Plasma Levels of Fluphenazine and Prolactin in Psychiatric Patients

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Summary. A total of 100 patients receiving fluphenazine (FPZ) decanoate for at least 12 months (96 schizophrenics and 4 other diagnoses) were investigated for plasma levels of FPZ and prolactin on the day of injection (day 0) and 7 days later (day 7). The plasma FPZ level significantly correlated with the weekly dose of FPZ. The plasma FPZ level per weekly FPZ dose multiplied by 100 (the FPZ ratio) showed a 20-fold variation. The FPZ ratio was significantly higher in the day- and in-patients (hospital-patients) than in out-patients. The plasma prolactin level significantly correlated with the plasma FPZ level but the prolactin to FPZ ratio negatively correlated with the plasma FPZ level. The prolactin to FPZ ratio was lower in the hospital patients than in the out-patients. This may suggest either that the high prolactin to FPZ ratio is an indicator of the therapeutic efficacy of FPZ or that there are at least two biologically distinct subgroups, one with a sharp prolactin response to FPZ, therefore with good prognosis, and another with the reverse direction.

Key words: Fluphenazine decanoate – Plasma level – Prolactin

Introduction

Many investigations have demonstrated that relapses of schizophrenia are greatly reduced by administering anti-psychotic medication. Fluphenazine (FPZ) decanoate and other depot anti-psychotics have been enjoying a reputation as effective maintenance therapy for schizophrenic disorders (Denham and Adam-

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son 1973; Hirsch et al. 1973; Hogarty et al. 1979; Tegeler and Lehman 1981).

The optimal dose of anti-psychotics remains debatable. Some authors claimed that much a higher dosage than usually prescribed alleviated the symptoms of refractory schizophrenic disorders (Dencker et al. 1978, 1981; Hollister and Kim 1982; Zarifian et al. 1982). Other investigators maintained that clinical effects could not be increased above a certain critical level of the dose (Donlon et al. 1980; Neborsky et al. 1981). More uncertain is the optimal dose of maintenance anti-psychotics. Ample evidence suggests that schizophrenic patients relapse when their maintenance medication is withdrawn (Andrews et al. 1976; Cheung 1981; Goldberg et al. 1977; Hogarty and Ulrich 1977; Johnson et al. 1983; Wistedt 1981). However, little is known about the therapeutic level of the dose needed to prevent relapses (Kane et al. 1983). It seems that the clinicians' intuition mainly determines the dose for individual patients.

It is feasible to assume that the plasma level of the drug is a much better predictor of its therapeutic efficacy than its dose because of a wide variability of the plasma drug level to its dose. For example, Wiles and Gelder (1979) examined the plasma FPZ level in 33 schizophrenics to find a 3- to 4-fold variation in the FPZ concentration in subjects receiving the same dose. Nevertheless, the relationship of the plasma level of anti-psychotics with the clinical improvement of schizophrenic symptomatology is still unclear. Possible determinants of the plasma drug level are pharmacological variables such as the dose of the drug, injection interval and the duration of treatment along with the demographic and clinical variables such as the patient's age, sex, race, status and diagnosis. In-

formation about the relationships of these variables with the plasma drug level may help clinicians determine the appropriate dose for individual patients.

The measurement of the plasma prolactin level is a second alternative to assess the clinical efficacy of anti-psychotics because the prolactin level reflects the degree of the blockade of the tubero-infundibular dopaminergic pathway (Gruen et al. 1978a, 1978b; Kolakowska et al. 1975, 1981) albeit at receptors on pituitary lactotrophs (Goldsmith et al. 1979; Besser et al. 1980; Brown et al. 1976). The blockade of the tubero-infundibular pathway may reflect that of the mesolimbic pathway, a suspected locus of schizophrenic disorder. The plasma prolactin level may therefore indicate the therapeutic efficacy regardless of the plasma drug level.

Wiles et al. (1976) reported a correlation of 0.84 between the plasma prolactin and FPZ levels. Brown and Laughren (1981) demonstrated a significant correlation between the plasma prolactin level and the duration of remission. However, Kolakowska et al. (1985) found that the schizophrenic groups with good and poor outcomes did not differ in the bio-availability of or the prolactin response to anti-psychotics. Again the variables described should be examined for their relationship with the plasma prolactin level and its ratio to the drug level if they are to be used in determining the optimal dose of the anti-pychotic drug.

