Br. J. clin. Pharmac. (1982), **13**, 353S–357S

ABRUPT WITHDRAWAL OF PINDOLOL OR METOPROLOL AFTER CHRONIC THERAPY

E. SZÉCSI, S. KOHLSCHÜTTER, W. SCHIESS & E. LANG

Carl-Korth-Institute for Cardiovascular Diseases, Erlangen, FRG

1 In an open controlled study a group of 18 healthy volunteers received either pindolol 10 mg three times daily or metoprolol 100 mg three times daily for 4 weeks. Before treatment, and after abrupt withdrawal the resting heart rate, the blood pressure, the exercise heart rate and the isoprenaline CD_{25} (dose of isoprenaline to increase the heart rate by 25 beats/min) were determined. Heart rates were continuously monitored by an ECG-coupled computer. The CD_{25} values were calculated by an off line computer procedure from the on line recorded data.

2 After metoprolol we found 6 out of 12 patients with a CD_{25} below baseline, in one case with a corresponding increase in heart rate during exercise. After pindolol we observed a CD_{25} below baseline only in one case with no corresponding reaction in the exercise test. In both groups we observed a reactive increase in resting heart rate and systolic blood pressure around day 5 after withdrawal.

3 We conclude that abrupt withdrawal of metoprolol in contrast to pindolol is associated with a higher risk of developing β-adrenergic receptor hypersensitivity.

Introduction

Severe coronary events and arrhythmias have been reported following the abrupt withdrawal of chronic therapy with propranolol (Gilfrich & Rahn, 1981; Lederballe *et al.*, 1979; Maling & Dollery, 1979; Miller & Olson, 1975; Ross & Lewis, 1979; Schofer & Bleifeld, 1981, Shand, 1975; Shand & Wood, 1978; Slome, 1973) and more recently also after metoprolol (Kristensen, 1979; Lederballe *et al.*, 1979; Meinertz *et al.*, 1979). So far no such effects have been reported following withdrawal of pindolol, a nonselective β-adrenoceptor blocker with marked intrinsic sympathomimetic activity (ISA). There is evidence that withdrawal phenomena may, at least partially, be caused by a reactive hypersensitivity of β-adrenoceptors (Lederballe *et al.*, 1979; Nattel *et al.*, 1979; Schofer & Bleifeld, 1981). The question remains open if this is a common property of all types of β-adrenoceptor blocking drugs or if there are differences due to selectivity or partial agonism (ISA).

In a recent study we observed that beneficial effects persisted for up to 14 days after withdrawal of a 4 week period of therapy with pindolol in patients with angina pectoris (Lang *et al.*, 1979).

The aim of this study was to follow the changes in β-adrenergic sensitivity after withdrawal of pindolol or metoprolol and to compare these effects with our clinical observations.

Methods

In an open controlled study 12 healthy male and 6 healthy female volunteers (mean age 24 years, 19–33) having given informed consent, received either pindolol 10 mg three times daily or metoprolol 100 mg three times daily for 4 weeks. Each of the groups consisted of 12 subjects, since 6 of the volunteers received both test drugs.

Resting heart rate (RHR), resting blood pressure (RBP; Riva-Rocci) and the isoprenaline CD_{25} (dose of isoprenaline required to increase the heart rate by 25 beats/min) (Cleaveland *et al.*, 1972; Nattel *et al.*, 1979) were determined twice before drug administration, during the treatment, and then each second or third day for up to 2 weeks, after withdrawal starting at the first day after cessation of the test drugs. Before administration of the β-adrenoceptor blockers and at the time of suspected hypersensitivity, exercise tests on a bicycle ergometer were performed. The HR was monitored and documented by an ECG-coupled on line computer procedure.

A catheter was inserted into the antecubital vein of the right arm and saline was infused (0.5 ml/min) during 0.5 h of rest. The mean resting heart rate (MRHR) was calculated by the computer from the last 10 min and this value was taken as baseline for the isoprenaline tests performed subsequently.

CD_{25}-values were determined by injecting bolus intravenous doses of isoprenaline (Aludrin,

0306–5251/82/130 353–05 $01.00

Boehringer Ingelheim). The dose range used was 0.1–600 μg of isoprenaline. Each isoprenaline dose was administered twice. The dose was then doubled and increased until the increase in heart rate above baseline reached 30–35 beats/min. After each injection 5 to 10 min were required for the HR to return to baseline.

