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FLUPHENAZINE DECANOATE IN ACUTE AND MAINTENANCE THERAPY OF SCHIZOPHRENIA

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Abstract

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1. The knowledge of the pharmacokinetic profile of fluphenazine decanoate (FPZ-D) suggested it was suitable for treatment of schizophrenic patients not just during the maintenance phase of the disease but also during acute relapses.
2. 27 acute schizophrenic in-patients (diagnosed according to the DSM III) were treated with FPZ-D, 25 mg i.m. with repeated administrations (after 2, 4, 30 days).
3. FPZ-D proved effective in all cases, already after the second day and particularly on Brief Psychiatric Rating Scale items such as delusion, hallucinations, hostility.
4. Extrapyramidal side-effects, appeared in about 40% of the patients.
5. The use of the drug both in the acute phase and maintenance schizophrenia therapy is envisaged, overcoming the problems deriving from the rejection by patients of any therapeutic tool and consequently the therapeutic "milieu".

Keywords: acute schizophrenia, fluphenazine decanoate, maintenance therapy.

Abbreviations: anticholinergic side effects (ACS), brief psychiatric rating scale (BPRS) extrapyramidal side effects (EPSE), fluphenazine decanoate (FPZ-D).

Introduction

The main problems faced in the therapeutic management of acute schizophrenic patients can be summarized as follows:

i) lack of insight, hostility and therefore, lack of therapeutic cooperation

ii) the presence of possible poisoning delusions and the consequent rejection of therapy.

Each feature and their summation often mean that oral drug therapies are not viable. Moreover, frequent parenteral treatment, repeatedly forcing the patient's will, enhance incidental delusional persecutory ideas thus jeopardizing the already fragile physician/

patient relationship.

On the other hand, in maintenance treatment of schizophrenia, the focal problem is represented by poor therapeutic compliance connected to the patient's more or less impaired insight.

The clinical introduction of long-acting neuroleptics has been the most relevant attempt to solve this latter problem and reduce relapses (Johnson 1979). Actually, the ideal anti-psychotic treatment should consist in the possibility of using the same compound in the acute and maintenance phases, thereby assuring a formal and substantial therapeutic continuity.

This result can be achieved in theory by using the conventional formulation of a certain compound in the acute phase and its long-acting preparation in the maintenance period. However, at this point, the difficulties mentioned above for acute treatment with a conventional compound,must be reconsidered,even when administered by the parenteral route. FPZ-D has been widely used since the seventies, surprisingly enough, without knowing its pharmacokinetic profile in humans. Preliminary data were supplied by Curry et al (1978) who demonstrated an early plasma peak of the drug 8-10 hours after administration, followed by a "plateau" of stable concentrations for 2-3 weeks. These data were confirmed in an experimental model (Altamura et al 1979) and in other human studies (Curry et al 1979, Javaid et al 1981, Wiles & Gelder 1979). On the basis of this peculiar pharmacokinetic profile a sensible hypothesis seems to be the use of FPZ-D not only during the maintenance period but also in acute schizophrenic episodes,assuring a considerable degree of therapeutic continuity. In former knowledge, the data concerning the use of FPZ-D in acute schizophrenia are scanty and involving other psychopathological conditions (Guarnieri et al 1979).

The purpose of the study was to assess the therapeutic efficacy and side-effects of a monotherapy with FPZ-D in schizophrenic patients both during the acute and maintenance phases of the disease.

Methods

Patients Population

The study included 27 schizophrenic in-patients of both sexes (12 females and 15 males), of age ranging from 20 to 62 years (mean age 33.88 ± 1.84 S.E.), with the follo-

wing DSM III diagnosis: Disorganized (295.14)= 9, Paranoid (295.34)= 9, Catatonic (295.24)= 1, Undifferentiated (295.94)= 8, in the phase of acute exacerbation (Tab 1). The mean duration of disease was 7.2 (± 1.11) years.

Drug Administration

After a week wash-out, at time 0, the patients were given FPZ-D in a dosage equal to 25 mg i.m., repeated after 2, 4, 30 days. The use of anticholinergic drugs or benzodiazepines was allowed only in cases of dire necessity.

