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PROPRANOLOL LA AND AMBULATORY BLOOD PRESSURE

STEWART MANN, M.W. MILLAR CRAIG, V. BALASUBRAMANIAN & E.B. RAFTERY

Department of Cardiology,
Northwick Park Hospital & Clinical Research Centre,
Watford Road, Harrow, Middlesex

1 The technique of continuous recording of intra-arterial blood pressure in ambulant hypertensives has been used to investigate the effects of a long-acting formulation of propranolol (propranolol LA).

2 Seven subjects with untreated essential hypertension were studied before and 2 months after commencing treatment with propranolol LA once daily in the morning, results showing that smooth control of blood pressure and heart rate occurred throughout 24 h.

3 Bicycle ergometry tests performed by these subjects during both studies showed significant blood pressure reduction by propranolol LA during the mild and moderate grades of dynamic exercise.

4 In a parallel study where six treated hypertensives were monitored before and after substitution of standard propranolol by the 'LA' form, close correspondence of blood pressure throughout the 24 h occurred with each regimen.

Introduction

Propranolol LA (long-acting) is a new preparation of propranolol ('Inderal', ICI) with slow-release characteristics which has been shown to provide therapeutically appropriate blood levels throughout 24 h following a single dose (McAinsh, Baber, Smith & Young 1978; Leahey, Neill, Varman & Shanks, 1980). In common with other β-adrenoceptor blocking agents that have slow-release characteristics, it has been developed in response to the finding that patient compliance in tablet taking is much improved by the restriction of the number of daily doses—preferably to once daily (Gatley, 1968; Marshall & Barritt, 1977). Using the 'Oxford' technique of ambulatory monitoring we have recorded the intra-arterial blood pressure and heart rate over the full day and night in hypertensive subjects following their normal daily routine. In many cases we have repeated the studies some two to three months after therapy with anti-hypertensive medication had been started. Several such studies have been made with β-adrenoceptor blocking agents and the degree of control of blood pressure during the night and early morning has been variable (Millar Craig, Kenny, Mann, Balasubramanian & Raftery, 1979; Millar Craig, Mann, Balasubramanian & Raftery, 1978; Mann, Millar Craig, Altman, Melville & Raftery, 1979). We report here a study performed in this manner using propranolol LA and also a parallel study examining the circadian trends in heart rate and blood pressure in hypertensives controlled with either the standard or LA formulations of propranolol.

Methods

Patients

All patients studied were recruited from the hospital hypertension clinic; the nature of the study was fully explained and informed consent obtained. The project had the approval of the Hospital Ethical Committee (EC 421). These subjects were freely ambulant outpatients; all worked normally during the day and slept at home at night.

Group 1 Twelve patients initially entered the first study, none had received anti-hypertensive medication prior to their first recording. All had clinic blood pressure levels greater than 145/100 mm Hg on at least two occasions. Four subjects were not re-studied due to technical problems (two patients) or side effects (two patients). A further subject was discarded from the analysis as his two studies had not been under comparable conditions. All remaining seven subjects were male and had a mean age of 45.4 years (range 35–57 years) old and mean blood pressure at entry of 150/111 mm Hg.

Group 2 Of eight subjects initially entering the comparability study, two were not re-studied due to technical problems producing unsatisfactory initial recordings. Of the remaining six all were male and the mean age was 54.2 years (range 36–68 years). Previous awareness of hypertension had been for a mean of 2.6 years (range 6 months to 7 years), and pre-treatment

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clinic blood pressure levels were all greater than 155/110 mm Hg (mean 181/117 mm Hg). All were well controlled at the time of recruitment, mean blood pressure being 143/88 mm Hg.

Drug administration

Group 1 After initial monitoring all were treated with propranolol LA 160 mg (one capsule) once daily except for three of the seven patients whose blood pressure had not fallen below 150/100 mm Hg after the first 4 weeks of therapy where dosage was increased to 320 mg (two capsules) daily.