The present study was concerned with the plasma levels of FPZ and prolactin. The main questions considered were:

1. What are the pharmacological and demographic variables that determine the plasma level of FPZ?

2. What are the pharmacological and demographic variables that determine the ratio of the prolactin level to the FPZ level?

Method

The Sample. Psychiatric patients registered at the depot anti-psychotic clinic (Modecate Clinic), All Saints Hospital, Birmingham, were selected if they met the following inclusion criteria: (1) they were aged less than 65 years; (2) they had received no anti-psychotics other than FPZ for at least 3 months prior to the investigation; (3) FPZ had been administered continuously for at least 12 months and (4) they had no mental subnormality, epilepsy or other organic brain diseases.

The subjects consisted of 68 men and 32 women; they were aged 22 to 62 with a mean of 44.5 ($\pm$ 9.7) years. There were 71 out-patients; 21 day-patients and 8 in-patients. Of the patients, 64 met the criteria of Feighner et al. (1973) for definite schizophrenia; 17 probable schizophrenia; 16 did not meet the Feighner criteria for schizophrenia but their clinical diagnosis was schizophrenia and 3 had a non-schizophrenic diagnosis (personality disorder). There was no significant correlation of the

subjects' diagnosis with status or sex. Of 32 women, 16 were premenopausal.

The FPZ dose per injection was 12.5 mg to 125 mg with a mean of 43.6 mg ($\pm$ 24.2 mg). The mode of the dose was 25 mg which was prescribed for 40 patients. The interval between injections was 1 to 6 weeks with a mean of 2.8 ($\pm$ 0.9) weeks. The mode of the injection interval was 2 weeks for 46 patients. The FPZ dose per week (weekly FPZ dose) was 2.083 mg to 62.5 mg with a mean of 18.0 $\pm$ 13.1 mg. The mode of the weekly FPZ dose was 12.5 mg for 27 patients. The duration of FPZ treatment was 1 year and 9 months to 11 years and 1 month with a mean of 7 years and 1 month.

In 20 patients no anti-parkinsonian agents were prescribed. Procyclidine was prescribed for 74 patients, trihexyphenidyl for 3; benztropine for 2 and orphenadrine for 1. Hypnotics were prescribed for 12 patients, nitrazepam for 9, flurazepam, diazepam and triazolam for 1 each. Other medications administered included tricyclic anti-depressants for 1 patient, benzodiazepine anxiolytics for 3, ferrous sulphate for 2, and franol and phenytoin for 1 each.

The Assessment. The subjects were interviewed by the senior author. Their clinical symptoms were assessed by applying the modified version of the Brief Psychiatric Rating Scale (BPRS) (Kolakowska 1976). Diagnosis was established acording to the research diagnostic criteria of Feighner et al. (1973). The extra-pyramidal side effects were rated using Simpson and Angus's (1970) rating scale.

A blood sample was obtained before an injection of FPZ on a day when the injection was due (day 0); a second sample was obtained 7 days later (day 7). Two samples on day 0 and 8 on day 7 were not analysed because they were lost. A written informed consent was obtained from every subject after the purpose and nature of this study were fully explained. No patients detained under the Mental Health Act were included.

The plasma level of FPZ was measured using the radio-immunoassay method of Wiles and Franklin (1978). Samples were assayed in triplicate. Precision (coefficient of variation) within assays was $< \pm 10\%$ and between assays was $< \pm 15\%$.

The plasma level of prolactin was measured by the homologous double antibody radioimmunoassay of McNeilly and Hagen (1974), using antibody obtained from the National Pituitary Agency (USA). Standard human prolaction was provided by the Medical Research Council (UK), 1 mg being equivalent to 18.02 milliInternational Units. Precision within assays was $< \pm 7\%$, and between assays $< \pm 12\%$. The normal range of the prolactin level for this assay was 1.7 to 17.0 ng/ml for men and 2.5 to 20.6 ng/ml for women.

The Statistical Analysis. The plasma FPZ level was divided by the weekly FPZ dose (mg/week) and then multiplied by 100 to yield the FPZ ratio (to indicate drug bio-availability). The FPZ ratio, therefore, reflected the FPZ level produced by a weekly FPZ dose of 100 mg. Since the plasma prolactin level was found to correlate with the plasma FPZ level, it was divided by the plasma FPZ level to yield the prolactin to FPZ ratio (to function as a measure of prolactin response).

