Brit. J. Psychiat. (1983), **142,** 579–583

Serum Concentration of Depot Neuroleptics in Tardive Dyskinesia

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Summary: Using radioimmunoassay techniques, serum levels of depot neuroleptics, fluphenazine and flupenthixol, were estimated in two groups of chronic schizophrenic patients with, and without, tardive dyskinesia. There were high correlations between drug dose and plasma concentration. There was no significant difference in dose-related serum levels of either drug between the groups.

The hypothesis that patients with tardive dyskinesia develop the syndrome because they do not metabolise neuroleptics as efficiently as those without the syndrome was not supported by the data.

Tardive dyskinesia (TD) can be defined as "a syndrome of involuntary movement arising in psychiatric patients taking neuroleptic drugs" (*Lancet,* 1979). The tardive element in the disorder implies that the syndrome arises after a time delay from the first prescription of neuroleptic drugs. Some patients, particularly the elderly, may, however, exhibit the syndrome (bucco-linguo-masticatory dyskinesia, the BLM triad) without the prior use of such agents (Brandon *et al,* 1971), which suggests organic as well as drug-induced changes in the aetiology. Some studies (Brandon *et al,* 1971; Famuyiwa *et al,* 1979) have indicated that both the length of exposure to neuroleptic treatment and high accumulated dose increase the chances of developing TD, others do not agree (Kane and Smith, 1982). Jeste *et al* (1979), in a study of oral neuroleptics in patients with tardive dyskinesia, claimed to find a significantly increased serum neuroleptic level in patients with TD, compared to patients without the disorder. Higher plasma levels could result not only from a higher dose but also from differences in drug metabolism between individuals. Tricyclic antidepressants have been potently illustrative of the variations in metabolism of drugs between patients, and such differences are likely to be of genetic origin (Braithwaite *et al,* 1982). Individuals who develop TD may metabolise neuroleptic agents more slowly than others on similar doses, and in consequence, they may generate higher blood concentrations of the drug. This study set out to determine whether, or not, chronic schizophrenics with tardive dyskinesia have higher serum levels of depot neuroleptic, in relation to the dose, than a control group without TD.

Methods

The study involved two depot neuroleptics, fluphenazine ("Modecate") and flupenthixol ("Depixol"). The patient population were all long-stay, had a case-note diagnosis of schizophrenia, and fulfilled the criteria of Feighner *et al* (1972) for such a diagnosis. The diagnosis of tardive dyskinesia was made by two psychiatrists who agreed independently on the finding of oro-facial dyskinetic movements and, specifically, bucco-linguo-masticatory dyskinesia. In all cases TD was considered to be secondary to neuroleptic administration. No case was included in which the movements were considered to be the result of neurological disease. There were 12 patients on fluphenazine, of whom 5 had TD; and, of 30 on flupenthixol, 15 had TD. All patients had been on depot neuroleptics for at least 2 years.

The patients in the study had their concurrent oral neuroleptic medication stopped five days before the blood samples were taken. Since the half-lives of orally administered fluphenazine hydrochloride and cis(z)-flupenthixol hydrochloride are about 15 hours (Curry *et al,* 1979) and 19–39 hours (Jørgensen, 1980), respectively, significant levels of these drugs are unlikely to be present in the serum of patients after a five day washout period. The continued prescription of anti-Parkinsonian drugs and benzodiazepines was allowed.

In order to obtain consistency in sampling in each patient, blood was taken off five days after he, or she, last received a depot injection. The blood samples were centrifuged immediately after sampling, and the sera placed on ice until ultrafiltration, using Amicon Diaflo PM 10 membranes at 37°C, was performed. Serum and ultrafiltrate were analysed for neuroleptic concentration by radioimmunoassay (Rowell *et al*, 1979). The assay, using tritiated fluphenazine or flupenthixol as labels, exhibited low cross-reactivities towards the major side-chain and ring metabolites of fluphenazine and flupenthixol, respectively. The total serum and unbound serum levels (in the case of fluphenazine), or, total levels (in the case of flupenthixol) were then calculated.

Results

In patients taking flupenthixol, there was no difference in the serum concentration of this drug between males with and without TD; the same was true for females with and without TD (Table I). Likewise, for patients taking fluphenazine, there was no difference in the total serum concentration of this drug between males and females with, and without, TD (Table II).

There was a high correlation of dose (mg/week or mg/kg/week) against serum concentration for male and female TD and non-TD groups receiving flupenthixol (Table I). There was no significant difference between the slopes of these correlations (Fig 1). For a dose of 19.2 mg/week of flupenthixol, in the non-TD group, a serum flupenthixol level was calculated as 8.4 ng/ml. For a similar dose in the TD group, a serum level of 9.3 ng/ml was obtained. From the regression data shown in Fig 1, the difference was not significant.