The ECG-coupled computer heart rate monitoring allowed the graphic on line plotting of each heart beat (Figure 1). Isoprenaline-induced peaks in heart rate were located on the graphs by a computerized plotter, the coordinates were transmitted to the computer and converted to absolute heart rate values.

The calculation of CD_{25} was based on a logarithmic regression line (Figure 1). When there was no obvious linear relationship, CD_{25} was calculated by extrapolation.

The exercise tests were performed on a Siemens ergometer bicycle. The work load was 2–3 watts/kg of body weight for 5 min. The conditions for both exercise tests were kept constant.

The exercise heart rate at the time of suspected hypersensitivity was compared with the exercise heart rate before treatment. For MRHR and RBP a comparison was done between the pretreatment values and the highest values reached after withdrawal. These changes were analysed for significance by the Wilcoxon matched pair signed rank test. Differences in the size of changes between the pindolol and the metoprolol group were investigated for significance by the Mann-Whitney-Wilcoxon-test. Isoprenaline CD_{25} was considered as hypersensitive when at least two-fold lower than the lowest individual pretreatment value and the results were analysed for significance in a 2 × 2 contingency table.

Results

Mean resting heart rate (MRHR)

The MRHR of 70 beats/min before treatment remained unchanged on pindolol, but decreased on metoprolol from 68 to 56 beats/min. After withdrawal the MRHR increased and was highest at the fifth day. The values for pindolol are 80 beats/min, for metoprolol 73 beats/min. When compared to pretreatment values this increase was significant for both groups ($P = 0.04$) (Figure 2). However, there was no

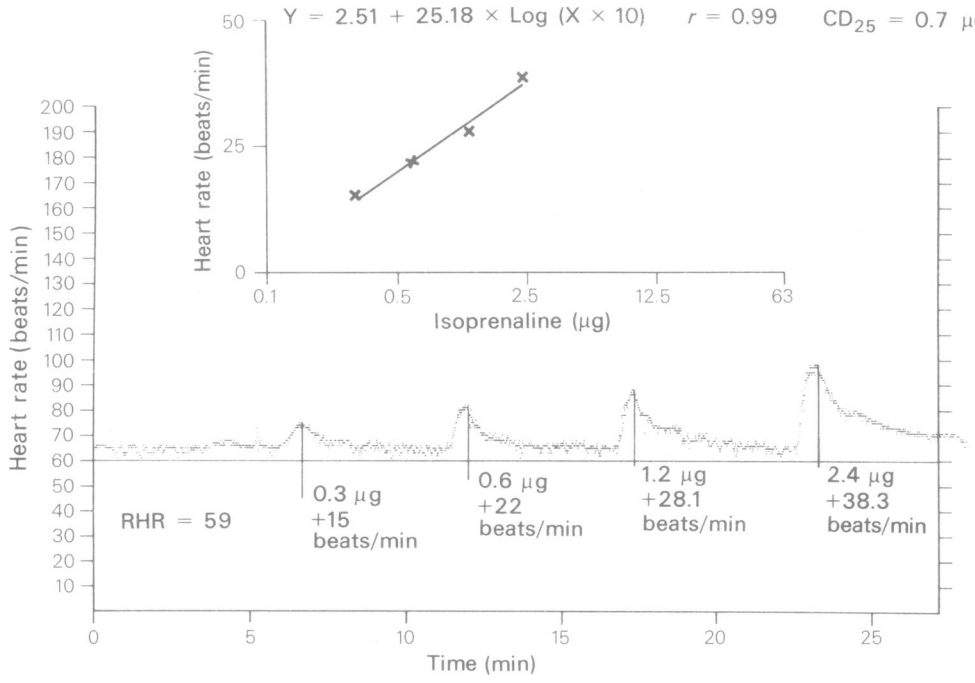

Figure 1 Documentation of the isoprenaline test and linear regression for determination of the isoprenaline CD_{25}. For each RR period heart rate was calculated by the computer and plotted 'on line' by a computerized plotter. Peaks induced by isoprenaline were located 'off line' with a computerized plotter and coordinates were transmitted to the computer. Determinations of heart rate increase, logarithmic regression and calculation of the CD_{25} were performed subsequently by the computer and documented graphically.

