Effect of a long acting beta-adrenoceptor blocker on diurnal variation of cardiac dysrhythmias

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Summary: To investigate circadian variation of cardiac arrhythmias ambulatory electrocardiogram monitoring was carried out before and after one week's treatment with a long acting beta-adrenoceptor blocker, nadolol, in 26 patients who presented with symptoms attributable to arrhythmias. Analysis of the 24 hour profile of premature ventricular contractions showed a significantly ($P < 0.05$) higher frequency during midday to midnight than between midnight and midday. The frequency of supraventricular tachycardia was significantly ($P < 0.05$) higher during the periods from 12.00 hours to 16.00 hours (11.0 ± 12) and 16.00 hours to 20.00 hours (11.3 ± 11) than during the periods of 00.00 hours to 04.00 hours (3.6 ± 3) and 04.00 hours to 08.00 hours (6.0 ± 8). The period of the highest incidence of all arrhythmias was between 16.00 hours to 24.00 hours, and that of lowest during the period between 04.00 hours to 12.00 hours ($P < 0.01$). After one week's treatment with nadolol the frequency of all arrhythmias was strikingly reduced but their pattern of occurrence remained unchanged. These studies suggest that patients who present with symptoms attributable to arrhythmias tend to have these more frequently during the physical and mental activities of the day and evening presumably due to the accompanying sympathetic overactivity.

Introduction

Most patients who present with palpitations as their chief complaint tend to be aware of such episodes during their waking hours. This apparent predilection for daylight could be either because the patients sleep during their nocturnal episodes, and the palpitations are as frequent during the night as they are during the day, or that there may be a real circadian variation. There is some evidence that dysrhythmias may be markedly suppressed during sleep (Lown *et al.*, 1975; Leach *et al.*, 1981; Kuzel, 1973), and an earlier study from our laboratory has shown a circadian rhythm of ventricular arrhythmias (Mir & Tirlapur, 1982). However, some patients with anxiety may have a low threshold for palpitations whereas ventricular tachycardia – a life-threatening arrhythmia – may never cause palpitations (Bigger, 1980; Hinkle *et al.*, 1969; Bleifer *et al.*, 1974). The purpose of this study was to investigate the distribution of arrhythmias within a 24 hour period in patients who presented mainly with palpitations, and to explore the effectiveness of once-a-day long-acting beta-adrenoceptor blocker, nadolol.

Methods

Patients

Twenty-eight consecutive patients with recurrent palpitations (22 patients) or dizziness (6 patients) thought to be due to dysrhythmias, were recruited from our general medical clinic into this study. There were 17 males and 11 females, and their ages ranged from 20 to 70 years (mean 48 ± 15 , s.d.). Since one of the objectives of the study was to explore a relationship between symptoms and Holter data, patients known to have valvular heart disease were not included because it was thought that their knowledge of the heart disease might have influenced their referral.

Protocol

All patients had a complete physical examination, a chest X-ray, a 12-lead electrocardiogram (ECG) and routine laboratory investigations including a full blood count and liver function tests. Other investigations such as thyroid function and barium studies were performed only when clinically indicated. A 24 hour ambulatory ECG Holter monitoring study was carried out before and after one week's treatment with a single

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daily 40 mg dose of nadolol. None of the patients received any other antiarrhythmic therapy or digitalis, either before or during the study and all were clinically stable. Holter monitoring of ECG was carried out with a Medilog II recorder (Oxford Medical Systems, UK) as described previously (Mir & Tirlapur, 1982).

Analysis of data

A Reynolds high speed ECG analyser trend system was used for the analysis of all tapes. The criteria for the identification of supraventricular tachycardia (SVT), ventricular tachycardia (VT) and premature ventricular contractions (PVC) were the same as detailed previously (Mir & Tirlapur, 1982). An hourly trend print out record was obtained showing the PVC and premature supraventricular contraction count, the hourly heart rate, and the number of SVT and VT episodes. In addition, all tapes were manually scanned and random samples of PVC and episodes of SVT and VT were verified on a rhythm strip.

Statistical methods

Standard statistical methods were used. Individual data series of all patients for each 4 hour period in the day were compared by paired *t* test with the corresponding period in the night (i.e. 12.00 hours to 16.00 hours against 00.00 hours to 04.00 hours). Student's paired *t* test was used in comparing the frequency of arrhythmias period by period before and after nadolol. All data have been expressed as mean and standard deviation.

Results

Although all patients with palpitations and dizziness had premature ventricular and supraventricular ectopic beats sometime during the 24 hour period of Holter monitoring, there was a large hour to hour and

intersubject variation. The mean PVC per hour per patient was not significantly different during the day between 08.00 hours and 20.00 hours (23) from during the night between 20.00 hours and 08.00 hours (20), but there were periods of high and low frequency of arrhythmias (Table I). The mean PVC during the 4 hour period of 16.00 hours to 20.00 hours (109 ± 60) was significantly higher than in the corresponding period of 04.00 hours to 08.00 hours (29 ± 23 ; $P < 0.001$). The frequency of supraventricular ectopics beats (data not shown) and PVC was significantly higher from 20.00 hours to 24.00 hours than during 08.00 hours to 12.00 hours ($P < 0.001$; Table I).

