (Glaubiger & Lefkowitz, 1977; Aarons *et al.*, 1980). The majority of case reports and formal studies concern withdrawal from propranolol, but other β-adrenoceptor blockers may also be implicated. Indeed, a few reports suggest withdrawal features after metoprolol (Lederballe Pedersen, 1976; Rangno *et al.*, 1982a), practolol (Nellen, 1969), oxprenolol (Nellen, 1969), and atenolol (Jackson *et al.*, 1979). It is unknown whether any difference in frequency or severity of the withdrawal phenomena is due to limited experience with other β-adrenoceptor blockers or to real differences in their pharmacology. We have completed studies in three groups of hypertensive patients and have shown differences after withdrawal from propranolol (non-selective) (Nattel *et al.*, 1978), metoprolol (selective) (Rangno *et al.*, 1982a) and pindolol (non-selective with intrinsic sympathomimetic activity) (Rangno *et al.*, 1982b). This paper is limited to a comparison of four measurements made in those three studies, namely cardiac β-adrenergic receptor sensitivity to isoprenaline, resting blood pressure, resting heart rate and symptoms. Gradual dose reduction schedules for propranolol and metoprolol were developed to prevent withdrawal manifestations (Rangno *et al.*, 1982a, c).

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Table 1 Patient characteristics and dose of β-adrenoceptor blocker

	Number of patients	*Age (years) median range*	*Dose (mg/day)*	*Post-withdrawal placebo*
Propranolol	9	48 (26–79)	240	No
Metoprolol	8	52 (42–82)	300	Yes
Pindolol	10	51 (28–64)	20	Yes

*Daily doses were divided into three times daily for propranolol and twice daily for metoprolol and pindolol.

Methods

Subjects

Ethical considerations precluded studies in patients with angina. Therefore the study population consisted of patients treated for mild to moderate essential hypertension, who were free of historical or ECG evidence of coronary artery disease. Table 1 shows the patient characteristics and drug doses before abrupt withdrawal. Some patients participated in more than one study. All patients were on therapy for at least 1 month before withdrawal. Seven patients receiving propranolol continued to take a thiazide diuretic throughout the study, while others received no other antihypertensive medication.

Design – Abrupt withdrawal

Patients were studied initially, on day 0, 12 h after their last dose of β-adrenoceptor blocker, and serially thereafter at the same time of the day at approximately 2 day intervals for 2 to 3 weeks. Patients refrained from tobacco and caffeine beverages for at least 12 h before each study.

Design – Gradual withdrawal

After completion of the abrupt withdrawal studies some patients again received propranolol or metoprolol as described before abrupt withdrawal. After 1 month of propranolol (240 mg/day), three patients had a stepwise 50% dose reduction at 3 day intervals