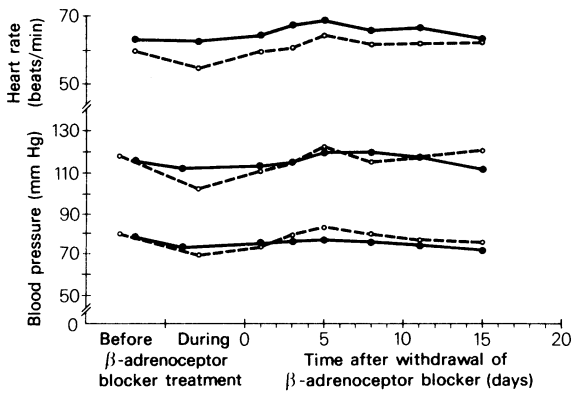

Figure 2 Resting heart rate and blood pressure changes after abrupt withdrawal of pindolol (●) or metoprolol (○). A slight reactive increase in resting heart rate and systolic blood pressure with maximum values at the fifth day after withdrawal occurred in both groups.

difference between the two β-adrenoceptor blocker groups. The MRHR normalized gradually and reached pretreatment values after some 14 days.

Resting blood pressure

The systolic blood pressure decreased on pindolol from 115 to 110 mmHg and on metoprolol from 117 to 105 mmHg. Withdrawal was followed in both groups by a gradual increase up to 120 mmHg in the pindolol and to 125 mmHg in the metoprolol group (Figure 2).

The diastolic blood pressure decreased on pindolol from 79 to 73 mmHg and on metoprolol from 80 to 72 mmHg. After withdrawal the diastolic BP normalized gradually. The mean values for metoprolol at day 5 were with 83 mmHg slightly higher than baseline values. In the pindolol group the diastolic BP was normal again at day 5 without any further increase. There was no statistically significant difference between the groups.

Table 1 Maximal heart rate after 5 min of bicycle exercise (2–3 watts/kg) before β-adrenoceptor blocker therapy and after withdrawal at the time of suspected hypersensitivity.

Subject	*Before pindolol*	*After withdrawal of pindolol at time of suspected hypersensitivity*
	(beats/min)	
BB	172	168
IB	175	175
ES	155	152
IO	165	167
RT	148	151
KH	142	148
JS	170	177
SG	159	156
TT	140	144
RK	171	168
SS	166	166
PD	158	162
Mean ± s.d.	160±11.9	161±10.8
	Before metoprolol	*After withdrawal of metoprolol at time of suspected hypersensitivity*
SS	162	169
SG	158	163
TT	142	168
WP	125	133
TE	156	156
SK	159	148
ES	158	156
TN	162	163
JB	151	154
JE	146	148
RK	128	136
RT	150	157
Mean±s.d.	150±12.5	154±11.4

