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Lowest effective dose of depot neuroleptics

SIR: We would like to support the statement of Marder *et al* (*Journal*, May 1991, **158,** 658–665) that monitoring of plasma levels is helpful to treat patients with the lowest effective dose of a depot neuroleptic such as fluphenazine. We have followed up stable out-patients on depot neuroleptics for between two and four years. Our data support the statement of Marder *et al* that plasma levels of fluphenazine should be between 0.53 and 3.0 ng/ml.

Our patient group consisted of 103 stable out-patients (mean age 42 years, range 18–72, mean weight 76 kg, mean height 1.75 m), receiving depot medication for at least six months (mean interval 13 days; range 7–28) and having no change in medication for three months.

All patients had schizophrenia or schizoaffective disorder as a primary diagnosis. The types of medication were: fluphenazine (FPZ) $n=27$; flupenthixol (FPX) $n=57$; and haloperidol (HAL) $n=19$.

Repeated measurements of plasma levels, one hour before injection, using a high pressure liquid chromatography or gas liquid chromatography method, were performed. No metabolites were determined. The coefficient of variation was less than 5% for FPZ, FPX and HAL, quantitation limit FPZ 0.2 ng/ml; FPX 0.5 ng/ml; HAL 0.5 ng/ml.

An estimated linear regression for all data was performed for each medication group. The 'kinetic' model used was the anticipated relationship between the administered dose at the previous visit divided by the number of weeks since the previous visit (i.e. interval) and the plasma concentration. The usual way to estimate the assumed linear relationship (with respect to time) is by use of a linear regression model with no respect to different variances at different dose levels.

Plots of estimated line, confidence limits and observations were made, 'B' representing the slope of the regression line in the case of one variable. The confidence interval of 95% is the interval of the regression line. The relationships between plasma level and dosage are shown below.

For fluphenazine: B = 0.04, 95% confidence interval = 0.027–0.0053. 52/58 observations (89.7%) of the plasma levels were within the 0.5–3.0 ng/ml range.

For flupenthixol: B = 0.05, 95% confidence interval = 0.038–0.06. 114/140 observations (81.4%) of the plasma levels were within the 0.5–3.0 ng/ml range.

For haloperidol: B = 0.05, 95% confidence interval = 0.02–0.07. 42–47 observations (89.3%) of the plasma levels were within the 0.5–4.0 ng/ml range.

The results show that in this stable group the plasma levels are within a definite range. The variation of haloperidol is higher than for flupenthixol and fluphenazine.

As Marder *et al* (1987) and Johnson *et al* (1987) have shown for fluphenzine and flupenthixol, lower dosage may be as effective as higher dosage in preventing relapse in maintenance therapy with depot neuroleptics.

However, both report that a 'too low' dosage leads in the long term (more than one year) to a statistically greater chance of relapse. Marder *et al* (1990) showed that lower plasma levels of fluphenazine (<1.0 ng/ml) do indeed significantly correlate with a relapse after six or nine months. They measured the plasma level at the day of injection using a RIA-method and report a range of 0.5–3 ng/ml.

Norman *et al* (1987) found in a comparable group of stable out-patients on long-term fluphenazine decanoate an average plasma level for males ($n=9$) of 1.3 µg/l and for females ($n=8$) 1.0 µg/l. They found no relationship between BPRS-scores and plasma levels over time.

In a preliminary analysis we found no influence of anxiolytics, anticholinergics, or sex on plasma level. We realise that our study is methodologically weak, but the results correlate quite well with the results of the study that Marder *et al* report in this journal. Furthermore, we think that our data do support the view that in future research on relapse prevention in maintenance therapy, more attention should be given to plasma levels, since patients receiving 20 mg or 40 mg of flupenthixol or fluphenazine per week may have the same plasma level. Individual, unique, metabolic factors may play a role in these differences. Other factors such as age, race, or co-medication might also influence the plasma levels.