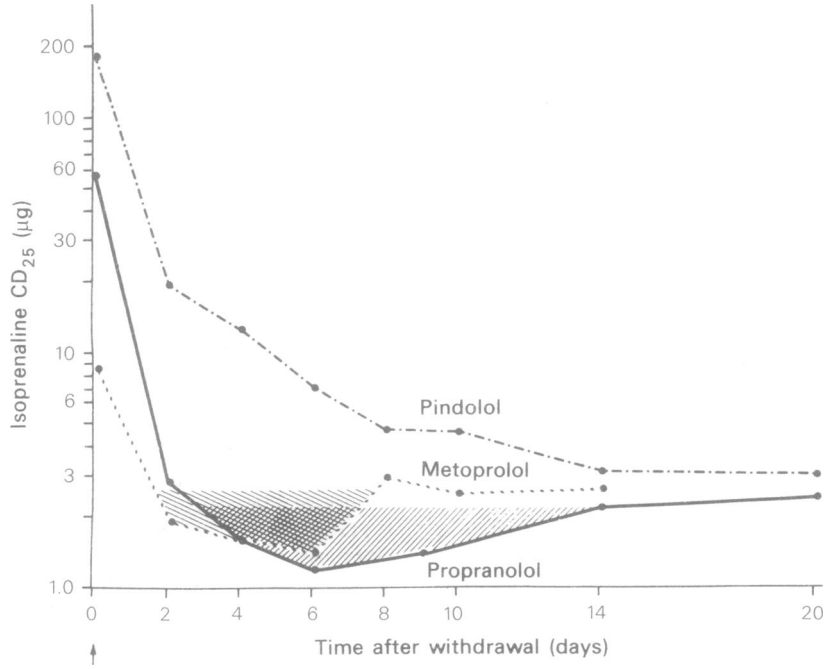

Figure 1 Median isoprenaline CD_{25} values (μg) after abrupt withdrawal of propranolol, metoprolol and pindolol. The dashed areas represent the period of increased β-adrenergic receptor sensitivity after propranolol and metoprolol. After propranolol and metoprolol, day 2 to 6 significantly less than day 20 ($P<0.05$).

and six patients received a prolonged low dose of 10 mg three times a day for 14 days. After 1 month of metoprolol (300 mg/day) seven patients received a prolonged low dose of 25 mg twice daily for 10 days. Placebo was substituted after propranolol and metoprolol were completely discontinued. Studies were performed on the last day of full dose and serially for 10 to 14 days during dose reduction and an additional 10 to 14 days during placebo.

Measurements

On each study day, the same procedure was performed. A brief history was taken using a checklist to elicit complaints possibly related to withdrawal. A 19-gauge butterfly needle was inserted into an antecubital vein. After 30 min of bed rest in a quiet room, blood pressure was measured three times by sphygmomanometer. The heart rate changes produced by small incremental doses of isoprenaline were measured to obtain an index of cardiac β-adrenergic receptor sensitivity, according to the method of Cleaveland *et al.* (1972). Before each dose of isoprenaline, baseline heart rate was obtained by measuring the two shortest RR intervals on a resting ECG strip. Isoprenaline 200 μg/ml was used, with 20 μg/ml and 2 μg/ml solutions obtained by serial 1:10 dilutions. Each bolus dose of isoprenaline was administered by a rapid intravenous push and followed by a rapid infusion of 20–30 ml of 5% dextrose solution. The logarithm of each isoprenaline dose was plotted against the resulting change in heart rate, to obtain a log dose-response curve. A minimum of four points was obtained and plotted by linear least-squares regression. The isoprenaline dose required to produce an increase in heart rate of 25 beats/min was obtained from this line of best fit. This dose will be referred to as the isoprenaline CD_{25} (chronotropic dose 25). The median CD_{25} on days 14 to 20 after withdrawal was considered the 'baseline CD_{25}' reflecting β-adrenergic receptor sensitivity off β-adrenoceptor blocker. A decrease of CD_{25} below baseline reflects a withdrawal-induced increase in cardiac β-adrenergic receptor sensitivity. The medians of heart rate and blood pressure on days 14–20 were termed 'baseline heart rate' and 'baseline blood pressure'.

Analysis of data

All data for the groups is expressed as median and range. Changes in measurements over time were analysed by the Friedman non-parametric analysis of variance with multiple comparison and one-tailed probability (Hollander & Wolfe, 1973). Statistical analysis was performed within each of the three drug groups and between the groups.

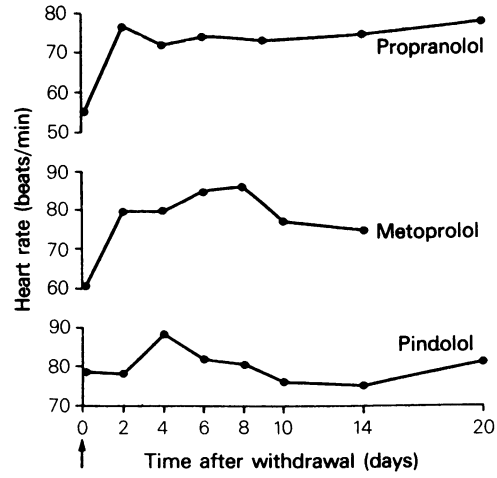

Figure 2 Median heart rates after abrupt withdrawal of propranolol, metoprolol and pindolol. After metoprolol, days 2 to 8 significantly greater than day 14 ($P<0.05$). After pindolol days 2 to 6 significantly greater than days 14 to 20 ($P<0.05$).