Group 2 Five subjects were taking propranolol at the time of recruitment. The dosages were 160 mg twice daily in two, 80 mg (twice daily in one and 40 mg three times daily in two subjects. In view of propranolol LA capsule size (160 mg) the last two actually slightly increased their total daily propranolol dose from 120 mg to 160 mg when transferred to the new regimen, all others maintained exact equivalence. Four patients were taking thiazide diuretics in addition and one was also taking hydrallazine 25 mg three times daily. All additional drugs were maintained in their original dosage regimen throughout the study. The sixth subject was recruited while taking propranolol LA 320 mg daily and re-studied on propranolol 160 mg twice daily.

Tablets and capsules were supplied by Clinical Trials Dispensary, ICI Pharmaceuticals Division.

Procedures and observations

Monitoring was performed using the 'Oxford' system; a transducer/perfusion unit being attached to an indwelling catheter placed percutaneously in the left brachial artery and signals recorded on a miniature cassette recorder. The method and equipment have been fully described elsewhere (Bevan, Honour & Stott, 1966; Millar Craig, Hawes & Whittington, 1978), and allowed subjects to be fully ambulant indulging in normal daily activities and sleeping at home. The subjects studied in Group 1 performed a short exercise protocol including bicycle ergometry—progressively increasing each 4 min to higher work levels (250, 400, 700 and 1,000 kpm/min). This was carried out shortly after cannulation in both first and second studies. All recordings were continued for at least 24 h.

Recordings were processed by a hybrid computer system (Cashman, Millar Craig & Stott, 1979) to yield hourly mean values of heart rate, systolic and diastolic pressure according to clock time for each subject and these means pooled according to the stage of the study. Circadian curves were later constructed joining the pooled values to demonstrate the trends over the 24 h day.

Clinic blood pressure was recorded in all cases using a standard sphygmomanometer operated by a trained nurse who had no knowledge of the trial status of the patient. Systolic and diastolic (phase V—disappearance of sounds) pressures were recorded after 5 min supine rest and 2 min standing. Levels quoted represent the mean of the two readings.

In Group 1 re-studies were performed between 5 and 11 weeks after the first recording (mean 8 weeks). Mean pre-restudy clinic blood pressure was 146/91 mm Hg.

In Group 2 transfer to the alternative propranolol regime was made immediately after the first study and re-studies were performed at a mean of 9 weeks later (range 6–17 weeks).

Results

Group 1

Curves constructed from the recordings of the seven patients studied before and after treatment with propranolol LA are shown in Figure 1. Vertical lines indicate the degrees of statistical significance of the difference in the change in hourly mean points using a

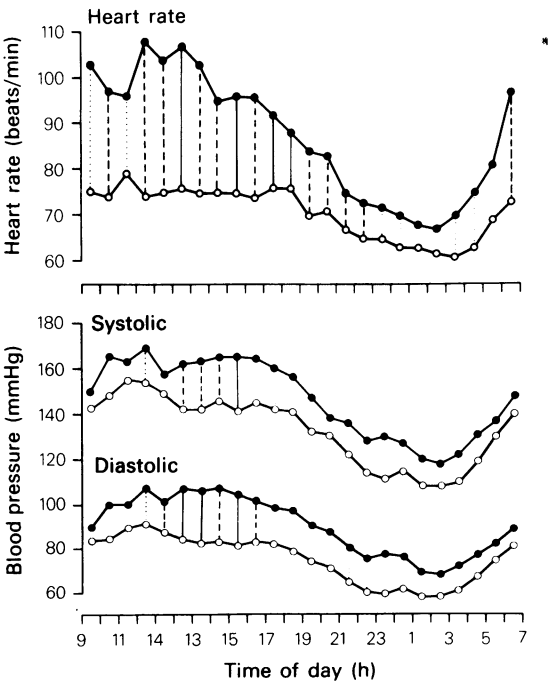

Figure 1 Circadian curves of heart rate, systolic and diastolic pressure before treatment (●) and while taking propranolol LA once daily each morning (○) in seven subjects. Lines join pooled hourly mean values. Vertical lines indicate the degree of statistical significance of the difference.

●·····○ $P<0.05$, ●- - -○ $P<0.01$, ●——○ $P<0.001$.

paired Student's *t*-test. Heart rate was reduced significantly throughout the 24 h; blood pressure reduction was also smooth throughout but with fewer significantly different points, most occurring during the daytime.

