The effect of nadolol on heart rate in hyperthyroidism.
A controlled trial

J. H. Lazarus1, J. C. Kingswood1 and R. John2

Departments of Medicine1 and Medical Biochemistry2,
University of Wales College of Medicine, University Hospital of Wales, Cardiff, Wales, UK

Abstract. Twenty hyperthyroid patients were randomly assigned in a double-blind fashion to receive either nadolol 80 mg/day or placebo for 2 weeks; all patients then took carbimazole as well from 2–6 weeks. Twenty-four hour Holter ECG recordings at 0, 2 and 6 weeks showed that nadolol reduced the mean maximum heart rate by 19.9% ($P < 0.0005$) at 2 weeks and by 30.3% ($P < 0.0005$) at 6 weeks compared to 5.2% (ns) and 18.3% ($P < 0.0005$) in patients taking placebo. There was no alteration of the normal circadian variation of heart rate by nadolol. The minimum heart rate before therapy was significantly correlated with FT$_4$ (r = 0.52) and with FT$_3$ (r = 0.44). The percentage of time per hour during which the heart rate was greater than 100 was reduced by 79% at week 2 by nadolol compared to 22% in the placebo group. At the 6 week point the placebo group still had a tachycardia (mean maximum heart rate 101.6 beats/min ± 15.2 sd) compared to the nadolol group (80.4 ± 7.7). Nadolol did not cause excessive bradycardia. It is effective in the early management of hyperthyroidism and should be given for at least the first 4–6 weeks.

Tachycardia is one of the cardinal manifestations of hyperthyroidism, but there are few data regarding the 24 h variation in heart rate in this disease and its response to beta-adrenoceptor blockade studied in detail. Jansson et al. (1984) recently studied 19 hyperthyroid patients by Holter electrocardiography and showed a 20% reduction in mean 24 h heart rate in patients rendered euthyroid but did not use β-blockers. Forfar et al. (1982) in an open study examined the relationship between the sympathetic nervous system and cardiovascular responses in 10 hyperthyroid patients before and during propranolol therapy. The aims of the present study were to evaluate the effect of nadolol, a non-selective β-blocker, on the heart rate during the early management of hyperthyroidism and to examine the characteristics of the heart rate in the disease. We have employed a double-blind placebo study and have used 24 h heart rate monitoring on three occasions during treatment.

Patients and Methods

Twenty hyperthyroid patients (5 males, 15 females, mean age 43.3 ± 10.4 sd, range 26–62) were studied. The diagnosis of hyperthyroidism was made by clinical examination and always confirmed by noting elevation of serum free thyroxine (FT$_4$) and free triiodothyronine (FT$_3$) which were both measured by the Amerlex method (Amersham plc, England). Reverse triiodothyronine ($rT_3$) was measured by radioimmunoassay (Hufner & Grussendorf 1976).

The aetiology of the hyperthyroidism was Graves' disease or toxic multinodular goitre. Patients were consecutively entered into the study, but no patient was entered into the study who had ischaemic heart disease, who was not in sinus rhythm or who had any medical contra-indication to β-blocker therapy. At the time of diagnosis patients were randomly allocated to one of two treatment groups in a double-blind manner. The patients therapy regime was contained in a sealed envelope which was opened after the patient had agreed to participate in the study. Numbered bottles containing identical looking tablets ensured that doctor and patient were both unaware of which medication was being prescribed. Group A received placebo tablets only.
for 2 weeks then carbimazole 10 mg q.i.d. and took these and the placebo until week 6. Group B received nadolol 80 mg once per day for the first 2 weeks then took carbimazole 10 mg q.i.d. together with the nadolol until week 6. Twenty-four hour Holter ECG monitoring was done at weeks 0, 2 and 6 in each patient. The patient was admitted to hospital for this procedure and encouraged to walk about during the day. The experimental protocol was approved by the local Ethical Committee and informed consent was obtained from each patient.

Twenty-four hour recording of heart rate was done by Medilog 4–24 (Reynolds Medical Ltd) which records on a C120 casette. Particular attention was paid to skin preparation and electrode attachment. Two ECG leads were positioned, one at the top of the sternum and the other at V-5. This ensured the presence of a large R wave and a small T wave which allowed better triggering of the analyser. The tapes were analysed by Hertford medical by the Pathfinder Analysis (STG K2). This is a tape replay system facility with a trend system incorporating a printer interface module. The print provided information on hourly heart rate (mean of 14 R-R intervals) for the maximum, average and minimum rates. The number of premature beats and aberrant beats was recorded and the number of min in every hour during which the heart rate exceeded 100 beats per min or was less than 48 beats per min was also recorded.

The statistical tests used were Student's t-test and linear regression analysis.

Results

The mean maximum heart rate (i.e. mean of 24 hourly values) before therapy in the 20 patients was 117.8 ± 10.3 SD beats per min. The mean average rate was 100.7 ± 10.8, and the mean minimum rate was 89.8 ± 11.5. The mean maximum heart rate between 10.00 and 17.00 h before therapy was 130.3 ± 15.3 (range 105–157) with a mean minimum heart rate between 03.00 and 06.00 h of 83.2 ± 10.9 (range 59–104). When the maximum hourly heart rate for each patient was noted the mean for all the patients before therapy was 147.6 ± 21.5 (range 112–198) and the mean minimum hourly heart rate was 74.5 ± 11.1 (range 51–94). The mean difference between these maximum and minimum heart rates was 73.2 ± 23.2 (39–126), and there was a significant

Fig. 1.