Assessment Instruments

At 0, 1, 2, 3, 4, 5, 14, 30 and 60 days, the psychopathologic symptomatology was assessed by means of BPRS (Overall & Gorham 1962) and extrapyramidal side-effects were evaluated by means of the modified Simpson & Angus Scale (EPSE)(1970)(items such as akathisia,disartria,acute dystonia were added). Anticholinergic side-effects were evaluated on the basis of a check list (ACS)(available on request) and the pulse rate and blood pressure (both in the supine and standing positions) were measured on the same occasions. Routine hematochemical tests were carried out at the beginning and at the end of the study.

Statistical Analysis

Data analysis was performed by means of the Friedman ANOVA and Newman-Keuls multiple-comparison tests.

Results

BPRS Mean Total Scores

A significant reduction (-16.42 % $p < 0.01$) of the BPRS mean total score was reported already on the second day of treatment (Table 1, Fig 1). From the third day on, a significant decrease in important items such as hallucinations (-33 % $p < 0.01$), hostility (-32 % $p < 0.01$), unusual thought content (-30 % $p < 0.01$), conceptual disorganization (-28 % $p < 0.05$) was observed (Fig 2). The improvement of all the items (which, in the majority of cases, peaked on the 14th day) remained steady up to the end of the trial, with a significant reduction of the mean global BPRS score equal to 48.37 % ($p < 0.01$) versus time 0. The items with the highest per cent decrease were conceptual disorganization (-70.89 %), unusual thought contents (-70.07 %) and hallucinations (-66.97 %).

Table 1

Characteristics of the Population under Survey Showing the BPRS and EPSE Scores

PT. nº	DIAGNOSIS*	SEX	AGE (yrs)	WEIGHT (kg)	DOSE (mg/kg)	BPRS TIME (days) 0	1	2	3	4	5	14	30	60	EPSE TIME (days) 0	1	2	3	4	5	14	30	60
1	D	F	35	61	0.41	62	60	51	43	36	34	31	40	40	0	4	8	9	18	18	23	19	15
2	D	F	23	68	0.37	78	79	62	47	36	30	29	53	51	0	0	16	15	30	25	29	24	24
3	P	M	48	66	0.38	72	72	69	69	69	62	46	34	31	0	3	0	1	0	1	2	0	0
4	P	M	26	80	0.31	69	53	44	38	29	22	27	41	38	0	3	16	15	14	4	4	4	4
5	P	F	40	64	0.39	84	83	81	66	59	57	41	42	40	0	0	6	17	14	23	23	27	24
6	U	F	43	62	0.40	52	52	52	47	42	35	27	25	23	0	1	2	2	2	2	1	0	0
7	D	F	22	61	0.41	80	80	62	57	43	38	27	31	40	0	0	7	20	20	19	19	17	25
8	U	F	35	50	0.50	66	62	54	50	35	25	23	22	24	0	4	6	16	16	13	12	24	17
9	D	M	38	75	0.33	96	71	57	42	34	26	24	23	30	0	4	14	13	11	4	7	13	6
10	D	F	34	54	0.46	61	62	55	42	39	36	34	34	31	0	0	1	1	1	0	0	1	1
11	U	M	20	65	0.38	66	64	54	39	30	27	26	34	37	0	2	6	3	2	19	29	31	23
12	D	M	32	70	0.36	76	66	49	41	38	26	25	29	33	0	5	17	16	20	29	14	11	10
13	D	F	39	60	0.42	68	60	48	39	30	25	24	33	36	0	2	7	4	5	10	5	4	4
14	P	F	38	66	0.38	76	76	76	59	47	47	41	53	57	0	0	17	21	22	25	23	33	35
15	P	F	32	74	0.34	75	75	56	49	42	35	35	39	49	0	0	24	34	34	39	43	36	34
16	C	M	62	64	0.39	79	79	76	68	67	60	56	54	56	9	9	7	6	8	8	8	8	8
17	U	M	34	81	0.31	74	70	67	66	64	64	71	72	75	0	0	2	3	1	2	2	1	1
18	P	F	32	55	0.45	85	75	56	51	46	34	27	21	26	0	8	16	16	16	14	18	29	23
19	P	M	41	76	0.33	63	63	63	61	60	46	42	42	42	0	0	1	1	1	2	1	1	1
20	P	M	48	84	0.29	65	65	65	65	63	63	63	55	38	0	0	0	2	1	2	2	0	1
21	P	M	32	61	0.41	50	49	48	43	43	38	30	25	23	0	1	1	2	1	1	1	1	1
22	D	F	36	85	0.29	69	56	41	31	25	24	24	33	28	3	9	12	14	15	15	17	17	17
23	U	M	22	91	0.27	66	66	58	57	56	35	23	22	22	0	0	1	1	1	0	0	0	0
24	U	M	24	74	0.34	68	68	68	68	63	36	16	11	11	0	0	0	3	3	3	1	2	0
25	D	M	35	100	0.25	73	55	46	41	32	32	24	25	27	3	9	18	15	23	24	17	22	21
26	U	M	20	66	0.38	74	74	74	73	72	63	45	40	40	0	0	1	1	3	3	5	7	7
27	U	M	24	68	0.36	84	71	82	79	70	71	58	52	49	0	0	0	4	5	7	9	9	9
	Mean		33.8	72.1	0.33	71.5	66.8	59.7*	53.0*	47.0*	40.4*	34.7*	36.4*	36.9*	0.5	2.3	7.6*	9.4*	10.6*	11.5*	11.6*	12.6*	11.5*
	± SE		1.84	2.24	0.013	1.93	1.78	2.19	2.48	2.83	2.87	2.67	2.62	2.57	0.35	0.60	1.38	1.63	1.90	2.00	2.17	2.29	2.14

