Schizophrenia Research, 1 (1988) 31–35
Elsevier

SRS 00010

Fluphenazine decanoate dose and severity of depression in patients with post-psychotic depression

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(Received 6 August 1987, revised received 28 August 1987, accepted 22 September 1987)

The authors examined the fluphenazine decanoate dose and the fluphenazine plasma levels in comparison with measures of severity of depression in schizophrenic and schizoaffective patients. All patients were selected for study on the basis of having stable, syndromally defined, antiparkinsonian non-responsive syndromes of post-psychotic depression. No meaningful relationships were found. The implications of this observation with regard to the notion that depressive symptomatology in such patients is neuroleptic-induced is discussed.

Key words: Fluphenazine; Neuroleptic; Depression; Post-psychotic depression; (Schizophrenia)

INTRODUCTION

It is a recognized clinical phenomenon that a substantial number of patients with schizophrenia, who require maintenance treatment with neuroleptic medication to reduce their vulnerability to psychotic relapse, experience a depression-like syndrome during that treatment and during that phase of their illness (McGlashan and Carpenter, 1976; Johnson, 1981; Knights and Hirsch, 1981; Siris et al., 1981; Hirsch, 1982; Mandel et al., 1982; Moller and Von Zerssen, 1982; Roy et al., 1983; Martin et al., 1985). The etiology, or etiologies, of these depression-like states, however, have been a matter of some controversy. It is unclear, for example, how much the patients' underlying diathesis may contribute to their vulnerability to this type of symptomatology (Galdi et al., 1981), how much the neuroleptic-induced akinesia syndrome may be involved in generating a depression phenocopy (Siris, 1987), and how much the psychosocial demoralization syndrome may be a factor (Frank, 1973). Further overarching these hypotheses, though, has been the unresolved controversy concerning to what extent neuroleptic medications themselves may be responsible for the induction of 'depression' in these patients (Ananth and Ghadirian, 1980; Hirsch, 1982). Therefore, in order to shed light on the potential induction of depression-like symptomatology in schizophrenic patients by neuroleptics, we examined the severity of depression, in relationship to neuroleptic doses and neuroleptic plasma levels, in a cohort of schizophrenic and schizoaffective patients with stable, antiparkinsonian non-responsive, syndromally diagnosed, post-psychotic depressions.

METHODS

Patients were evaluated who gave informed consent and met syndromal criteria for post-psychotic depression (Siris et al., 1981, 1987b). These criteria included a diagnosis of either schizophrenia or

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schizoaffective disorder by Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) for their most recent psychotic episode, a current status in which they were either non-psychotic or only residually psychotic (RDC definition), a current syndrome 'in cross-section' meeting RDC for either major or minor depression, a Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) score of 12 or more – not counting the items for derealization or paranoia, and maintenance of both the syndrome and the HDRS score for a minimum of three consecutive weekly ratings. Furthermore, all patients studied had maintained their syndromes and HDRS score criteria despite treatment with adjunctive benztropine mesylate at a dose of 2 mg p.o. t.i.d. All patients were receiving their clinically best-adjusted dose of fluphenazine decanoate at a dose which had been stable for a minimum of three weekly injections at the time of the evaluation.

Clinical evaluations were performed with the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978; Endicott et al., 1981), Present State Examination and the Brief Psychiatric Rating Scale (Overall and Gorham, 1962). Blood was drawn for fluphenazine determination at the time of clinical evaluation and 1 week after the most recent intramuscular fluphenazine decanoate injection. It was immediately centrifuged and the plasma frozen at $-20^{\circ}C$ until assayed (Suckow and Cooper, 1981).

RESULTS

46 patients participated in this study. Their demographic and clinical characteristics appear in Table 1.