Since previous investigations indicated that the prolactin level increased with increasing level of dopaminergic antagonists, the plasma prolaction to FPZ ratio rather than the prolactin level per se was examined further. The plasma prolactin to FPZ ratio was examined separately for men and women because the prolactin response to the administration of dopamine antagonists was known to differ between men and women.

The plasma FPZ level, FPZ ratio, plasma prolactin level and prolactin to FPZ ratio were examined in relation to each

other and to the FPZ dose per injection, the injection interval in weeks, the weekly FPZ dose (i.e. FPZ dose per injection divided by the injection interval in weeks), the duration of the FPZ treatment and the subject's age. They were also compared between men and women, between Caucasians and non-Caucasians, between hospital-patients (in-patients and day-patients combined) and out-patients and between the patients with definite schizophrenia and other diagnoses. A few missing values for each variable caused reduction in the number of cases in each analysis. This number is noted wherever appropriate.

Correlations between two variables were examined using Pearson's product moment, and comparisons between two categorical groups using the t-test. When correcting for normative and categorical variables, the analysis of covariance was applied.

Results

FPZ Level

The plasma level of FPZ varied greatly from 0.4 ng/ml to 12.4 ng/ml, and was found to correlate positively with the weekly FPZ dose (day 0, $r = 0.793$, $n = 98$, $P < 0.001$; day 7, $r = 0.780$, $n = 92$, $P < 0.001$).

In order to examine the influences of the FPZ dose per injection and the injection interval on the plasma FPZ level, multi-linear regression analysis was performed with the plasma FPZ level on day 0 as the dependent variable with the weekly FPZ dose, the FPZ dose per injection and the injection interval as independent variables. The majority of the variance of the plasma FPZ level on day 0 (66%) was found to be accounted for by the weekly FPZ dose followed by the injection interval (3%) and the dose per injection (1%). The analysis of the plasma FPZ level on day 7 was almost identical. It was therefore obvious that the plasma FPZ level was determined mainly by the weekly dose of FPZ.

FPZ Ratio

The FPZ ratio varied from 2.00 to 40.00 (mean ± SD 15.93 ± 6.40) on day 0 and from 2.00 to 41.40 (mean ± SD 19.78 ± 7.86) on day 7. The duration of FPZ treatment did not correlate with the FPZ ratio. The subject's age showed a significant correlation with the FPZ ratio on day 7 ($r = 0.258$, $n = 89$, $P < 0.01$). This correlation was still significant, though to a lesser degree, when corrected for the weekly FPZ dose by using the partial correlation method ($r = 0.219$, $P < 0.05$).

The FPZ ratio did not differ between men and women or between Caucasians and non-Caucasians (Table 1). It was, however, found to be significantly higher in the hospital-patients than in the out-patients both for days 0 and 7, and in the patients with

Table 1. The fluphenazine (FPZ) ratio and the demographic variables

	FPZ ratio	
	Day 0	Day 7
Sex		
Male	15.4 ± 6.5 (66)	19.1 ± 7.1 (60)
Female	17.0 ± 6.1 (32)	21.0 ± 9.1 (32)
t-test	NS ($t = 1.11$)	NS ($t = 1.06$)
Race		
Caucasian	15.7 ± 5.4 (79)	19.8 ± 7.5 (77)
Non-Caucasian	17.0 ± 9.5 (19)	19.8 ± 9.9 (15)
t-test	NS ($t = 0.59$)	NS ($t = 0.02$)
Status		
Hospital-patients	18.6 ± 6.5 (29)	22.5 ± 8.1 (27)
Out-patients	14.8 ± 6.1 (69)	18.7 ± 7.6 (66)
t-test	<0.01 ($t = 2.73$)	<0.05 ($t = 2.15$)
Diagnosis		
Definite schizophrenia	15.0 ± 6.4 (62)	17.8 ± 6.2 (59)
Other diagnoses	17.5 ± 6.2 (36)	23.3 ± 9.3 (33)
t-test	NS ($t = 1.83$)	<0.01 ($t = 3.39$)

Parentheses indicate the number of subjects

other diagnoses compared with those with definite schizophrenia only for day 7.

