

Fluphenazine decanoate

Its steady-state pharmacologic profile and relationship to tardive dyskinesia

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A sensitive radioimmunoassay was developed to determine the steady-state, fixed-dose pharmacokinetic profile of fluphenazine decanoate in nine outpatients. To see if neuroleptic blood levels measured by this assay correlated with a clinical event, we performed a cross-sectional study of fluphenazine blood levels in 11 patients with and 17 patients without tardive dyskinesia. The results do not support the hypothesis that fluphenazine decanoate serum levels correlate with TD occurrence.

Key words: Fluphenazine decanoate; Pharmacokinetics; Tardive dyskinesia

INTRODUCTION

Fluphenazine decanoate (FPZ dec), a long-acting neuroleptic, is administered parenterally for treatment of patients with chronic psychoses. In spite of its proven efficacy, relatively little is known about its pharmacokinetic characteristics. Of the investigations of FPZ dec levels to date (Nasrallah et al., 1978; Curry et al., 1979; Wiles and Gelder, 1979; Dysken et al., 1980; Tune et al., 1980; Dudley et al., 1983; Ereshefsky et al., 1984; Viala et al., 1984; Altamura et al., 1985; Brown and Silver, 1985; Chang et al., 1985; Jann et al., 1985; Marder et al., 1986; Midha et al., 1987), few have used single-dose strategies (Nasrallah et al., 1978; Curry et al., 1979; Viala et al., 1984; Altamura et al., 1985; Chang et al., 1985; Midha et al., 1987) and obtained blood samples at enough time points during the FPZ dec injection interval (Nasrallah et al., 1978; Altamura et al., 1985; Chang et al., 1985) to allow conclusions about the steady-state pharmacokinetic profile of

the drug. Furthermore, the steady-state, fixed-dose pharmacokinetic studies utilized assays with limited sensitivities. To better characterize FPZ dec pharmacokinetics, we developed a sensitive radioimmunoassay (RIA) that gave reproducible results over a wide range of concentrations. We decided to conduct a pilot study to measure steady-state serum levels between a 2 week injection interval in nine chronic psychiatric outpatients receiving a fixed dose of this medication. In an effort to see if these RIA measurements of FPZ dec blood levels correlate with clinical phenomena, we conducted a separate cross-sectional study of 28 chronic outpatients with and without tardive dyskinesia (TD) to determine if there is a correlation between serum FPZ dec level and the occurrence of TD.

SUBJECTS, MATERIALS AND METHODS

Study procedure

For the pharmacokinetic study, we selected nine symptomatically stable outpatients with psychotic diagnoses who had been receiving FPZ dec parenterally. All patients gave written informed consent as per the procedure devised by the Yale Human Investigation Committee. Prior to drug adminis-

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tration, each patient volunteered a medical history, and received a physical examination, and complete battery of clinical laboratory tests to assess renal, hematopoietic and hepatic function. Each patient then received a single 1 ml injection of 25 mg of FPZ dec intramuscularly every 2 weeks for five doses. After a sixth dose, serum samples for fluphenazine determination were obtained at 0, 2.0, 4.0, 6.0, 24.0, 48.0, 96.0, 168.0, 240.0, and 336.0 h.

In a separate cross-sectional study, 28 chronic psychiatric outpatients receiving various doses of FPZ dec (range 12.5–75 mg every 2 weeks) in the context of low contact supportive individual or group psychotherapy gave written informed consent to participate. Of the 28 patients, 11 (39%) received a diagnosis of TD via the TD Clinic (Glazer and Moore, 1981; Glazer, 1986) where they had been found to be receiving FPZ dec maintenance without other neuroleptic medications for 6 months, a total Abnormal Involuntary Movement Scale (AIMS) (Smith et al., 1979) score of 3 or more with one of the seven anatomical items scored as 2 or more, and the absence of other medical conditions that could cause chorea. All patients had been noted to meet these criteria on two or more exams at least 3 months apart. The 17 non-TD cases were group-matched to the TD subjects. They were included if (1) they were receiving at least 6 months of FPZ dec maintenance without other neuroleptic medication; (2) they had never been referred for an evaluation in the TD Clinic; (3) they had no mention of having involuntary movements in their medical record; (4) they had no sign of TD on AIMS exam performed prior to venipuncture.

A trained research assistant administered the AIMS, performed the venipuncture and reviewed the patients record for the appropriate demographic and clinical information. Blood samples were obtained 10 min prior to patients receiving their usual injection of FPZ dec.

Assay procedure

The serum was assayed using the following radioimmunoassay procedure. 100 μ l of fluphenazine antisera and 200 μ l of 125 I-radiolabeled fluphenazine-carboxy-histamine were added to the standards (0.0–10.0 ng of fluphenazine/ml) and 50 μ l of unknown serum samples. After mixing, the tubes were incubated for 2 h at room temperature (37°C).

