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Fluphenazine plasma level monitoring for patients receiving fluphenazine decanoate

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Abstract

Background: Finding a dose of an antipsychotic for maintenance therapy that is both safe and effective can be difficult because clinicians are unable to titrate dose against clinical response in patients who are already stable. Therapeutic monitoring of antipsychotic plasma levels has the potential for helping clinicians in dosage selection. With this in mind, we evaluated the usefulness of monitoring fluphenazine plasma levels for patients with schizophrenia who were receiving maintenance treatment with fluphenazine decanoate.

Method: Thirty-one patients with schizophrenia were randomly assigned to low, medium, or high (0.1–0.3, 0.3–0.6, 0.6–1.0 ng/ml) plasma levels of fluphenazine. The dose of fluphenazine decanoate was adjusted in order to maintain patients in their assigned range. Side effects, psychopathology, and psychotic exacerbations were measured during the year following randomization.

Results: All of the psychotic exacerbations occurred during the first eight weeks following randomization, before patients had adequate time to reach their plasma level assignments. We did not find a relationship between plasma levels of fluphenazine and clinical outcomes or side effects.

Conclusion: Our results do not provide support for the usefulness of monitoring fluphenazine plasma levels for patients receiving fluphenazine decanoate.

Keywords: Schizophrenia; Antipsychotic; Fluphenazine

1. Introduction

Finding the best dose of long-acting antipsychotics can be a time consuming and uncertain process. These agents can take three to six months to reach a stable state (Marder et al., 1989). Moreover, these agents are usually prescribed to prevent relapse in stabilized patients. The clinician is unable to titrate dose against clinical effects in patients who are stable. As a result, it would be helpful if the clinician could use information such as plasma concentrations of the antipsychotic for assistance in dose finding.

There is only limited data available regarding the usefulness of plasma concentrations for patients treated with a depot antipsychotic (Brown et al., 1982; Wistedt et al., 1982) although the available studies suggest that plasma level monitoring may be useful. Using logistic regression, we (Marder et al., 1991) found a relationship between fluphenazine (FLU) plasma levels and the risk of psychotic exacerbations

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Table 1
Mean (SD) fluphenazine plasma concentrations in three dosing groups

	BL	4 week	8 week	12 week	16 week	26 week	38 week	52 week
Low	0.28 (0.09)	0.32 (0.10)	0.19 (0.10)	0.12 (0.10)	0.26 (0.11)	0.30 (0.11)	0.25 (0.10)	0.18 (0.10)
	$N=7$	$N=8$	$N=8$	$N=7$	$N=5$	$N=7$	$N=8$	$N=7$
Medium	0.36 (0.08)	0.48 (0.10)	0.23 (0.08)	0.26 (0.09)	0.23 (0.09)	0.33 (0.09)	0.40 (0.09)	0.35 (0.09)
	$N=11$	$N=8$	$N=10$	$N=8$	$N=8$	$N=9$	$N=9$	$N=7$
High	0.49 (0.09)	0.42 (0.09)	0.43 (0.10)	0.43 (0.09)	0.45 (0.10)	0.50 (0.11)	0.65 (0.12)	0.79 (0.12)
	$N=10$	$N=8$	$N=7$	$N=9$	$N=6$	$N=5$	$N=4$	$N=4$

in patients receiving 5 or 25 mg of fluphenazine decanoate (FD) every two weeks. These findings suggested that monitoring steady state plasma levels of FLU and adjusting the dose based on these levels might decrease the risk of psychotic relapse. The study presented in this report was designed to test this theory by assigning patients to plasma level ranges that were hypothesized to be above, below, or within the range that appeared to be most effective. In that study, we found that FLU levels (measured by radioimmunoassay (RIA)) of approximately 0.8–1.5 ng/ml were within the therapeutic range. In this report we measured FLU levels by high pressure liquid chromatography, a more sensitive and specific method that yields lower levels. As a result, we redefined the most effective plasma range of FLU as 0.4–0.7 ng/ml based upon a pilot study.

2. Methods

Subjects for this study were 31 outpatients from the West Los Angeles VA Medical Center with a schizophrenia disorder diagnosed by the Structured Clinical Interview for DSM-IV (First et al., 1997). Inclusion criteria required that subjects have had at least two documented episodes of acute schizophrenia and they are considered as candidates for maintenance antipsychotic treatment. After signing written informed consent, subjects were randomly assigned to one of three plasma level ranges of FLU: 0.1–0.3, 0.3–0.6, 0.6–1.0 ng/ml. Patients were gradually changed from their current oral or depot to FD by starting patients on 5, 15, or 30 mg of FD according to their assignment and gradually decreasing the dose of their current medication until it was discontinued in about three months. FLU plasma levels were monitored on a monthly basis and the dose was adjusted accordingly. For this study, the treating psychiatrist who ordered the FD and the nurse who administered the injection were aware of the patient's assignment. The unblinded psychiatrist and nurse did not participate in any of the ratings. The remainder of the study staff, all of the raters, and the patient were blind to the patients dose and plasma level.