Weekly intramuscular fluphenazine doses were compared with the four extracted SADS summary scales for depression, the SADS 'depressed mood' item, the BPRS 'depression' item, and the BPRS scales for 'anxious depression' and 'withdrawal/retardation' using the Pearson product moment correlation. The results of these analyses are shown in Table 2. Similar comparisons involving plasma fluphenazine levels are shown in Table 3 for the 36 patients for whom these data were also available. No statistically significant, trend level, or near trend level relationships were found with the exception of a trend level relationship between the BPRS anxious-depression score and the plasma fluphenazine level. Given the number of analyses performed, one or more trend level relationships would be expected by chance alone, so little weight can be attributed to this one isolated trend-level finding. Visual inspection of the plots suggested no other relationships (i.e., curvilinear) which needed to be tested.

The Pearson product moment correlation between the weekly fluphenazine decanoate dose and

TABLE 1

Patients with the post-psychotic depression syndrome who were assessed (n = 46)

Age	32.3 ± 8.9
Sex (M/F)	24/22
In/Outpatient	6/40
Residually psychotic/non-psychotic	15/31
Duration since most recent flagrant episode of psychosis	49.0 ± 89.4 weeks
Fluphenazine decanoate (weekly dose)	0.65 ± 0.43 ml
Plasma fluphenazine level	0.99 ± 0.76 ng/ml
Benztropine mesylate (daily dose)	5.8 ± 1.1 mg
SADS-extracted Hamilton Rating Scale score	22.8 ± 6.9
Global Assessment Scale (GAS) score	42.2 ± 9.0
BPRS total scores	40.2 ± 0.8

TABLE 2

Comparisons of weekly fluphenazine doses with measures of depression (n = 46)

	Pearson product moment correlation	
	r	P
SADS-extracted Hamilton Depression Rating Scale score	−0.003	0.98
SADS-Depressive Mood and Ideation Scale	−0.155	0.30
SADS-Endogenous Features Scale score	−0.026	0.87
SADS-Depressive Associated Features Scale score	0.016	0.92
SADS-Depressed Mood item	−0.074	0.62
BPRS Depression item	−0.003	0.98
BPRS Anxious Depression score	0.081	0.59
BPRS Withdrawal/Retardation score	0.037	0.81

TABLE 3

Comparisons of plasma fluphenazine levels with measures of depression (n = 36)

	Pearson product moment correlation	
	r	P
SADS-extracted Hamilton Depression Rating Scale score	0.177	0.30
SADS-Depressive Mood and Ideation Scale	0.056	0.75
SADS-Endogenous Features Scale score	0.115	0.50
SADS-Depressive Associated Features Scale score	0.236	0.17
SADS-Depressed Mood item	0.054	0.75
BPRS Depression item	0.112	0.51
BPRS Anxious Depression score	0.282	0.095
BPRS Withdrawal/Retardation score	0.023	0.89

the plasma fluphenazine level was $r = 0.72$, $P = 0.0001$. The intra-assay variability of the plasma fluphenazine assay was 2.7%, and interassay variability was 5.0%.

DISCUSSION

We found no meaningful evidence for a relationship between the severity of depression in schizophrenic and schizoaffective patients with post-psychotic depression syndromes and either the dose or the plasma level of the fluphenazine decanoate they were receiving. This study therefore complements others which showed no difference in neuroleptic dosages when schizophrenic patients with and without depression were compared (Roy, 1984) and which found that depressive symptoms actually often decreased when schizophrenic patients were treated with neuroleptics (Dencker et al., 1973; Donlon et al., 1976; Knights and Hirsch, 1981; Moller and Von Zerssen, 1982; Strian et al., 1982). Other previous reports have also failed to support any relationship between neuroleptic (Knights and Hirsch, 1981) or fluphenazine decanoate (Knights et al., 1979, Schooler et al., 1980) usage and depressive symptomatology in schizophrenia. Moreover, in a relevant observation, a recent review documented that neuroleptic drugs may actually have therapeutic activity in at least some cases of depression (Robertson and Trimble, 1982). On the other hand, several other reports are still frequently cited in the literature, implicating neuroleptic medications (Floru et al., 1975; Singh, 1976), and particularly fluphenazine decanoate (DeAlarcon and Carney, 1969; Johnson and Malik, 1975; Carney and Sheffield, 1976; Faloon et al., 1978; Hogarty et al., 1979; Johnson, 1984), in the etiology of 'depressed' states in schizophrenic patients; and these reports are rendered plausible by the putative role of dopamine in affective regulation (Gerner et al., 1976; Post, 1977; Randrup and Baestrup, 1977; Bunney, 1978).

