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EFFECTS OF SULTOPRIDE AND SULPIRIDE ON SERUM PROLACTIN LEVEL IN SCHIZOPHRENIA

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Abstract: Sultopride or sulpiride was administered to 26 schizophrenic patients. In the male patients, there was a significant correlation between serum concentrations of sultopride and sulpiride and prolactin response. In the female patients, there was no significant correlation between them. In sultopride treatment, prolaction response was suggested to be predictive of a good therapeutic response.

Index Terms

schizophrenia, sultopride, sulpiride, prolactin, dopamine

INTRODUCTION

The ability of neuroleptics to influence the endocrine system is well documented. Matsuoka et al[1] reported that 65 % of schizophrenic female patients with amenorrhea, 78 % of schizophrenic patients with galactorrhea and 58 % of schizophrenic male patients developed hyperprolactinemia, in which all of those patients were under the chronic neuroleptic treatment.

The prolactin hormone (PRL) is under doparminergic inhibitory control so that neuroleptics increase its secretion[2]. The role of PRL concentration as an indicator of doparminergic activity has yielded controversial results. It has been reported that a single dose of haloperidol produces a weaker PRL secretion response in schizophrenic patients than in normal controls[3], and Kulkarni et al[4] reported a significant inverse relationship between the PRL response and severity of delusional symptoms.

Sultopride and sulpiride are antipsychotic drugs belonging to the class of substituted benzamides. Sulpiride is reported to be very potent in stimulating PRL release in rats[5] and humans[6], while sultopride, like sulpiride, also stimulates PRL secretion in rats[7] and humans[8].

In the present study, we wanted to investigate the clinical profile or difference of these drugs and also to determine whether changes in PRL response to neuroleptics, in serum PRL levels also reflect central doparminergic activity.

SUBJECTS AND METHODS

The study comprised 26 patients with a mean age of 41.5±12.4 year (16 males with a mean age of 41.8±15.4, and 10 females with a mean age of 42.5±11.7, of whom 10 had an irregular

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menstrual cycle and 2 had a regular menstrual cycle), who were diagnosed with schizophrenia based on DSM-IIIR criteria and had been receiving treatment at Nara Medical University Hospital. There was no significant difference as to mean age and period of illness between the

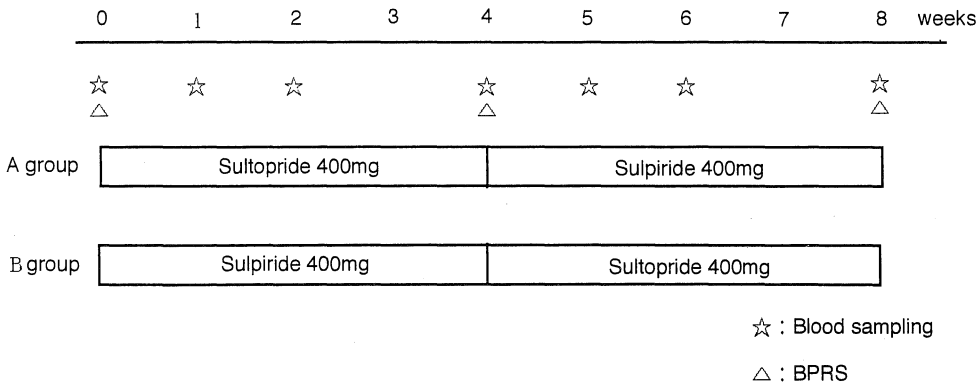

Fig. 1. Schedule of the study.

