

SULPIRIDE STIMULATION OF PROLACTIN SECRETION IN ADOLESCENTS WITH GYNECOMASTIA: RELATION TO THE CIRCULATING LEVELS OF ESTRADIOL

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SUMMARY

Basal levels of prolactin (PRL) and estradiol (E_2) were studied in 10 adolescents with gynecomastia who were at stages II to IV of their sexual development. In 7 of the 10 patients, the hypophyseal response of PRL to the administration of sulpiride was assessed: 5 of the 7 received 25 mg i.m., and the remaining 50 mg i.m. The 10 cases were compared with 12 control boys without gynecomastia matched for stage of sexual development. Five of the controls were given 25 mg of sulpiride i.m. and the other 50 mg. Basal PRL levels were the same in both groups. Sulpiride stimulates the secretion of PRL in boys with and without gynecomastia. However, a significantly increased circulating E_2 level was found in patients with gynecomastia.

Idiopathic pubertal gynecomastia is a relatively frequent occurrence which generally has a spontaneous resolution. There are several papers that study the behaviour of different hormones¹⁻³, but the results have not allowed us to reach any definite conclusions as regards the etiopathogenesis of the process. In a longitudinal study Lee et al¹ reported an increase in the circulating prolactin (PRL) levels prior to the appearance of gynecomastia. The results obtained by the authors at the time of the development of breast tissue show that: 1) PRL levels are the same as those found in normal adolescents during the same developmental stage, and 2) there is a significant increase both in blood estradiol (E_2) concentrations and in the E_2 : testosterone ratio. However, very little is known about the dynamic behaviour of PRL in this clinical condition.

The aim of the present paper is to evaluate the effect of a dopaminergic antagonist (Sulpiride) on PRL secretion in the adolescent with gynecomastia occurring at different stages of his sexual maturation. We have also assessed the circulating E_2 levels in the same group of patients in order to correlate them with the PRL response to the stimulus and study its possible changes according to the timing of breast development.

MATERIAL AND METHODS

Ten patients with gynecomastia were studied. Their sexual development ranged between stages II and IV according to Tanner's classification⁴, and their age range was 12-16. In 7 of the 10 patients, a sulpiride test was performed. None of the patients studied had received any medication or had a family history of gynecomastia or of any

other pathology. Routine laboratory tests, as well as the X-ray plate of the sellar region, were normal. Sexual chromatin taken from buccal smears was negative in all cases. Breast hyperplasia with a diameter of 2.5-5 cm was observed in all the patients. In 3 of the 10 patients gynecomastia was unilateral. Five patients received 25 mg of sulpiride i.m. and another two 50 mg i.m..

Twelve normal volunteers matched for age and sexual development were used as controls. Five of these 12 controls received 25 mg of sulpiride i.m. and the remaining seven 50 mg i.m..

Blood samples were drawn from all cases 15 min and immediately before (time 0) the injection of sulpiride and then 30 and 60 min after its administration. The test was performed at 8 a.m.. Serum was separated through centrifugation and stored frozen at -20°C until it was processed.

In all the samples PRL was determined by a double antibody radioimmunoassay (RIA). The antigen for iodination, standard and antiserum, was kindly furnished by NIH (NIAMDD). Results were expressed in ng/ml of the standard V.S.L.1 from human hypophysis. The intra-assay variation coefficient was 8%.

In the 10 patients with gynecomastia and in 11 of the 12 controls E_2 was determined in a pool of 2 samples drawn at 15-minute intervals. A RIA which employed E_2 isotopically labelled with ^{125}I was used according to a previously described procedure. The iodination of E_2 was performed in cold with chloramine T., with an efficiency of 60-75%. The labelled steroid was purified through Sephadex LH-20 column chromatography. Elution was performed with benzene: methanol (85:15). Antibody against E_2 was obtained by multiple inoculations to rabbits with 6 oxime- E_2 -bovine serum albumin. Quality control results showed that the antibody was specific for the several steroids studied⁵. Sensitivity was of 25 pg and its accuracy was demonstrated by the parallelism between the standard curve and the progressive serum dilutions of pregnant women. Intra- and inter- assay coefficient variations were 5% and 10% respectively.

