The effects of metoprolol on ambulatory blood pressure


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Summary

1. Continuous monitoring of arterial pressure was performed via an indwelling cannula over 24 h in 12 hypertensive patients before treatment and again 2–4 months after starting metoprolol (100 mg twice daily).
2. During treatment, heart rate and systolic and diastolic pressures were significantly reduced.
3. The circadian patterns of heart rate and blood pressure changes were similar before and during therapy.

Key words: arterial pressure, circadian rhythm, metoprolol.

Introduction

Although β-adrenoceptor-blocking agents are commonly used in the management of hypertension, the mechanism of their antihypertensive action is still unclear (Prichard, 1978). They reduce cardiac output and tend, at least initially, to raise peripheral resistance, the latter effect being slightly less marked with cardioselective agents (Lund-Johansen & Ohm, 1977). The antihypertensive action is generally of slow onset, over several days or weeks, unlike the cardiac slowing, which appears immediately. Similarly the loss of antihypertensive activity after cessation of treatment appears to be slow and there is considerable debate about the need for multiple daily doses of the drugs. Little is known, however, about the effects on nocturnal blood pressure.

Ambulatory monitoring of intra-arterial pressure has been used in various departments over the past 15 years to study blood pressure of subjects during normal activities in their own environment (Bevan, Honour & Stott, 1969). It also fulfils a useful role in the assessment of action of vasoactive drugs both in acute use and, by later restudy, during chronic treatment (Mann, Millar Craig, Balasubramanian, Melville & Raftery, 1979). Among the studies we have performed is one using the cardioselective β-adrenoceptor-blocking agent, metoprolol, reported here. In addition to observing blood pressure and heart rate throughout the 24 h cycle we have taken advantage of the presence of an indwelling arterial cannula to record accurately changes in pressure during isometric and dynamic exercise.

Methods

Twelve patients with mild or moderate untreated essential hypertension were recruited from the outpatient clinic. Their mean age was 54 years (range 38–62 years) and mean pretreatment clinic blood pressure was 165/105 mmHg (range 140/100–185/115 mmHg). Informed consent was obtained, the study having approval from the hospital ethical committee.

Monitoring of the ECG and intra-arterial pressure was carried out with standard methods (Millar Craig, Bishop & Raftery, 1978a). Patients were cannulated between 09.00 and 10.00 hours and an exercise protocol was carried out. Afterwards they returned to normal daily activities, visiting the hospital briefly for an equipment check during the evening. In six patients the cannula was removed after 24 h of normal activity but the other six continued for a further 24 h, having started therapy with metoprolol (100 mg twice daily).

During the exercise period six patients underwent a bicycle ergometer test at increasing workloads of 250, 400, 700 and 1000 kpm/min. The other six performed an isometric exercise test (50%
maximal handgrip sustained for 2 min) and a graded treadmill exercise test (4% increases in gradient every 3 min at a constant speed of 3 m.p.h.). Bicycle and treadmill tests were limited by the patient's exercise tolerance.

After the first study, patients were followed in the outpatient clinic while the standard dosage regimen was maintained. Restudies were performed between 2 and 4 months later along the lines of the pretreatment studies, including appropriate exercise tests but only 24 h of free ambulatory monitoring.

Recordings for 24 h were analysed with a hybrid computer system (Cashman, Millar Craig & Stott, 1979) to obtain hourly mean values of heart rate and systolic and diastolic pressure. Results were pooled for all patients undergoing similar phases of the study and circadian curves plotted to compare pre- and post-treatment values. Data were also replotted with the time of awakening used as a reference point to examine trends in heart rate and blood pressure at this time.

Records taken from the periods of standardized exercise were replayed at higher speed with an ultraviolet-light chart recorder and measurements made directly from this. Results were pooled as before. Statistical comparison of pre- and post-treatment data was made by the paired Student's t-test.

**Results**

All 12 patients completed the trial, none developing significant side-effects and all agreeing to a re-study. Mean interstudy interval was 11 weeks (range 7–17 weeks) and clinic pressures before restudy indicated reasonable control for most of the group (mean 138/86 mmHg, range 125/82–167/104 mmHg).

**Circadian curves (Fig. 1)**

Reduction in heart rate and blood pressure was smooth and continuous throughout the day. The reduction reached statistical significance ($P < 0.05$) for nearly all hourly mean values. There was good reduction throughout the night and normalization to the time of waking showed smooth parallel reduction at this time even though the slopes of the curves were similar. The general pattern of each curve reflected trends described previously in other studies (Millar-Craig et al., 1978b).

**Exercise tests**

Mean peak pressures achieved during the isometric test were 204/116 mmHg pretreatment and 181/97 mmHg on the restudy. This reduction did not achieve statistical significance ($P > 0.05$).

Reduction of heart rate and blood pressure at all grades of bicycle and treadmill exercise was statistically significant ($P < 0.05$) except at the highest grades of each, where only two patients completed tests on both occasions.

**Discussion**

Considerable debate has recently taken place over the trends in blood pressure in the early morning and the possible association with a peak incidence of pathological cardiovascular events occurring at this time of day (Millar Craig et al., 1978a; Littler & Watson, 1978). Concern has been voiced that in ambulatory trials of other β-adrenoreceptor-blocking agents, notably atenolol (Millar Craig, Kenny, Mann, Balasubramanian & Raftery, 1979) and oxprenolol (Millar Craig et al., 1978b), little reduction of pressure has been shown at this time. A further similar trial of atenolol (Floras, Fox, Hassan, Jones, Sleight & Turner, 1979) has by contrast shown good reduction of pressure during the night and early morning.
With twice-daily metoprolol we found a smooth reduction in blood pressure throughout the 24 h period. With no intra-patient crossover it is difficult to make firm inferences when comparing results of similar trials as differences in results may have been due to patient factors rather than the properties of the drug studied; the invasive nature of this study limits this possibility severely. One possibly important difference between the group of patients studied here and those in our atenolol study (Millar Craig et al., 1979) was the pretreatment blood pressure, which was higher in the latter (179/113 mmHg). Similar trials of β-adrenoceptor blockers performed in other centres, where smooth 24 h reduction of pressure was shown, have also included patients with more moderate hypertension (Floras et al., 1979; Watson, Stallard & Littler, 1979). Criteria for pressure control before restudy have also varied, but although this study was of a fixed dose of metoprolol with no such qualifying criteria, good 24 h control was patently achieved. Clearly further work is required to aid interpretation.

The pattern of reduction of blood pressure and heart rate by metoprolol during exercise concurs with the work of others in this field (Claussen, Damsgaard & Mellemgaard, 1979; Nyberg, 1976). β-Adrenoreceptor-blocking agents appear to be more effective in reduction of exercise pressures than centrally acting agents, but pressure rises during isometric exercise are little affected (Taylor, Watt & Goldstraw, 1978). The persistence of these peak blood pressures even after 'adequate' control suggests that additional advice to patients to limit this activity may be valuable.

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References