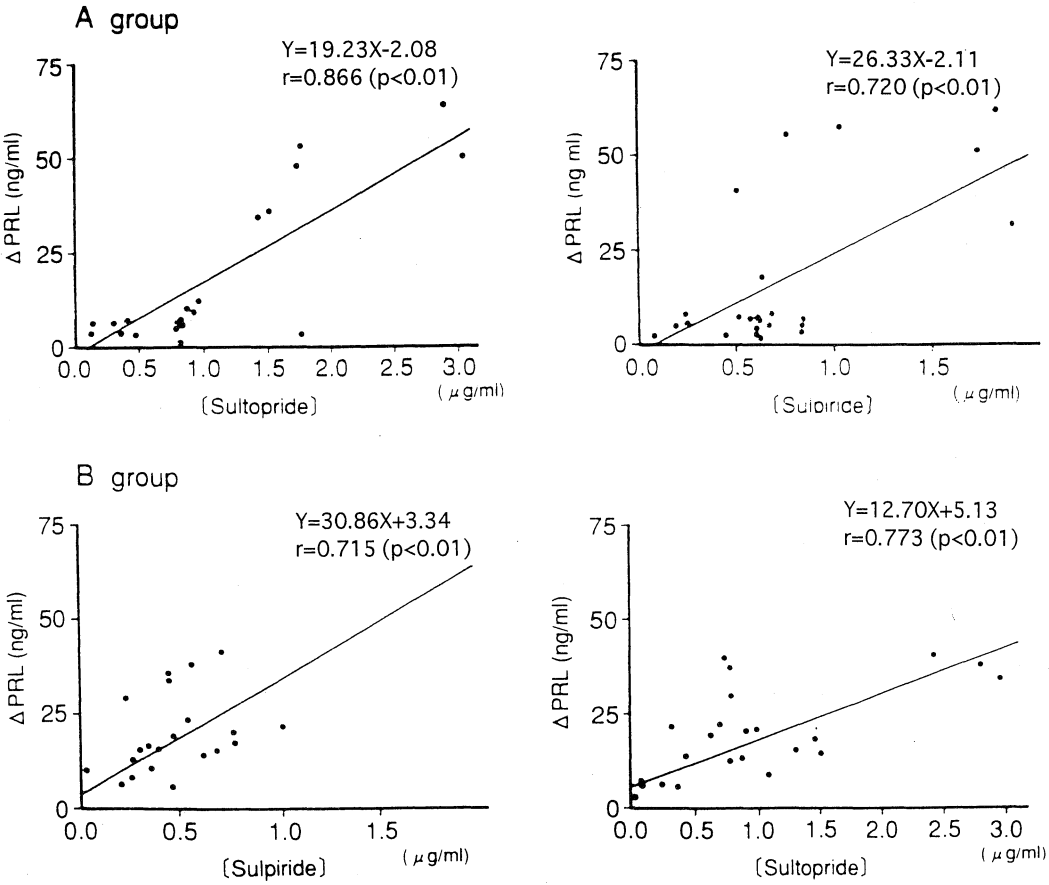

Fig. 2. Significant correlation between ΔPRL (Y ng/ml) and concentration (X μg/ml) of drugs in the male patients.

male group and the female group. All patients gave informed consent to this study.

Subjects were divided into two groups, A and B, and were administered sultopride or sulpiride according to fixed dose crossover method (Fig. 1). A : Sultopride 400 mg/day was administer-