Results

Isoprenaline CD_{25} values – abrupt withdrawal

The comparative changes in CD_{25} values after withdrawal from propranolol, metoprolol and pindolol are shown in Figure 1. Comparable and reproducible stable baseline CD_{25} values were achieved by days 14–20. The values were 2.4 μg (range 1.4 to 7.6) after propranolol, 2.6 μg (range 0.9 to 5.1) after metoprolol and 3.0 μg (range 1.6 to 16.7) after pindolol. This contrasts with initial CD_{25} of 57 μg (range 4.6 to 355), 8.7 μg (range 3.1 to 24) and 181 μg (range 16.0 to 800) measured 12 h after the last dose of propranolol, metoprolol and pindolol respectively. Not only these initial values but also the subsequent course of CD_{25} values differed notably between drugs. After propranolol, the period of increased β-adrenergic receptor sensitivity extended from day 3 to 13. This was manifested by a median CD_{25} value below baseline during this interval, with all nine subjects having a value 2 to 5 fold below baseline (i.e. increased sensitivity) somewhere between day 5 and 9 ($P<0.05$). A similar pattern in CD_{25} values was observed in each patient after withdrawal of metoprolol, but differed from propranolol by an earlier onset and shorter duration of increased β-adrenergic receptor sensitivity. Median CD_{25} values were significantly below baseline between day 2 and 8, with individual values 2 to 3 fold below baseline for the eight subjects ($P<0.05$). After pindolol, the median CD_{25} fell gradually to the ultimate baseline, and in

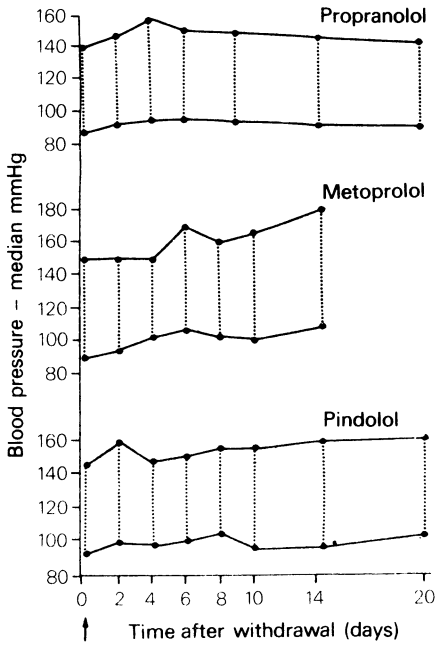

Figure 3 Median systolic and diastolic blood pressures after abrupt withdrawal of propranolol, metoprolol and pindolol. After propranolol, systolic and diastolic pressure on day 6 significantly greater than on day 20 ($P<0.05$).

none of the ten subjects was the CD_{25} on days 0 to 10 lower than on day 14 or 20.

Heart rate – abrupt withdrawal

Comparative changes in resting heart rate after drug withdrawal are shown in Figure 2. Two days after propranolol, heart rate had returned to baseline of 78 beats/min (range 60 to 105), from an initial value of 55 beats/min (range 48 to 70) on day 0. Four patients showed a rebound increase in heart rate of about 6 beats/min between days 2 to 8. After metoprolol, patients had a comparable initial heart rate of 61 beats/min (range 54 to 79) on day 0, and all patients had a significant rebound between days 2 to 8 during the period of increased β-adrenergic receptor sensitivity (median 6 beats/min, $P<0.025$). Pindolol did not produce the same bradycardia as propranolol and metoprolol, the median initial heart rate being 79 beats/min (range 74 to 86). After pindolol withdrawal, a significant rebound of heart rate occurred in nine of ten patients between day 2 and day 6 varying from 6 to 22 beats/min (median 10) ($P<0.05$).

