THE EFFECTS OF PROPRANOLOL AND ACEBUTOLOL ON THE OVERNIGHT PLASMA LEVELS OF ANTERIOR PITUITARY AND RELATED HORMONES

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- 1 The effects of single evening doses of the β -adrenoceptor blocking agents propranolol (80 mg orally) and acebutolol (200 mg orally) on plasma levels throughout the night of prolactin, growth hormone, luteinising hormone, follicle stimulating hormone, cortisol and testosterone have been studied in seven healthy male volunteers.
- 2 Three way analysis of variance showed that acebutolol significantly reduced circulating levels of prolactin and follicle stimulating hormone, but did not alter the levels of the other hormones studied.
- 3 Propranolol significantly reduced follicle stimulating hormone and testosterone, and significantly increased circulating levels of cortisol, but caused no change in the other hormones studied.
- 4 Prolactin, luteinising hormone, testosterone and cortisol showed a significant variation with time indicating the existence of a diurnal rhythm in the pattern of their secretion.
- 5 There was a significant inter-subject variability in all the hormones studied.
- 6 There was a significant between-subject variation in response to both propranolol and acebutolol.
- 7 Different subjects showed significant variations with respect to time in prolactin, growth hormone and cortisol levels.
- 8 Neither propranolol nor acebutolol significantly altered the time course of secretion of any of the hormones studied.
- 9 Possible relationships of these β -adrenoceptor blocker-induced changes in anterior pituitary and related hormones to the antihypertensive mechanism of acebutolol and propranolol are discussed.

Introduction

In searching for the mode of action of β -adrenoceptor blocking drugs as antihypertensive agents it has become evident that they have actions on the central nervous system. Their possible effects on anterior pituitary hormones has received little attention although such hormones as prolactin and adrenocorticotrophic hormone could influence blood pressure control. We therefore studied the acute effects of ($\pm$)-propranolol and of acebutolol on blood levels of various anterior pituitary and related hormones in healthy volunteers.

We have previously found no change in plasma prolactin or growth hormone following long term control of blood pressure with oxprenolol in patients with essential hypertension (Lewis *et al.*, 1979). We recognised, however, that this failure to demonstrate any change in the level of these hormones could have been related to 'noise' because of their responsiveness to external stimuli (Meites, 1977) or to diurnal

variation. Accordingly blood samples were taken during the hours of nocturnal sleep in the present study.

Methods

Seven healthy male medical students were studied (age range 21-23 years). Informed consent was obtained from each subject after approval for the study from the local Ethical Committee had been received. Indwelling venous cannulae were used to minimise the disturbance of blood sampling during sleep. The cannulae were inserted 2 h before taking the first sample and were kept patent by the slow continuous infusion of 250 ml of heparinised saline over the 12 h sampling period. The volunteers were given single blind cross-over treatment with a capsule of lactose, acebutolol (200 mg) and propranolol (80

mg) on three separate occasions 2 weeks apart. The three capsules were given in randomised order, at 20.00 h. Blood sampling began at 22.00 h after all subjects had been in the recumbent position for 30 min. Fifteen 5 ml blood samples were taken between 22.00 h and 09.00 h (see Figures 1–6) the venous line being emptied of heparinised saline before each sample was taken. The 5 ml blood sample was added to a tube containing ethylene-diamine-tetraacetic acid-potassium (EDTA), the plasma separated within 30 mins and stored at -18°C until assayed for prolactin, growth hormone luteinising hormone (LH), follicle stimulating hormone (FSH), cortisol and testosterone. All hormones were measured by radio-immunoassay (Groom, 1977; Dyas, Read & Riad-Fahmy, 1979; Riad-Fahmy *et al.*, 1979). All the samples for each hormone were assayed at the same time to eliminate errors due to inter assay variability. Three way analysis of variance was used for statistical analysis of the results. The 'main effects' of subject, drug and time on the hormone levels were analysed. The 'two way interactions' of subject and drug, subject and time, and drug and time, on the hormone levels were also analysed. *F* values were calculated for each of the variables. Where a two-way interaction was found to be significant, this data was used to recalculate the significance of the 'main effect' to give a more 'conservative' figure for the *F* value.

Results

The results are expressed graphically (Figures 1–6.) A summary of the statistical analyses is given in Table 1.

Prolactin

Figure 1 illustrates the time course of changes in the plasma level of prolactin in the seven subjects studied

Figure 1 The overnight time course of plasma levels of prolactin after placebo (■) and single doses of propranolol 80 mg (▲) and acebutolol 200 mg (●). Each point shows the mean $\pm$ s.e. mean of seven subjects.