The FPZ ratio was then analysed by the analysis of covariance with the patient's sex, status (hospital- vs out-patients) and diagnosis (definite schizophrenia vs other diagnoses) as independent variables together with the subject's age, and weekly FPZ dose as covariates both for days 0 and 7. It emerged that the subject's status (day 0, $df = 1$, $F = 9.301$, $P < 0.01$; day 7, $df = 1$, $F = 8.460$, $P < 0.01$), but not sex or diagnosis influenced the plasma FPZ ratio significantly (though diagnosis showed a slightly significant influence on the day 7 FPZ ratio, $df = 1$, $F = 6.459$, $P < 0.05$). The plasma FPZ ratio on day 7 adjusted for the other independent variables and covariates was 23.18 and 18.54 for the hospital- and out-patients, respectively.

The total score of the side effect rating scale was 0 to 11 with a mean of 0.15 (± 1.3); 65 patients showed no side effects and 99 patients had a total score of 3 or less. Since most of the patients were assessed as having few side effects, no further analyses were carried out for the relationship of the side effects with the pharmacological and hormonal variables. The administration of anti-parkinsonian drugs did not affect the FPZ ratio. The total score of the BPRS ranged between 0 and 23; 91 patients had a total score of 13 or less. No further analyses were conducted because most of the patients remitted.

Prolactin Level

The plasma prolactin level on day 0 was 4.2 to 55.5 ng/ml with a mean of 12.6 (± 8.9) ng/ml for men, and 3.9 to 73.5 ng/ml with a mean of 26.1 (± 20.7) ng/ml for women. On day 7 it was 4.3 to 68.1 ng/ml with
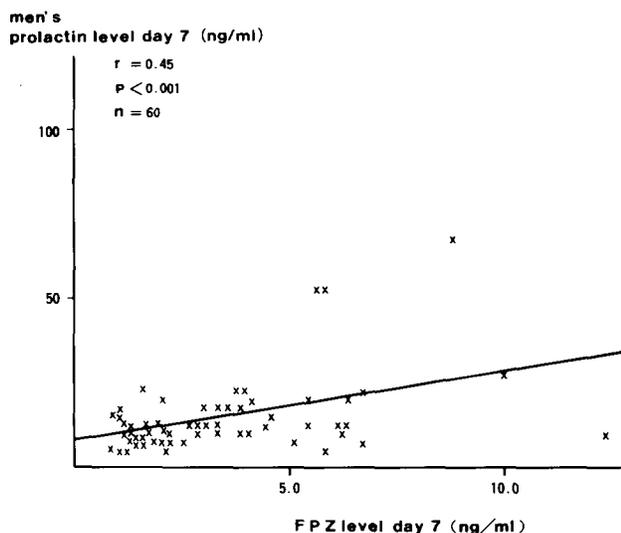
men' s
prolactin level day 7 (ng/ml)

r = 0.45
P < 0.001
n = 60

Fig. 1. The plasma levels of prolactin and FPZ in male patients on day 7

women' s
prolactin level day 7 (ng/ml)
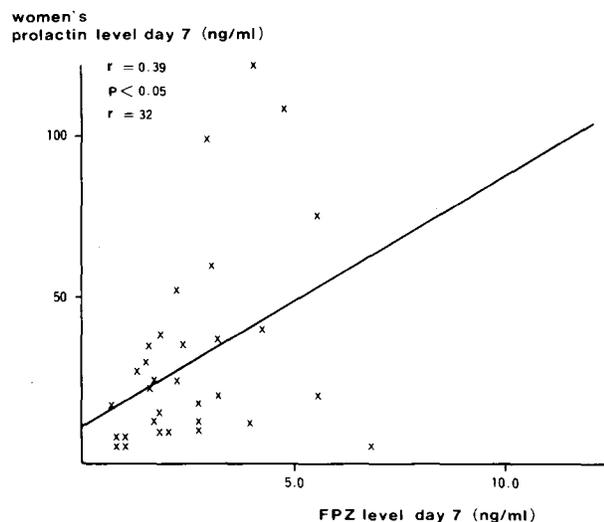

r = 0.39
P < 0.05
r = 32

Fig. 2. The plasma levels of prolactin and FPZ in female patients on day 7

a mean of 14.6 (± 11.4) ng/ml for men, and 5.6 to 120.0 ng/ml with a mean of 31.8 (± 29.9) ng/ml for women. In 17 of the 68 men and 6 of the 32 women the prolactin level was higher than the normal range.