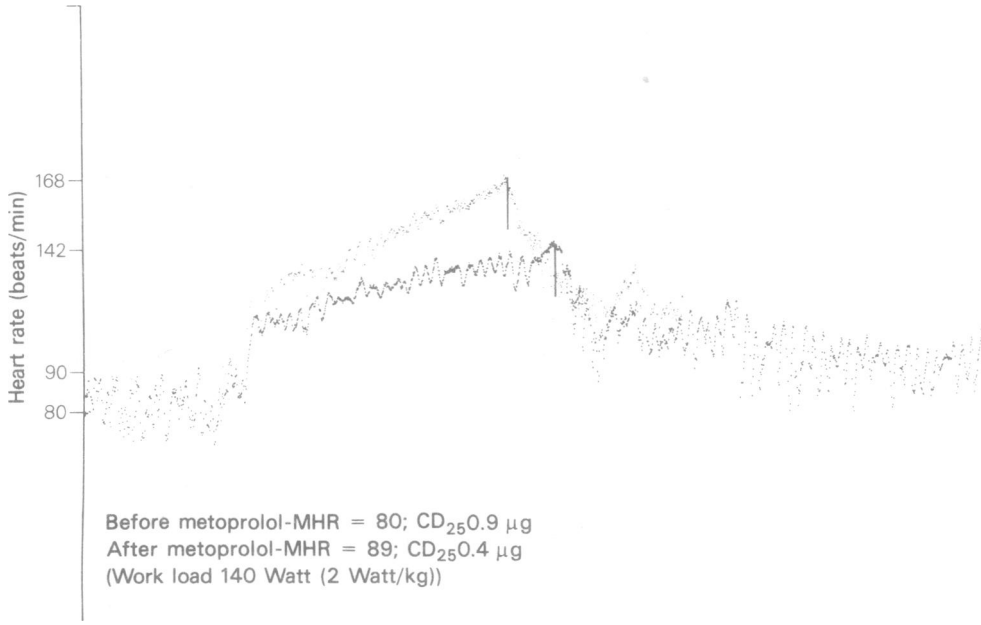

Figure 3 Exercise heart rate before metoprolol and 3 days after withdrawal (CD_{25} 0.4 μg) in one patient with a reactive heart rate increase of 26 beats/min; baseline CD_{25} was 0.9 μg.

Exercise heart rate

The heart rates at the end of 5 min of bicycle ergometer exercise are shown in Table 1. The mean values did not show any statistically significant increase during the time of withdrawal. However, we found one case in the metoprolol group with a significant increase in exercise heart rate from 142 to 168 beats/min, associated with a corresponding isoprenaline hypersensitivity (0.9 μg → 0.4 μg) (Figure 3).

β-adrenoceptor sensitivity by isoprenaline CD_{25}

The isoprenaline CD_{25} values before, during and after abrupt withdrawal of β-adrenoceptor treatment are shown in Figure 4. The CD_{25} baseline was 0.58 μg for the pindolol group and 0.67 μg for the metoprolol group. During β-adrenoceptor blockade the CD_{25} increased for pindolol to 390 μg (100–600) and to 10.7 μg (3.16–22) for metoprolol. These values were determined 2–6 h after the last dose of the β-adrenoceptor blocker. After withdrawal the CD_{25} quickly normalized and returned to baseline around day 7 in the metoprolol group. In the pindolol group CD_{25} decreased more slowly and at day 15 was still above baseline (1 μg).

After metoprolol withdrawal we found isoprenaline CD_{25} values below baseline in 8 out of 12 patients. Only 6 of these 8 cases were considered to be clearly hypersensitive with a minimum CD_{25} during withdrawal 2–3 fold lower than their baseline CD_{25}.

After pindolol we observed only one case with a CD_{25} value after withdrawal below baseline (0.3 μg, baseline 0.6 μg). This difference between the two groups was significant ($P = 0.1$, contingency table).

Discussion

We assume that the slight increases in resting heart rate and systolic blood pressure in both groups after withdrawal are not of clinical relevance. There were also no statistically significant differences between the pindolol and the metoprolol group.

The long-term β-adrenoceptor antagonistic effect seen after withdrawal of pindolol, which may be the basis of its long-lasting therapeutic effect in angina pectoris, is of special interest.

There was a clear difference in the behaviour of the two β-adrenoceptor blockers in terms of β-adrenoceptor sensitivity. After metoprolol in 6 out of 12 cases we found a hypersensitivity with CD_{25} values 2–3 fold lower than baseline. In one case there was also a corresponding reactive overshoot in HR during exercise. In the pindolol group one out of 12 cases showed a CD_{25} two-fold below baseline without a reactive increase in HR during exercise.