Blood pressure – abrupt withdrawal

Comparative changes in resting blood pressure after drug withdrawal are shown in Figure 3. After propranolol, six of the nine patients experienced a significant rebound of both systolic and diastolic pressures ($P<0.05$); the median of these six subjects were 135/85 mm Hg initially, 154/98 mm Hg at peak and 139/86 mm Hg at ultimate baseline. Median pressures for all nine patients were 140/87 mm Hg (range 97/74 to 159/100) initially, 145/95 mm Hg (range 128/84 to 180/107) on day 6 and 140/89 mm Hg (range 112/79 to 180/120) at baseline. After metoprolol, systolic and diastolic pressure rose progressively from 149/90 mm Hg (range 131/74 to 187/108) on day 0 to 178/107 mm Hg (range 147/91 to 206/125) on day

Table 2 Symptoms after withdrawal of β-adrenoceptor blockers

	Propranolol (n = 9)	*Metoprolol* (n = 8)	*Pindolol* (n = 10)
Headache	3	1	1
Tremulousness	1	1	1
Anxiety	1	1	0
Chest pain	1	0	0
Total	6	3	2

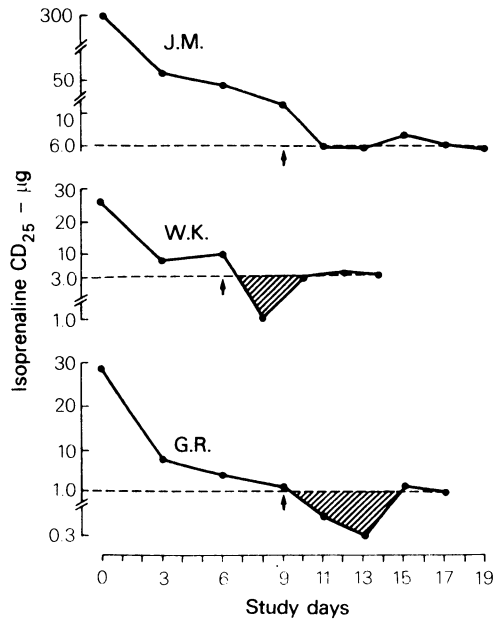

Figure 4 Serial changes in β-adrenergic receptor sensitivity, as measured by isoprenaline CD_{25} (μg) in patients withdrawn from propranolol by serial dose reduction (group A). The dashed horizontal line indicates the ultimate stable CD_{25}. Values below the stable CD_{25} (hatched area) indicate increasing β-adrenergic receptor sensitivity seen in patients WK and GR. Arrows indicate the end of propranolol dose tapering schedule.

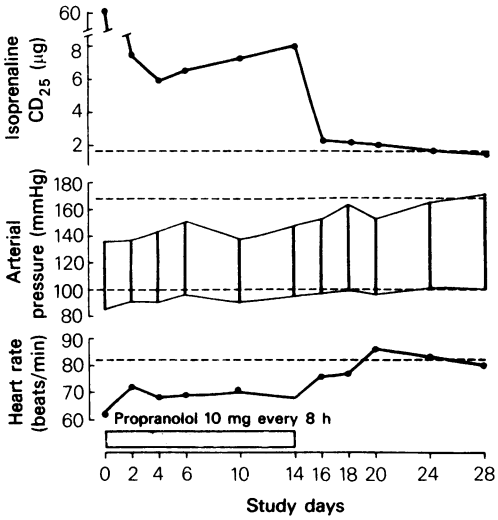

Figure 5 Median isoprenaline CD_{25} (μg) median arterial blood pressure (mmHg) and median heart rate (beats/min) during and after prolonged low dose propranolol withdrawal in group B patients ($n = 6$). Dashed horizontal lines represent the ultimate stable values.

14. There was no rebound except for one subject, on day 8 (systolic and diastolic). The same progressive rise was observed after pindolol from 144/90 mm Hg (range 130/70 to 184/116) on day 0 to 161/102 mm Hg (range 140/80 to 190/122) on day 20.

Symptoms – abrupt withdrawal

Clinical symptoms suggestive of withdrawal were described by six patients after propranolol, by three after metoprolol and by two after pindolol (Table 2). These were of variable duration, but did not last for more than 4 days except in two patients who had progressive headache concomitant with a rise in their blood pressure after withdrawal of metoprolol or pindolol.

CD_{25}, heart rate, blood pressure and symptoms – gradual withdrawal

Figure 4 shows that stepwise dose reduction of propranolol prevented hypersensitivity to isoprenaline in only one of three patients. Figure 5 shows that prolonged treatment with a low dose of propranolol largely prevented all the changes in isoprenaline hypersensitivity and rebound in heart rate and blood pressure.