Hourly maximum heart rates before therapy in Group A (placebo •—•) and Group B (nadolol o—o) and after 2 weeks of treatment with placebo (•—•) or nadolol (o—o). SD are not shown because of clarity.
correlation between these differences and the maximum heart rates ($r = 0.88, P < 0.001$).

There was no significant difference before treatment in the mean maximum heart rate between groups A and B (Fig. 1). The efficacy of nadolol in reducing the heart rate is shown by the fact that it caused a mean reduction in the maximum heart rate of 19.9% after 2 weeks (from 115.3 ± 9.52 sd to 92.3 ± 6.05, $P < 0.0005$) compared to 5.2% from 124.3 ± 17.3 to 117.8 ± 13.9, $P > 0.1$ ns) in the placebo group. At the end of the 6 week period there was a 30.3% reduction in mean maximum heart rate in group B (from 115.3 ± 9.5 to 80.4 ± 7.7) but only 18.3% in group A (from 124.3 ± 17.3 to 101.6 ± 15.2 (Fig. 2). Inspection of the maximum heart rates during the 24 h period in both groups at 0 and 2 weeks (Fig. 1) and in group B at 0, 2 and 6 weeks showed that the circadian variation was maintained with the expected minimum values being observed between the hours of 01.00 and 06.00. Although the mean number of min per hour (expressed as the mean value of 24 hourly readings in min) during which the heart rate was greater than 100 beats/min was higher in group A (39.1 range 10.9–60.0) compared to group B (29.3 range 11.8–50.8) before therapy, the difference was not significant. A reduction of 79.2% in the mean duration by week 2 to 6.1 min (range 0.3–13.5) was seen in group B compared to a 22.5% reduction in group A to 30.3 min (range 0.6–52.6). Even at 6 weeks (after 4 weeks of carbimazole) there was a mean of 14.8 min per hour of heart rate > 100 in group A (range 0–46.2) compared to 0.2 min per hour in group B (range 0–2.5). This represents a 62.1% reduction in min per hour of heart rate > 100 in group A between 0–6 weeks compared to a reduction of 99.3% in group B. At the end of the 6 week experimental period there was no significant difference between the mean number of min per hour when the heart rate was less than 48 beats per min (Group A 0.34 vs Group B 0.57). No patient in either group had significant numbers of aberrant beats at any stage of the analysis.

Prior to therapy the mean minimum heart rate for each patient was significantly correlated with serum FT$_4$ ($r = 0.46, P < 0.01$) and with FT$_3$ ($r =$

Fig. 2.
Mean maximum heart rates (±sd) in the two groups at 0, 2 and 6 weeks.
0.44, \( P < 0.05 \). There were no significant correlations between maximum heart rate and thyroid hormone levels or between heart rate and T₃/T₄ ratio or reverse T₃ concentrations.

Discussion

The genesis of tachycardia in hyperthyroidism is related to the interaction of thyroid hormone with a probably increased number of myocardial β-receptors (Williams & Lefkowitz 1983) as well as resulting from the direct effect of thyroid hormone on the sinoatrial node (Morkin et al. 1983). β-adrenoreceptor blocking drugs are of proven efficacy in the reduction of heart rate in hyperthyroidism (Utiger 1984; Feely & Peden 1984). Nadolol, a non-selective β-blocker, has been recently shown to be effective in the control of hyperthyroid symptoms (Wilkinson & Burr 1981; Peden et al. 1982). In a study of cardiac sinus rate in euthyroid patients using Holter monitoring, Attuel et al. (1981) found that nadolol had a more powerful β-blocking effect than propranolol and acebutolol. The present study documents the effectiveness of nadolol in reducing cardiac rate throughout the day in hyperthyroidism confirming the previous small open study of Adam et al. (1981), and shows that the pattern of heart rate variation is similar to that seen in untreated patients. At the 6 week point, after the addition of carbimazole therapy, the maximal heart rates in the nadolol group were significantly lower than the placebo although both groups were clinically and biochemically euthyroid. Furthermore, there was no evidence of excess bradycardia in the nadolol group.

The wide range of maximum and minimum heart rates that may be observed in the hyperthyroid state was noted by Jansson et al. (1984). However, in our patients the normal circadian variation in heart rate was not different from that observed in normal persons (Attuel et al. 1981), but it was set at a higher level. The range of minimal heart rates observed before treatment indicates that although the rate does not fall below 80/min some thyrotoxic patients may have a sleeping pulse rate less than this level. In view of the high maximum hourly heart rates it was perhaps surprising not to find much evidence of ectopic activity. Jansson et al. (1984) only found ectopic beats in 4 out of 19 patients which agrees with our findings although Bantle et al. (1980) found some patients to have up to 3000 ectopic beats over 12–24 h. Previous studies have shown significant correlations with heart rate and free T₃ index (Jansson et al. 1984; Forfar et al. 1982; Bantle et al. 1980), and we have confirmed the correlation between minimum heart rate and thyroid hormone concentrations.

The main clinical feature in hyperthyroidism, the increased cardiac rate, results from the as yet unclear relationship between the thyroid hormones and the adrenergic system. The present study has defined the variability of heart rate in hyperthyroidism and indicated that β-blockade produces heart rate characteristics which are not different from those in normal persons. As it is desirable to reduce the heart rate in hyperthyroidism a drug such as nadolol should be given for at least 4 weeks in the early management of this disease.

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References


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Dr J. H. Lazarus,
Department of Medicine,
University of Wales College of Medicine,
University Hospital of Wales,
Heath Park,
Cardiff CF4 4XN.