In conclusion the risk of developing β-

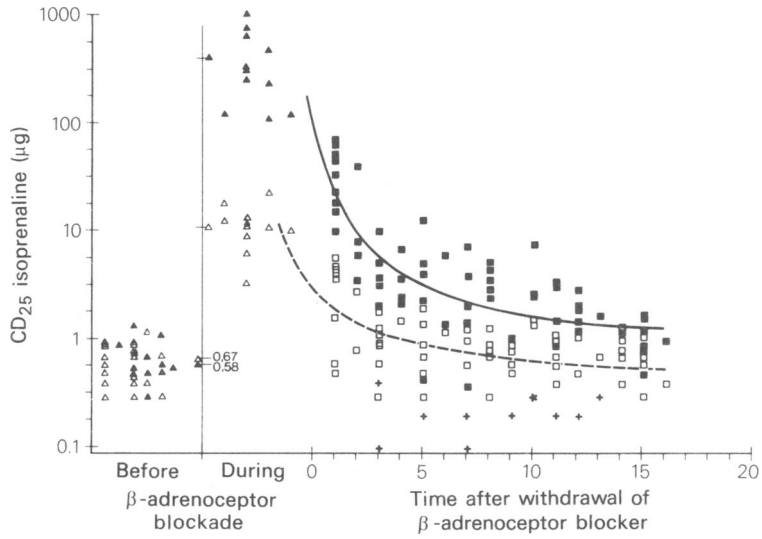

Figure 4 Isoprenaline CD_{25} before, during and after abrupt withdrawal of chronic β-adrenoceptor blockade (−, *, ▲, ■ pindolol ---, +, △, □ metoprolol). The mean CD_{25} of 0.58 μg increased on pindolol to 390 μg and for metoprolol from 0.67 to 10.7 μg. After abrupt withdrawal 6 out of 12 patients of the metoprolol group showed 2–3 fold lower CD_{25} (+) than the individual baseline values while after pindolol withdrawal we observed a 2 fold lower CD_{25} (*) in only one single case.

adrenoceptor hypersensitivity with its potential clinical implications is higher after metoprolol than after pindolol withdrawal. However neither drug should be withdrawn abruptly. These results confirm our earlier clinical observation of a persistant antianginal effect after withdrawal of pindolol (Lang *et al.*, 1979).

References

CLEAVELAND, C.R., RANGNO, R.E. & SHAND, D.G. (1972). A standardized isoproterenol sensitivity test. *Arch. Intern. Med.*, **130**, 47–52.

GILFRICH, H.J. & RAHN, K.H. (1981). Absetzphänomene bei Beendigung einer Therapie mit Beta-Rezeptorenblockern. *Med. Welt Bd.*, **32**, 1036–1037

KRISTENSEN, B.Ø. (1979). Beta-blocker withdrawal syndrome? *Lancet*, **i**, 554.

LANG, E., PITSCHA, P. & SCHIESS, W. (1979). Der Beta-Blocker Pindolol in der Therapie der Angina pectoris. *Wiener Med. Wschr.*, **129**, 484–488.

LEDERBALLE PEDERSEN, MIKKELSEN, E., LAHNG NIELSEN, J. & CHRISTENSEN, N.J. (1979). Abrupt withdrawal of beta-blocking agents in patients with arterial hypertension. Effect on blood pressure, heart rate and plasma catecholamines and prolactin. *Eur. J. clin. Pharmac.*, **15**, 215–217.

MALING, T.J.B. & DOLLERY, C.T. (1979). Changes in blood pressure, heart rate, and plasma noradrenaline concentration after sudden withdrawal of propranolol. *Br. med. J.*, **2**, 366–367.

MEINERTZ, TH., JUST, H., KASPER, W., KERSTING, F. & BREUING, K.-H. (1979). Beta-blocker withdrawal syndrome? *Lancet*, **i**, 270.

MILLER, R.R., OLSON, H.G., AMSTERDAM, E.H. & MASON, T. (1975). Propranolol withdrawal rebound phenomenon. *New Engl. J. Med.*, **293**, 416–418.

NATTEL, S., RANGNO, R.E. & VAN LOON, G. (1979). Mechanism of propranolol withdrawal phenomena. *Circulation*, **59**, 1158–1164.

ROSS, P.T., LEWIS, M.J. & HENDERSON, A.H. (1979). Beta-blocker withdrawal syndrome. *Lancet*, **i**, 875.

SCHOFER, J. & BLEIFELD, W. (1981). Erhöhtes Risiko nach abruptem Absetzen von Beta-Rezeptorenblocker? *Dtsch. med. Wschr.*, **106**, 563.

SHAND, D.G. (1975). Propranolol withdrawal. *New Engl. J. Med.*, **293**, 449–450.

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

SLOME, R. (1973). Withdrawal of propranolol and myocardial infarction. *Lancet*, **i**, 156.