THE RELATIONSHIP BETWEEN CHANGES IN 5-HT INDUCED PLATELET AGGREGATION AND CLINICAL STATE IN PATIENTS TREATED WITH FLUPHENAZINE

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- 1 Platelet aggregation responses to 5-HT and adenosine diphosphate were examined in a population of eighteen patients treated with fluphenazine decanoate for longer than one year.
- 2 5-HT induced aggregation was enhanced in ten subjects. This enhancement was similar to that previously described in patients receiving chlorpromazine.
- 3 Patients who showed enhanced 5-HT induced aggregation showed less rateable psychopathology and less extrapyramidal side-effects than patients who did not show enhancement.
- 4 These findings suggest that platelet aggregation responses could be used to identify patients who could be safely withdrawn from long-term neuroleptic therapy.

Introduction

Chlorpromazine has been shown to inhibit platelet aggregation induced by 5-hydroxytryptamine *in vitro* (Boullin, Grahame-Smith, Grimes & Woods, 1975a) and to enhance aggregation *in vivo* (Boullin, Woods, Grimes, Grahame-Smith, Wiles, Gelder & Kolakowska, 1975b). Inhibition of aggregation *in vitro* has also been shown with fluphenazine and α -flupenthixol (Boullin, Grimes & Orr, 1975).

Boullin *et al.* (1975b) have suggested that the enhancement of 5-HT induced platelet aggregation in patients receiving chlorpromazine could be related to therapeutic effects and prove to be a useful pharmacological tool in monitoring chlorpromazine therapy.

In view of the *in vitro* findings with fluphenazine and flupenthixol, both widely used depot neuroleptics in the maintenance treatment of schizophrenia, we have examined the effect of fluphenazine on 5-HT-induced platelet aggregation *in vivo*, and we have tried to relate changes in platelet aggregation to clinical symptoms and to the presence of extrapyramidal side-effects. We have found that aggregation was enhanced in ten

of the eighteen patients tested and that those patients who showed enhancement of aggregation differed clinically from those patients who did not.

Methods

The subjects were eighteen chronic schizophrenic patients (six in-patients and twelve day patients) who had been receiving fluphenazine (FPZ) for at least 6 months. The mean age of the sample was 40.1 years and the age range was 19-56 years. The dosage regime for fluphenazine varied from 25 mg fortnightly to 25 mg monthly. All the patients were receiving anti-parkinsonian medication under supervised conditions—benzhexol in doses of 4-15 mg/day or orphenadrine in doses of 150-300 mg/day, together with nitrazepam (10 mg) at night as required; these drugs did not affect platelet aggregation responses when added to platelet rich plasma (PRP) *in vitro*.

Blood samples were taken immediately before the drug was given, 2 h after and 2 weeks later.

Figure 1 Platelet aggregation responses to 20 μ M 5-HT in a fluphenazine treated patient and normal control subject. Aggregation is expressed as changes in light transmittance through platelet rich plasma (mv, ordinate) stirred at 1000 rev/min at 37°C, in relation to time (abscissa). (a) response of control subject; (b) response of fluphenazine treated patient. The baseline responses prior to addition of 5-HT are superimposed.

Blood was collected into 0.129 M sodium citrate, platelet rich plasma (PRP) was prepared, and platelet aggregation studies were carried out as described by Boullin, Green & Price (1972). Aggregation was induced by 10 to 50 μ M 5-hydroxytryptamine (5-HT), or adenosine diphosphate (ADP) in similar concentrations, added to PRP stirred at 1000 rpm and maintained at 37°C.

We confirmed earlier work (Boullin *et al.*, 1975b) that maximal aggregation responses were produced with 20 μ M 5-HT and that higher concentrations did not cause inhibition. ADP responses were normal.

Rates of change in optical density of the PRP following the addition of 5-HT or ADP were expressed as μ v/min from recordings on an X-Y recorder.

Overall aggregation responses were measured by the total change in optical density over the first 300 s after addition of 5-HT or ADP to PRP. The area under the aggregation curve record (Δ OD) was measured with a compensating polar planimeter and expressed in arbitrary units in relation to ADP responses (see below).

5-HT responses were expressed as a % of ADP responses in order to compensate for individual variations in the optical density of PRP samples, and for variations which could arise from using equipment of different sensitivity.

Clinical rating was carried out using the Brief Psychiatric Rating Scale (BPRS) (Overall & Goreham, 1962). Extrapyramidal symptoms were rated on the scale devised by Simpson & Angus (1970). Ratings were carried out on each patient at each sampling point.

Results

5-HT induced aggregation rate was increased and aggregation was irreversible in ten of the patients; aggregation responses in the remainder of the sample were normal. Figure 1 shows the normal aggregation response to 5-HT, which is reversible, and the enhanced response with increased rate of aggregation and irreversibility seen in about 55% of our patients. This response was qualitatively and quantitatively similar to that described in patients receiving chlorpromazine.

Though there were differences between patients in rates of aggregation and total change in optical density induced by 5-HT, intra-individual values were highly reproducible and there was no consistent pattern of change in aggregation before,

Table 1 Aggregation rates produced by 5-HT in patients receiving fluphenazine (FPZ), chlorpromazine (CPZ) and in controls

	Controls*	FPZ patients with reversible aggregation	FPZ patients with irreversible aggregation	CPZ*
Rate (μ v/min)	771 $\pm$ 192 (13)	834 $\pm$ 128 (8)	2598 $\pm$ 458 (10)	1819 $\pm$ 241 (9)
5-HT rate as % ADP rate	22.6	25.5 $\pm$ 2.91	61.4 $\pm$ 6.49	52.8

The data show mean $\pm$ s.e. mean values for aggregation rate obtained in normal subjects compared to those obtained with blood taken from FPZ and CPZ treated patients 2 h after drug administration. The values in parenthesis refer to the number of patients investigated.

