Adrenergic hypersensitivity after beta-blocker withdrawal

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SUMMARY We investigated the possibility of a rebound increase in sympathetic response after stopping beta-blocker treatment by measuring heart rate under conditions of increased sympathetic drive, as provided by standing with vasodilatation, or the Valsalva manoeuvre. Significant rebound increases in heart rate were observed after stopping propranolol given for one or more weeks but not when given for only four days. The amplitude of the rebound heart rate relative to the control heart rate off beta-blockers was similar after propranolol, atenolol, oxprenolol, or acebutolol, and in hyperthyroid subjects.

A propranolol withdrawal syndrome has been suggested by many anecdotal reports. Formal evidence of such an underlying beta-adrenergic hypersensitivity was originally lacking,¹⁻⁵ but two reports published after we started our study have now provided such evidence.^{6,7} We measured heart rate under conditions of increased sympathetic drive, during and after stopping treatment with different beta-blocking drugs, given for differing periods of time, and in euthyroid or hyperthyroid groups of subjects.

Methods

The heart rate, measured from electrocardiograms, was recorded as an index of sympathetic activity, as follows: (i) supine (after resting supine for ≥ 20 min), (ii) standing (after standing for 3 min), (iii) standing with vasodilatation (3 min after 1 mg sublingual glyceryl trinitrate given after measuring the standing heart rate, or, in patients already taking long acting nitrate preparations, after standing for 3 min), and in some subjects (iv) during the Valsalva manoeuvre. All measurements were made at the same time of day, three hours or more after a meal, and at least six hours after caffeine, alcohol, smoking, or strenuous exercise. The Valsalva manoeuvre was performed supine, after familiarisation with the technique.⁸ The maximum heart rate achieved during the forced expiratory phase was measured, and the mean

value obtained in three consecutive manoeuvres performed at 10 minute intervals calculated. Heart rates were measured during treatment with beta-blocking drugs and daily after their single blind substitution by placebo. Control values off beta-blocker treatment were those measured six days after stopping treatment (10 days after stopping atenolol), preliminary studies having confirmed that heart rate responses had returned to normal after these intervals. Separate studies showed that there was no change in the heart rate response to standing with vasodilatation by glyceryl trinitrate when this was repeated daily for six days in six subjects.

Heart rate responses were measured in different groups of subjects as indicated in the Results section. Patients on long-term (3 months or more) treatment with propranolol 80 mg bd for angina constituted one group. Other groups consisted of healthy male volunteers treated with twice daily doses of dl-propranolol (160 mg/day), atenolol (200 mg/day), oxprenolol (160 mg/day), or acebutolol (400 mg/day), for four days, one week, or six weeks as indicated. A further group consisted of patients with proven, untreated hyperthyroidism given dl-propranolol (160 mg/day) or oxprenolol (160 mg/day) for six weeks. The number of subjects in each group is given in the captions to the figures.

Data for each group are given as the mean $\pm$ standard error. Data within groups are compared by Student's *t* test for paired data, and data from different groups are compared by Student's *t* test for unpaired data. The limit of significance is taken as $p < 0.05$.

Fig. 1 Heart rates lying (●—●), standing (○—○), and standing with vasodilatation (□—□) measured daily after stopping propranolol (160 mg/day) given to (a) euthyroid patients for three months or more ($n=5$), (b) normal subjects for six weeks ($n=12$), (c) normal subjects for one week ($n=6$), (d) normal subjects for four days ($n=6$). Day 1 is on beta-blocker treatment (12 hours after last dose), subsequent days represent 24 hour intervals from day 1, and day 6 represents control values (see text). Asterisk indicates significant difference ($p < 0.05$) compared with control heart rate.

Fig. 2 Heart rates lying (●—●), standing (○—○), standing with vasodilatation (□—□) measured daily after stopping (a) atenolol (200 mg/day) given to normal subjects for six weeks ($n=6$), (b) oxprenolol (160 mg/day) given to normal subjects for one week ($n=6$), (c) acebutolol (400 mg/day) given to normal subjects for one week ($n=6$). (Conventions as in Fig. 1).

Results

Fig. 1 shows heart rates measured supine, standing, and standing with vasodilatation, daily after stopping propranolol (80 mg bd) in four groups of subjects—(a) patients treated with propranolol for three months or more, who were also taking long acting nitrates; and normal subjects treated with propranolol for (b) six weeks, (c) one week, and (d) four days. The rebound increase in heart rate was greatest on standing with vasodilatation. The phenomenon has accordingly been characterised in each group throughout this study by the peak heart rate measured under these conditions. The size of the rebound is expressed relative to the respective control value off beta-blocker treatment. The maximum size of the rebound in groups (a)–(d), respectively, was 17 ± 4 per cent, 17 ± 3 per cent, 31 ± 8 per cent ($p < 0.05$ in each case), and 13 ± 6 per cent (NS). The timing of the peak rebound was similar in groups (a)–(c) at 2.8, 2.7, and 2.3 (range 2 to 5) days.

