

Fluphenazine Enanthate Induced Decompensations

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INTRODUCTION

Intramuscular fluphenazine enanthate is an effective phenothiazine. It appears to be significantly superior in the drug reluctant patient, and is an effective substitute for daily oral psychotropic drugs in both hospitalized and non-hospitalized schizophrenics.¹⁻⁴

Adverse behavioral reactions to fluphenazine enanthate have been reported.⁵ "Severe depressive mood changes"^{6,7} and "the fulminating acute onset of schizophrenic symptomatology"⁸ have been attributed to fluphenazine enanthate. Allan and White⁹ reported a case of catatonic-like stupor and disturbed temperature regulation precipitated by a large dose (100 mg) of fluphenazine decanoate. Goldberg et al,¹⁰ on the basis of a controlled study, concluded that fluphenazine enanthate "appears to be significantly superior to oral phenothiazines in the drug reluctant patient." They noted, in their analysis of covariance of Brief Psychiatric Rating Scale data, that some patients became worse on fluphenazine enanthate. Specifically, in a subgroup of patients who did *not* hallucinate or were *not* uncooperative, 32% of patients started to hallucinate, and 44% of patients became uncooperative. Also, some developed increased blunting of affect, increased suspicion, increased tension, and increased depression.

This paper focusses on nine schizophrenic patients who experienced dramatic exacerbations of their original psychosis on fluphenazine enanthate in conventional dosages. These exacerbations of psychosis appear to be extrapyramidally based, and can be reversed by intramuscular biperiden (Akineton)—an anticholinergic drug. Response to biperiden is so prompt that it can be used as a diagnostic test.

METHOD

Observations were made over a nine-month period on a 30-bed psychiatric unit in a university affiliated veterans hospital. The emphasis is on active treatment, and staff-patient ratio is high.

Thirty-eight patients with clearcut schizophrenia were switched to fluphenazine enanthate. The usual reason for the switch was drug reluctance to oral phenothiazines. Fluphenazine enanthate was administered in conventional dosages—6-25 mg., I.M. every

two weeks; prophylactic antiparkinson medication was not administered.

Especially those patients on fluphenazine enanthate were watched around the clock for exacerbations of psychosis or conspicuous regressions. Once a deterioration of mental status was reported, an attempt was made to establish consensus between the treating resident, nursing staff, and director that a definite deterioration had actually occurred. Biperiden (Akineton) 5 mg., I.M. or a placebo was then administered in double blind fashion on an every-other-incident basis, if there was even subtle evidence of extrapyramidal involvement, such as mild tremor, akinesia, or evidence of restlessness suggestive of an akathisia. "Double blind" was not successful, however, since spontaneous complaints of dry mouth invariably tipped off at least the rater. Biperiden, 5 mg., I.M. was chosen because of its prompt onset of action and documented effectiveness in reversing drug induced EPS.¹¹ The patient was evaluated by a brief interview and BPRS¹² by two experienced clinicians, both before and one to two hours after the injection of biperiden (Akineton). Since these exacerbations were often sudden and at odd times, it was not always possible to have two raters. In that event, the patient was rated by the senior investigator.

RESULTS

Out of the 38 patients switched to fluphenazine enanthate, nine patients experienced dramatic exacerbations of psychosis. These exacerbations occurred within 2-8 days after the injection (mode 5 days). The decompensations were in the direction of the original psychosis and did not resemble a toxic psychosis. During fluphenazine induced exacerbations thought processes became disorganized, secondary symptoms recurred, quality of contact deteriorated, and many complained of an abject fear or terror that was difficult to articulate. Onset was often sudden, and some attacks were self-limited. Most important, all decompensations were associated with subtle and evanescent extrapyramidal symptoms—usually either a subtle akathisia or an oculogyric crisis.

Decompensations were reversed by biperiden, 5 mg., I.M. in all cases. In one case, however, biperiden was very effective in reversing some sudden regressions but was ineffective at other times. Clinically, peak action occurred at about 1 hour and duration of effect was about 4 hours. Reversal of regression was dramatic. Quality of contact improved, secondary symptoms abated, thinking became more reality oriented and pa-

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tients invariably stated that they felt more "at ease", "relaxed", "calmer", and "less tense".