The plasma levels of prolactin and FPZ significantly correlated for men both on day 0 ($r = 0.452$, $P < 0.001$) and day 7 ($r = 0.446$, $P < 0.001$) (Fig. 1). They also significantly correlated for women on day 0 ($r = 0.443$, $P < 0.01$) and day 7 ($r = 0.392$, $P < 0.05$) (Fig. 2). As will be seen from Figs. 1 and 2, the prolactin rise was much steeper for women than for men.

The correlation of the plasma prolaction level with the FPZ dose was slightly lower than that with the plasma FPZ level for women but not for men. The correlations of the plasma prolaction level with the FPZ dose were for men $r = 0.438$ on day 0 ($P < 0.001$) and $r = 0.439$ on day 7 ($P < 0.001$), and for women $r = 0.355$ on day 0 ($P < 0.05$) and $r = 0.295$ on day 7 (NS).

Prolactin to FPZ Ratio

The prolactin to FPZ ratio was significantly higher for women than for men both on day 0 (12.7 ($n = 32$) vs 5.7 ($n = 66$) $t = 4.96$, $P < 0.000$) and on day 7 (12.5 ($n = 32$) vs 5.1 ($n = 60$) $t = 4.90$, $P < 0.000$). Table 2 shows the correlations of the prolactin to FPZ ratio with the other pharmacological variables and the subject's age. The duration of the FPZ treatment and the subject's age did not correlate with the prolactin to FPZ ratio. The inverse correlation between the prolactin to FPZ ratio and the FPZ level was strong in men but no so in women.

When corrected for the plasma FPZ level by using the partial correlation method, correlation of the prolactin to FPZ ratio with age for day 7 in male patients increased to -0.323 ($P < 0.01$) whilst those with the remaining variables did not increase.

The prolactin to FPZ ratio was higher for out-patients both on days 0 and 7 for men and women (Table 3). When the prolactin to FPZ ratio was examined separately for men and women by the analysis of covariance with the patient's status and diagnosis as independent variables and the weekly FPZ

Table 2. Correlation of the prolactin to FPZ ratio with the other correlates

Correlates	Male		Female	
	Day 0	Day 7	Day 0	Day 7
Duration of FPZ treatment	−0.044 (65) NS	−0.058 (59) NS	−0.019 (31) NS	−0.077 (31) NS
Plasma FPZ level	−0.540 (66) ***	−0.442 (60) ***	−0.259 (32) NS	−0.118 (32) NS
Age	−0.066 (64) NS	−0.224 (58) *	0.034 (31) NS	0.264 (31) NS

Parentheses indicate the number of subjects. Correlation is expressed by Pearson's product moment
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 3. The prolactin to FPZ ratio and the demographic variables

	Prolactin to FPZ ratio	
	Day 0	Day 7
Males		
Race		
Caucasian	5.64 ± 3.76 (51)	5.14 ± 3.48 (49)
Non-Caucasian	5.76 ± 3.13 (15)	4.76 ± 2.33 (11)
t-test	NS ($t = 0.11$)	NS ($t = 0.34$)
Status		
Hospital-patients	3.40 ± 2.07 (19)	3.31 ± 1.98 (17)
Out-patients	6.59 ± 3.70 (47)	5.76 ± 3.46 (43)
t-test	<0.001 ($t = 4.45$)	<0.01 ($t = 3.44$)
Diagnosis		
Definite schizophrenia	5.35 ± 3.43 (43)	4.81 ± 2.77 (40)
Other diagnoses	6.27 ± 3.92 (23)	5.59 ± 4.17 (20)
t-test	NS ($t = 0.98$)	NS ($t = 0.76$)
Females		
Race		
Caucasian	12.27 ± 7.86 (28)	12.09 ± 8.14 (28)
Non-Caucasian	15.73 ± 5.55 (4)	15.55 ± 9.74 (4)
t-test	NS ($t = 0.85$)	NS ($t = 0.78$)
Status		
Hospital-patients	7.72 ± 6.53 (10)	7.74 ± 8.13 (10)
Out-patients	14.97 ± 7.09 (22)	14.69 ± 7.81 (19)
t-test	<0.05 ($t = 2.74$)	<0.05 ($t = 2.36$)
Diagnosis		
Definite schizophrenia	13.05 ± 7.20 (19)	12.85 ± 7.81 (19)
Other diagnoses	12.18 ± 8.48 (13)	12.04 ± 9.19 (13)
t-test	NS ($t = 0.31$)	NS ($t = 0.27$)

