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WITHDRAWAL OF LONG-TERM THERAPY WITH ATENOLOL IN HYPERTENSIVE PATIENTS

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1 The offset of effects on blood pressure and heart rate after cessation of long-term therapy (19 ± 3.6 months) with atenolol (200 mg once/daily) was studied in six hypertensive patients.

2 Withdrawal of atenolol resulted in a gradual return of lying, standing and post-exercise systolic and diastolic blood pressure levels and heart rate towards the baseline value. The offset of effect greatly exceeded the time for elimination of atenolol.

3 No significant differences in the pharmacokinetic profile of atenolol were evident between the values obtained following chronic dosing and an acute single-dose study.

4 The lack of clinical evidence of increased cardiac adrenergic sensitivity or rebound hypertension following withdrawal of atenolol contrasts with reports of a withdrawal syndrome following cessation of therapy with propranolol. Nevertheless until the mechanism of the propranolol-withdrawal syndrome is better understood caution is required when stopping therapy with atenolol in patients with severe coronary artery disease.

Introduction

Recently attention has been drawn to a possible state of β-adrenergic receptor supersensitivity following abrupt cessation of treatment with propranolol (Nattel, Rangno & Van Loon, 1979). The clinical importance of this observation may be considerable and requires evaluation for both nonselective and selective β-adrenoceptor blockers.

We have studied the offset of effects on lying, standing and post-exercise blood pressure and heart rate following abrupt withdrawal of long-term therapy with atenolol, a cardioselective β-adrenoceptor antagonist without partial agonist activity.

Methods

Six patients (4 male) with established hypertension took part in the study. Their average age was 48 years (range 31–61). Our procedure for selection of patients with mild hypertension has been described previously and involves both inpatient and outpatient assessment (Petrie *et al.*, 1975; Jeffers *et al.*, 1978). After 1 month outpatient run-in period on placebo the mean pre-treatment lying blood pressure (Hawksley random-zero sphygmomanometers; diastolic blood pressure – phase 4) was 169/107 mmHg.

At the time of the study all patients were taking atenolol 200 mg, once daily (mean duration of treatment 19 ± 3.6 months). None of the patients suffered from airways obstruction, overt ischaemic heart disease, hepatic dysfunction or significant renal impairment. The study was approved by the local Area Ethical Committee and all patients gave informed written consent to participate in this study.

Patients attended the ward at 08.00 h on the morning of day 1, 24 h after their last dose of atenolol, having fasted for 10 h. Before and at intervals after a further 200 mg dose of atenolol taken with 100 ml water, lying, standing and post-exercise blood pressures and heart rates and whole blood atenolol concentrations were measured. The heart rate was measured by electrocardiography. Blood pressures were measured in the right arm using a Hawksley random-zero sphygmomanometer. On each occasion the mean of two readings was recorded after the patient had been lying for 5 min, after standing for 2 min and a single measurement was recorded immediately following completion of a standardized two-step exercise test. Blood samples were drawn from an indwelling cannula into lithium heparin tubes. Four hourly urine samples were also collected over a 24 h period. Samples were stored at 4°C and analysed within 1 month of sampling. Whole blood atenolol concentrations were measured by gas liquid chromatography with electron capture detection (Scales & Copsey,

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1975). Creatinine clearances were also measured.

An acute dosing pharmacokinetic study (200 mg atenolol in 100 ml water) was also carried out 4 weeks after cessation of the long-term atenolol therapy.

The Wilcoxon test for pair differences was used to assess the effects on blood pressure and heart rate. The baseline value was taken as the mean value seven days after the last dose of atenolol.

The area under the curve from 0 to 24 h ($AUC_{0\to24\,h}$) was calculated using the trapezoidal rule. Peak blood concentrations, $AUC_{0\to24\,h}$ and elimination half-life ($T_{\frac{1}{2}}$) were compared in the chronic and acute dosing regimens, using a paired *t*-test.

Results

Blood pressure and heart rates

The mean lying, standing and post-exercise systolic and diastolic blood pressures and heart rates at intervals after the withdrawal of long-term atenolol are shown in Table 1 for the six patients studied. The mean supine blood pressure at 7 days (168/104 mmHg) was similar to the mean supine pretreatment pressure (169/107 mmHg).

Systolic blood pressure The lying blood pressures were controlled (> 10% reduction) for 48 h after cessation of therapy. The standing and post-exercise measurements showed more variability, but significant reduction in systolic blood pressure was seen 48 h post-dosing (14% reduction standing; 12% reduction post-exercise).

Diastolic blood pressure Reduction in blood pressure was maintained for 72 h, this result being most significant for the post-exercise diastolic blood pressures.

Heart rates Heart rates returned to baseline values in linear fashion over 72 h, the rate of recovery being approximately 10% per 24 h. The mean percentage reductions 48 h post-dosing were 9.5 (lying), 16.5 (standing) and 20.0 (post-exercise) respectively. The comparable values 60 h post-dosing were 9.5, 13.5 and 10.0 respectively. Evidence of possible adrenergic supersensitivity was also sought by examination of the results from individual patients. In only one patient on one occasion (72 h value) did the post-exercise heart rate exceed the 7-day rate (150:138 beats/min).

