THE EFFECT OF PROPRANOLOL ON LUTEINISING HORMONE AND PROLACTIN PLASMA CONCENTRATIONS IN HYPERTENSIVE WOMEN

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- 1 Chronic propranolol treatment has been previously shown to lower the plasma concentrations of LH and prolactin in normal male volunteers.
- 2 The effect of 2 weeks treatment with propranolol (80 mg twice daily) on the plasma concentrations of LH and prolactin has now been investigated in five post menopausal hypertensive women.
- 3 There was no significant effect of propranolol treatment on the basal plasma concentrations of either hormone. Both hormones showed significant increases in plasma concentration following GnRH stimulation and these increases were also unaffected by propranolol treatment.

Introduction

It has recently been demonstrated that 6 weeks treatment with propranolol (80 mg twice daily) significantly lowered the overnight plasma concentrations of luteinising hormone (LH) and prolactin in a group of young healthy male volunteers (Dart *et al.*, 1981). The mechanism of this effect was not elucidated but was thought likely to be a central (CNS) effect of propranolol. It was also speculated that a lowering of prolactin concentration might contribute to the hypotensive action of propranolol. However, extrapolation of these findings to hypertensive subjects, and particularly to hypertensive women in whom effects of β -adrenoceptor blocker treatment on gonadotrophin and prolactin concentrations might be of more practical importance, may not be justified. Therefore, the effect of two weeks treatment with propranolol (80 mg twice daily) on the plasma concentrations of LH and prolactin in a group of post-menopausal hypertensive women has now been studied.

The effect of propranolol treatment on the LH response to gonadotrophin-releasing hormone (GnRH) has also been investigated. If the action of propranolol were due to a central (CNS) effect, it would be expected to leave the response to exogenous GnRH unchanged. However, an alteration in pituitary function, e.g. by β -adrenoceptor blocker-induced changes in pituitary blood flow, might be expected to alter the response to exogenously administered GnRH. The action of propranolol on an LH 'surge', such as occurs at mid-cycle in pre-menopausal women, was also studied since an effect might have important implications with regard to fertility.

Methods

The study group comprised five post-menopausal women (age 53–62 years, 3–19 years post menopause) who were on long term follow up for borderline hypertension, having been referred with initial blood pressures $> 160/95$ mm Hg. Approval for the study was obtained from the local Ethics Committee and all subjects gave their informed consent prior to participation. At the time of the study none of the subjects had received any antihypertensive medication for at least 1 year. All subjects were studied at an initial pre-treatment visit. They were then allocated, double-blind, to consecutive 2-week treatment periods with propranolol (80 mg twice daily) and placebo. Studies were performed on the last day of each treatment period. No pulse or blood pressure measurements were made during the study.

On each study day subjects arrived at 08.00 h after an overnight fast and an indwelling plastic cannula was inserted into an antecubital vein. Subjects remained fasting and recumbent throughout the study. Blood sampling was begun at 09.00 h and samples were withdrawn every 20 min until 13.00 h. On each occasion the first 3 ml withdrawn was discarded and 10 ml samples were then taken into lithium heparin tubes. At 11.30 h, 150 mg GnRH (Gonadorelin, Ayerst) was given by bolus injection. Fluid replacement was made after each sampling with 0.9% saline containing 2 iu/ml heparin. The samples were centrifuged and the plasma separated and stored at -20°C until assayed. Samples were assayed, in duplicate, for LH and prolactin using commercially available radio-immunoassays (Serono Biodata Diagnostics). The

sensitivity of the assay for LH was 0.5–2.0 mIU/ml and the intra-assay coefficient of variation was 4%. For prolactin, the sensitivity of the assay was 16–32 μ IU/ml and the intra-assay coefficient of variation was 7%.

Samples for LH estimation had to be diluted prior to assaying. Dilution was performed with pooled male plasma with a mean LH concentration of 3.5 mIU/ml. In four patients dilution was 1:4 whilst in the remaining patient a 1:2 dilution was used. The LH concentrations were subsequently corrected to allow for the LH content of the diluent. Statistical evaluation was performed using an analysis of variance technique with repeated measures (BMDP, 1981) by which the contributions of inter-patient variability, time and drug treatment to any observed differences could be determined.

Results

The results are shown in Figures 1 and 2. Propranolol did not have a statistically significant effect on the pre- or post-GnRH-stimulated concentrations of either LH or prolactin ($P > 0.4$). Both the prolactin and LH series showed statistically significant differences ($P < 0.001$) in the hormone concentrations between subjects both before and after GnRH stimulation. During the pre-stimulation period there

was a time dependent fall in the plasma concentration of prolactin but not of LH (see Figures 1 and 2) whilst following GnRH stimulation the plasma concentrations of both prolactin and LH showed significant increases ($P < 0.001$).

Discussion

This study failed to demonstrate any effect of 2 weeks treatment with propranolol on the plasma concentrations of LH or prolactin in hypertensive post-menopausal women. Although blood pressure was not measured during this study (in order to preserve the double-blind conditions) and therefore direct correlations could not be made, it seems unlikely that a fall in prolactin levels is of importance in the anti-hypertensive effect of propranolol. Furthermore, the failure of propranolol to inhibit the rise in plasma LH concentrations induced by GnRH suggests that propranolol would not interfere with the mid-cycle surge of LH which occurs during the pre-menopausal menstrual cycle. The demonstration of a rise in prolactin concentrations in response to GnRH confirms the recent report of Casper & Yen (1981).

Although the findings in this study are not in accord with those reported previously (Dart *et al.*, 1981) direct comparison between the studies is not possible because of marked differences in the study groups as

Figure 1 Pre- and post-GnRH-stimulated plasma concentrations of prolactin. Results are mean values ($n = 5$) $\pm$ s.e. mean. ■ placebo, □ propranolol 80 mg twice daily, ▼ pretreatment.

Figure 2 Pre- and post-GnRH-stimulated plasma concentrations of luteinising hormone. Results are mean values ($n = 5$) $\pm$ s.e. mean. ∇ pre-treatment, $\blacksquare$ placebo, $\square$ propranolol 80 mg twice daily.

well as differences in the time for which propranolol was administered, the time of day at which the study was performed and the shorter blood sampling time in this study. However, a marked effect of propranolol on LH and prolactin concentrations is unlikely to be manifest only during the night and this assumption would be expected to apply particularly to LH which does not show a diurnal variation in plasma concentration. Similarly, it seems unlikely that there would be major differences between 2 and 6 weeks treatment with propranolol. Both prolactin and LH are secreted in irregular 'pulses' (Parker *et al.*, 1973; Yen *et al.*, 1974), at approximately 90 min intervals and have plasma half-lives of approximately 20 min, so it

is likely that 20 min sampling over several hours will have given a reliable indication of the mean plasma concentrations. Hence the most likely explanation for the difference between the findings in this study and those reported previously lies in the marked differences between the two study groups. Whatever the explanation for the different findings, it seems unlikely that the previously demonstrated fall in plasma prolactin concentrations during propranolol treatment is of importance in the mechanism of the hypotensive action of propranolol.

Our thanks are due to Mrs P. Cunningham for excellent technical assistance. Financial assistance towards the study from ICI is also gratefully acknowledged.

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(Received April 19, 1982,
accepted July 27, 1982)