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THE PROLACTIN RESPONSE IN PATIENTS RECEIVING NEUROLEPTIC THERAPY. THE EFFECT OF FLUPHENAZINE DECANOATE

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Abstract

1. Fluphenazine decanoate (FD) 50 mg was administered to 15 patients. The patient population was divided into three groups: i) Group A including 5 subjects who had never been treated before; ii) Group B including 5 subjects treated with neuroleptics for at least one year, but who had discontinued the drugs for at least three months and iii) Group C including 5 subjects who had been chronically treated with neuroleptics for at least two years.
2. The increase in plasma level of the hormone prolactin (PRL) after the administration of FD was different in the three groups. The patients never treated before showed the highest "PRL response", which had a great variability among all patients.
3. The "PRL response" did not correlate neither with psychopathological changes nor with extrapyramidal side effects.
4. The "PRL response" did not seem to be a useful tool in predicting the appropriate dosage and interval of the FD administration in a given patient.

Keywords: fluphenazine decanoate, neuroleptics, prolactin response, schizophrenia

Abbreviations: BPRS: Brief Psychiatric Rating Scale; EPSE: Extrapyramidal Side Effects; FD: Fluphenazine decanoate; PRL: Prolactin

Introduction

The prolactin secretion induced by neuroleptics has been widely investigated in recent studies. Some authors have suggested the possibility of using the variations of the plasma PRL levels, after the injection of fluphenazine decanoate, to establish the appropriate dosage and the interval between injections of depot neuroleptics (Meltzer and Stahl, 1976; Sachar et al., 1976; Nasrallah et al., 1978).

In a first study (unpublished data) we have investigated the increase of PRL plasma concentration above "baseline" concentration at zero time (the time of neuroleptic administration): the "PRL response" (Langer and Sachar, 1977).

The most interesting result was a marked difference in the "PRL response", after an injection of 25 mg FD, between patients who had received neuroleptic therapy for a long period and those who had never been treated before with this kind of drugs.

The "PRL response" was much more evident and longer lasting in the second class of patients, suggesting the possible development of "tolerance" to the neuroleptics in the "PRL response". However in one patient, treated for five years with chloropromazine, the injection of 50 mg of FD has provoked a much higher "PRL response" than a dose of 25 mg, confirming the importance of the neuroleptic dosage for the "PRL response". The highest PRL values were observed ten days after the injection of FD.

On the basis of these preliminary data, we carried out the present, more systematic study. The purpose of this study was to verify the possibility of using "the PRL response", after the administration of FD, for a more rational use of FD in clinical psychiatry.

Methods

Patient population

Three groups of male schizophrenic patients were formed on the basis of the neuroleptic therapy previously received (Table 1).

Table 1

Characteristics of the patient population

GROUP	A	B	C
SCHIZOPHRENIA.....	5	5	5
(PARANOID).....	(3)	(2)	(3)
ACUTE.....	3	3	3
CHRONIC.....	2	2	2
AGE 20-30.....	3	3	1
AGE 30-40.....	2	2	4
MEAN LENGTH OF ILLNESS (YEARS)	1	9	8

Group A: Patients never treated before - Group B: Patients continually treated
Group C: Patients treated before, but without therapy for at least three months

Group A consisted of five patients who had never received neuroleptics before the experiment.

Group B consisted of five patients who had been chronically treated with neuroleptics for at least two years; they were switched to "placebo" four days before the beginning of the experiment.

Group C consisted of five patients who had been treated before with neuroleptics for at least one year, but who had stopped after having taken this kind of drug for at least three months.

The clinical diagnosis was made in accordance with the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM.II). Table 1 shows the characteristics of the patient population of the three groups: it may be seen that the ratio of acute patients versus chronic patients was the same (3:2), and that the age was comprised between 20 and 40 years. The mean length of illness varied from one year in Group A, to nine years in Group B and eight years in Group C.

