β -ADRENOCEPTOR HYPERSENSITIVITY AFTER STOPPING OXPRENOLOL: DISCREPANT FINDINGS NOT ATTRIBUTABLE TO METHODOLOGY

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Using isoprenaline and glyceryl trinitrate (GTN) induced tachycardia we have compared the rebound β -adrenoceptor hypersensitivity on stopping slow-release and conventional oxprenolol in young normotensive subjects. Heart rate on standing with GTN rose after stopping slow-release and conventional oxprenolol to peak levels on day 2 or 3 significantly greater than corresponding control levels off treatment on day 5. The isoprenaline CD_{25} (the dose required to increase heart rate by 25 beats/min) fell after stopping conventional oxprenolol to a significantly lower level on day 3 than the control level off treatment on day 5. Contrary to a recent report describing no rebound β -adrenoceptor hypersensitivity on stopping slow-release oxprenolol we have demonstrated it after stopping slow release as well as conventional oxprenolol.

Keywords β -adrenoceptor hypersensitivity oxprenolol

Introduction

Absence of β -adrenoceptor antagonist withdrawal hypersensitivity following slow-release oxprenolol was recently reported (Bolli *et al.*, 1981), leading to the suggestion that the phenomenon does not occur after β -adrenoceptor antagonists possessing partial agonist activity. A similar lack of withdrawal hypersensitivity has been reported in some studies with pindolol (Rangno & Langlois, 1982; Szecsi *et al.*, 1982) and in particular a down regulation of human lymphocyte β -adrenoceptor density has been noted with this drug and attributed to its partial agonist activity (Molinoff *et al.*, 1982). In contrast we have previously reported that the phenomenon does occur after stopping oxprenolol (Ross *et al.*, 1981). One possible explanation for these differing results lies in the use of the direct chronotropic response to isoprenaline in these negative studies whereas we had used the reflex chronotropic response to standing with glyceryl trinitrate (GTN). We have accordingly compared these two methods in groups of normal subjects treated with conventional or with slow release oxprenolol.

Methods

Six normal subjects (men aged 21–23 years) took two 2-week courses of oxprenolol 80 mg twice daily with an intervening 2-week treatment-free period. The

chronotropic response to standing with GTN was measured following the first course of treatment and the chronotropic response to isoprenaline was measured following the second course of treatment. A further six normal subjects (men aged 21–23 years) took slow-release oxprenolol 160 mg in the morning for 2 weeks, following which the chronotropic response to standing with GTN was measured.

In all cases measurements were made under constant conditions, at 12.00 h; strenuous exercise, cigarette smoking and a heavy meal were avoided on the morning of a measurement and alcohol consumption was avoided during the preceding 24 h. Measurements were made at 18 h after the last conventional oxprenolol tablet, and 28 h after the last slow-release oxprenolol tablet, and thereafter at 24 h intervals for 5 days. Measurements 5 days after stopping either of these agents were shown to be the same as pretreatment (Ross *et al.*, 1981), and therefore provided the control data 'off treatment'.

Heart rate was measured from the electrocardiogram. In the standing GTN protocol, heart rate was measured for 1 min 4–5 min after standing and again for 1 min 4–5 min after placing a sublingual GTN (1 mg) tablet under the tongue. To determine the dose of isoprenaline needed to increase heart rate by 25 beats/min (CD_{25}) supine heart rate was measured for 1 min 4–5 min after lying down, and again at peak following each of a series of bolus intravenous (i.v.)

injections (through an indwelling i.v. cannula) of isoprenaline in increasing doses from 0.05 μg , through 0.1, 0.25, 1, 2, 5, 10, 20, to 40 μg as necessary; peak heart rate (shortest R-R interval) was measured following each injection and heart rate was allowed to return to its original base line before giving each next dose. The CD_{25} was calculated from the best fit linear regression line of each isoprenaline dose-response curve.

Data are given as the mean $\pm$ s.e. mean. Group mean data on a given day were used for comparison rather than mean data for individual peak responses which might occur on different days and whose use would be statistically improper. Wilcoxon Signed Rank test was used for statistical analysis. Results are considered significantly different when $P < 0.05$.

Results

Figure 1 shows that heart rate on standing with GTN rose after stopping oxprenolol or slow-release oxprenolol to peak levels on day 2 or 3 significantly greater than corresponding control levels off treatment on day 5. Figure 2 shows that CD_{25} fell after stopping conventional oxprenolol to a low level on day 3 which was significantly lower than the control level off treatment on day 5.

Figure 1a) Heart rate in normal subjects measured standing before (●—●) and after (○—○) glyceryl trinitrate, 1 to 5 days after stopping a 2 week course of oxprenolol 80 mg twice daily, mean $\pm$ s.e. mean ($n = 6$). Significantly greater heart rate responses were seen on day 2 than on day 5 (* $P < 0.05$). **b)** Protocol and legend as in Figure 1a, but measurements made after stopping a 2 week course of slow release oxprenolol 160 mg one tablet in the morning. Significantly greater heart rate responses were seen on day 3 than on day 5 (* $P < 0.05$).

Figure 2 Dose of intravenous isoprenaline required to increase heart rate by 25 beats min^{-1} (CD_{25}), 1 to 5 days after stopping a 2 week course of oxprenolol 80 mg twice daily given to normal subjects, mean $\pm$ s.e. mean ($n = 6$). Significantly lower CD_{25} was seen on day 3 than on day 5 (* $P < 0.05$).

Discussion

These findings confirm our earlier observations (Ross *et al.*, 1981) that a rebound increase in β -adrenoceptor sensitivity can be demonstrated under conditions of increased sympathetic drive after abruptly stopping oxprenolol, as after β -adrenoceptor blockers without partial agonist activity. They show also that rebound hypersensitivity is similarly present after stopping the slow-release formulation of oxprenolol: this is as expected because the peak of this rebound effect occurs 2–3 days after stopping either slow release or conventional oxprenolol, when plasma levels are negligible in each case (Bolli *et al.*, 1981). We therefore failed to confirm the negative findings reported by Bolli *et al.* (1981) after slow release oxprenolol.

One possible explanation for the difference in findings might have lain in the different methods used to demonstrate the phenomenon and it was for this reason that we compared the direct chronotropic response to isoprenaline (as used by Bolli *et al.* (1981)) and the reflex sympathetic response to standing with

GTN (as used in our earlier study (Ross *et al.*, 1981): we found no difference between these methods. Our subjects were given oxprenolol only for 2 weeks but we have previously shown that the phenomenon is manifest after as little as 1 week's treatment (Ross *et al.*, 1981). It may be relevant that Bolli *et al.* (1981) studied hypertensive patients aged 27–53 years whereas we used younger normotensive subjects in the present study: Bertel *et al.* (1980) have reported that the CD₂₅ of the chronotropic response to iso-

prenaline is slightly depressed both by age and by the presence of hypertension. This seems unlikely though to provide the whole explanation for the lack of rebound hypersensitivity observed by Bolli *et al.* (1981).

We conclude that the rebound increase in β -adrenoceptor sensitivity after stopping chronic β -adrenoceptor blocker treatment cannot be avoided by using oxprenolol with its partial agonist activity.

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