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Prolactin response to low dose sulpiride

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1 Prolactin levels in response to sulpiride were studied in healthy volunteers.
2 Oral doses of 1 mg—50 mg sulpiride or placebo were given.
3 A 3 mg sulpiride dose produced similar levels to those achieved with both 10 mg and 50 mg.
4 Circadian effects were studied showing no significant differences in the prolactin response to sulpiride.
5 Acute or chronic responses showed an attenuation with chronic sulpiride treatment to 50% of the peak levels attained with acute treatment.
6 These results indicate that sulpiride retains its potent ability to produce prolactin release even at the low doses studied here.

Keywords sulpiride prolactin low dose

Introduction

Sulpiride is a substituted benzamide which selectively blocks postsynaptic dopaminergic neurones, affecting only non adenyl cyclase linked (D_2) receptors. Its chief clinical role is an antipsychotic agent used in the treatment of schizophrenia in doses of 800–2400 mg. Like other drugs in this class it causes prolactin release.

Two other potential clinical uses for sulpiride have been proposed, namely its ability to enhance defective milk production during lactation (Aono *et al.*, 1979; Ylikorkala *et al.*, 1982) and to potentiate progestagen only contraception (Payne *et al.*, 1985). In both of these circumstances, the clinical effect may depend, at least in part on the prolactin releasing effect of sulpiride, and it would be important therefore to define the minimal effective dose. Accordingly, the present investigation was designed to establish: (1) The prolactin sulpiride dose response curve at lower, presumably less sedative, single oral doses (1 mg–50 mg) in healthy female volunteers. (2) The circadian variation, if any, in prolactin response to sulpiride. (3) The prolactin response to chronic sulpiride dosing.

Methods

Study 1

Seven healthy female volunteers aged 18–23 years with height range 1.520–1.740 m and weight range 54.2–68.4 kg completed the investigation. Five of the subjects were taking a combined oral contraceptive during the study. Subjects were free from other medication (except the oral contraceptive pill) for 2 weeks prior to the study. Ethics Committee approval and informed consent were obtained.

The subjects were admitted after an overnight fast at 08.45 h on five successive weeks. Blood samples were withdrawn through a heparinised cannula at −30, −15 min and immediately predose to establish basal prolactin levels. Sulpiride

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suspensions of 1, 3, 10, 50 mg and matching placebo were given according to a randomised crossover design. Standardised meals were provided at 1, 3 and 8 h after treatment.

Venous blood samples (10 ml) were collected at 30, 60, 90, 120, 240, 360, and 480 min after treatment and plasma was stored at −20° C.

Sulpiride treatments were specially prepared in the form of suspensions, with matching placebo suspension by the Pharmacy, Ninewells Hospital and Medical School, Dundee. These were prepared freshly each week from crushed sulpiride tablets with the addition of methylhydroxybenzoate, glycerol, peppermint oil, syrup and sterile water, suspended in sodium carboxymethylcellulose.

The prolactin assay was performed using a kit produced by the Chelsea Hospital for Women which employs the solid phase separation procedure. The interassay coefficient of variation was 5.9% at 300 miu l^{-1} and the intraassay coefficient of variation was 3.8% at 300 miu l^{-1}.

Study 2

Five healthy female volunteers aged 19–21 years completed the study. The height range was 1.630–1.740 m and the weight range was 55.6–68.9 kg. Four of the subjects were taking the combined oral contraceptive pill.

Subjects were admitted at 08.30 h (morning) or 21.00 h (evening) on 5 successive weeks and remained for 10 h. Treatment was given on the first 4 weeks on a single-blind cross over design as follows: single doses of 1 mg sulpiride in the morning, placebo in the morning, single dose of 1 mg sulpiride in the evening, and placebo in the evening. During week 5 1 mg sulpiride was given each evening for 7 consecutive days with blood sampling being carried out on the seventh evening. Morning doses of sulpiride were administered after an overnight fast, followed by meals at 1, 3 and 8 h. Evening doses were administered after a 5 h fast, followed by meals at 1 and 10 h.

On each study day blood samples were withdrawn through a heparinised cannula at −30 min and immediately predose to establish basal prolactin levels. Sulpiride suspensions containing 1 mg 5 ml^{-1} and matching placebo suspensions were prepared freshly each week by the Pharmacy, Ninewells Hospital and Medical School. The suspension was prepared from sulpiride base lot 83-27 NI720 10 Juillet 83 supplied by Delagrange with the addition of the same compounds listed in Study 1 and suspended in the same way. Blood samples (10 ml) were taken at 30, 60, 90, 120, 360 and 600 min after treatment.

Statistical analysis of prolactin levels was performed on log transformed data using the paired *t*-test, with the Bonferroni correction factor for multiple comparisons.