Paroxysmal tachyarrhythmias

During a single 24 hour ambulatory monitoring period there were 1390 episodes of supraventricular tachycardia; 813 of these occurred during the day and 577 during the period between 20.00 hours and 08.00 hours as shown in Table I. The mean of supraventricular tachycardia episodes was significantly higher during the period from 16.00 hours to 20.00 hours than during 04.00 hours and 08.00 hours (11.3 ± 11 vs 6 ± 8 ; $P < 0.05$). The period after midnight tended to have low frequency with the mean rate being 3.6 ± 2.9 . The highest rate was recorded during 20.00 hours to 24.00 hours (12.0 ± 10 ; $P < 0.001$). Of the total episodes of ventricular tachycardia (186), 112 occurred during the day and 74 during the night. The highest number of VT episodes occurred during 16.00 hours to 24.00 hours (82) and the lowest number occurred during the hours between 00.00 hours and 08.00 hours (37) but there was no significant difference between various periods (Table I). The hourly episodes of palpitations and dizziness as recorded by patients on their diaries showed better agreement with PVC ($r = 0.45$; $P < 0.01$) than with tachyarrhythmias ($r = 0.02$). Many episodes of dysrhythmias, particularly at night, went unnoticed by the patients.

Table I Premature ventricular beats, supraventricular and ventricular tachycardia in 4 hour periods before and after nadolol in 26 patients (Data means $\pm$ s.d.)

Time	Premature ventricular ectopic beats		Paroxysmal tachycardia episodes			
			Supraventricular		Ventricular	
	Before	After	Before	After	Before	After
04.00–08.00 h	29 ± 23	*** 13 ± 10	$6.0 \pm 8\ddagger$	$3.0 \pm 4.0^*$	0.7 ± 1.5	0.6 ± 1.0
08.00–12.00 h	50 ± 32	** 15 ± 13	9.0 ± 10	$3.0 \pm 5.0^*$	1.0 ± 2.0	0.9 ± 2.0
12.00–16.00 h	101 ± 60	** 38 ± 40	11.0 ± 12	$4.0 \pm 4.0^*$	1.4 ± 2.0	0.8 ± 1.5
16.00–20.00 h	$109 \pm 60\ddagger$	** $38 \pm 42\ddagger$	11.3 ± 11	3.4 ± 5.0	1.7 ± 2.2	$0.70 \pm 1.3^*$
20.00–24.00 h	$163 \pm 80\ddagger$	** $80 \pm 89\ddagger$	12.0 ± 10	6.0 ± 5.0	1.4 ± 1.8	$0.40 \pm 0.8^*$
00.00–04.00 h	74 ± 45	* $41 \pm 43\ddagger$	3.6 ± 3	$1.6 \pm 1.9^{**}$	1.0 ± 0.7	$0.5 \pm 0.9^{**}$

Paired *t*: * = $P < 0.02$; ** = $P < 0.01$ compared with before nadolol; *** = $P < 0.001$; $\ddagger$ = $P < 0.001$ compared with the corresponding time period (i.e. p.m. vs a.m.)

Effect of nadolol

In two patients nadolol had to be withdrawn within 3 days because of severe bradycardia (pulse rate <30 beats/min). Both required artificial pacing. Further investigations revealed that one patient, a 42 year old female, had polymyositis with cardiac involvement and the other, a 70 year old male, had sinoatrial disease. Eight of the 10 patients with recurrent palpitations, 2 of the 3 with the prolapse of posterior mitral valve cusp and all the 5 patients with thyrotoxicosis reported considerable relief from palpitations after nadolol. The Holter monitoring results of a one week treatment with 40 mg nadolol a day in the 26 patients are summarized in Table I. The frequency of PVC was significantly reduced but the periods of maximum frequency were still the same as before the therapy. The incidence of ectopics was higher during the period between 12.00 hours and 24.00 hours than 0.00 hours and 12.00 hours (Table I). Five patients (2 with ischaemic heart disease and diabetes mellitus, one with hypertension, 1 with phobic state and 1 with prolapse of posterior mitral valve cusp) responded poorly to nadolol and continued to have ectopic beats as well as paroxysmal tachyarrhythmias; 3 of these responded to amiodarone but 2 others showed very little response to disopyramide, mexiletine and amiodarone tried in turn. These two patients had more episodes of VT after nadolol between 04.00 hours and 08.00 hours.