* DSM III: D = Disorganized (295.1) C = Catatonic (295.2) P = Paranoid (295.3) U = Undifferentiated (295.9) * $p < 0.01$

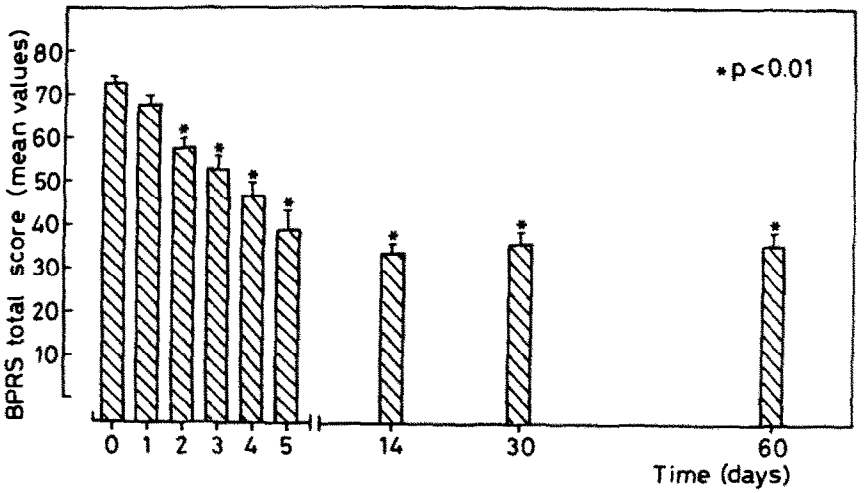

Fig 1. Pattern of the total BPRS score (mean values) recorded in the course of the study, indicating a significant drop in BPRS scores ($p < 0.01$ vs time 0) as from the 2th day.