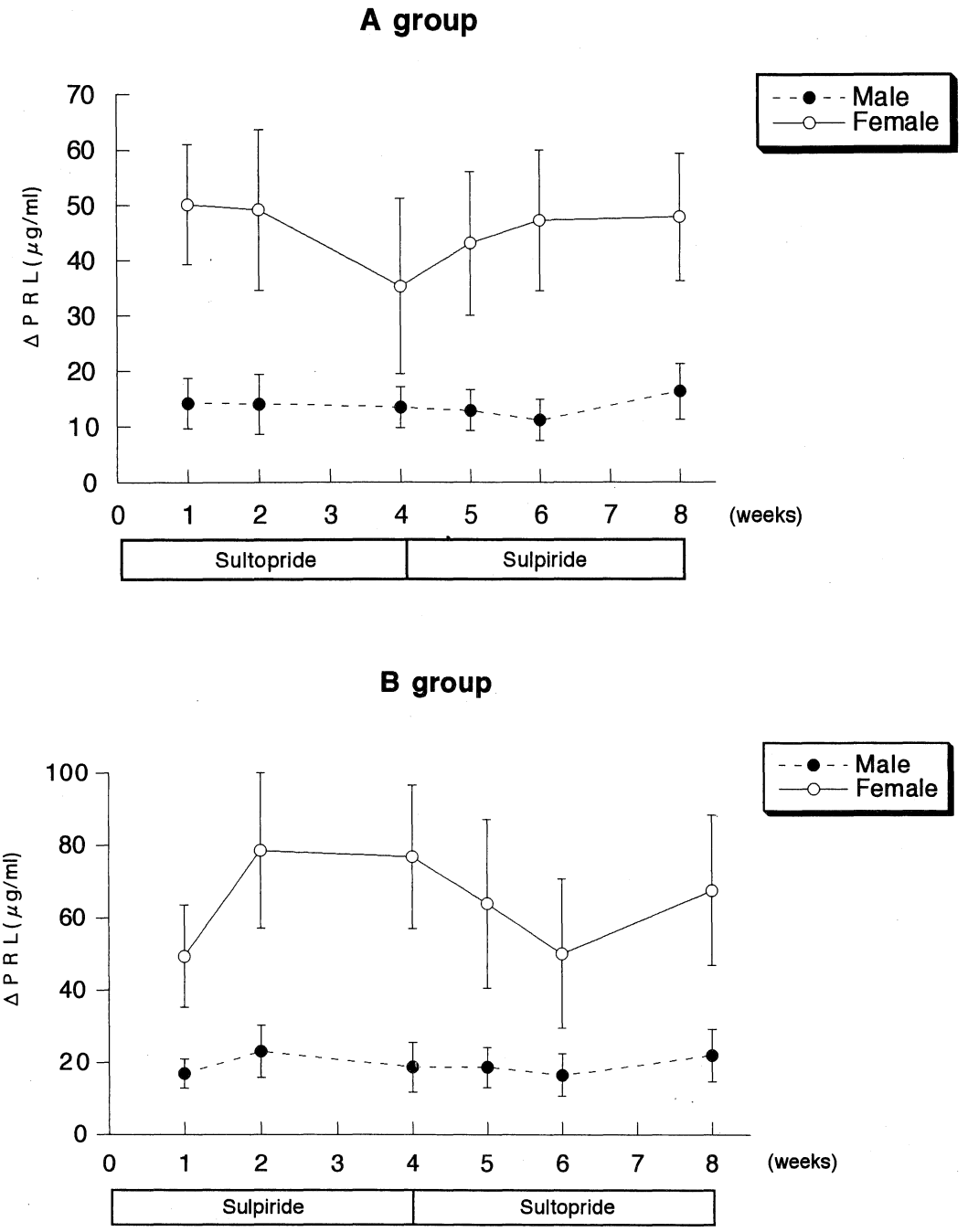

Fig. 3. Time course of ΔPRL response to admisistration of sultopride and sulpiride. ΔPRL is defined as the increment of PRL compared to base level (0 week).

ed orally for the first 4 weeks and then sulpiride 400 mg/day was administered orally for 4 weeks. B: Sulpiride 400 mg/day was administered orally for the first 4 weeks and then sultopride 400 mg/day was administered orally for 4 weeks. Medication regimens prior to this study were continued without any change.

Once the subjects were enrolled in the study, their symptoms were rated on the 18-item Brief Psychiatric Rating Scale (BPRS)[9] by their primary physician at 0, 4, and 8 weeks of the study. This was based on earlier five-dimensional model BPRS subtypes[10], which include the dimensions of 1) Anxiety-Depression (somatic concern, anxiety, guilt feelings, and depressive mood); 2) Anergia (emotional withdrawal, motor retardation, blunted affect, and disorientation); 3) Thought Disturbance (conceptual disorganization, grandiosity, hallucinatory behavior, and unusual thought content); 4) Activation (tension, mannerisms and posturing, and excitement); 5) Hostile-Suspiciousness (hostility, suspiciousness, and uncooperativeness).

In order to determine whether changes in PRL during treatment were predictive of therapeutic response to neuroleptics, we investigated the correlation between ΔPRL at 1 week and the degree of improvement of BPRS total score at 4 weeks or between them at 5 weeks and 8 weeks.

Blood samples were taken routinely at 8 : 30 a. m.; just before the daily medication in 0, 1, 2, 4, 5, 6, and 8 weeks after the beginning of the study for estimating serum PRL levels, sultopride levels and sulpiride levels. PRL was measured by radioimmunoassay using Spac-S prolactin Kit, Daiichi Radioisotope Laboratories., Tokyo. Serum concentrations of sultopride and sulpiride were measured by performing high-performance liquid chromatography with electrochemical detection (HPLC-ECD) by Teijin Bio Laboratories, Inc. Tokyo.