Drug administration

In the experiment a single i.m. injection of two 25 mg phials of FD (Moditen depot; Squibb) was administered. No other drug was administered with the exception of one 30 mg capsule per os of Flurazepam (Dalmadorm; Roche), at 21 h., as hypnotics, in 8 patients.

Experimental design

All patients and four healthy volunteers were tested for PRL basal values for two consecutive days at 8 h., after an overnight fast, and at 12 h.

The patients were awakened at 6.30 h. Twenty minutes before starting each test, an indwelling catheter was placed in an anticubital vein. Blood was immediately centrifuged at 4°C. Serum was stored at -21°C until assay. After the injection of FD (50 mg), the blood samples were taken every morning with the same procedure at 8 h. for ten days, then, again at 8 h., every five days until the end of the experiment (42 days).

The changes related to the circadian rhytm were studied on the 10^{th} day, at four hour intervals for 24 hours.

On the same day of the PRL assay, psychiatric symptoms were rated with the BPRS (Overall and Gorham, 1962), and EPSE with the Mindham's rating scale (Mindham, 1976). Throughout the study, clinicians were blind to laboratory data.

A general view of the design is given on Table 2.

Assessment instruments

A) Psychiatric symptoms were rated with the BPRS (Overall and Gorham, 1962), in the eighteen items and eight points (from 0 to 7) version.

EPSE were rated with the Mindham's rating scale (Mindham, 1976), which uses four points (from 0 to 3) to evaluate facial expression, stiffness, tremor, associated walking movements and physical status condition.

B) The assessment of PRL values was performed with the Radio-Immuno-Assay (R.I.A.)

Data analysis

The statistical method used in this study was the Student's 't' test.

Results

The prolactin response

The mean basal PRL values did not differ among the 15 patients nor between patients and the

Table 2

Experimental design

	8 h.	12 h.	16 h.	20 h.	24 h.	4 h.
day 1	PRL, BPRS, EPSE	PRL				
2	PRL, BPRS, EPSE	PRL				
3	PRL, BPRS, EPSE, FD					
4	PRL, BPRS, EPSE					
5	PRL, BPRS, EPSE					
6	PRL, BPRS, EPSE					
7	PRL, BPRS, EPSE					
8	PRL, BPRS, EPSE					
9	PRL, BPRS, EPSE					
10	PRL, BPRS, EPSE					
11	PRL, BPRS, EPSE					
12	PRL, BPRS, EPSE	PRL	PRL	PRL	PRL	PRL
17	PRL, BPRS, EPSE					
22	PRL, BPRS, EPSE					
27	PRL, BPRS, EPSE					
32	PRL, BPRS, EPSE					
37	PRL, BPRS, EPSE					
42	PRL, BPRS, EPSE					

[1] We have indicated with PRL the determination of PRL level, with BPRS the administration of BPRS, with EPSE the administration of Mindham's rating scale, with FD the injection of 50 mg of FD i.m.

controls: 10 ng/ml (S.D. ± 5).

The "PRL response" was present in all patients after the injection of FD. The highest PRL values were present between the 9th and the 12th day.

The "PRL response" was much more evident in patients treated before with neuroleptics as compared with patients already treated for a long time with these kind of drugs. The patients already treated with neuroleptics, but free from therapy since at least three months showed an intermediate "PRL response" (Fig. 1).

Among patients of each group a clear "PRL response" variability was present (Fig. 2).

The PRL values tended to return to "baseline" values after 30 days.

The circadian variations of PRL assessed on the 10th day showed the same differences among the three groups observed for the total "PRL response".

The physiological peaks are maintained. In groups B and C, the PRL values are once again lower than in group A, but superior to physiological values (Fig. 3).