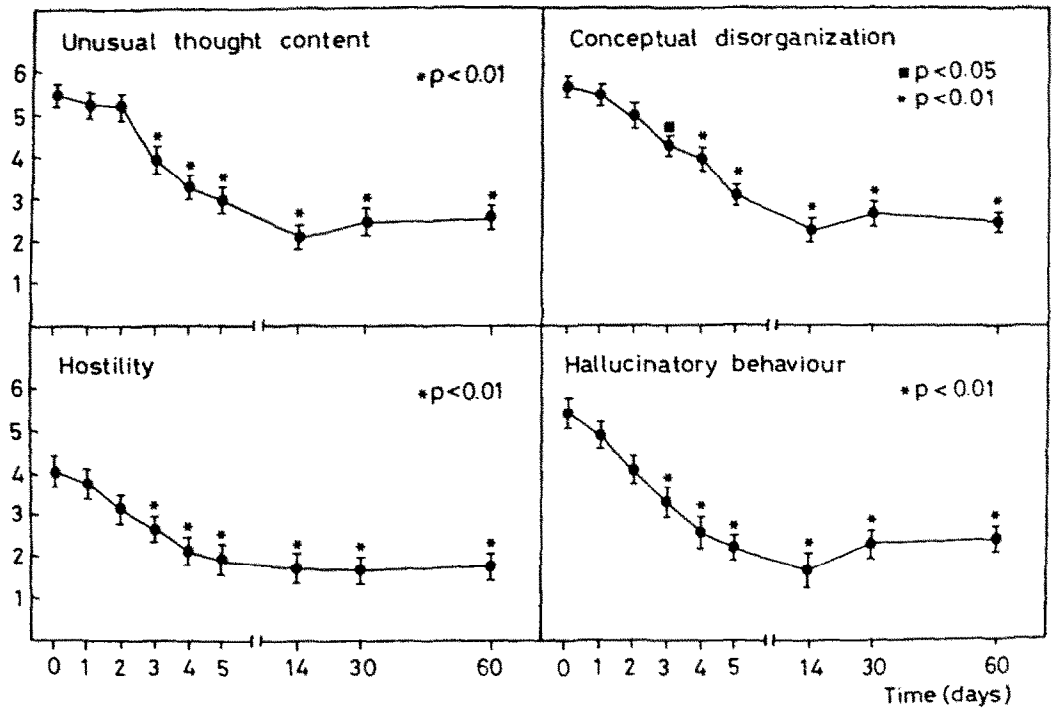

Fig 2. Pattern of the total score (mean values) of 4 BPRS items recorded in the course of the study, each of which decreased significantly (vs time 0) as from the 3th day.

The patients' mood improved during the study (-44.33% on the 60th day). The drug developed no particular sedative effect, as shown by the pattern of items such as anxiety and excitation (-45.2% and -39.28% at the end of the study).

ESPE Total Scores

Table 1 and Fig 3 illustrate the pattern of the mean EPSE total scores of side-effects: starting from the second day, 40.7% of the patients'score was higher than 3 ($p < 0.01$). This score reached the peak value on the 30th day, but involved a smaller number of patients (33.3%) thereafter, to the end of the study. Such symptoms as tremors, akathisia and rigidity were particularly evident. Fig 4 shows the pattern of the total score (mean values) of four EPSE items recorded during the course of the study. Acute dystonia due to the neuroleptic drug was observed in 4 patients. Combinations of anticholinergic or benzodiazepine drugs were given to 6 patients only, because of marked extrapyramidal side-effects.

Anticholinergic and Cardiovascular Effects

Anticholinergic effects (mouth dryness, constipation) also increased significantly ($p < 0.05$) from the second day, peaking on the 14th day (plus 88.13% from time 0)(Fig 5).

Blood pressure changed significantly only in terms of systolic values in both the supine (maximum drop, -7 %) and standing (maximum drop, -10 %) positions, as shown in Fig 5. No significant effects on the pulse rate was observed. Hematochemical tests showed no abnormalities.

Discussion

Antipsychotic Activity

FPZ-D was found to be effective in the survey population and in particular on symptoms, such as delusion, auditory hallucinations and hostility. No important sedative effects were observed, in agreement with data from literature, which confirms a less sedative profile of the drug than other phenothiazines such as chlorpromazine or thioridazine (Abuzzahab 1983, Poldinger 1984). The early clinical action of the drug cannot be regarded as an early full antipsychotic one, but rather as the partial improvement of some target symptoms. It is well-known fact that a proper antipsychotic effect occurs no earlier than 10-15 days of continous neuroleptic treatment (Cotes et al 1978).