Figure 2 The overnight time course of plasma levels of FSH after placebo (■) and single doses of propranolol 80 mg (▲) and acebutolol 200 mg (●). Each point shows the mean $\pm$ s.e. mean of seven subjects.

over the 12 h sampling period. Analysis of the main effects (subject, time, drug) showed (Table 1) that there were significant differences in prolactin levels between the subjects studied, taking into account the effects of the drugs and the effects of time. There was also a significant alteration in prolactin levels with time over the 12 h period studied, despite the difference between subjects and the effects of the drugs, indicating a diurnal variation in the pattern of prolactin secretion. Acebutolol significantly reduced the blood levels of prolactin, whereas propranolol did not, analysed over the 12 h period; a small reduction in prolactin levels after propranolol is apparent (Figure 1) but only more than 6 h after giving the drug.

Analysis of the two-way interactions (Table 1) showed that the response in prolactin levels to the two drugs studied was significantly different between subjects. Different subjects showed significant variations

Figure 3 The overnight time course of plasma levels of LH after placebo (■) and single doses of propranolol 80 mg (▲) and acebutolol 200 mg (●). Each point shows the mean $\pm$ s.e. mean of seven subjects.

Figure 4 The overnight time course of plasma levels of testosterone after placebo (■) and single doses of propranolol 80 mg (▲) and acebutolol 200 mg (●). Each point shows the mean $\pm$ s.e. mean of seven subjects.

in prolactin levels with respect to time in the absence of either drug. Neither acebutolol nor propranolol significantly altered the time course of prolactin levels in any individual subject.

Gonadotrophins (FSH and LH)

FSH and LH levels also showed significant differences between subjects. There was no significant alteration with time in the pattern of FSH levels (Figure 2), but LH levels showed significant evidence of a diurnal rhythm (Figure 3). FSH levels were significantly reduced by propranolol and by acebutolol, but LH levels were not altered by either drug.

Both FSH and LH showed significant subject-drug interactions, i.e. the responses to the two drugs studied were significantly different between the subjects. There was no interaction between subject and

Figure 5 The overnight time course of plasma levels of testosterone after placebo (■) and single doses of propranolol 80 mg (▲) and acebutolol 200 mg (●). Each point shows the mean $\pm$ s.e. mean of seven subjects.

Figure 6 The overnight time course of plasma levels of cortisol after placebo (■) and single doses of propranolol 80 mg (▲) and acebutolol 200 mg (●). Each point shows the mean $\pm$ s.e. mean of seven subjects.

time, nor between drug and time on the levels of these two gonadotrophins.

Testosterone

Testosterone levels again varied between subjects, and with time, indicating the presence of a diurnal rhythm. Propranolol, but not acebutolol, significantly reduced the secretion of this hormone (Figure 4).

There was a significant subject-drug interaction but no interaction between subject and time or drug and time.

Growth Hormone

Again there was a significant variation between subjects with respect to the blood levels of growth hormone. No diurnal rhythm was evident. Neither acebutolol nor propranolol altered growth hormone levels.

There was a significant subject-drug interaction and a significant subject-time interaction but neither drug significantly altered the time course of growth hormone levels (Figure 5).

Cortisol

In common with the other hormones studied there was a significant difference between subjects in the blood levels of cortisol. A diurnal rhythm was obvious (Figure 6). Propranolol but not acebutolol significantly increased blood levels of cortisol.

Subject-drug and subject-time interactions were seen but no drug-time interaction.

Table 1 A summary of the results of statistical analyses of data.

Main effects	Prolactin	FSH	LH	Testosterone	GH	Cortisol
Subject	< 0.01	< 0.01	< 0.01	< 0.01	< 0.05	< 0.01
Time	< 0.01	NS	< 0.01	< 0.01	NS	< 0.01
Drug (Propranolol)	NS	< 0.01	NS	< 0.01	NS	< 0.05
(Acebutolol)	< 0.01	< 0.01	NS	NS	NS	NS
<i>Two-way interactions</i>						
Subject/Drug (Propranolol)	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.05
(Acebutolol)	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.05
Subject/Time	< 0.01	NS	NS	NS	< 0.01	< 0.01
Drug/Time (Propranolol)	NS	NS	NS	NS	NS	NS
(Acebutolol)	NS	NS	NS	NS	NS	NS

Figures indicate *P* values. NS = result not statistically significant. *P* values given for main effects are based on 'conservative' *F* values (see text).