The bicycle ergometry test results are shown for six of the seven patients (one record was technically unsatisfactory) in Table 1. Pooled values of heart rate and blood pressure for the last minute of each grade of exercise are shown, statistical significance of treatment effects being assessed again by the paired Student's *t*-test. Significant reduction of heart rate and blood pressure was seen at the lower grades of exercise (250, 400 and 700 kpm/min). Although five patients managed to continue throughout the highest grade (1000 kpm/min), significant reduction of systolic pressure was not achieved. Pooled results are given in Table 1.

Group 2

The curves constructed from the recordings of the six patients studied during propranolol LA and during propranolol therapy are shown in Figure 2. The points were not significantly different throughout most of the 24 h but slightly better control was seen during the propranolol LA phase, especially for heart rate.

Drug tolerance

No serious side effects were noted. Two patients complained of symptoms of gastritis whilst on propranolol LA and in one instance (a newly treated patient) this was sufficiently severe to cause cessation of therapy. One of the newly treated patients also developed a cough and wheeze associated with a viral infection, and propranolol LA was stopped and this patient removed from the study.

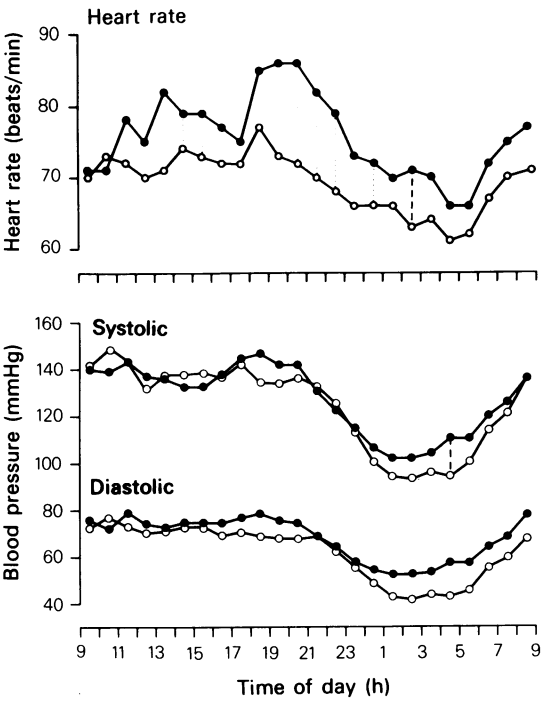

Figure 2 Circadian curves of heart rate, systolic and diastolic pressure derived from six hypertensive patients taking standard propranolol twice or thrice daily (●) or the equivalent dose of propranolol LA once daily each morning (○).
●····○ $P<0.05$, ●– – –○ $P<0.01$.

Discussion

Anti-hypertensive effects and other aspects of β-adrenoceptor blockade are usually assessed with non-invasive methods involving an artificial situation such as a hospital visit which may include exercise tests (Reybrouck, Amery, Fagard, Jousten & Lijnen, 1978). By using ambulatory monitoring techniques we have been able to record blood pressure and heart rate during normal daily activities, most subjects being able to attend their work normally and sleep at home. The invasive method of monitoring is known to be accurate and reliable (Millar Craig, Hawes *et al.*, 1978), features not yet established with non-

Table 1 Blood pressure levels (mm Hg) and heart rate (beats/min) at various grades of bicycle exercise before (Pre) and during (Post) therapy with propranolol LA in subjects in Group 1. Figures shown are mean levels ± s.d. for those completing each grade.

Grade	*Systolic*		*Diastolic*		*Heart rate*		
(kp/min)	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	n
Pre-Ex	176±25	154±34*	177±22	88±22**	104±11	80±8**	6
250	194±22	166±24**	120±23	96±19**	120±12	98±8**	6
400	205±25	175±28**	123±23	99±20***	134±16	107±10**	6
700	225±26	194±35*	133±24	106±20**	163±13	129±26*	6
1000	239±22	205±34	133±19	113±18*	178±11	151±22*	5

* $P<0.05$, ** $P<0.001$, *** $P<0.001$.

invasive equipment. Unfortunately the technique has posed certain limitations on the design of trials such that limited number of studies (usually two) can be performed on each subject and ethical considerations have precluded placebo and long-term reproducibility studies. However, the short term reproducibility of the above techniques of recording and analysis has been established (Mann, Millar Craig, Melville, Cashman, Altman and Raftery, 1980).