The statistic study was performed according to Student's Test for matched samples⁶.

RESULTS

Figure 1 shows the PRL hypophyseal responsiveness to stimulation with sulpiride in the group of patients with gynecomastia compared with that in the control group. The PRL response obtained with sulpiride varied greatly in all the subjects except in the 2 patients with gynecomastia who received 50 mg of the drug. With the administration of 25 mg of sulpiride i.m., a positive response was obtained in both groups. In the control group the maximum response was observed 60 min. after the administration of the drug in all cases but one. In 6 of the 7 patients with gynecomastia, the maximum response occurred 30 min. after the injection. In the remaining case the response was observed at 60 min. The administration of 50 mg of sulpiride i.m. elicited a positive response both in the control group and in the 2 patients with gynecomastia. Four of 7 cases of the control group had a maximum response at 30 min. and the remaining 3, at 60 min. In the 2 patients with gynecomastia, the highest levels of PRL were observed 30 min. after the administration of the drug.

As can be seen in figure 2, mean basal levels of PRL in the patients with gynecomastia do not differ from those in the control group. Fifty mg of sulpiride resulted in a significantly greater response than that obtained with 25 mg in the control group ($p < 0.001$). Sixty minutes after the administration of 25 mg of sulpiride, a maximum of 29.9 ng/ml was obtained. This response was significantly greater than that obtained at 30 min. ($p < 0.01$). In the 2 patients with gynecomastia who were given 50 mg of sulpiride a maximum of 120 and 107.5 ng/ml, respectively, was observed at 30 min.

As can be seen in figure 3 the circulating E_2 levels in the patients with gynecomastia were significantly higher than those in the control group ($p < 0.001$).

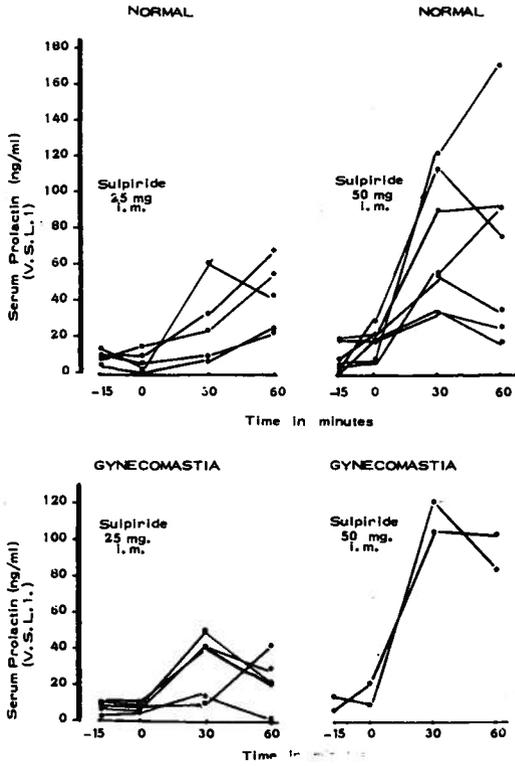


Figure 1 — Individual PRL responses to stimulation with 25 and 50 mg of sulpiride in normal and gynecomastic patients.

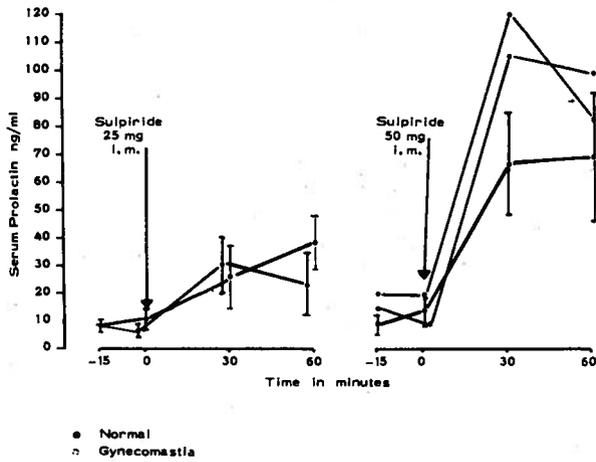


Figure 2 — $M_{\text{mean}} \pm S.E.$ in PRL concentration after stimulation with 25 and 50 mg of sulpiride in normal (o) and gynecomastic (o) patients.