Discussion

The blood levels of prolactin, LH, testosterone and cortisol showed characteristic changes with time during the relatively undisturbed hours of nocturnal sleep, whereas those of FSH and growth hormone remained constant. Similar underlying patterns have generally been described previously for these hormone levels individually—prolactin (Parker, Rossman & VanderLaan, 1973), cortisol (Krieger, 1979), FSH (Judd, 1979), and growth hormone (Parker *et al.*, 1979), though a recent study with more frequent sampling showed no consistent diurnal variation in LH levels (Judd, 1979). Our study showed the inter-subject variability in hormone levels, both on and off β -adrenoceptor blocking drugs, that is to be expected from biological variation, but the underlying time course of changes in any hormone level remained unaltered by either drug.

The levels of prolactin were lowered by acebutolol but not significantly by propranolol. The smaller effect of propranolol could be related to differences between the haemodynamic effects of acebutolol, with its partial agonist and cardioselective properties, and those of propranolol, with neither. Alternatively it could be attributable to inadvertent use of a lower β -adrenoceptor blocking dose, given the wide inter-subject variation in the pharmacokinetic properties of propranolol (Shand, Nuckolls & Oates, 1970), although this explanation seems unlikely in view of its effects on cortisol levels as discussed below. We have previously reported that oxprenolol did not alter prolactin levels in patients with essential hypertension (Lewis *et al.*, 1979) but only single samples at clinic attendances were measured in that study. Little has been known of the role of beta adrenoceptors in controlling prolactin secretion, though isoprenaline

infusion has been reported to increase prolactin levels (Imura & Kato, 1974). Chronic treatment of rats with propranolol can result in increased brain levels of dopamine (Morinan & Leonard, 1977) which in turn could reduce prolactin secretion (del Pozo & Flückiger, 1973), and some β -adrenoceptor blockers affect 5-hydroxytryptamine receptors which might influence prolactin secretion through this possible relationship remains unresolved (Frantz, 1979).

LH levels were unaltered by the β -adrenoceptor blocking drugs but FSH levels were lowered. This contrasts with data showing that propranolol increased LH but had no effect on FSH levels in animals (Borrell *et al.*, 1977). The influence of beta blockers on these gonadotrophins has been little studied in man, though propranolol is reported to have had no effect on the pulsatile release of LH (Yen *et al.*, 1974). Testosterone levels generally follow those of LH (Rowe *et al.*, 1975). In the present study propranolol lowered testosterone levels while not altering LH. Acebutolol in contrast had no effect on testosterone levels. These apparent discrepancies could be attributed to the haemodynamic effects of acute doses of these drugs. Thus propranolol is likely to cause greater reduction of cardiac output with arterial vasoconstriction than acebutolol (Gibson, 1974; Lewis *et al.*, 1973; Basil *et al.*, 1973) and changes in testicular blood flow are known to influence Leydig cell response to gonadotrophins (Eik-Nes, 1964). These haemodynamic differences may also explain the observation that propranolol increased cortisol levels whereas acebutolol did not.

Growth hormone levels were highest during the early hours of sleep, as previously recognised (Parker *et al.*, 1979), but were unaltered by either beta blocking drug. The control of growth hormone secretion is

complex: it has been suggested that adrenergic mechanisms participate as well as dopaminergic and serotonergic mechanisms (Imura & Kato, 1974) but the present findings lend no support to this.

The present study of hormone levels measured serially during the hours of sleep shows that acute doses of β -adrenoceptor blocking drugs can lower blood levels of prolactin and FSH. In the light of our earlier report that oxprenolol did not alter prolactin levels as measured in single samples, these results emphasise the need to take account of random (Meites, 1977) and circadian variation when seeking such effects. The direction of the effect on prolactin levels is such that it would tend to lower blood pressure, since prolactin causes renal retention of salt and water (Horrobin *et al.*, 1971), and enhances

arterial vasoconstrictor responses to noradrenaline (Horrobin, Manku & Burstyn, 1973). Changes in the levels of testosterone and cortisol were also induced, though it seems possible that these could have been secondary to haemodynamic effects. The clinical relevance and haemodynamic consequences of these acute effects of β -adrenoceptor blockers on hormone levels is of course difficult to evaluate. The effects of long term treatment with β -adrenoceptor blockers may prove to be more relevant to therapeutic considerations.

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