Clinical outcome was measured during the first three months following randomization and every three months thereafter. Outcome instruments included the Brief Psychiatric Rating Scale (BPRS) with scales scored from one to seven (Overall and Gorham, 1962), the Schedule for Assessment of Negative Symptoms (SANS) (Andreasen, 1982), the Simpson–Angus Rating Scale (Simpson and Angus, 1970), and the Barnes Akathisia Scale (Barnes, 1989). Patients were continued in the study for 52 weeks or until they met the criteria for a psychotic exacerbation (which was defined as a worsening of three points or more on BPRS cluster scores for thought disturbance or paranoia) or until they developed extrapyramidal side effects that could not be adequately managed with antiparkinson medications.

FLU plasma concentrations were measured using a high pressure liquid chromatography with electrochemical detection (HPLC-ECD) method previously described by Luo et al. (1997). The lower limit of determination of the assay was 0.05 ng/ml of FLU. The within-day and between day assay variations were less than 10%. The standard curve was linear over the range of 0.05–5 ng/ml of FLU in plasma. The validity of the assay was confirmed by inter-lab quality control samples.

3. Results

The mean age of the 31 subjects randomized in the

Table 2
Fluphenazine dose, plasma concentrations, and outcomes

Subject	Duration in study (weeks)	Mean fluphenazine dose (mg/14 days)	Mean fluphenazine concentration (ng/ml)[a]	Baseline BPRS 24	Final BPRS 24	Critical outcomes
1	52	22.1	0.23	44	47	
2	52	21.1	0.34	47	38	
3	52	33.1	0.42	31	34	
4	8	30.0		32	30	EPS
5	52	4.0	0.24	32	26	
6	52	4.0	0.23	24	25	
7	8	30.0		52	52	EXAC
8	52	19.3	0.35	32	31	
9	8	4.0		48	57	EXAC
10	52	23.0	0.33	43	47	
11	24	30.0	0.32	57	50	EPS
12	6	15.0		62	92	EXAC
13	52	4.1	0.14	33	36	
14	52	40.8	0.55	36	40	
15	39	16.3	0.30	44	34	
16	20	30.0	0.37	52	34	
17	52	4.2	0.16	46	42	
18	48	6.5	0.14	51	46	
19	2	8.3		26	75	EXAC
20	52	5.1	0.15	49	24	
21	52	46.2	0.85	60	34	
22	52	47.1	0.81	32	30	
23	52	9.2	0.17	48	46	
24	52	11.2	0.25	49	29	
25	52	30.0	0.66	32	25	
26	52	21.3	0.40	48	43	
27	24	32.5	1.00	42	29	
28	20	35.0	0.63	49	55	
29	40	18.0	0.25	54	52	EPS
30	2	4.0		26	26	EXAC
31	52	17.5	0.39	33	34	

[a] Fluphenazine concentrations are included beginning at three months.

study was 42.4 (SD, 7.3); the mean duration of illness was 17.5 years (SD, 7.8); and the mean number of years of education was 12.2 (SD, 0.4). The ethnicity of subjects was 64.5% African–American, 19.4% Caucasian, 12.9% Hispanic–American, and 3.2% Asian–American. Among the subjects 74% were single, 3.2% were married and 22.6% were divorced. The mean total BPRS at baseline was 42.4 (SD, 10.5) for the 24 item version. There were no significant differences for any of these variables among the three dosage groups. Fifteen of the subjects (48%) were receiving either haloperidol or FD prior to study entry. Medication status and medication doses were not related to treatment outcomes.

Table 1 describes the plasma levels of patients who were randomized to the three treatment groups. Levels in the high group changed significantly during the study year with a slope of 0.007 ng/ml/week ($t = 5.32$, $df = 6$, $p = 0.002$). Levels in the low and medium group did not change significantly during the year. Table 2 displays FLU dosing, plasma levels, and selected outcomes for the 31 patients in the study. FLU concentrations include levels beginning at three months since this is the approximate time required for reaching steady state for patients receiving FD. Among the 31 patients who were randomized, five experienced a psychotic exacerbation, three dropped out because of EPS, two left the study for

drug abuse, and three left for other reasons (two became noncompliant and one wanted another drug). Eighteen patients completed the 52 week protocol.

We evaluated the relationship between psychopathology and side effects and FLU level with a series of covariance analyses. The dependent measures were four BPRS subscales and total, SANS total, Barnes global score, and Global Parkinsons score. We used all available observations between weeks one and 52 as the repeated measures and the level of FLU as the time dependent within cell covariates. None of the analyses indicated a significant association.

All of the exacerbations occurred within the first eight weeks of being assigned to a treatment group. When we compared plasma levels prior to an exacerbation among patients who experienced an exacerbation (0.19–0.46 ng/ml) with those who did not at the same time point (0.31–0.37), the levels were not significantly different. We also failed to find a relationship between dose of FD and the risk of exacerbations.