Results of the Brief Psychiatric Rating Scale¹² (Table I) confirm the clinically observed reversals of regression with biperiden. These results are based upon 14 episodes of decompensation in 7 different patients. The BPRS was administered by two independent raters immediately before akineton injection and one hour post injection. The results indicate a significant overall reversal of regression; specifically increased reality contact (Conceptual Disorganization, Unusual Thought Content, and Somatic Concern Scales), improved quality of contact (Blunted Affect, Suspiciousness, Hostility, Emotional Withdrawal and Uncooperativeness Scales), and decrease in dysphoric affective state (Anxiety, Tension, Depressive Mood, and Excitement Scales).

BPRS ratings were collected for 8 cases of pre- and post-placebo injections. These ratings show no post-placebo improvement. Statistical analysis on this small number of cases was not deemed meaningful.

ILLUSTRATIVE CASES

Case I: Fulminant psychosis precipitated by fluphenazine enanthate.

This 38 year old, never married, white female with the diagnosis of chronic paranoid schizophrenia was admitted because of inability to cope and bizarre somatic delusions. She was convinced that her muscles were "wasting away" and that she was "turning into a skeleton". She did not respond to the interactional therapies, but did show sustained improvement on thioridazine, 200 mg. q.i.d., and trifluoperazine, 20 mg. q.i.d.

Because of drug reluctance she was switched to fluphenazine enanthate, 25 mg., I.M. every two weeks. On the fifth day after the injection she developed a florid exacerbation of psychosis. She threw herself on the floor with such force that she severely bruised her shoulder. She drank a bottle of perfume and repeatedly prostrated herself in the middle of the floor. She tried to strangle the examiner and seemed to experience terror and anxiety of annihilation proportions. No rational contact could be established. She moaned "I have come to the end now. It's the end of the world for me. I am so weak . . . I have no muscles. I'm wasting away." She also experienced auditory hallucinations for the first time — "They are like religious voices saying this is the end of the world." The only suggestions of extrapyramidal involvement were a mild akinesia as reflected by decreased facial expression, a barely noticeable fine tremor, and a subtle and evanescent akathisia as manifested by fidgetiness and intermittent crossing and uncrossing of her legs. Biperiden, 5 mg., I.M., produced a dramatic improvement in mental status. One hour after the injection she was in good spirits, appropriate and able to converse rationally. The next day she again experienced a sudden and dramatic regression. A placebo injection produced no objective or subjective improvement; biperiden again produced a dramatic improvement. The same double-blind biperiden-placebo injections were repeated several more times with very consistent results.

Case II: Withdrawal, which simulated depression, precipitated by fluphenazine enanthate.

This 22-year old, single, unemployed, caucasian male was admitted on numerous occasions because of inability to cope and LSD or amphetamine induced psychotic exacerbations. He carries the diagnosis of simple schizophrenia and has a long history of arrests for vagrancy. He has intermittently been on chlorpromazine and/or thioridazine in conventional dosages. Response to oral phenothiazines was difficult to assess because of his pronounced drug reluctance. Accordingly, he was given fluphenazine enanthate, 25, mg. I.M. For the next three days he was his usual self, viz, he would mostly sit around the dayroom, engage in desultory conversation when approached, and appeared "spiritually dead." On the fourth and fifth post injection day he exhibited transient, lopsided shoulders, arched back and intermittent restless pacing. When questioned about these extrapyramidal symptoms he indicated that he was not disturbed by them. On the sixth, seventh and eighth day he spent most of the time "sleeping" in bed. During the individual interview there was no evidence of extrapyramidal involvement. He was withdrawn, had a most silly and inappropriate grin (suggestive of drug ingestion or hebephrenia) and gave mostly monosyllabic answers. A placebo injection produced no subjective improvement. Thirty minutes after biperiden, 5 mg. I.M., he was a "changed person." The quality of contact improved dramatically and inappropriate grinning ceased. He was talkative, made sense and seemed, for once, interested in "help." He played an animated and skillful game of chess, of which the staff did not think him capable. He stated that on the fluphenazine he had "felt nervous as hell; I've never felt like that before. I couldn't sleep and I'm always a good sleeper. I felt very irritable and impatient. The only way I could handle it was to go to bed."

This dramatic improvement on biperiden was replicated on the tenth and eleventh day. All this time he had an evanescent mild akathisia, as manifested by feelings of anxiety, irritability, and impatience.