The current study differs from previously reported work in several important respects. Firstly, it makes a systematic attempt to rule out the potentially confounding syndrome of neuroleptic-induced akinesia with a trial of adjunctive benztropine 2 mg p.o. t.i.d. Akinesia is an extrapyramidal neuroleptic side effect whose features can strongly mimic depression (Rifkin et al., 1975; Van Putten and May, 1978), to the point, at times, of producing a clinically indistinguishable phenocopy (Siris, 1987). The reports which most strongly argue that there is a neuroleptic-induced 'depression', however, made no attempt to control for akinesia and may therefore have been observing this phenomenon rather than any other type of depression. Secondly, this is the only report to have gathered for examination cases with syndromally defined, temporally stable episodes of post-psychotic depression. Stable, *syndromally defined* depression in schizophrenia or schizoaffective disorder may be more likely to respond to an adjunctive antidepressant than mere *symptomatically defined* depression (Siris et al., 1978, 1987a,b), which adds drug response validity to this form of depression construct. Thirdly, this is the only report systematically to have examined the issue of neuroleptic dosage or neuroleptic plasma levels in relationship to the severity of depressive symptoms or depressive syndromes, allowing a dimensional dose versus clinical variable comparison. If, indeed, fluphenazine decanoate were to play a causative role in such depressive syndromes, a relationship with dose might be expected. Although this study was not of a randomized, blind, fixed dose design, which would

have been an even stronger test of the issue, the clinical adjustment of patients' doses was based on achieving a satisfactory antipsychotic response rather than adjusted to their affective state, so that the dosing was not particularly biased in this manner. Furthermore, non-blindness would have only biased toward the finding of a relationship had raters been influenced to rate more extremely the depressions of those patients receiving higher fluphenazine decanoate doses. Such a finding, of course, was not the case.

It is likely that the syndrome of depression in schizophrenia, even as presently defined, is a heterogeneous entity (Siris and Rifkin, 1983; Siris et al., 1987a). Some patients may experience depression-like symptomatology as a fundamental feature of their biological diathesis. Others may possibly experience at least some degree of akinesia even on ostensibly 'full' doses of antiparkinsonian medication, at least in part due to the marked variability in the rapidity of metabolism of anticholinergic antiparkinsonian drugs between individuals (Tune and Coyle, 1980). Akathasia is another extrapyramidal side effect which has been associated with dysphoric affect (Van Putten et al., 1984; Siris, 1985) and it is one that is less likely to be responsive to anticholinergic antiparkinsonian medication (Van Putten et al., 1984). Yet other patients certainly experience a depression-like demoralization syndrome (Frank, 1973), based on social and vocational disappointments, personal embarrassment, and/or family and community ostracism. It is still possible, given this heterogeneous situation, that certain individual patients may experience a depression-like syndrome causally linked to neuroleptic exposure. The present study generates evidence, however, that this is not a factor of sufficient magnitude or incidence as to be easily detectable among syndromally grouped patients with post-psychotic depressions, and that neuroleptics would therefore appear not to be the major etiologic factor in most cases of syndromally defined post-psychotic depression which occur during the course of schizophrenia or schizoaffective disorder.

ACKNOWLEDGEMENTS

This work was supported by NIMH Grants nos. MH-34309 and MH-03092.

The authors thank Magali Torres for excellent secretarial assistance.

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