Patients who dropped out because of EPS tended to do so throughout the course of the study. The first of the three individuals who dropped out due to EPS left the study after eight weeks; the last drop out for this reason occurred at 40 weeks. Again, we did not find a relationship amongst EPS, the plasma level of FLU or the dose of FD. In reviewing the FLU levels for patients who developed EPS we noted that two of the three had a relatively steep increase in their concentrations over the course of the study in comparison with patients who did not develop EPS.

4. Discussion

Our results did not support our hypothesis that the monitoring of FLU plasma levels can assist clinicians who are managing patients on FD. We failed to find an association between FLU levels and either clinical response or side effects. The lack of a relationship between plasma levels and psychopathology or side effect ratings is probably explained by our design. Patients were stable at entry to the study. As a result, changes in psychopathology usually consist of worsening at the time of an exacerbation. Since there were very few exacerbations in the study and since we intervened whenever we found that patients had a worsening in their clinical state, we did not anticipate that plasma levels at regular intervals would be associated with psychopathology. We also treated patients at the first sign of side effects, particularly EPS. If EPS did not respond to anticholinergic medications or beta blockers, patients were removed from the study. This would also explain the lack of a relationship between side effects and plasma levels.

We were surprised at the difficulty we experienced in adjusting FD doses to meet our target plasma levels. As noted in a previous report (Marder et al., 1989), FLU plasma concentrations require more than three months to reach a stable state. This is consistent with other trials (reviewed in Marder et al., 1989) which noted that this is a property of long-acting haloperidol as well as FLU. In reviewing individual cases, we also noted that many patients continued to have rising levels for the first six months following randomization. As a result, it may be that the lag time between changes in dose and the effects of those changes on plasma level made these manipulations difficult. It is conceivable that plasma level monitoring for depot drugs may be helpful for confirming that patients have an adequate plasma level rather than for targeting a particular plasma concentration.

Our plasma levels of FLU were substantially lower than those from our prior report (Marder et al., 1991). This is probably explained by a change in the analytical method from RIA in the previous study to the more specific and sensitive HPLC-ECD method. The main disadvantage of RIA methods is the possible cross reaction of the antibody with other interfering compounds. The more specific and sensitive HPLC-ECD method only detects the concentration of FLU itself.

The levels we found suggest that FLU concentrations in the range of 0.25–0.80 are probably adequate for maintenance therapy. These levels are consistent with those found by Miller et al. (1995) who measured FLU using a gas chromatography/mass spectrometry (GCMS) assay. They found that the mean FLU concentration was 0.5 ng/ml in a population of patients who received doses of FD from 12.5 to 100 mg per month. Only two of 24 patients had levels greater than 1.0. In contrast, Levinson et al. (1995) studied plasma levels of FLU in patients treated with oral FLU who had experienced acute exacerbations of

schizophrenia. They found that FLU concentrations below 0.5 were suboptimal and that the greatest improvements occurred at levels above 1.0 ng/ml. This suggests that levels of depot drug for maintenance treatment are probably lower than those needed for acute treatment with oral FLU.

Other studies support the effectiveness of relatively low doses of FD. Most studies have found that lowering the dose of antipsychotic by about 80% is relatively safe although relapse rates are higher when doses are reduced (Marder et al., 1987; Hogarty et al., 1988). These doses were in the range of 4–10 mg of FD administered every two weeks. Lowering the dose below these levels led to relapse rates that may have been excessively high (Kane et al., 1983). These results were supported by the Treatment Strategies in Schizophrenia multicenter study in which an 80% dosage reduction led to relapse levels that were slightly higher than more conventional doses, but that were in an acceptable range (Schooler et al., 1997). In this report our low plasma level group received doses as low as 4 mg of FD every two weeks which appears to be an acceptable level for some individuals.

The small sample size of this trial limits the ability to draw conclusions from its results. The results are clearly vulnerable to a Type II error. For example, using a one way analysis of variance and a three group comparison, a sample of 84 patients would be needed to detect a medium effect size at $p = 0.05$, and 36 patients would be required to detect a large effect. In other words, our sample size of 31 is barely adequate for detecting a large effect.

Two factors made it difficult to recruit patients for this study. Firstly, the introduction of second generation antipsychotics made it much more difficult to recruit subjects for this trial. Secondly, we were concerned that the lowest level of FD would not provide adequate protection for some patients. As a result, patients were only selected when we were confident that their safety would not be compromised by low dose treatment. Ironically, we did not find that the lowest plasma level condition was associated with an increased relapse risk. However, this lack of an association between low plasma levels and relapse could, in part, be explained by the very careful selection of patients.

In summary, our findings failed to support our hypothesis that plasma levels of FLU were related to clinical outcome or side effects. However, the small sample size and our reluctance to place patients on very low doses of medication could explain our negative findings. On the other hand, our findings support other studies which indicate that many patients with schizophrenia can be protected from relapse on low doses and low plasma levels of FD. In practical terms, the data suggest that patients who are experiencing side effects with FLU levels above, for example, 0.5 ng/ml may continue to do well with fewer side effects if their dose is reduced.

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