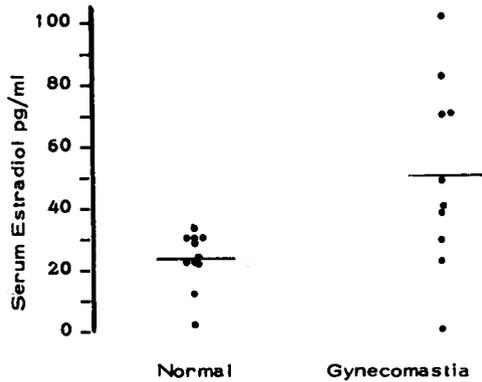


Figure 3 — Circulating E_2 concentration in normal and gynecomastic patients. The line shows the mean in each group.

DISCUSSION

Our results demonstrate that in the patients with gynecomastia basal PRL levels remain unchanged, whereas circulating E_2 concentrations are significantly high. These findings are in agreement with those previously reported by Lee in studies performed in male adolescents at the beginning of their mammary development¹.

PRL levels studied longitudinally in those adolescents who developed gynecomastia were significantly higher prior to its appearance as compared with those found in the subjects without mammary development¹. It is possible to say then that gynecomastia could be caused by the hypersecretion of E_2 (glandular production or peripheral conversion). The breast would be probably sensitized to the estrogenic action (increased number of receptors) by high and transitory levels of prolactin which could be present previously to the development of gynecomastia.¹

The stimulating effect of the hypophyseal secretion of PRL achieved by inhibitors of the dopaminergic tone was demonstrated. Sulpiride, administered intravenously, induced a greater PRL release in the boys with gynecomastia⁷.

There are no significant differences between the groups in the PRL values obtained after stimulation with 25 mg of sulpiride although, in general, the response in those with gynecomastia occurs earlier. D'Agata et al⁸ have reported a greater PRL release in adolescents with gynecomastia using the same dose but a different way of administration (i.v.). These discrepancies in results could be explained by the different route employed and by the different stage of sexual development of the adolescent when the study was performed. The use of 50 mg of the drug does not allow us to draw any conclusions because it was administered in only two patients and it will be necessary to evaluate a greater number of cases.

In Conclusion:

- 1) Sulpiride stimulates the secretion of PRL in boys with and without gynecomastia.
- 2) Within the limits of the dosages employed this is a dose dependent effect.
- 3) Boys with gynecomastia have higher basal E_2 levels than the controls.

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RESUMO

Procedeu-se ao doseamento dos níveis basais de prolactina (PRL) e estradiol E₂ em 10 adolescentes com ginecomastia que se encontravam entre os graus II e IV do seu desenvolvimento sexual. Em 7 dos 10 doentes a resposta hipofisária da prolactina à administração de sulpiride foi avaliada: 5 destes 7 doentes receberam 25 mg i.m. e os restantes 50 mg i.m.. Os 10 casos foram comparados com 12 rapazes sem ginecomastia que serviram de controle e cujo desenvolvimento sexual era equiparável. Cinco dos indivíduos do grupo controle receberam 25 mg de sulpiride i.m. e os restantes 50 mg. Os níveis basais de PRL eram semelhantes em ambos os grupos. O sulpiride estimula a secreção de PRL nos rapazes quer tenham ou não ginecomastia. Contudo, verificou-se a presença de um aumento significativo dos níveis circulantes de E₂ nos doentes com ginecomastia.

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