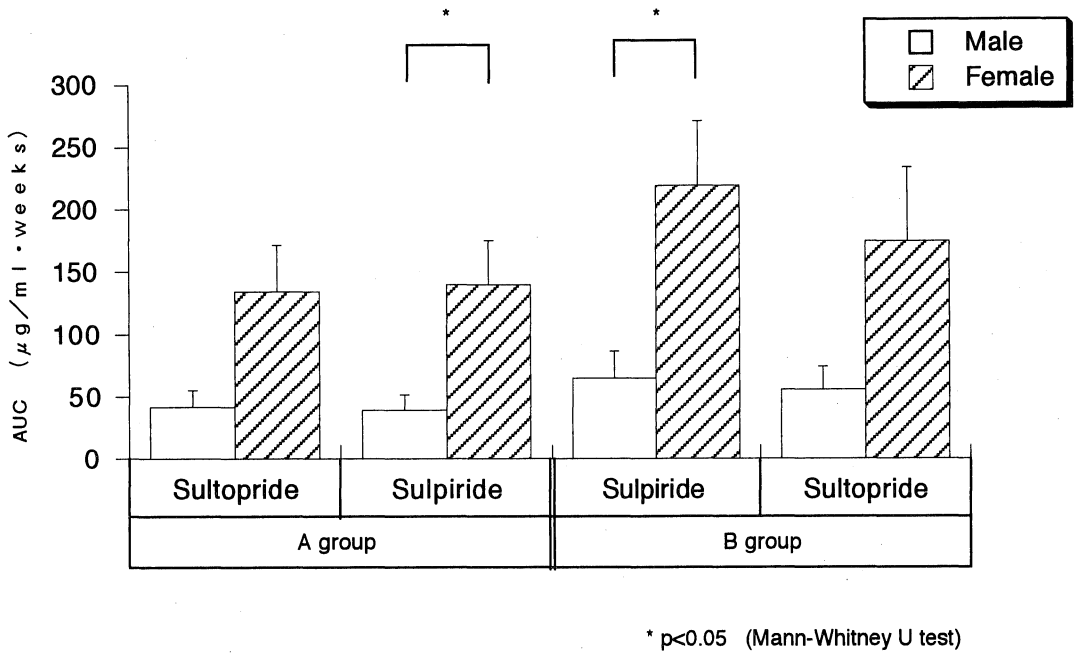

Fig. 4. Area under the curve (AUC) of Fig. 3 was illustrated.