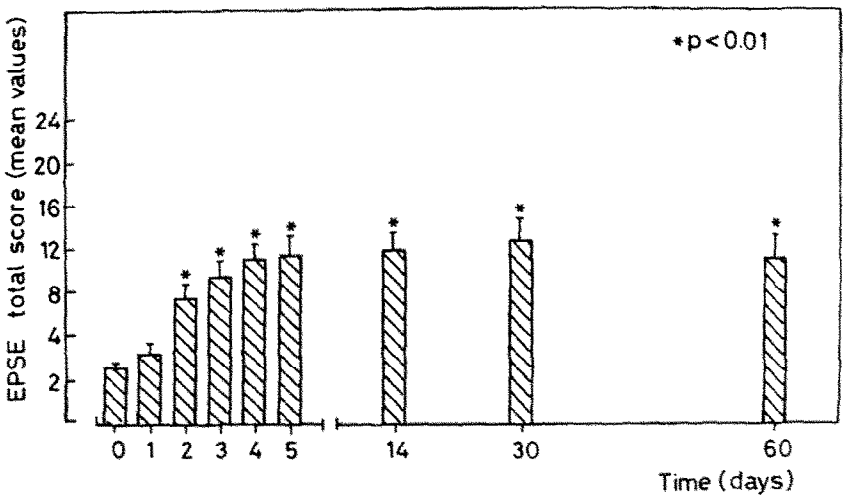

Fig 3. Pattern of the total EPSE score (mean values) recorded in the course of the study: its increase is significant ($p < 0.01$ vs time 0) as from the 2th day.

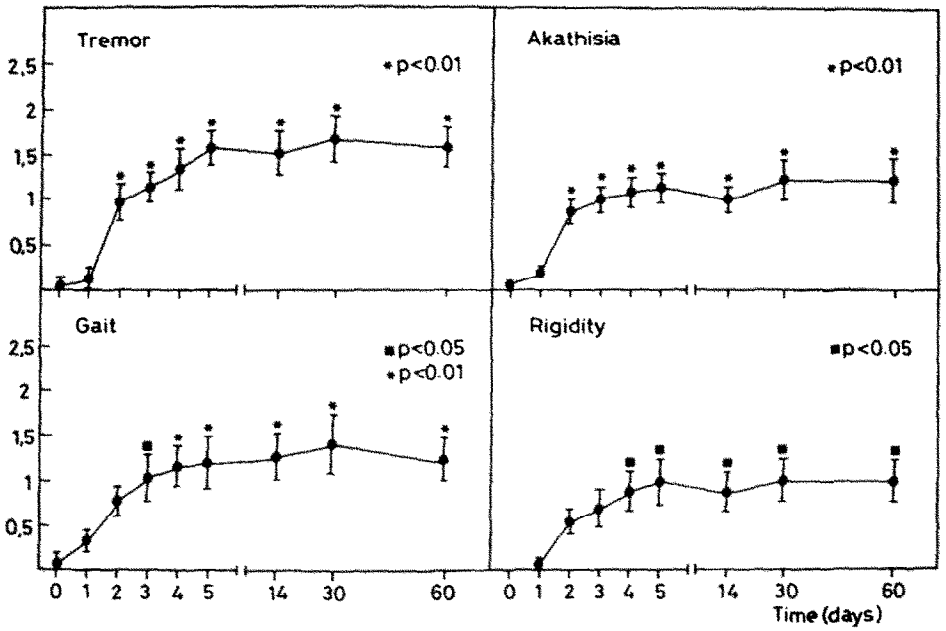

Fig 4. Pattern of the total score (mean values) of 4 EPSE items, each of which increased significantly (vs time 0) in the course of the study.