* Data from Boullin *et al.* (1975b)

2 h after the injection of the drug, or 2 weeks later. The rate of platelet aggregation and the total change in optical density induced by 5-HT in those patients who showed an enhanced response were similar to those seen in patients receiving chlorpromazine. The patients who did not show an enhanced response were not different from controls.

Table 1 shows that the rate of aggregation in patients receiving FPZ, but showing reversible aggregation, was similar to that of controls. The rate seen in patients on FPZ but showing irreversible aggregation was more than doubled to 61.4% of the maximal ADP-induced rate, and similar to the rates found by Boullin *et al.* (1975b) in chlorpromazine treated patients.

Table 2 shows that the total change in optical density in fluphenazine treated patients with reversible aggregation was within the normal range, whereas that seen in patients who showed irreversible aggregation was similar to that seen in chlorpromazine treated patients.

There were clinical differences between patients showing normal reversible aggregation to 5-HT and those showing atypical irreversible responses. Table 3 shows mean scores on the BPRS and the rating scale for extrapyramidal symptoms for each of the two groups. Patients who showed no

enhancement of aggregation had significantly higher scores on both scales than patients who showed enhancement; there was thus a higher incidence of rateable psychopathology and of extrapyramidal side-effects in patients with normal reversible aggregation. These differences were not related to the dose of fluphenazine given, or to the interval between injections.

BPRS scores did not vary significantly within patients over the three sampling points. Some patients showed an increase in extrapyramidal signs—mainly rigidity and tremor, 2 h after receiving the drug but the changes were not marked or consistent. Scores on the rating scale for extrapyramidal side-effects were not related to the dose of fluphenazine in this group of patients or to the type or amount of anti-parkinsonian medication administered.

Discussion

Patients receiving depot neuroleptics such as fluphenazine or flupenthixol are usually part of a chronic schizophrenic population in whom psychotic symptoms are controlled to a greater or lesser degree. The purpose of treatment with these drugs is to maintain such control, and the absence

Table 2 Total changes in optical density of PRP produced by 5-HT (ΔOD) in patients receiving fluphenazine (FPZ), chlorpromazine (CPZ) and controls

	Controls	FPZ patients with reversible aggregation	FPZ patients with irreversible aggregation	CPZ patients*
ΔOD 5-HT % ADP	11.2 (28)	12.76 (8)	57.5 (10)	85.2 (21)
ΔOD ADP	± 1.7	± 1.24	± 9.42	± 6.3

The data show mean $\pm$ s.e. mean values for change in optical density (ΔOD) obtained in normal subjects compared to those obtained with blood taken from FPZ and CPZ treated patients 2 h after drug administration. The values in parenthesis refer to the number of patients investigated.

* Data from Boullin & Grimes (1976)

Table 3 Brief Psychiatric Rating Scale (BPRS) and Extrapyramidal Symptoms Rating (EPS) Scale scores in FPZ treated patients with reversible and irreversible aggregation

Score on rating scale	Patients with reversible aggregation (n = 8)	P	Patients with irreversible aggregation (n = 10)
BPRS	13.36 $\pm$ 2.52	<0.001	6.2 $\pm$ 1.4
EPS	16.9 $\pm$ 2.5	<0.001	3.24 $\pm$ 0.98

The values are the mean $\pm$ s.e. mean of individual scores on the rating scales indicated.

The patients are divided into two groups on the basis of their aggregation responses.

of clinical changes within patients over the 4 weeks spanned by a single injection is therefore not surprising. The patients tested had been on phenothiazines or thioxanthenes for a long period and no detectable clinical changes within patients over the period of the investigation were expected.

It is well known that some patients respond well to phenothiazine therapy and some do not; there are few criteria which enable one to accurately identify potential responders to fluphenazine and virtually no guidelines available for monitoring chronic neuroleptic therapy. A further problem with the depot neuroleptics is that there are no biochemical or other means which enable us to identify those patients in whom the drug could be safely withdrawn.

There are a number of possible implications of the findings on platelet aggregation enhancement with chlorpromazine and fluphenazine. Platelet aggregation enhancement does represent a peripheral tissue effect of neuroleptic drugs which could reflect a central effect manifest clinically as antipsychotic activity. The presence of an enhanced aggregation response to 5-HT could indicate that the drug was having an antipsychotic effect, while the absence of an enhanced response in spite of treatment would indicate that the drug was not having the desired central effect. Patients who are clinically improved but who do not show

an enhanced aggregation response might therefore be those who could stop taking the drug, whereas improved patients who showed enhancement of aggregation would be at greater risk of relapse if the drug were to be withdrawn.

This hypothesis will need testing, but our findings indicate that patients on depot neuroleptics who did not show an enhanced aggregation response displayed more symptoms and more extrapyramidal side-effects than patients who showed enhancement. This suggests that clinical change due to the drug rather than to other factors is more likely to be seen in patients who show an enhanced response. Such clinical change does not seem to be associated with extrapyramidal side-effects. The pharmacology of the enhanced platelet aggregation response in patients receiving neuroleptics is still not fully understood. It may involve changes in the nature of receptors on the platelet membrane (Boullin, Green & Grimes, 1975; Boullin & Grimes, 1976) and changes in prostaglandin synthesis (Boullin & Orr, 1976) but the precise mechanism whereby neuroleptics cause enhancement of aggregation remains obscure.

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