Figure 6 shows that prolonged low dose metoprolol administration largely prevented all of the changes in isoprenaline hypersensitivity and rebound in heart rate.

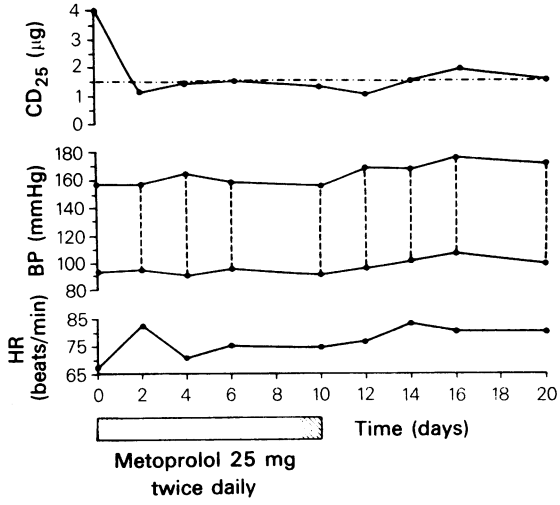

Figure 6 Effect of gradual metoprolol withdrawal on the dose of isoprenaline required to increase chronotrophy 25 beats/min (CD_{25},-a), blood pressure (BP, b) and resting heart rate (HR, c). Full dose metoprolol (150 mg twice daily) was gradually reduced to 25 mg twice daily for 10 days before being completely withdrawn and replaced with placebo. All the data points are median values for the group ($n = 7$).

Discussion

There were substantial differences in cardiac responsiveness as measured by isoprenaline and resting heart rate between withdrawal of propranolol, metoprolol and pindolol. The explanation for these divergent observations may lie in the hypothesis of Ariens & Simonis (1976) and the recent observations of Bryan *et al.* (1981) and Bake *et al.* (1980). These investigators propose that cardiac β-adrenoceptors are primarily stimulated by local adrenergic neurone release of neurotransmitter noradrenaline (hence 'β-T' receptors) while cardiac β_2-adrenoceptors are primarily stimulated by the circulating hormone adrenaline (hence 'β-H' receptors). Resting heart rate would be a measure of β_1-adrenoceptor responsiveness and the isoprenaline test a measure of β_2-adrenoceptor responsiveness. Differing adaptive changes may occur in these receptors after chronic exposure to β-adrenoceptor blockers with different pharmacological properties. After abrupt withdrawal and rapid elimination of β-adrenoceptor blockers these changes in receptor responsiveness may be unmasked.

After propranolol withdrawal there was a common, marked and prolonged rebound sensitivity to isoprenaline but a less common, mild and short lived rebound in resting heart rate. This would be consistent with an increase in β-receptor density as shown

by others (Glaubiger & Lefkowitz, 1977; Aarons *et al.*, 1980) but with a greater change of β_2- *v* β_1-adrenoceptors. This suggests that propranolol's greater antagonist action is at the β_2-adrenoceptor and that it is non-selective.

After metoprolol withdrawal there was a common, marked and prolonged sensitivity to both isoprenaline and resting heart rate. This would be consistent with a more equal increased density of both β_1- and β_2-adrenoceptors. This is in keeping with the known β_1-adrenoceptor selectivity of metoprolol and the fact that progressive β_2-adrenoceptor blockade occurs at greater doses such as used in this study.

After pindolol withdrawal there was a brief, small rebound in resting heart rate at the same time as directly opposite common, marked and persistent decrease in isoprenaline responsiveness. This would be consistent with mild enhanced β_1-adrenoceptor density and marked suppressed β_2-adrenoceptor density. This latter phenomenon has been shown after chronic administration of the β_2-adrenoceptor agonist terbutaline (Galant *et al.*, 1978; Wolfe *et al.*, 1977). The known partial agonist activity of pindolol at higher concentrations could occur predominantly at β_2-adrenoceptors and result in down regulation. There could be a much lower effective concentration of pindolol at the β_1-receptor since there is a relatively much greater concentration of agonist (noradrenaline) at this site (Frishman *et al.*, 1979). Thus a predominant antagonist action of pindolol at low concentration could result in up regulation of the β_1-receptor.