The circadian trends of heart rate and blood pressure in the untreated groups in this study are similar to those obtained in other studies of hypertensive patients (Millar Craig, Bishop & Raftery, 1978) and indeed the changes produced by propranolol LA are similar to those seen when patients have been treated with other β-adrenoceptor blocking agents. Using the same methods to study 200 patients before and after thrice daily oxprenolol therapy, Millar Craig, Mann *et al.* (1978) reported substantial daytime blood pressure reduction but little effect at night and especially when blood pressure was rising in the early morning. Six patients taking once daily atenolol showed the same reduction pattern (Millar Craig *et al.*, 1979) and it did not appear that altering the dosage time from morning to evening made any substantial difference. A similar result has been reported by different authors (Mehta, Walsh & Goldberg, 1980) who studied patients before and after therapy with once daily acebutalol.

Other similar studies have however shown smooth and significant control throughout the 24 h; these include a study of 12 patients who took twice daily metoprolol (Mann *et al.*, 1979) and one where a similar number of hypertensives took atenolol once daily (Floras, Fox, Hassan, Jones, Sleight & Turner, 1979). Watson, Stallard & Littler (1979) reported similarly smooth 24 h control when analysing the pooled results of 17 patients taking either propranolol, metoprolol or acebutalol once daily. Control shown by propranolol LA in this study certainly appeared satisfactory throughout the 24 h period.

The exercise tests were timed at between 3 and 4 h after the last dose of propranolol LA and not designed to test the efficacy of the drug beyond 24 h. They were however comparable in protocol to those we have performed to assess other β-adrenoceptor blockers and indeed produced comparable results. Significant reduction of blood pressure levels achieved during the lower work grades of bicycle ergometry but not at the highest grade has been found with metoprolol (Mann *et al.*, 1979), oxprenolol and atenolol (Millar Craig, 1979). This may be because fewer subjects are able to sustain this work load or because a degree of isometric exercise is involved in pedalling at 1000 kpm/min. Evidence from previous studies has shown that most antihypertensive drugs are less effective during this type of activity (Taylor, Watt & Goldstraw, 1979).

The cross-over study showed that substituting propranolol LA for the standard formulation of propranolol produced equivalent, if not improved control of both heart rate and blood pressure. As compliance was not specifically checked here, an improvement in this may be partially responsible. The two patients who had a slight increase in total daily dosage of propranolol when changed to the LA formulation did not show greater blood pressure reduction on the later study. A bias due to study order could be an explanation for the better performance of propranolol LA; however the one patient who started on this form had slightly higher pressures when taking the standard formulation of propranolol during this re-study.

With evidence that once-daily administration of conventional beta blockers produces effective blood pressure control over 24 h the need for 'long-acting' and 'slow-release' preparations may be questioned. However, although blood pressure control is the factor of greatest prognostic importance (Veterans Administration Co-operative Studies, 1967 and 1970), this may not be the only mechanism of the benefit that β-adrenoceptor blockers specifically provide in hypertension. Leahey *et al.* (1980) found that control of heart rate, especially during exercise, seemed to be more closely related to plasma levels of the drug and the necessary pharmacodynamics behind the rather ill-defined 'cardio-protective' effect are unknown. A further advantage, not seen in this study, is the theoretical possibility that avoidance of high peaks of drug levels in the plasma may avoid some side effects.

In conclusion we have shown that 24 h control of blood pressure with propranolol LA in formerly untreated hypertensives is similar to that shown by multiple daily dosage regimens of conventional β-adrenoceptor blockers. Blood pressure reduction during dynamic exercise is also similar. In the cross-over study we have demonstrated equivalent control of blood pressure and heart rate when twice or thrice daily dosage with conventional propranolol was replaced by once daily propranolol LA.

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