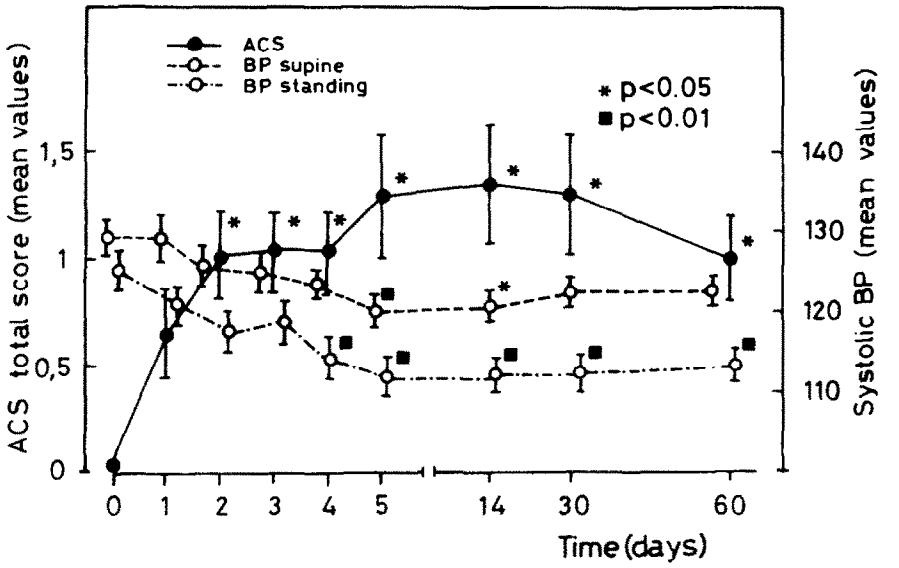

Fig 5. Pattern of the total ACS score (mean values) and the mean values of systolic blood pressure (BP) - both supine and standing - recorded in the course of the study. The significant variations are expressed vs time 0.

It must be stressed that no depressogenic effects, which could be related to FPZ-D, were recorded: a depressogenic effect, if any, actually seems to occur after longer periods of therapy (Alarcon and Carney 1969, Ayd 1975).

The anti-hallucinatory and anti-delusional action of FPZ-D could suggest that it is suitable for use in acute schizophrenic relapses with positive symptoms but no severe psychomotor agitation.

The rationale underlying the early clinical effect of FPZ-D is the pharmacokinetic profile of this drug, characterized by an early plasma peak and surprisingly enough, the clinical data on the acute effect of FPZ-D, which are rather scarce and concern mixed populations of subjects affected by schizophrenia and mania (Guarnieri et al 1979).

Unwanted Side Effects

The early plasma peak after administration of FPZ-D also caused unwanted side-effects, essentially of the extrapyramidal type (tremor, akathisia, rigidity) and which in the course of the study appeared in about 40% of subjects. However, the incidence of these effects was not greater than that mentioned in other studies on various neuroleptic

agents (Altamura et al 1986, Ayd 1961, Johnson 1978, Moleman et al 1982).

It is important to point out that neither anticholinergic drugs nor benzodiazepines were administered on a routinary basis, but only to patients showing severe extrapyramidal symptoms. Hypotension and anticholinergic side-effects were also present, as reported in previous studies (Altamura et al 1985). Since a relationship between the plasma levels of the drug and frequency of side-effects, extrapyramidal in most cases, was reported (Altamura et al 1985), a routine plasma assay of fluphenazine could prove useful in reducing side-effects especially in high-risk patients.

Conclusions

Our study primarily seems to demonstrate that the use of a single agent for the treatment of the acute and maintenance phases of schizophrenic psychoses is possible, thus assuring a formal and substantial therapeutic continuity which could influence the patient's compliance with the therapeutic plan. Moreover, the use of FPZ-D in the acute phase could improve the patient/physician relationship and acceptance of the "therapeutic milieu", which are among the most important non-pharmacological factors capable of affecting the outcome of treatment with antipsychotic agents (May 1976).

Finally, the quality and quantity of side-effects did not differ significantly from those recorded during treatment with conventional drugs, although the peculiar pharmacokinetic profile of FPZ-D suggests caution in treating patients prone to acute extrapyramidal or cardiovascular side-effects.

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