There was also a high correlation between dose (mg/week or mg/kg/week) against total serum fluphenazine concentration for both the TD and non-TD groups (Table II). Again, there was no significant difference between the slopes of these correlations (Fig 2). For a dose of 15.2 mg/week in the non-TD group, a serum fluphenazine level was calculated as 5.1 ng/ml. For a similar dose in the TD group a serum level of 5.8 ng/ml was obtained from the regression data shown in Fig 2. The difference was not significant. Unbound serum fluphenazine levels were also determined, and there was a significant correlation between dose and unbound drug levels in serum (Table III). The mean unbound serum concentration was not significantly different between the TD and non-TD groups; however, the sera from only three TD patients were examined in this study. No significant correlation between age and unbound serum fluphenazine was observed.

Partial correlation coefficients between age and dose, and age and total serum levels, were calculated, partialling out serum levels and dose levels respectively. This was done for males and females and for those with and without TD. The coefficient, r, did not differ significantly on any of these variables, i.e. serum level in relation to dose did not increase with age, sex, or whether, or not, the patient had TD.

Discussion

The incidence of TD in hospital populations in-

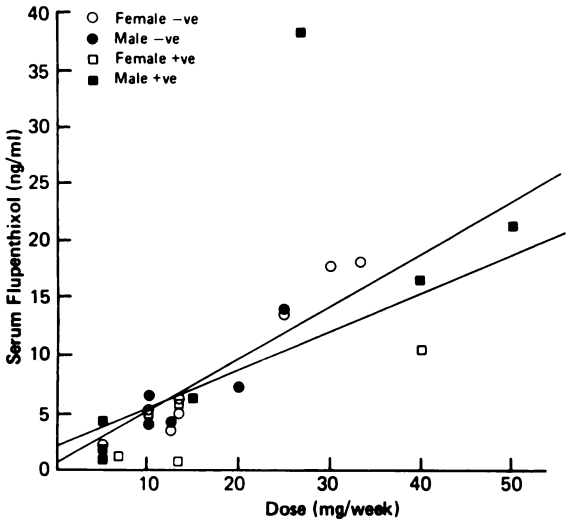

FIG 1.—Best fit linear regression analysis of dose mg/week against serum flupenthixol concentration.
A = male and female without TD (r = 0.88, P <0.0091, N = 17).
B = male and female with TD (r = 0.66, P <0.02, N = 12).

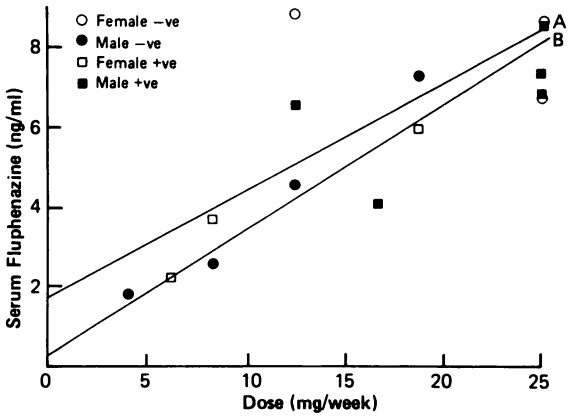

FIG 2.—Best fit linear regression analysis of dose (mg/week) against serum fluphenazine concentration (ng/ml).
A = male and female without TD (r = 0.76, P <0.005, N = 7).
B = male and female with TD (r = 0.99, P <0.001, N = 10).

https://doi.org/10.1192/bjp.142.6.579 Published online by Cambridge University Press

TABLE I

Concentrations of flupenthixol in male and female patients with and without TD

N	Age (Mean±SE)	Sex	TD	Dose (mg/week)	Dose (mg/kg/week)	Serum conc. (ng/ml)	Correlation coef. r*		Significance	
							(mg/week)	(mg/kg/week)	(*i*)	(*ii*)
7	51±4.2	M	—	22.5±9.1	0.218±0.192	8.6±3.1	(*i*)0.82	(*ii*) 0.94	P <0.02	P <0.001
7	57±4.7	M	+	21.0±7.0	0.345±0.138	12.8±5.1	(*i*) 0.67	(*ii*) 0.59	P <0.01	NS†
10	49.1±3.9	F	—	16.2±3.0	0.246±0.057	8.1±1.9	(*i*) 0.98	(*ii*) 0.91	P <0.001	P <0.001
5	65±3.8	F	+	16.7±6.0	0.312±0.114	4.5±1.8	(*i*) 0.84	(*ii*) 0.82	P <0.05	P <0.05

* Correlation coefficient, r, obtained from linear regression analysis of dose (mg/week) against serum concentration (*i*), or dose (mg/kg/week) against serum concentration (*ii*).
† Not significant.