The offset of effects on post-exercise blood pressure and heart rate are summarized in Figure 1.

Table 1 Blood pressure and heart rate (mean ± s.e.mean, $n = 6$) after cessation of long-term atenolol therapy (200 mg/day).

	Time (h) 0	12	24	36	48	60	72	168
Systolic blood pressure (mm Hg)								
lying	144** ± 8	142** ± 11	134** ± 10	153** ± 12	151* ± 13	164 ± 12	149** ± 12	168 ± 9
standing	130** ± 8	153 ± 12	133** ± 10	149* ± 10	146** ± 13	161 ± 12	155 ± 14	164 ± 14
post-exercise	162** ± 11	166* ± 14	156** ± 12	180 ± 11	168** ± 15	193 ± 11	179 ± 17	190 ± 11
Diastolic blood pressure (mm Hg)								
lying	91* ± 5	88** ± 3	79** ± 6	90* ± 4	88** ± 5	98* ± 3	90* ± 5	104 ± 3
standing	92** ± 5	98* ± 5	93* ± 5	102* ± 7	96** ± 4	105 ± 4	101* ± 3	108 ± 4
post-exercise	100* ± 4	96* ± 6	92** ± 6	104 ± 10	96** ± 3	100** ± 6	100** ± 6	112 ± 6
Heart rate (beats/min)								
lying	61** ± 3	58** ± 1	64** ± 1	73 ± 2	76* ± 3	76 ± 4	86 ± 2	84 ± 4
standing	64** ± 2	61** ± 3	70** ± 4	77* ± 3	80* ± 4	83** ± 4	89 ± 3	96 ± 1
post-exercise	86** ± 6	92** ± 5	98** ± 4	109** ± 7	114** ± 3	127* ± 5	133 ± 6	142 ± 7

*$P<0.1$, **$P<0.05$ by Wilcoxon test for pair differences. The base line value is the mean at 168 h.

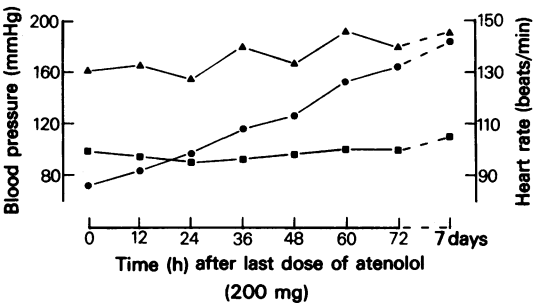

Figure 1 Recovery of post-exercise heart rate (●) and blood pressure (▲ systolic, ■ diastolic) after withdrawal of chronic atenolol therapy (19±3.6 months; dose 200 mg orally.

Pharmacokinetics

There were no significant differences in peak blood concentrations, $AUC_{0\to 24\,h}$, elimination half-life ($T_{\frac{1}{2}}\beta$) or creatinine clearance between the values obtained following chronic dosing, and in the acute single-dose study (Figure 2 and Table 2). Renal clearance of atenolol was always in excess of creatinine clearance, the mean atenolol/creatinine clearance ratio being 1.52±0.15.

Table 2 Pharmacokinetic profile of atenolol (mean±s.e.mean, $n=6$) after chronic (19±3.6 months) or acute oral dosing (200 mg).

	Chronic dosing	*Acute dosing*
Peak blood concentration (μg/ml)	1.84±0.35	2.27±0.36
$AUC_{0\to 24\,h}$ (μg ml^{-1} h)	17.8±3.1	17.4±3.1
$T_{\frac{1}{2}}\beta$ (h)	9.7±0.8	9.3±0.8

Discussion

This study shows that abrupt discontinuation of long-term therapy with atenolol in hypertensive patients was followed by a gradual return of blood pressure levels and heart rate towards pretreatment values over the seven day study period. The time of offset of effect of atenolol greatly exceeded the time for drug elimination. No other study following cessation of long-term therapy with atenolol has been reported.

A propranolol-withdrawal syndrome has been reported in some patients with severe coronary artery disease (Miller *et al.*, 1975). Recently transient supersensitivity to the chronotropic effects of incremental bolus doses of isoprenaline has been shown at a median time after propranolol withdrawal of four days (Nattel *et al.*, 1979). The lack of evidence of