Case III: Exacerbations of psychosis can occur even when extrapyramidal symptoms are suppressed with antiparkinsonian medication. The following case illustrates a fluphenazine in-

Table 1: Analysis of Brief Psychiatric Rating Scale administered pre and post injections of biperiden for 14 cases.

| BPRS Item | Mean Pre | Mean Post | Variance | t |
|----------------------------|----------|-----------|----------|----------|
| Somatic Concern | 4.25 | 2.14 | 1.71 | 4.61**** |
| Anxiety | 5.14 | 2.93 | 1.41 | 5.89**** |
| Emotional Withdrawal | 4.00 | 3.14 | 1.39 | 2.30* |
| Conceptual Disorganization | 4.36 | 3.25 | 1.24 | 3.34*** |
| Guilt Feelings | 2.82 | 2.68 | 1.03 | 0.52 |
| Tension | 4.54 | 2.64 | 1.11 | 6.37**** |
| Mannerisms and Posturing | 2.14 | 1.46 | 1.26 | 2.01 |
| Grandiosity | 1.14 | 1.14 | 0.00 | 0.00 |
| Depressive Mood | 4.43 | 2.93 | 1.22 | 4.59**** |
| Hostility | 2.79 | 1.21 | 1.74 | 3.38*** |
| Suspiciousness | 2.57 | 1.36 | 1.53 | 2.97** |
| Hallucinatory Behavior | 1.86 | 1.21 | 1.34 | 1.79 |
| Motor Retardation | 3.39 | 2.46 | 1.19 | 2.92** |
| Uncooperativeness | 2.46 | 1.36 | 1.86 | 2.23* |
| Unusual Thought Content | 4.61 | 2.79 | 1.43 | 4.75**** |
| Blunted Affect | 4.07 | 3.07 | 1.18 | 3.18*** |
| Excitement | 3.61 | 1.21 | 1.82 | 5.06**** |
| Disorganization | 1.14 | 1.07 | 0.27 | 1.00 |
| Elevated Mood | 1.00 | 1.00 | 0.00 | 0.00 |

*P < .05 **P < .02 ***P < .01 ****P < .001

duced decompensation and the subsequent breakthrough of subtle extrapyramidal symptoms with an associated exacerbation of psychosis.

This 25-year old white male was admitted because he jumped out of a second story window in response to command hallucinations. He has a history of LSD and amphetamine abuse and carries the diagnosis of chronic paranoid schizophrenia of the "process" or non-reactive type. Because of phenothiazine reluctance, he was placed on fluphenazine enanthate, 12.5 mg. I.M., every two weeks. On the seventh day after the injection he became withdrawn and spent most of his time in solitary pacing. On interview he appeared terror stricken and thoughts were so disorganized that no rational contact could be established. One hour after biperiden, 5 mg. I.M., he was a changed person. He conversed rationally and stated "I was extremely nervous. I felt like jumping out of my skin. I've never felt like this before. I wanted to die. I couldn't feel comfortable in any position." After it was established that a placebo injection produced no relief, he was started on trihexyphenidyl (Artane), 4 mg. t.i.d., and fluphenazine enanthate was reduced to 6 mg. I.M., every two weeks. Despite this rather high dose of trihexyphenidyl and a low dose of fluphenazine enanthate, subtle deterioration of mental status regularly occurred within the five days following fluphenazine injection. The deterioration consisted of episodic extreme anxiety, withdrawal, and disorganization of thought processes, and a rather "weird staring at patterns on the floor" (nurses' quote). In view of his history of drug abuse, LSD intoxication was entertained. The patient finds it difficult to articulate this terror stricken state and can only tell us "It feels like I'm going insane again. It's a horrible feeling . . . my eyes are sort of drawn to the patterns on the floor. I can stop it if I want to." The subtle oculogyric crisis and associated deterioration of mental status were readily reversed by biperiden, 5 mg. I.M. Placebo injections had absolutely no effect.

Case IV: Deteriorations of mental status can occur when maintenance antiparkinsonian medications are discontinued.

This 24-year old, divorced negro male was admitted because of strange behavior. At the time of admission he was suspicious, guarded, hostile and was frightened by voices accusing him of being "queer." Because of drug reluctance, he was maintained on fluphenazine enanthate, 12.5 mg. I.M., every two weeks. A very mild akathisia manifested by restless tossing and turning at night and vague complaints of muscle tension during the day was easily suppressed by trihexyphenidyl (Artane), 4 mg. b.i.d. Nine weeks later the trihexyphenidyl was stopped. Over the next several days a subtle deterioration of mental status occurred. He became more withdrawn and experienced a "strong fear" that he could not further articulate and had never experienced before . . . It's like I'm getting paranoid again. I'm scared of people. It's weird . . ." In addition, he experienced peculiar and frightening hallucinations of "tires screeching", as opposed to the accusatory hallucinations at admission. A subtle akathisia consisting of frequent crossing and uncrossing of his legs was noted. Biperiden, 5 mg. I.M., dramatically improved the mental status. Placebo injections had no effect. He was placed back on trihexyphenidyl, 4 mg. b.i.d., and feels "a hundred percent."