Parentheses indicate the number of subjects

dose as a covariate, it emerged that the patient's status still contributed significantly to the difference in the prolactin to FPZ ratio. Thus the ratio on day 0 was 3.92 and 6.38 for hospital- and out-patients in men ($df = 1$, $F = 9.152$, $P < 0.01$), and 8.11 and 14.78 for hospital- and out-patients in women ($df = 1$, $F = 4.773$, $P < 0.05$). The ratio on day 7 was 3.75 and 5.59 for men ($df = 1$, $F = 4.529$, $P < 0.05$) and 7.24 and 14.92 for women ($df = 1$, $F = 4.791$, $P < 0.05$).

Discussion

FPZ Level

The present study showed that the plasma FPZ level fairly significantly correlated with the weekly dose. However, the bio-availability of the FPZ, expressed as the FPZ ratio, showed a 20-fold variation. This is greater than that reported by Wiles and Franklin (1978).

When administering medication for a substantially long period, one must always be aware of possible tapering of the plasma drug level. Anti-psychotic maintenance therapy is usually continued over several years. The present study, however, demonstrated that both the plasma FPZ level and the FPZ ratio did not correlate with the duration of FPZ treatment. Thus there seems little possibility of progressive reduction in the FPZ level over a maintenance period. The enzyme induction, if it occurred, may have taken place in the very early phase of the FPZ treatment, therefore need not be considered further.

Presence or absence of anti-parkinsonian drugs did not correlate with the FPZ ratio. Some investigators reported reduction in the plasma level of anti-psychotic drugs by the administration of anti-parkinsonian agents (Bamrah et al. 1986). These studies were for acute administration of the drugs. The effect of anti-parkinsonian agents may disappear when they are administered chronically.

Although the patient status and diagnosis showed, among their subgroups, different FPZ ratios, only the former was found in analysis of covariance to be an independent variable significantly influencing the FPZ ratio. Thus the FPZ ratio adjusted for the other variables and covariates was higher for hospital-patients than for out-patients. It may be speculated that FPZ is either absorbed less or metabolized more rapidly among those who could be discharged from hospital. Despite its clinical significance, this issue has been little studied so far.

Prolactin Level

The plasma prolactin level was found to correlated with the plasma FPZ level for men and women; the prolactin to FPZ ratio was much higher for women. These are consistent with previous studies. The prolactin to FPZ ratio negatively correlated with the plasma level of FPZ. This may reflect that the increase in the plasma prolactin level is reduced with increasing plasma FPZ level.

It has already been argued that the nigro-striatal dopaminergic tract develops tolerance to the administration of anti-psychotics but the tubero-infundibular tract does not (Chouinard et al. 1981). The present finding that the prolactin to FPZ ratio did not correlate with the duration of FPZ treatment is consistent with those findings. An alternative explanation may be, however, that the prolactin tolerance occurred quite early in the course of the drug treatment with no further progression of the tolerance. Even so, these findings and those with the FPZ level

suggest that both the plasma FPZ level and prolactin response to it develop little progressive tolerance over the course of FPZ treatment.

Although a different prolactin to FPZ ratio for sex differences was anticipated, it was of interest that the prolactin to FPZ ratio was higher for out-patients than for combined day- and in-patients. If the prolactin to FPZ ratio was an indicator of how efficient FPZ is for individual patients, one might argue that the prolactin to FPZ ratio is higher for those patients who have been successfully treated and therefore are now out of hospital. Brown and Laughren (1981) demonstrated that a low plasma prolactin level correlated with later relapse of the illness.

An alternative hypothesis is that the sample of patients studied in this investigation consisted of at least two biologically distinct subgroups, one with a good prognosis with a high prolactin to FPZ ratio, and another with a poor prognosis with a low prolactin to FPZ ratio. The patient status at the time of the present examination may be partly due to this biological subcategorization, though schizophrenic outcome is also known to be determined by psycho-social variables. This issue may be clarified when the patients are followed up.

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