TABLE II

Total serum concentrations of fluphenazine in patients with and without TD

N	Age (Mean±SE)	Sex	TD	Dose (mg/week)	Dose (mg/kg/week)	Serum conc. (ng/ml)	Correlation coef. r*		Significance	
							(mg/week)	(mg/kg/week)	(*i*)	(*ii*)
7	53.1±4.0	M & F	—	15.2±3.0	0.115±0.028	5.8±1.1	(*i*) 0.76	(*ii*) 0.72	P <0.05	P <0.05
10	55.4±2.6	M & F	+	26.9±11.2	0.367±0.180	8.8±3.6	(*i*) 0.99	(*ii*) 0.99	P <0.001	P <0.001

* Correlation coefficient, r, obtained from linear regression analysis of dose (mg/week) against serum concentration (*i*), or dose (mg/kg/week) against serum concentration (*ii*).

TABLE III

Unbound serum concentrations of fluphenazine in patients with and without TD

N	Age (Mean±SE)	Sex	TD	Dose (mg/week)	Dose (mg/kg/week)	Unbound serum conc. (ng/ml)	Correlation coef. r*		Significance		% Unbound†
							(mg/week)	(mg/kg/week)	(*i*)	(*ii*)	
7	53.1±4.0	M & F	—	15.2±3.0	0.115±0.028	0.45±0.074	(*i*) 0.71	(*ii*) 0.68	P <0.05	P <0.01	7.8
3	55.7±4.8	M & F	+	18.7±6.2	0.121±0.029	0.38±0.094	(*i*) 0.997	(*ii*) 0.97	P <0.01	P <0.05	6.9

* Correlation coefficient, r, obtained from linear regression analysis of dose (mg/week) against unbound serum concentration (*i*), or dose (mg/kg/week) against unbound serum concentration (*ii*).
† % Unbound values expressed as [unbound serum concentration (ng/ml): total serum concentration (ng/ml)]×100.

creases markedly with age, with a maximum in the 61–70 age group (Brandon *et al,* 1971). There is also an increased incidence in female patients. The suggestion has been made in the past that TD may be due to drug-induced dopaminergic supersensitivity, or to an organic (degenerative) cause, or to a combination of both (Famuyiwa *et al,* 1979). The Famuyiwa study indicated that both cognitive impairment and CT-scan change were commoner in a group of patients with TD than in those without, which suggested the importance of a degenerative component in the development of the condition. The role of drugs, on the other hand, is obscure; for the total drug exposure and duration of treatment is reported to be higher in the TD groups in some, but not all, studies. This suggests, either, that there is an idiosyncrasy in individuals with TD; or, that with a given dose of drugs, and for metabolic reasons, the TD patients achieve higher, and potentially more toxic, levels of psychotropic drugs, compared to individuals who do not develop TD.

Our studies show quite clearly that the TD group do not develop inappropriately high serum concentrations of drugs, in relation to dose, than the non-TD group. It is also clear that changes in the incidence of TD with age are not related to higher serum levels of neuroleptic, again relative to the dose of drug given. Similarly female patients do not have higher serum levels than males, when given comparable drug doses.

The studies indicate a very clear and significant relationship between dose and serum levels of both fluphenazine and flupenthixol. The indications are that the rate of release of the depot preparation is the limiting factor in the final serum level, rather than the subsequent metabolism of the drug (Jørgensen, 1980). These drugs are strongly bound in plasma. A potential source of variation between patients might be the percentage of the drug which is unbound and, presumably, in equilibrium with tissue levels. From the limited number of investigations, this does not appear to be the case for fluphenazine. The values obtained for percentage unbound fluphenazine in serum agree with *in vitro* values (Rowell *et al,* 1980). Although a significant correlation between age and unbound serum fluphenazine concentration has been reported *in vitro* (Rowell *et al,* 1980), no corresponding correlation has been observed in this study in the sera from the non-TD group of patients. It is possible that the age-binding relationship is altered by schizophrenia. Or, that metabolites of fluphenazine, which were not co-incubated in the *in vitro* experiment, obscure the relationship *in vivo*. Alternatively, schizophrenics may have different pharmacokinetics, drug metabolism and elimination than non-schizophrenics.

This study does not, then, promote the view that higher serum levels of neuroleptic drugs occur in patients with TD (Jeste *et al,* 1979). The Jeste *et al* study did however involve the use of oral medication and piperidine-type phenothiazines, and further studies are necessary to look in particular at this route of administration and type of neuroleptic. It does not seem very likely that the route of administration of neuroleptic is important, since we can anticipate that, because of their high dopamine blockade, depot neuroleptics are more potent in producing TD than oral preparations.

Our studies do not answer the question whether, or not, the organic changes in TD are the primary cause which render individuals on drug therapy to be more susceptible to the syndrome, or whether the drugs which produce TD also produce organic and cognitive changes.

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(Received 30 September; revised 26 November 1982)