Relationship between the PRL response and the data collected by the psychiatric scales

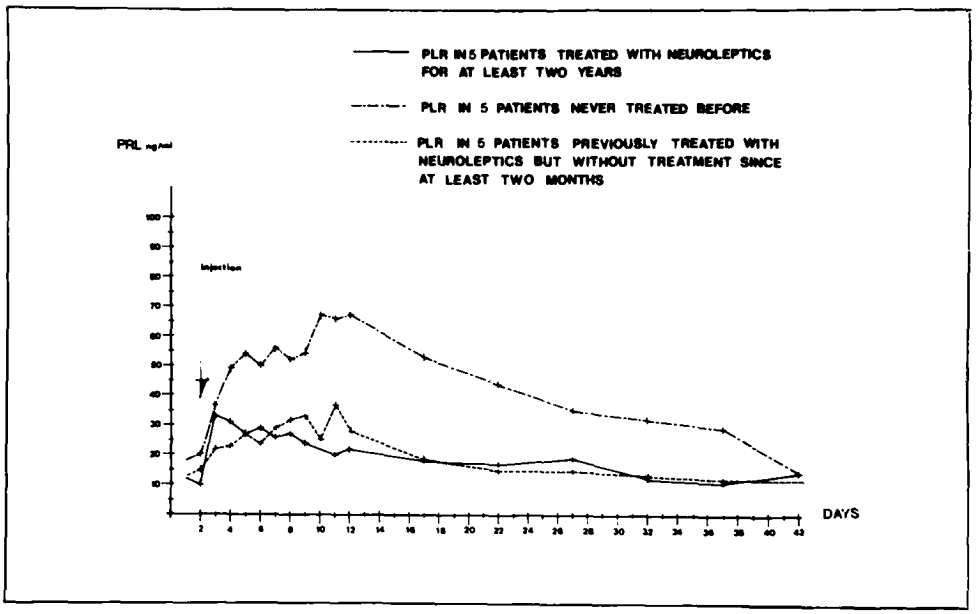

Fig. 1 - Mean values of "PRL response" in the patients of Group A (—— - —— -), the patients of Group B (————), the patients of Group C (- - - -), after injection of 50 mg of FD i.m. The Group A (patients never treated before with neuroleptics) shows the highest "PRL response".

The rank order correlations between the mean PRL values and the total scores of the BPRS, in the groups, were negative for Group A (- 0.35) and very weak for Groups B and C (+ 0.41 and + 0.11).

The rank order correlation between the mean PRL values and the total scores of the Mindham's rating scale for EPSE were negative in the three groups (-0.25; -0.33 and -0.17 respectively).

Discussion and Conclusions

The PRL value in pharmacopsychiatry

The results of this study are negative in relation to the hypothesized possibility of using the "PRL response" as a valuable tool for a more rational therapy with FD in a single patient. The main reason is the great inter-patients variability in the "PRL response" to the same dose of the depot neuroleptics, as already noted for oral neuroleptics (Sachar et al., 1976). The second reason is the marked difference in the "PRL response" between patients treated for the first time with neuroleptics and patients treated with this kind of drugs. The presence of these two factors makes it very difficult, if not impossible, to use the "PRL response" as a biological index of the therapeutic action of the neuroleptics, in other words to use the "PRL response" as a substitute of the plasma levels of the neuroleptics, which are, anyway, difficult to correlate with the psychotherapeutic effect of the neuroleptics

(Marvin et al., 1978).