Fig. 2 shows heart rates measured daily after

stopping beta-blocker treatment in three groups of normal subjects treated with (a) atenolol (200 mg/day) for six weeks, (b) oxprenolol (160 mg/day) for one week or (c) acebutolol (400 mg/day) for one week. The maximum size of the rebound in groups (a) to (c), respectively, was 14 ± 5 per cent, 18 ± 7 per cent, and 27 ± 6 per cent ($p < 0.05$ in each case), none of which is significantly different from the corresponding findings with propranolol given for similar periods of time (Fig. 1b and c). The peak rebound was reached at five (range four to seven) days after atenolol which is significantly later than after propranolol (Fig. 1b, $p < 0.001$), and at three (range two to five days) after both oxprenolol and acebutolol, which is similar to the findings with propranolol (Fig. 1c).

Fig. 3 shows heart rates measured daily after stopping beta-blockers in two groups of hyperthyroid patients, treated for six weeks with—(a) propranolol (160 mg/day), (b) oxprenolol (160 mg/day). The maximum size of the rebound was 11 ± 3 per cent and 15 ± 6 per cent ($p < 0.05$ in each case), respectively, neither of which differs

Fig. 3 Heart rates lying (●—●), standing (○—○), and standing with vasodilatation (□—□) measured daily after stopping (a) propranolol (160 mg/day) given for six weeks ($n=5$) or (b) oxprenolol (160 mg/day) given for six weeks ($n=4$) in hyperthyroid patients. (Conventions as in Fig. 1).

Fig. 4 Heart rates measured during the Valsalva manoeuvre daily after stopping propranolol (160 mg/day) given to normal subjects for six weeks ($n=6$). (Conventions as in Fig. 1).

significantly from the findings with propranolol in euthyroid subjects (Fig. 1b). Peak rebound occurred at four and three days, respectively.

Fig. 4 shows the maximum heart rates achieved during the Valsalva manoeuvre after stopping propranolol (160 mg/day) given for six weeks. There was again a significant peak rebound of 17 ± 5 per cent ($p < 0.05$), occurring at three days.

Discussion

The present study shows that a significant rebound increase in beta-adrenergic response can be shown regularly after stopping beta-blocker treatment given for one week or more. No difference in the size of the phenomenon, expressed as the increase in heart rate relative to the heart rate of beta-blockers, was observed after any of the different beta-blockers studied. Likewise, hyperthyroidism did not increase the relative size of the rebound, despite higher absolute heart rates.

The phenomenon is likely to be the result of increased beta-receptor responsiveness. Propranolol withdrawal has now been reported to be associated with about a 50 per cent increase in the sensitivity of the heart rate response to isoprenaline,⁶ and animal experiments have shown that treatment with this drug causes a compensatory increase in myocardial beta-receptor numbers,⁹ providing an explanation of the pharmacological phenomenon of "denervation hypersensitivity".^{10, 11} Treatment with propranolol in man has also now been shown

to increase beta receptor numbers on lymphocytes by about 50 per cent over five days, the number declining to normal over five days after stopping the drug.

The clinical manifestation of beta-adrenergic hypersensitivity will clearly depend on the degree of increased beta adrenergic responsiveness (as receptor numbers decline towards normal) and on the degree of receptor activation, which will in turn depend on the sympathetic drive and declining plasma levels of the beta-blocking drug. Earlier failures to demonstrate the phenomenon are probably because measurements were made under resting conditions. Abnormally high levels of beta adrenergic activity could occur earlier than the time of the peak heart rate response observed under the conditions of the present study, if very high levels of sympathetic drive were to override residual beta-blockade during the period of increased responsiveness. Whether the continuation of very small doses of a beta-blocking drug are sufficient to counteract this increase in beta-adrenergic responsiveness¹² under all circumstances must await studies of the complete dose-response which characterises this state. An increase in the ceiling of the dose-response is likely on theoretical grounds, in which case stimulation to this level could cause an abnormally high level of adrenergic activity which might not be fully counteracted by small doses of beta-blocking drugs. It is nevertheless reassuring that in such circumstances small doses of propranolol continued throughout cardiac surgery have been reported to reduce clinical features of beta-adrenergic activity.¹³

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