Bradycardia

Two episodes of bradycardia (heart rate under 50 beats/minute) were observed in the night in 2 patients before nadolol. After nadolol the mean heart rate fell significantly during each 4 hour period. There were 23 episodes of bradycardia in 7 patients after nadolol; 2 of these complained of dizziness, 2 dizziness and tiredness and 2 complained of tiredness alone. However, the symptoms were not severe enough to warrant withdrawal of nadolol in any of these patients during the week of treatment.

Side effects

Apart from severe symptomatic bradycardia in the 2 patients in whom nadolol had to be withdrawn, side effects were not troublesome in any others. Four patients complained of dizziness, 4 tiredness, 3 of cold peripheries and 1 of headaches. One patient, a male aged 47 years, complained of impotence which improved after the termination of the treatment period. The 5 patients with thyrotoxicosis experienced a considerable improvement in their symptoms during the week of nadolol.

Discussion

Day to day and intersubject variations limit the usefulness of a single 24 hour monitoring in establishing a pattern of occurrence of arrhythmias. Despite these variabilities, all arrhythmias showed a higher frequency in the evening than in the morning, in the afternoon than after midnight and during waking than during sleeping hours. A previous study from our laboratory showed an overwhelming predominance of PVC during the day in 13 subjects. In this study with twice the number of patients, the day versus night frequency of arrhythmias was much less impressive, but there was an obvious increase during the day than night.

Various investigators have observed that sleep has a suppressive effect on ventricular arrhythmias which tend to occur more frequently during the day than night (Lown *et al.*, 1975; Leach *et al.*, 1981; Kuzel, 1973; Mir & Tirlapur, 1982; Lown *et al.*, 1973; Winkle *et al.*, 1977). The reason for a high frequency of arrhythmias during the strenuous hours of the day may be related to a heightened sympathetic activity associated with the daytime activity. Taggart *et al.* (1969; 1973) have demonstrated an increased ectopic activity associated with the stress of driving a car or speaking before an audience, and Coumel *et al.* (1981) have shown that some arrhythmias are mediated through sympathetic overactivity. However, there does not seem to be a straightforward relationship between physical activity and arrhythmias; the frequency of ventricular ectopics and tachyarrhythmias was greater from 20.00 hours to 24.00 hours than during the physically active period of 08.00 hours to 12.00 hours (Table I). This high frequency in the evening may be related to psychological stress since the end of the day represents the culmination of the day's stresses and strains, and the time to ruminate on the entire day's unpleasant experience. Psychological stress in the evenings and brooding about past events have been known to cause increased ectopic activity (Stevenson *et al.*, 1949; Sigler, 1967). Beta-blocking drugs have been shown to be most beneficial in patients with some evidence of an increased sympathetic activity (Hope *et al.*, 1974). In this study, nadolol, a long-acting beta-blocker, suppressed arrhythmias throughout the 24 hour period in 21 of the 26 patients. However, in considering the effectiveness of this drug, one must take into account the marked variability of arrhythmias seen in this study as has been reported by other workers in the past (Sheps *et al.*, 1977; Morganorth *et al.*, 1978; Sami *et al.*, 1980; Winkle *et al.*, 1977). Morganorth *et al.* (1978) have suggested a reduction of greater than 80% in PVC necessary to accept a therapeutic effect, and Sami *et al.* (1980) have argued for 65% reduction to show the effectiveness of a drug. As these reports on variability have shown either an

increase or a decrease in the occurrence of arrhythmias in corresponding hours on repetition of the 24 hour monitoring studies, the strongest criterion set for this study was a *reduction* in arrhythmias in over 70% of the corresponding hours. An hour by hour analysis showed that the actual figure was between 83 and 92%, i.e., all arrhythmias showed a reduction in corresponding hours in over 83% of the hours.

Although previous studies have shown that arrhythmias tend to occur more frequently during the day than night, in this study many episodes of VT were recorded during the small hours of the morning (Table I). Nadolol has a long half-life of 24 hours (Vukovich *et al.*, 1975), and after a single dose of 160 mg, effective beta blockade and high blood concentrations have been observed 24 hours after in patients with angina pectoris (Jones & Mir, 1981). The results of this study

have shown that a single dose of 40 mg/day can suppress arrhythmias throughout the 24 hour period. However, nadolol may induce severe bradycardia in patients with latent cardiac disease, as happened in 2 of our patients; in the male patient sinoatrial disease could not have been suspected before treatment.

In conclusion, Holter monitoring is an effective method of establishing the diagnosis in patients who present with complaints attributable to cardiac arrhythmias. These arrhythmias show a diurnal variation and tend to occur more during the day and evening than night and morning. Nadolol in a single daily dose of 40 mg is effective in most patients, but a high index of suspicion must be maintained for any underlying occult myocardial disease, as a troublesome bradycardia may be precipitated by a normal therapeutic dose.

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