The rebound in heart rate or blood pressure and the symptoms as part of the withdrawal features after propranolol, metoprolol and pindolol were statistically significant in some instances but we believe were of potential clinical significance even if they occurred in only one patient. Because the patients were resting during our observations, both the frequency and magnitude of the changes could have been underestimated. Some authors have suggested that increased adrenergic sensitivity will only become clinically manifest when the sympathetic drive is elevated, as for example by assuming a standing position, exercising or using a vasodilator (Lewis *et al.*, 1979). In addition, our relatively healthy patients without measurable cardiac disease, probably had a higher threshold to possible life-threatening consequences of these changes. The clinical implications of these withdrawal features are quite different in patients with ischaemic heart disease or arrhythmia. It has been shown that in a given patient, the onset of angina tends to occur at the same degree of myocardial oxygen demand, of which systolic pressure and heart rate are important determinants (Robinson, 1967). For ethical reasons, we limited our study to a hypertensive population, but the results can be extrapolated to all patients with overt cardiac disease and to hypertensive patients who may have ischaemic heart disease masked by their β-adrenoceptor blocker therapy.

The duration of increased cardiac sensitivity, 2 to 8 days after metoprolol, 3 to 13 days after propranolol and 2 to 6 days after pindolol suggests that none of these drugs should be discontinued rapidly. We have shown that tapering of propranolol in less than 9 days does not prevent withdrawal phenomena (Nattel *et al.*, 1978; Rangno *et al.*, 1982), while a prolonged low dose over 2 weeks prevents the increase in cardiac sensitivity and most of the other withdrawal features (Rangno *et al.*, 1982; Frishman *et al.*, 1979). Similarly, prolonged low dose metoprolol prevented most of the changes observed after abrupt withdrawal. We did not study a gradual withdrawal schedule for pindolol but based on the rebound in resting heart rate we would suggest a dose of 2 to 3 mg daily for 2 weeks before complete discontinuation.

The controversy over the prevalence, or even the existence, of a β-adrenoceptor blocker withdrawal phenomenon is partly explained by our data. The magnitude of increased cardiac responsiveness after propranolol, metoprolol or pindolol would probably go unnoticed in an individual without heart disease. So also the mild, infrequent and almost non-specific symptoms would be unlikely to raise suspicion. The same may be so for a patient with mild ischaemic heart disease. However, the patient with more severe ischaemic or arrythmic heart disease, through a further decrease in cardiac threshold, could experience an adverse cardiac event either at rest or after a previously tolerated physical-emotional stress. Such an event would be typical of, and therefore attributable to, the underlying disease without question of medication withdrawal. Patients should be informed of these risks to enhance medication compliance.

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References

AARONS, R.D., NIES, A.S., GAL, J., HEGSTRAND, L.R. & MOLINOFF, P.B. (1980). Elevated of β-adrenergic receptor density in human lymphocytes after propranolol administration. *J. clin. Invest.*, **65**, 949–957.

ARIENS, E.J. & SIMONIS, A.M. (1976). Receptors and receptor mechanisms. In *Beta adrenoreceptor blocking agents*. pp. 4–27. Amsterdam, North Holland: Elsevier.

BAKE, S.P., BOYD, H.M. & POTTER, L.T. (1980). Distribu-

tion and function of beta adrenoreceptors in different chambers of the canine heart. *Br. J. Pharmac.*, **68,** 57–63.

BOUDOULAS, H., LEWIS, R.P., KATES, R.E. & DALAMANGAS, G. (1977). Hypersensitivity to adrenergic stimulation after propranolol withdrawal in normal subjects. *Ann. int. Med.*, **87,** 433–436.

BRYAN, L.J., COLE, J.J., O'DONNEL, S.R. & WANSTALL, J.C. (1981). A study designed to explore the hypothesis that beta-1 adrenoreceptors are 'innervated' receptors and beta-2 adrenoreceptors are 'hormonal' receptors. *J. Pharmac. exp. Ther.*, **216,** 395–400.

CLEAVELAND, C.R., RANGNO, R.E. & SHAND, D.G. (1972). A standardized isoproterenol sensitivity test: the effects of sinus arrhythmias atropine and propranolol. *Arch. int. Med.*, **130,** 47–52.