We propose for future studies concerning relapse prevention in maintenance therapy that plasma levels of flupenthixol of 0.5–3.0 ng/ml, fluphenazine 0.5–3.0 ng/ml and haloperidol 1.0–4.0 ng/ml are studied.

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MARDER, S. R., VAN PUTTEN, T., MINTZ, J., *et al* (1987) Low-and-conventional-dose maintenance therapy with fluphenazine decanoate. *Archives of General Psychiatry*, **44,** 518–521.

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Soft neurological dysfunction and gender in schizophrenia

SIR: Evidence from the literature suggests that male and female schizophrenics differ in terms of: age at onset, clinical picture, response to neuroleptics (DeLisi *et al*, 1989), frequency of early brain injury, family history of psychosis, preponderance of positive as opposed to negative symptoms (Nasrallah & Wilcox, 1989) and neuromorphological abnormalities (e.g. Flaum *et al*, 1990). The most plausible explanation for these differences, according to Castle & Murray (1991), is that more male than female schizophrenics have a form of disease due to neurodevelopmental anomaly.

Nasrallah & Wilcox (1989) suggest that neurological factors may play an important aetiological (causative and/or additive) role in the development of schizophrenia in males, while hereditary factors may be more important for schizophrenia in females.

A group of 64 patients with schizophrenic disorder (43 males, 21 females) diagnosed according to DSM–III–R critera were included in the present study. All the patients were consecutively admitted to our university ward from the catchment area served by the hospital.

Inclusion critera were: age between 18 and 50; informed consent; no history of neurological disorder, drug abuse or alcoholism. Male and female schizophrenics had been ill for a mean of 7.75 years (s.d. 5.17) and 9.20 years (s.d. 7.54) respectively. Their ages ranged from 20 to 50 years (mean (s.d.) 30.04 (7.48)) for males and from 21 to 50 years (mean (s.d.) 34.28 (8.22)) for females. All the patients were on neuroleptic medication (dose range 200–3000 mgEq/chlorpromazine; mean (s.d.) 354 (289) for males and 357 (277) for females).

Patients were assessed by a standardised neurological examination focused on neurological soft signs (NSS) which was developed by our own research group and used in a previous study on schizophrenic patients, their first-degree relatives and healthy controls (Rossi *et al*, 1990). A revised form developed from its longer parent instrument (Rossi *et al*, 1990) was used in the present study. Twelve items of the original 19 formed the present NSS scale. No informative items were excluded from the instrument after the first study.

A two-tailed *t*-test for independent samples was performed. The alpha level was *a priori* fixed at 0.05.

Comparing the groups, a significant difference was found in age ($t = -2.24$, 69 d.f., $P = 0.028$). No significant differences were found in duration of illness ($t = -0.95$, 68 d.f., $P = 0.343$ NS) or current drug dosage ($t = -0.04$, 66 d.f., $P = 0.96$ NS) between the two groups. No between-group difference was found for NSS total score ($t = -0.30$, 69 d.f., $P = 0.76$ NS).

Female schizophrenics were found to have the same NSS total score compared with males, after age and mgEq/CPZ were taken into account using these two variables as covariates in the ANCOVA (main effects: $F = 0.941$, 3, 64 d.f., $P = 0.42$ NS). However age and mgEq/chlorpromazine were not significantly related to NSS total score (multiple regression analysis: no variable entered at 0.05 limit in the total sample and in male and female groups separately).

Our results failed to support the hypothesis of gender differences at neurological examination in schizophrenia, contrasting with Nasrallah & Wilcox's (1989) hypothesis of a pre-eminent role of neurological factors in the aetiology of schizophrenia in males, based on a retrospective evaluation of childhood brain injury. Since we found an excess of NSS in schizophrenics and their first-degree relatives in our previous study (Rossi *et al*, 1990), minimal brain damage can be considered as a potential marker of a gender-independent vulnerability.

Other factors (perhaps genetic) may play a differential role in eliciting schizophrenia in both sexes, or in modulating schizophrenia in males and females with a spread of neuromorphological and outcome differences.

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