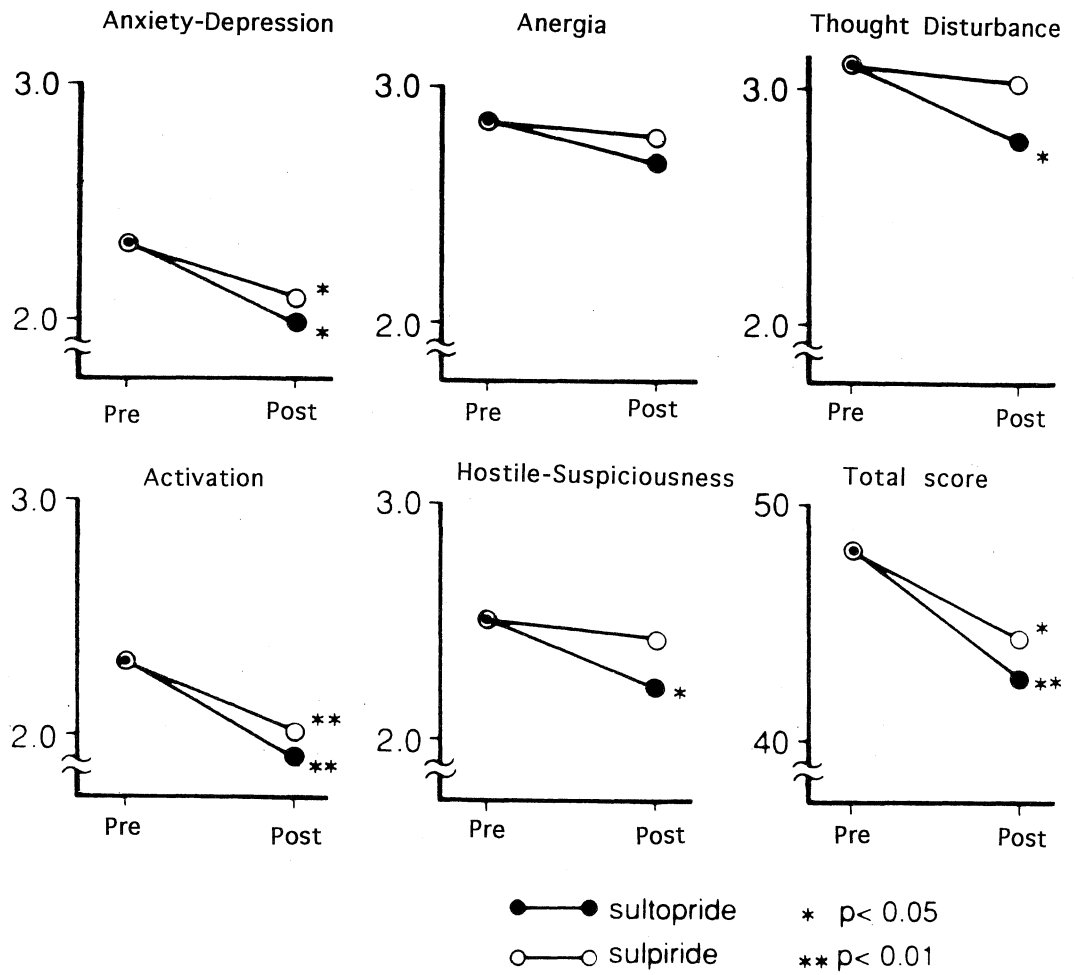

Fig. 5. BPRS cluster analysis of clinical effect of sultopride and sulpiride.

Stastistical analysis of the data was performed with the paired t-test and Mann-Whitney U -test. Values of $p<0.05$ were considered to be significant.

RESULTS

Sultopride in A group and sulpiride in B group were not detectable at 5 weeks in all patients. In the males, there was a significant correlation between serum concentrations of sultopride or sulpiride and ΔPRL in both A and B groups (Fig. 2). ΔPRL was defined as the increment of PRL compared to base level (0 week). The severity of drug-induced hyperprolactinemia was significantly correlated with drug concentration in peripheral blood in the males. On the other hand, in the females, there was no significant correlation between them. Time courses of drug levels and ΔPRLs are presented in Fig. 3. From Fig. 3, the area under the curve (AUC) is calculated and illustrated in Fig. 4. AUC of sulpiride in the females was significantly greater than in the males in both A group and B group, although AUC of sultopride did not significantly differ between genders. In each gender group, there was neither any significant difference between AUC of sultopride in A group and AUC of sultopride in B group, nor any significant

difference between AUC of sulpiride in A group and AUC of sulpiride in B group.

To investigate the clinical profiles of these benzamide drugs, we compared these antipsychotic effects by evaluating BPRS (Fig. 5). BPRS total scores were significantly decreased by sultopride administration and by sulpiride administration. For each BPRS cluster, "Anxiety-Depression" and "Activation" were significantly ameliorated by both administration of sultopride and sulpride, "Thought Disturbance" and "Hostile-Suspiciousness" were significantly ameliorated only by administration of sultopride.

There was a significant correlation between ΔPRL at 1 week and the degree of improvement of BPRS total score at 4 weeks in A group (sultopride). There was no significant correlation between them at 5 weeks and 8 weeks in A group (sulpiride), and there was no significant relationship between them in B group (sulpiride and sultopride). It was suggested that the greater ΔPRL at 1 week of treatment might be a predictor of a better response to 4 weeks sultopride treatment.

DISCUSSION

Sultopride and sulpiride were potent to induce hyperprolactinemia in both male and female patients. In the male patients, there was a significant correlation between the serum concentration of both drugs and ΔPRL, which suggested a peripheral blood effect on doparminergic activity of the anterior lobe of the pituitary. In the female patients, ΔPRL was greater than in the male patients and there was no relationship between serum concentration and ΔPRL, which is consistent with the report of Miyachi et al[8] and inconsistent with the report of Bjerkenstedt et al[11]. The mechanism of PRL secretion response in females be complicated, since fluctuating PRL levels throughout the menstrual cycle are well documented[12].

Both sultopride and sulpiride decreased BPRS total score, Anxiety-Depression score and Activation score. Sulpiride also decreased Thought Disturbance score and Hostile-Suspiciouness score, while sulpiride did not decrease these scores. It was suggested that sultopride had a more potent and wider spectrum than sulpiride.

There was a significant correlation between ΔPRL and the results of treatment with sultopride in A group. This might suggest great ΔPRL might be predictive of a good therepeutic response to neuroleptic treatment. However, there was no significant correlation between them with sulpiride treatment in A group and B group, with sultopride treatment in B group. In might be that benzamide derivatives have some effect on serotonergic activity, since the general consensus in the literature in that serotonin directly stimulates the release of PRL-releasing factor (PRF)[13,14]. Some caution must be applied in interpreting ΔPRL as an indicator of doparminergic activity.

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