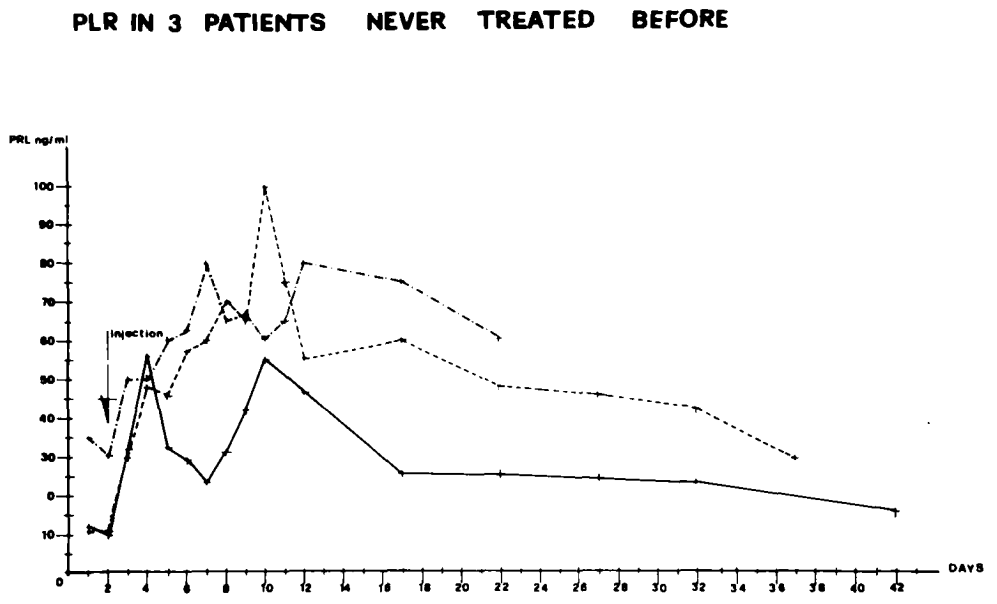

Fig. 2 Values of "PRL response" after injection of 50 mg of FD i.m., in 3 patients never treated before with neuroleptics (Group A).

Relationship between the PRL response and the psychiatric scales

Moreover in this study the modifications of the psychopathology induced by the neuroleptics measured with the BPRS, do not correlate in a significant way with the "PRL response" after the FD injection. In fact the possibility that the "PRL response" can be a valid indicator of the therapeutic action of neuroleptics is not conclusively established.

The results of the studies in this particular field are controversial. Some authors have found a positive correlation (Meltzer and Fang, 1976), whils others have reported no correlation between PRL levels and clinical response (Langer et al., 1978). It is possible that the neuroleptic does not exert a similar or a synchronous dopamine receptor blockade in the two regions of the brain which are supposed to be the site of action of the psychotropic effects (the mesolymbic-mesocortical region) and of the PRL release (the tubero-infundibular regulatory system). A different dopamine receptors blockade on the striatum and on the mesolymbic region has been demonstrated for thioridazine (Crow and Gillbe, 1973).

The difference in the "PRL response" between patients already treated with neuroleptics and those who have never been treated with this kind of drugs can be attributed to the development of a "tolerance" to the neuroleptics in the "PRL response", a fact that has been hypo-

hesized by some authors (De Rivera et al., 1976) and denied by others (Gruen et al. 1978).