Subject 7 (Study 1) and subject 1 (Study 2) both dropped out for personal reasons unrelated to the study. Their results were not included.

Results

All treatments were well tolerated with no evidence of sedation either observed or reported.

No significant changes in screening biochemistry or haematology were observed at the end of the study.

Prolactin responses to graded doses of sulpiride

The prolactin responses induced by placebo, 1 mg, 3 mg, 10 mg and 50 mg of sulpiride (Study 1) are presented in Figure 1 (geometric mean prolactin levels). Prolactin levels fell in all subjects following the stress induced by cannula insertion, and increased prolactin levels were induced by all doses of sulpiride. The mean peak prolactin response to 50 mg sulpiride occurred at 60 min, to 10 mg and 3 mg at 90 min and to 1 mg at 120 min. Comparison of the geometric mean peak prolactin levels with 95% confidence limits (Figure 2) showed no significant differences between treatment with 3 mg, 10 mg and 50 mg sulpiride, but the 1 mg dose produced reduced levels by comparison (1 mg *vs* 10 mg and 1 mg *vs* 50 mg, $P < 0.01$; 1 mg *vs* 3 mg NS).

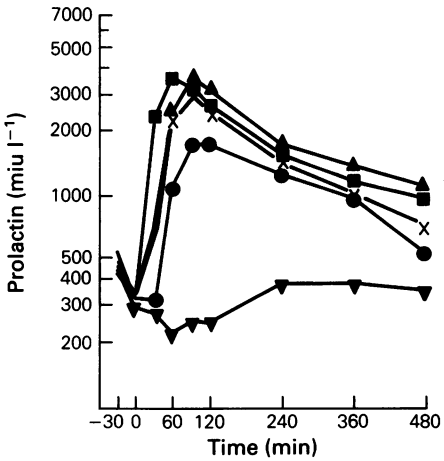

Figure 1 Geometric mean prolactin levels against time in response to placebo (▼, 1 mg (●), 3 mg (×), 10 mg (▲) and 50 mg (■) oral sulpiride ($n = 7$).

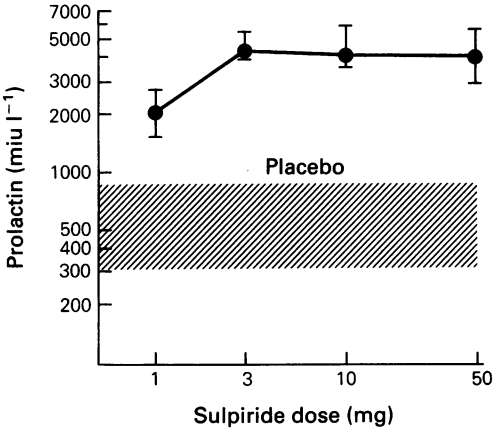

Figure 2 Geometric mean peak prolactin levels and 95% confidence limits in response to placebo, 1 mg, 3 mg, 10 mg and 50 mg oral sulpiride (n = 7).

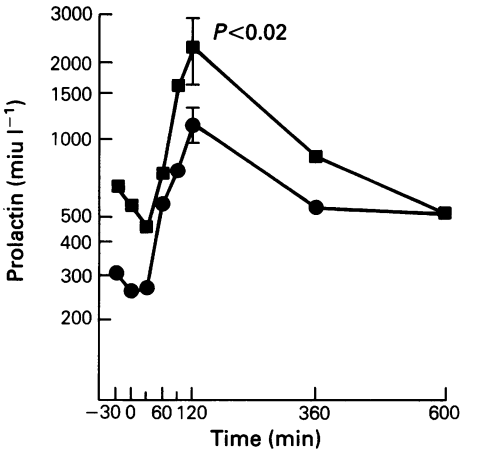

Figure 3 Geometric mean prolactin levels in response to an acute dose of 1 mg oral sulpiride given in the morning (■), compared with chronic dosing with 1 mg oral sulpiride for 7 days (●) (n = 5).

The mean area under the curve for prolactin for the different doses of sulpiride showed no significant differences between 3 mg, 10 mg and 50 mg but the response to 1 mg was 49% of the maximum response and was significantly less than the response to the other doses (1 mg *vs* 50 mg $P < 0.04$, 1 mg *vs* 10 mg $P < 0.03$, 1 mg *vs* 3 mg $P < 0.02$). The mean prolactin responses to sulpiride in the volunteers taking oral contraception showed no differences from those on no treatment.

Prolactin responses to morning and evening doses of sulpiride

Marginally higher initial levels of prolactin and lower post treatment levels at 600 min were seen in response to morning treatment in comparison with evening treatment which did not reach statistical significance. A comparison of the responses to 1 mg sulpiride given in the morning and evening showed slightly higher basal and lower 600 min post treatment values in response to the morning dose, which failed to attain statistical significance (similar to the placebo response). There were no differences in peak prolactin responses.

