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RAPID COMMUNICATION

Stimulation of Human Prolactin Secretion by Sulpiride

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Synopsis

Intramuscular injection of 100 mg of sulpiride significantly raised plasma human prolactin (hPRL) levels in all of 7 normal subjects examined. The mean (±SE) peak value was 78.0±16.6 ng/ml, which was observed 30 min after the injection. Daily administration of sulpiride (50 mg tid po) raised plasma hPRL levels in all 7 patients with peptic ulcer, with peak values obtained within 2 weeks. Lactation occurred in 2 of these patients. It is concluded that sulpiride stimulates hPRL secretion in man.

Recent studies have demonstrated that psychotropic drugs such as reserpine and chlorpromazine cause a significant increase in plasma human prolactin (hPRL) levels, frequently inducing galactorrhea (Frantz *et al.*, 1972). Chlorpromazine is now commonly used as a means of stimulating hPRL secretion in man (Friesen *et al.*, 1972; Turkington, 1972).

Borenstein *et al.* (1968) first reported that galactorrhea occurred following sulpiride administration in patients with metal disorders. Sulpiride, a new type of tranquilizer, differs from phenothizine derivatives (Laville and Margarit, 1968) and has a beneficial effect on peptic ulcers (Cornet and Grivaux, 1968).

This paper describes our studies on the effect of sulpiride on plasma hPRL concentrations in man.

Materials and Methods

Seven male volunteers, aged 18 to 31, were used in this experiment. They were non-obese and apparently normal in endocrine and metabolic function. After overnight fasting and absolute bed rest for at least 30 min, they received an injection of sulpiride* (Fujisawa Co. Ltd., 100 mg im), chlorpromazine (Shionogi Co. Ltd., 25 mg im) or TRH (Tanabe Co. Ltd., 500 μg iv). These studies were repeated at one-week intervals.

During the experiments the subjects were kept recumbent. Venous blood was collected in a heparinized syringe through an indwelling needle at 30 min intervals for 120 min following the injection.

Blood samples were also collected at 9 AM once a week from 7 patients with proven gastric ulcer (5 females and 2 males) during treatment with sulpiride (50 mg tid po) for 5 weeks.

Plasma was promptly separated and frozen at −20°C for assay of hPRL concentrations, which were determined by homologous radioimmunoassay as previously described (Kato *et al.*, 1974). Highly purified hPRL (Friesen #1) and anti-hPRL serum (Friesen #1) were kindly supplied by the NIAMDD. Statistical analysis was performed by Student's *t* test.

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* N-(1-ethyl-2-pyrrolidinylmethyl)-2-methoxy-5-sulfamoyl-benzamide.

Results

Plasma hPRL responses to sulpiride, chlorpromazine and TRH in normal subjects (Fig. 1)

The intramuscular injection of sulpiride caused a significant increase in plasma hPRL in all of 7 normal subjects examined. The mean (±SE) peak value obtained 30 min after the injection was significantly higher than the mean basal value of plasma hPRL (78.0±16.6 ng/m*l* *vs* 12.8±3.3 ng/m*l*, $P<0.01$).

Plasma hPRL levels also increased significantly after chlorpromazine or TRH injection in normal subjects, the mean peak values being 47.8±6.8 ng/m*l* and 48.8±5.8 ng/m*l*, respectively. These values were significantly higher than their respective basal hPRL levels ($P<0.01$).

The maximum responses of plasma hPRL to these three stimuli were not significantly different from each other, but the peak appeared earlier after sulpiride and TRH than after chlorpromazine.

The hypnotic effect often observed after chlorpromazine was not noted after sulpiride. One of 7 normal subjects complained of transient nausea after TRH injection. No other side effect was observed.

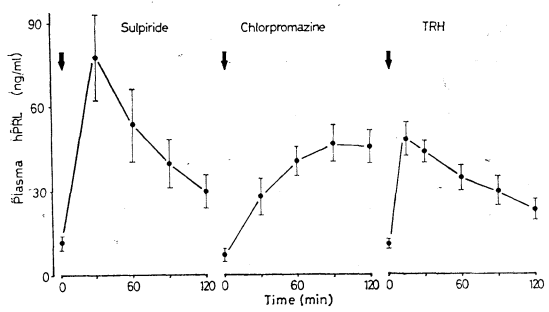

Fig. 1. Plasma human prolactin (hPRL) levels following injection of sulpiride (100 mg im). chlorpromazine (25 mg im) and TRH (500 μg iv) in 7 normal subjects. Mean±SE are shown.