Each sample was assayed in duplicate. Cross-reactivity results according to Abraham's (1969) criteria were: fluphenazine 100%, fluphenazine sulfoxide 5%, 7-hydroxyfluphenazine 12%, 8-hydroxyfluphenazine 0, fluphenazine-mono-*n*-oxide 29%, fluphenazine-di-*N*-oxide 11%, and *N*-des-hydroxyethyl fluphenazine 1.9%. Separation of bound and free radioactivity was accomplished by the addition of polyethylene glycol goat anti-rabbit gamma globulin (1 ml) followed by centrifugation. A phosphate buffer (pH 7.2, 0.1 M) was used. The resulting supernatants were decanted completely, and the bound fraction was counted in a standard well-type gamma scintillation counter with discriminator settings of 20–50 keV. Fluphenazine concentrations in serum were determined from a standard curve constructed by plotting counts per minute (cpm) standard/cpm blank (0 ng/ml) against the standard concentration. The working limit of quantification for this assay was 0.25 ng/ml using a 50 μ l plasma sample (12.5 pg).

The RIA method employed in this study was compared to the GC-MS method with specimens from bioavailability studies of oral and depot fluphenazine preparations. The results of this comparison, which will be presented in another article showed that the methods were correlated, but that the RIA-measured blood levels were considerably higher than the GC-MS-measured levels.

Statistical methods

For the pharmacokinetic study, mean steady-state parameters, such as the pre-dose minimum concentration (C_{\min}), maximum level (C_{\max}), time of C_{\max} (T_{\max}) and area under the serum-level curve (AUC) over the 336 h time course were calculated from complete serum-level vs. time curves for the nine available patients.

In the cross-sectional study, the hypothesis was that FPZ dec is more likely to cause TD, and that serum levels in TD patients could be significantly higher (or lower if FPZ dec masks TD) than non-TD patients. Dose of FPZ dec was expressed in chlorpromazine equivalents (CPZE) and normalized for dosing interval according to the method of Hollister (Hollister, 1977).

Differences between the TD and non-TD groups were tested for significance using χ^2 , *t*-test (two-tailed) and ANOVA statistics.

RESULTS

Pharmacokinetic study

Mean serum level data is depicted graphically in Fig. 1. Mean concentrations ranged from a C_{\min} of $0.96 (\pm 0.18)$ ng/ml to a C_{\max} of $2.18 (\pm 0.27)$ ng/ml. On an individual basis, the lowest C_{\min} was 0.40 ng/ml and the highest C_{\max} was 3.40 ng/ml. For most patients, T_{\max} occurred between 4 and 6 h after dosing with some individuals having a T_{\max} as early as 2 h. The mean area under the curve was 433.4 ng-h/ml (range 224–788 ng-h/ml).

TD study

Table 1 displays the demographic and clinical characteristics of the TD and non-TD groups. The only difference between the two groups was increased age in the TD group (mean 43.1 years) compared to the non-TD group (mean 33.2 years) $P = 0.011$. The TD patients had a non-significant

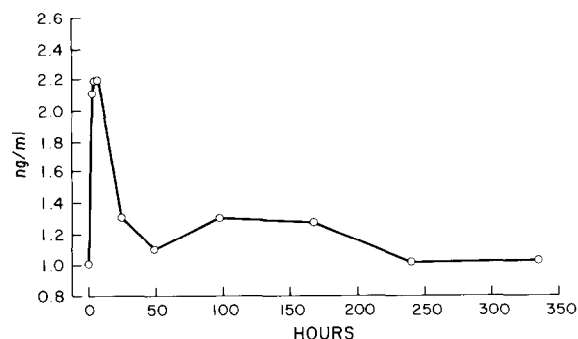


Fig. 1. Mean FPZ dec concentrations (ng/ml) over 2 week period in serum of nine patients treated for at least 3 months with 1 ml i.m. (25 mg/ml) every 2 weeks.

increase in FPZ dec levels (mean 2.3 ng/ml, SD 2.2) as compared to the non-TD group (mean 2.0 ng/ml, SD 1.8). The Pearson correlation between the FPZ dec dose and blood level was significant ($r = 0.60$, $P = 0.003$) for the entire group, and there was no difference between the TD and non-TD groups.

To determine if there was an age and/or TD effect on FPZ dec levels, we dichotomized age (≤ 37 versus > 37) and looked for differences in serum level by TD status. Older patients with TD had higher FPZ dec levels (mean level = 2.3 ng/ml, CI 0.3–4.3) as compared to non-TD patients (mean level = 1.4 ng/ml, CI 0.5–2.2). However, two-way analysis of variance for the effect of age and TD status on FPZ dec levels revealed no significant direct effects or interactions. The Pearson correlation between age and FPZ dec level ($r = 0.18$) was not significant ($P > 0.10$). There was no direct effect or interaction between patient sex and TD status on FPZ dec level. The ANOVAs of FPZ dec levels in the TD versus non-TD groups controlling for race, dosage in CPZE and concomitant use of antiparkinsonian agent was not significant.