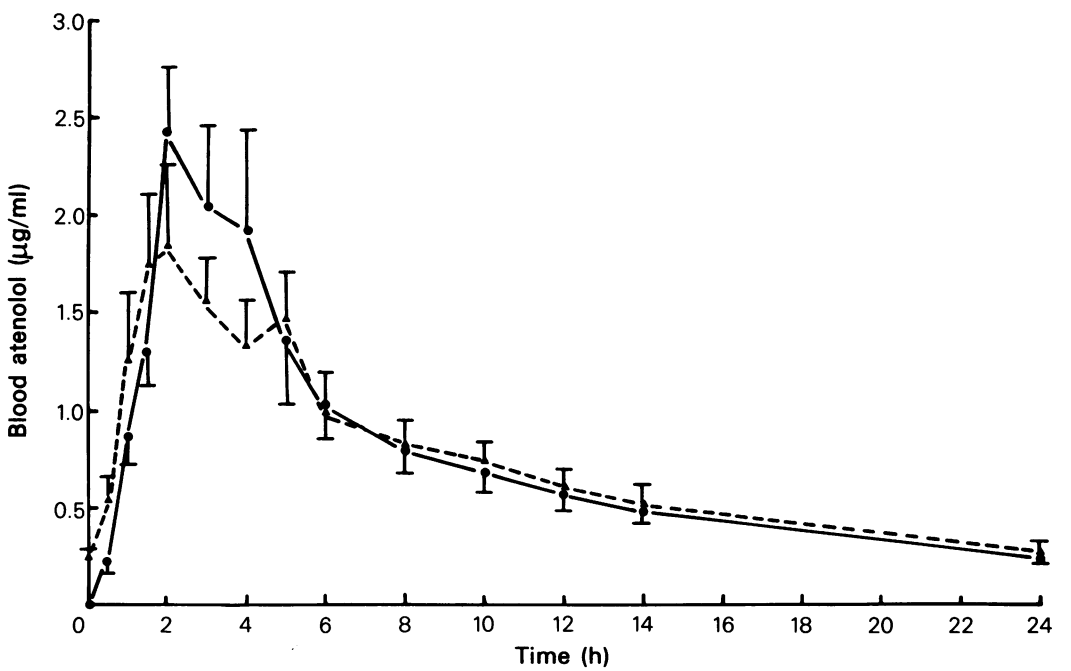

Figure 2 The whole blood concentration time curves of atenolol following chronic (▲) and acute (●) dosing (mean±s.e.mean, $n=6$). Dose 200 mg p.o.

increased cardiac adrenergic sensitivity or rebound hypertension in our study in the interval 24–72 h post-dosing or at 7 days post-dosing is reassuring although the degree of exercise chosen was not maximal, having been designed to achieve an untreated post-exercise heart rate of only 140 beats/min. Such an exercise test was considered appropriate for our middle-aged group of patients and we were reluctant to exceed it because of the uncertainty of the likely effects of withdrawal of therapy with atenolol, and because severe exercise is not a prerequisite for the propranolol-withdrawal syndrome. Heart rate increases of up to 140 beats/min partly reflect withdrawal of vagal tone. This level of exercise is also associated with significant cardiac beta adrenergic stimulation and catecholamines are liberated into coronary sinus blood (Hansen, Christensen & Hesse, 1978; Cousineau *et al.*, 1977). Although increased cardiac β-receptor sensitivity may be most easily demonstrated by isoprenaline dose-response studies if such a phenomenon were clinically relevant in our patients on long-term therapy then it should also be reflected in an exaggerated cardiac response to endogenous sympathetic stimulation. Further studies between 72 and 164 h post-dosing are now necessary following the report by Nattel *et al.* (1979).

Our study also shows that the pharmacokinetic profile of atenolol is not changed after chronic therapy. If cardiac β-adrenergic receptor supersensitivity is a feature of long-term β-adrenoceptor blockade, changes in β-receptor number or affinity are more likely to be implicated than altered drug disposition. Until the mechanism of the propranolol-withdrawal syndrome is better understood caution is required when stopping therapy with atenolol in patients with severe coronary artery disease.

References

COUSINEAU, D., FERGUSON, R.J., de CHAMPLAIN, J., GAUTHIER, P., COTÉ, P. & BOURASSA, M. (1977). Catecholamines in coronary sinus during exercise in man before and after training. *J. appl. Physiol.*, **43**, 801–806.

HANSEN, J.F., CHRISTENSEN, N.F. & HESSE, B. (1978). Determinants of coronary sinus noradrenaline in patients with ischaemic heart disease: Coronary sinus catecholamine concentration in relation to arterial catecholamine concentration, pulmonary artery oxygen saturation and left ventricular end-diastolic pressure. *Cardiovascular Res.*, **12**, 415–421.

JEFFERS, T.A., WEBSTER, J., REID, B., PETRIE, J.C. & BARKER, N.P. (1978). Atenolol and metoprolol in mild hypertension. *Br. med. J.*, **2**, 1269–1270.

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

NATTEL, S., RANGNO, R.E. & VAN LOON, G. (1979). Mechanism of propranolol withdrawal phenomena. *Circulation*, **59**, 1159–1164.

PETRIE, J.C., GALLOWAY, D.B., WEBSTER, J., SIMPSON, W.T. & LEWIS, J.A. (1975). Atenolol and bendrofluazide in hypertension. *Br. med. J.*, **4**, 133–135.

SCALES, B., & COPSEY, P.B. (1975). The gas chromatographic determination of atenolol in biological samples. *J. Pharm. Pharmac.*, **27**, 430–433.

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