FRISHMAN, W., KOSTIS, J., STROM, J., HOSSLER, N., ELKAYAM, V., GOLDNER, S., SILVERMAN, R., DAVIS, R., WEINSTEIN, J. & SONNENBLICK, E. (1979). Clinical Pharmacology of the new beta-adrenergic blocking drugs. Part 6. A comparison of pindolol and propranolol in treatment of patients with angina pectoris. The role of sympathomimetic activity. *Am. Heart J.*, **98,** 526–535.

GALANT, S.P., DURISETI, L., UNDERWOOD, S. & INSEL, P.A. (1978). Decreased beta-adrenergic receptors on human polymorphonuclear leukocytes after adrenergic therapy. *New Eng. J. Med.*, **299,** 933–936.

GERBER, J.G. & NIES, A.S. (1979). Abrupt withdrawal of cardiovascular drugs. *New Eng. J. Med.*, **301,** 1234–1235.

GLAUBIGER, G. & LEFKOWITZ, R.J. (1977). Elevated beta-adrenergic receptor number after chronic propranolol treatment. *Biochem. Biophys. Res. Comm.*, **78,** 720–725.

HOLLANDER, M. & WOLFE, D.A. (1973). *Non-parametric statistical methods*, pp. 138–155. New York: John Wiley & Sons.

JACKSON, G., SCHWARTZ, J., KATES, R.E. & HARRISON, D.C. (1979). Physiologic basis for beta blockade rebound: Atenolol vs. propranolol. *Clin. Res.*, **27,** 444.

LEDERBALLE PEDERSON, O. (1976). Comparison of metoprolol and hydrochlorothiazide as antihypertensive agents. *Eur. J. clin. Pharmac.*, **1,** 381–385.

LEWIS, M.J., ROSS, P.J. & HENDERSON, A.H. (1979). Rebound effect after stopping beta-blockers. *Br. med. J.*, **2,** 606–608.

MILLER, R.R., OLSON, H.G., AMSTERDAM, E.A. & MASON, D.T. (1975). Propranolol-withdrawal rebound phenomenon. Exacerbation of coronary events after abrupt cessation of antianginal therapy. *New Eng. J. Med.*, **293,** 416–418.

MIZGALA, H.F. & COUNSELL, J. (1976). Actue coronary syndromes following abrupt cessation of oral propranolol therapy. *Can. med. Ass. J.*, **114,** 1123–1126.

NATTEL, S., SHANKS, J. & RANGNO, R.E. (1978). Propranolol withdrawal. *Ann. int. Med.*, **89,** 288.

NATTEL, S., RANGNO, R.E. & VAN LOON, G. (1979). Mechanism of propranolol withdrawal phenomena. *Circulation*, **59,** 1158–1162.

NELLEN, M.S. (1969). Trial of two beta-blockade drugs, Ciba 39089 and ICI 50172 in angina pectoris. *S. Afr. med. J.*, **2,** 155–163.

O'BRIEN, E.T. & MACKINNON, J. (1972). Propranolol and polythiazide in treatment of hypertension. *Br. Heart J.*, **34,** 1042–1050.

RANGNO, R.E., LANGLOIS, S. & LUTTERODT, A. (1982a). Metoprolol withdrawal phenomena: Mechanism and prevention. *Clin Pharmac. Ther.*, **31,** 8–15.

RANGNO, R.E., LANGLOIS, S. & STEWARTT, J. (1982b). Cardiac hyper- and hyporesponsiveness after pindolol withdrawal. *Clin Pharmac. Ther.*, (in press).

RANGNO, R.E., NATTEL, S. & LUTTERODT, A. (1982c). Prevention of propranolol withdrawal phenomena by gradual dose reduction. *Am. J. Cardiol.* (in press).

ROBINSON, B.F. (1967). Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. *Circulation*, **35,** 1073–1082.

SHAND, D.G. & WOOD, A.J.J. (1978). Propranolol withdrawal syndrome – Why? *Circulation*, **58,** 202–203.

WOLFE, B.B., HARDEN, T.K. & MOLINOFF, P.B. (1977). *In vitro* study of β-adrenergic receptors. *Ann. Rev. Pharmac. Tox.*, **17,** 575–604.