DISCUSSION

The steady state pharmacokinetics of FPZ dec

This study demonstrates fixed-dose, steady-state FPZ dec concentrations in serum from nine chronic psychiatric outpatients. It is clear that the pharmacokinetic profile displayed in Fig. 1 represents steady state kinetics because the first (time 0) and last (336 h) time points are almost

TABLE 1

Demographic and clinical characteristics of 28 patients with and without TD receiving maintenance depot neuroleptic therapy

Variable	TD (n = 11)	No TD (n = 17)	P value
Mean age in years (SD)	43.1 (10.9)	33.2 (7.5)	0.011 ^a
n males (%)	8 (73%)	16 (94%)	NS ^b
n white (%)	5 (45%)	5 (29%)	NS ^b
Mean daily FPZ dec dose in chlorpromazine equivalents (SD)	487 (320)	498 (286)	NS ^a
Mean total AIMS score (SD)	4.7 (2.5)	0	–
Mean FPZ level (ng/ml) (SD) drawn 10 min prior to next scheduled FPZ dec injection (SD) interval	2.3 (2.2)	2.0 (1.9)	NS ^a

^a Student's *t*-test (two tailed).

^b χ^2 .

identical. The range in area under the curve in individual patients (224–788 ng-h/ml) as well as steady state levels (0.7–2.3) indicates that the inter-patient variability in FPZ dec serum levels is about three-fold. This variability is consistent with the range in C_{\min} values reported by Wiles and Gelder (1979) and is considerably narrower than the variability seen with oral fluphenazine (Dysken et al., 1981).

The best time to obtain serum levels of FPZ dec appears to be anywhere from 3 to 14 days after at least the sixth consecutive biweekly injection. In agreement with results from the present work, prior studies have shown that FPZ dec reaches a peak concentration before the first 24 h following the injection (Nasrallah et al., 1978; Curry et al., 1979; Wiles and Gelder, 1979; Ereshefsky et al., 1984; Altamura et al., 1985; Chang et al., 1985; Midha et al., 1987). The cause and clinical significance of early peak is still unclear (Altamura et al., 1979; Curry et al., 1979; Jann et al., 1985). It is interesting to compare the pharmacokinetic profile in our study to the ones reported by Midha et al. (1987) for parent fluphenazine and the fluphenazine sulf-oxide metabolite. In the latter study, a transient, mild peak of fluphenazine and fluphenazine sulf-oxide was found within the first few hours following a 5 mg challenge dose of fluphenazine decanoate. However, the magnitude of this peak was not as great as the one reported in the present study (Fig. 1). Since our RIA cross-reacted with several metabolites of parent fluphenazine, i.e., 7-hydroxy-fluphenazine, fluphenazine-mono-*n*-oxide and fluphenazine-di-*n*-oxide, it is reasonable to assume that one of these metabolites, or an as yet unmeasured metabolite, is the major contributor to this early peak.

FPZ dec and tardive dyskinesia

The results of our cross-sectional study did not support the hypothesis that FPZ dec levels are significantly higher in TD versus non-TD patients. Three previous studies (Barnes and Wiles, 1983; Csernansky et al., 1983; Fairbairn et al., 1983) have looked for a relationship between fluphenazine blood levels and TD. Barnes and Wiles (1983) reported that higher FPZ dec levels were associated with 'masked' TD. Csernansky et al. (1983) and Fairbairn et al. (1983) were unable to demonstrate differences in FPZ dec levels in TD and non-TD

patients as determined by radioreceptor assay and radioimmunoassay. It is important to recognize that the measurement of FPZ dec serum levels is only an approximate measure of FPZ dec metabolism in TD and non-TD patients. An ideal design to see if TD correlates with FPZ dec use would be either a single-dose or a fixed-dose, steady-state comparison of TD and non-TD patients matched for variables such as, age, sex, race, diagnosis, weight, height and exposure to neuroleptic medication. In addition, it would be helpful to rule out a masking effect of FPZ dec by discontinuing this medication in non-TD patients.

The finding that TD patients were older than non-TD patients is consistent with many previous studies. To date, no study has shown an effect of age on FPZ dec levels. In this study, FPZ dec levels appear to be lower in older patients without TD as compared to older patients with TD. This observation failed to reach statistical significance on analysis of variance but the sample size limited the statistical power of the test, particularly regarding a type 2 error. Future studies with a greater number of patients will help clarify the relationship between age, TD and FPZ dec levels.

In conclusion, we have utilized a radio-immunoassay to measure FPZ dec blood levels in a chronic fixed-dose pharmacokinetic study as well as a cross-sectional study of patients with and without TD.

Pharmacokinetic parameters found with this assay are consistent with previous studies. Future studies need to clarify the relationship of parent fluphenazine and its metabolites to clinical activity. FPZ dec levels do not appear to correlate with TD occurrence, although a prospective study of the pharmacokinetics of this neuroleptic in TD and non-TD patients is indicated.

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