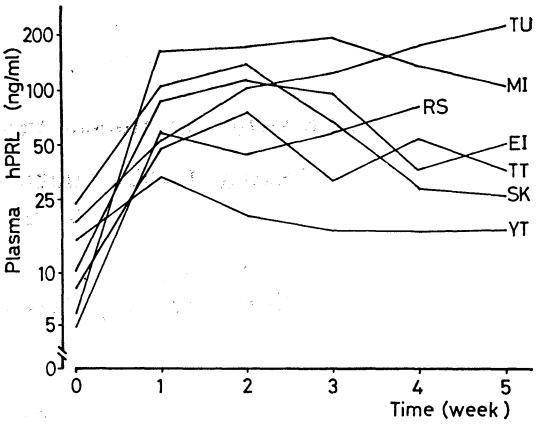

Fig. 2. Basal levels of plasma hPRL in 7 patients with gastric ulcer during treatment with sulpiride (50 mg tid po). Letters are initials of the patients.

Plasma hPRL levels during treatment with sulpiride in patients with peptic ulcer (Fig. 2)

Basal plasma hPRL levels in 7 patients with gastric ulcer ranged from 5.0 ng/m*l* to 24.0 ng/m*l* and increased significantly during treatment with sulpiride to peak levels of 34.0 ng/m*l* to 234 ng/m*l*. These plasma hPRL values were reached within 2 weeks, and then they decreased slightly in 5 of 7 patients. In the other 2 patients, plasma hPRL continued to rise gradually during the administration of sulpiride.

Galactorrhea occurred in 2 (RS, EI) of 5 female patients, 2 and 4 weeks, respectively, after the start of sulpiride administration. Another female patient (MI) complained of tenderness and swelling of the breasts without lactation after 1 week of treatment, but this disappeared in spite of the continued administration of the drug. No significant side effects were observed in 2 male patients (TT, YT).

Discussion

We have demonstrated in the present studies that sulpiride injection (100 mg im) stimulates hPRL release in man. The effec-

tiveness of sulpiride as a hPRL stimulator was comparable to that of chlorpromazine (25 mg im) and TRH (500 μg iv), which are frequently used to stimulate hPRL release (Bowers *et al.*, 1971; Frantz *et al.*, 1972; Friesen *et al.*, 1972; Jacobs *et al.*, 1971). The maximal increase in plasma hPRL after sulpiride injection occurred much earlier than after chlorpromazine.

Sulpiride proved to be a strong antagonist of the central effect of apomorphine (Laville and Margarit, 1968). Apomorphine stimulates central dopamine receptors (Roos, 1969) and inhibits hPRL secretion in man (Lal *et al.*, 1973). The inhibitory effect of apomorphine on hPRL secretion is blocked by pretreatment with chlorpromazine (Lal *et al.*, 1973), which raises plasma hPRL levels possibly by blocking dopamine receptors (Horn and Snyder, 1971). It is plausible, therefore, that hPRL release induced by sulpiride is due to its inhibitory effect on dopaminergic receptors either in the central nervous system or in the pituitary.

Kamberi *et al.* (1971) reported that dopamine inhibited PRL secretion and raised the hypothalamic content of PRL release-inhibiting factor (PIF) in rats. On the basis of these findings, chlorpromazine-induced hPRL release was explained by the decreased PIF due to hypothalamic catechlolamine depletion by the drug (Friesen and Hwang, 1973).

However, Takahara *et al.* (1974) recently demonstrated that serum PRL levels significantly decreased following catecholamine infusion into the portal vessel of rats. This suggests that catecholamines take part in control of PRL secretion not only as transmitters which trigger the release of PIF, but also by direct action on the pituitary cells. It has also been reported that apomorphine inhibits PRL release from the rat pituitary incubated *in vitro* (MacLeod and Lehmeyer, 1974). The present observation that sulpiride stimulates hPRL release as quickly as does TRH (Lister *et al.*, 1974) also suggests the possible direct action of this drug on the pituitary gland.

Sulpiride is reported to be useful in the treatment of peptic ulcer (Cornet and Grivaux, 1968), although the exact mechanism is not clear. In the present study, the daily administration of sulpiride significantly raised plasma hPRL levels in patients with gastric ulcer during treatment. It suggests, therefore, that lactation caused by sulpiride in some of these patients is due to hyperprolactinemia. Sulpiride treatment was associated with radiographic improvement in 2 and symptomatic relief in 3 of 7 patients with gastric ulcer. However, the relationship between plasma hPRL levels and the curative effect of sulpiride on peptic ulcer remains unclear.

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