Even on trihexyphenidyl, 4 mg. b.i.d., extrapyramidal symptoms and an associated decompensation broke through at times of stress. On his way to a court appearance, he became acutely terrified. "I thought the voices had gone away, but all of a sudden the voices started yelling and screaming—real loud. Then my eyes wanted to go up to the sky." These mild oculogyric crises and associated decompensations are self limited to about fifteen minutes.

DISCUSSION

The prompt reversal of these fluphenazine induced exacerbations of psychosis by biperiden—an antiparkinsonian drug—suggests that these exacerbations are extrapyramidally based. In this connection, Boardman and Fullerton¹³ have observed a "psychic extrapyramidal syndrome" (with oral phenothiazines) consisting of "depression, guilt feelings, apathy or agitation," which often passed for a "relapse". The "psychic extrapyramidal syndrome" could precede the motor manifestations and promptly responded to an antiparkinson drug (disipal).

Additional evidence that these exacerbations of psychosis are extrapyramidally based is that they are associated with subtle extrapyramidal symptoms—notably an akathisia. Akathisia is a subjective state and "refers not to any type or pattern of movement, but rather to a subjective need or desire to move."¹⁴ This urge to move is always accompanied by affective distress and, objectively, is usually manifested by restless pacing, inability to sit still, fidgetiness, and continuous alterations in posture. With the subtler akathisias, the patient may not pace or use the word "restless", and complain instead of "nervousness", "irritability", "impatience", feeling "keyed-up", or of an inability to feel "comfortable". Akathisia—because of its subjective nature—may thus be difficult to diagnose and can be mistaken for an exacerbation of the original mental illness.^{15,16} Kalinowsky¹⁷ states that akathisia can be "more difficult to endure than any of the symptoms for which (the patient) was originally treated", and cautions that akathisia may be mistaken for an "agitated depression". Fouks¹⁸ refers to akathisia as the "syndrome of impatience" and stresses that it often is associated with severe anxiety, peculiar bodily sensations, and bizarre mentation.

Mental manifestations do occur in documented basal ganglia disease. Schwabb, et al,¹⁹ have reported paroxysmal attacks of anxiety, depression, paranoid thinking and attacks of depersonalization in parkinson's disease. These paroxysmal attacks of altered mental functioning are often associated with oculogyric crisis and frequently disappear when antiparkinsonian drugs are administered. Schwabb¹⁹ mentions that these patients suddenly experienced an "abject terror of a sort they never experienced before"; this same feeling of terror was reported by several patients in this study. Davison and Bagley²⁰ also report an increased incidence of schizophrenia-like psychoses in such basal ganglia disorders as Huntington's chorea, Wilson's disease, torsion spasm, essential hereditary tremor, and mid-brain reticulosis. They conclude that "basal ganglia dysfunction often has a prominent mental component which may take a psychotic form".

Patients on fluphenazine enanthate should be

watched carefully for deteriorations in mental status. These deteriorations are often sudden and may be self limited. If an exacerbation of psychosis occurs—with or without obvious extrapyramidal symptoms—biperiden, or a similar antiparkinson drug, should be administered intramuscularly as a diagnostic test. Prompt improvement suggests that the exacerbation of psychosis is extrapyramidally based and mandates an increase in antiparkinsonian medication.

SUMMARY

Thirty-eight schizophrenic patients were switched to intramuscular fluphenazine enanthate in conventional dosages. Prophylactic antiparkinsonian medication was not used. Nine patients experienced dramatic exacerbations of psychosis. These decompensations appear to be extrapyramidally based, and can be reversed by intramuscular biperiden (Akineton) an antiparkinsonian drug.

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The value of having schizophrenic patients in therapy: Not only do they have a greater ability than most therapists to interpret the language and symbolism of the unconscious; they also often put their fingers with penetrating keenness on weaknesses and pretenses in the therapist's personality.

Freda Fromm-Reichmann

(Quoted by Judd Marmor, M.D.—*Psychiatry in Transition*—

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