Prolactin response to acute and chronic dosage with sulpiride

The prolactin responses to an acute dose of 1 mg sulpiride were compared to the response after 7 consecutive days of dosing with 1 mg sulpiride (Figure 3). The lower basal levels after chronic treatment did not differ significantly from the levels before acute treatment. The response to chronic treatment was 50% of the response to acute treatment in respect of the peak prolactin levels ($P < 0.01$) but did not differ for the area under the curve.

Discussion

Sulpiride has been shown to be a potent stimulator of prolactin release whether by oral (Sugnaux *et al.*, 1983) or intramuscular administration (Mancini *et al.*, 1976). The lowest sulpiride dose available in a commercially available preparation is a 50 mg tablet and although this is known to stimulate prolactin release, the dose response characteristics to lower sulpiride doses have not been defined. This study has demonstrated the remarkable retention of the prolactin releasing properties of sulpiride at doses as low as 1 mg, which induced a prolactin response of approximately 50% of that achieved with 10 mg and 50 mg. At the upper end of the doses used in this study, the responses to 3 mg, 10 mg and 50 mg showed no significant differences.

It would appear that the prolactin response to sulpiride reaches a maximum at 3–10 mg and thereafter, further doses achieve minimal if any, further increase in prolactin release and the rates of decay in the prolactin levels were similar for both 10 mg and 50 mg of sulpiride. Further studies would be required to establish whether higher doses of sulpiride would have greater effects on prolactin levels, either in peak response or duration of effect.

Although there were no differences in area under the curve, the prolactin response to 1 mg sulpiride after 7 days dosing was only 50% (peak levels) of that seen on the first day of exposure to the drug. This attenuation of response after chronic treatment complements the observations of Tormey *et al.* (1981) and Cohen *et al.* (1983) who demonstrated a refractory period in the response of prolactin to sulpiride at 2, 8 and 24 h after dosage. The reason for this is not clear, but it is possible that dopamine turnover increases in response to blockade, as has been demonstrated in the rat (Annunziato *et al.*, 1980) such that with chronic therapy, an increased amount of drug is required to produce the same effect. Alternatively the reduction in prolactin response could reflect down regulation of dopamine receptors. Further work is required to clarify whether this attenuation of the prolactin response will progressively increase or decrease with time, or whether this attenuation is displayed across the full dose range. Prolactin levels are known to show a circadian variation (Nokin *et al.*, 1972), and the characteristically higher night time levels were confirmed in this study. After allowing for this diurnal variation, the prolactin responses induced by sulpiride given in the morning and in the evening were similar, suggesting that, in any therapeutic usage, night time administration of sulpiride would be preferable as any sedative effect would not be noticed. However, the range of doses used in this investigation were well tolerated, irrespective of the time of day at which they were administered.

An important aspect of this study was the absence of sedative effects in association with the low doses of sulpiride used. At higher doses, sulpiride is known to have sedative effects (Liljequist *et al.*, 1975) which would considerably limit the potential for long term clinical use. In addition to the absence of sedative effects with the 1 mg–50 mg dose range studied here, no adverse biochemical or haematological changes were observed.

Oestrogens are known to potentiate prolactin secretion in rats (Cramer *et al.*, 1979), but the effect of the combined oral contraceptive pill does not affect prolactin levels in humans (Davis *et al.*, 1984). In our study, the prolactin responses to sulpiride were similar in both users and non-users of oral contraceptives.

One of the potential applications of sulpiride is its ability to potentiate the progesterone only pill (Payne *et al.*, 1985), offering the possibility of improving a non-oestrogenic contraceptive preparation. The dose of sulpiride used in that study was 50 mg twice daily but this report opens the possibility that much lower doses of sulpiride might be able to achieve the desired contraceptive effect in combination with the progesterone only pill.

Another potential application for sulpiride is the augmentation of inadequate lactation (Aono *et al.*, 1979; Ylikorkala *et al.*, 1982). In the report of Aono *et al.* (1979), a maternal dose of 50 mg sulpiride daily resulted in 1 $\mu g\ ml^{-1}$ of sulpiride being excreted in the breast milk 2 h after ingestion of the drug. Our study raises the possibility that a daily exposure to sulpiride within that dose range might have a substantial prolactin releasing impact on new-born infants. Although there is no evidence that sulpiride would cause harm to these infants, it would seem desirable to employ the lowest effective dose of drug required. This study raises the possibility that the desired therapeutic effect might be achieved with much lower doses of sulpiride without transferring measurable sulpiride to the baby.

This investigation suggests that low doses of sulpiride are well tolerated and that the potency of their prolactin releasing properties may have far reaching implications. Apart from the potential clinical applications, studies of the prolactin responses to low doses of sulpiride may prove a useful tool in the clarification of the dopaminergic control of prolactin secretion.

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