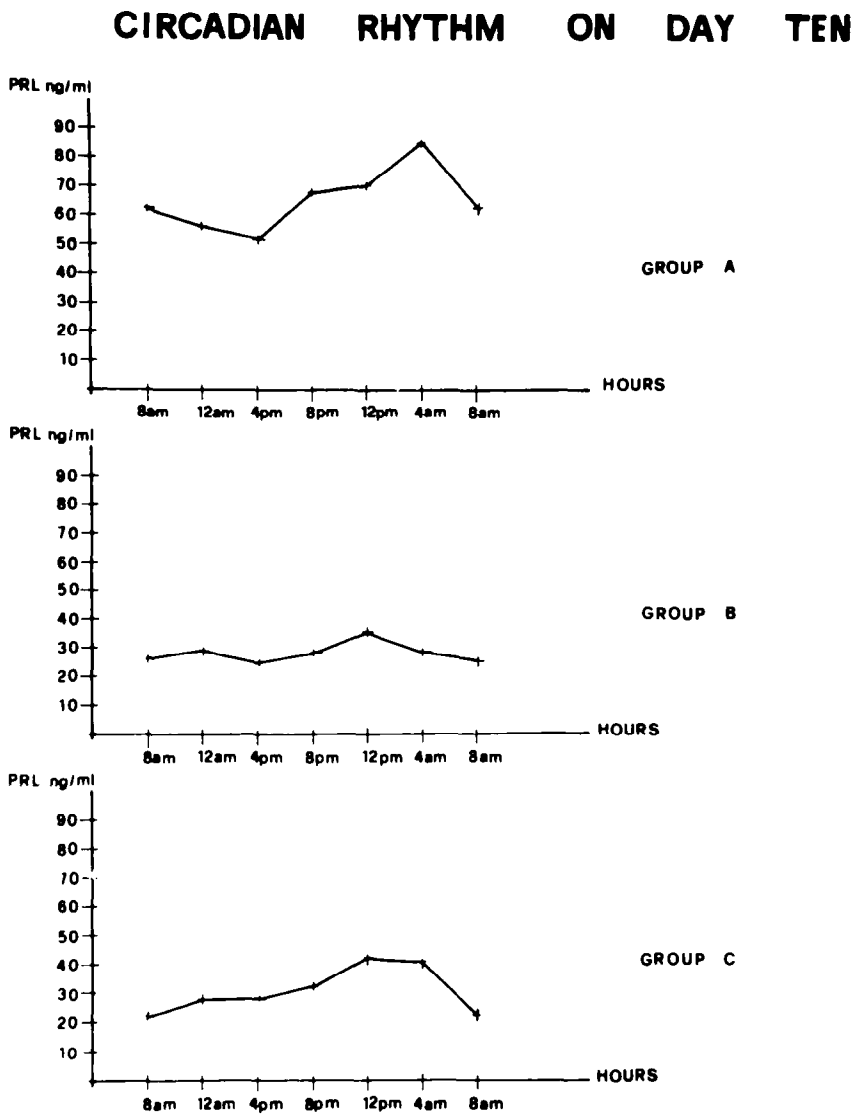

Fig. 3 Circadian variations of PRL values, ten days after the injection of 50 mg of FD i.m.

A more simple explanation could be an accelerated hepatic metabolism of the neuroleptics in patients already treated, due to an enzymatic induction, with a consequent lower plasma level of the neuroleptics and a lowered "PRL response". To verify this hypothesis, we intend to measure the plasma level of FD in the same population using a radioimmuno assay method. However the date presented by Nasrallah et al. (1978) about this correlations are not very encouraging. Another variable that could influence the "PRL response" is the duration of the

illness, which was shorter in group A than in the two other groups. Another limitation is represented by the sex of the patients (all males). Siris et al. (1978) have found a higher correlation between PRL increment and psychosis improvement in women treated with pimozide, than in men.

The negative correlation between the mean PRL values and the scores of the Mindham's rating scale for EPSE is, in a way, even more surprising considering that the EPSE is a relatively more objective parameter of the neuroleptic action in the CNS. Also in this case one could imply that the dopamine receptor blockade by the neuroleptics in the "striatum" and in the tubero-infundibular regulatory system is not parallel. We did not attempt to correlate the EPSE with the "therapeutic" effect because this was not one of the objects of the present study and because of the extreme complexity of this problem (Alpert et al., 1978).

We are now extending the study to a larger population to operate a factor analysis, the result of which will eventually permit to isolate the variables influencing the "PRL response" in patients treated with depot neuroleptics.

Conclusions

The present research data indicate no statistically significant correlation between "PRL response" and psychopathological changes, as measured with BPRS, after administration of FD.

We didn't find either any correlation between "PRL response" and EPSE, as measured with Mindham's rating scale.

Our data show high individual variability in PRL response to therapy with FD and significantly higher "PRL response" in patients never treated before, in comparison with the values obtained with patients previously treated.

Our study does not confirm the hypothesis of a possible use of "PRL response" as a valuable tool for a more rational therapy with FD.

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