THE EFFECTS OF NEUROLEPTIC DRUGS ON 5-HYDROXYTRYPTAMINE INDUCED PLATELET AGGREGATION IN SCHIZOPHRENIC PATIENTS

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- 1 The effects of treatment with a range of neuroleptic drugs on 5-hydroxytryptamine (5-HT) induced platelet aggregation *in vivo* were examined in a group of recently admitted psychiatric patients and in a larger group of chronic schizophrenic patients.
- 2 Five of seven recently admitted patients treated with chlorpromazine showed enhanced aggregation. Four of seven patients treated with fluphenazine, flupenthixol, trifluoperazine and haloperidol showed enhancement.
- 3 Enhanced aggregation responses were observed in only 20% of chronic schizophrenic patients being treated with a neuroleptic drug.
- 4 The relationship between changes in platelet aggregation and clinical changes in recently admitted patients was variable and platelet aggregation responses were not predictive of response to treatment.
- 5 Chronic schizophrenic patients with enhanced aggregation showed significant week to week variation in platelet aggregation response. Variability of responses was not related to the drug used or to the dose administered. There was some evidence that higher plasma concentrations of neuroleptic drugs were associated with enhanced platelet aggregation responses.
- 6 Treatment with neuroleptic drugs leads to enhancement of platelet aggregation responses induced by 5-HT. The frequency and reliability with which such responses can be elicited is unpredictable and the value of platelet aggregation responses as an empirical guide to treatment with neuroleptic drugs is therefore open to question.

Introduction

We have recently reported enhancement of platelet aggregation induced by 5-hydroxytryptamine (5-HT) in schizophrenic patients being treated with chlorpromazine (CPZ) (Boullin, Woods, Grimes, Grahame-Smith, Wiles, Gelder & Kolakowska, 1975) and fluphenazine (Orr & Boullin 1976). We have also reported a temporal relationship between changes in platelet aggregation responses and clinical changes in some recently admitted patients treated with chlorpromazine for the first time; in these patients, platelet aggregation enhancement was observed at the same time that symptoms became less marked. In chronic schizophrenic patients in whom maintenance treatment with chlorpromazine was withdrawn, enhanced platelet aggregation responses returned to normal at the same time that symptoms reappeared (Boullin, Orr & Peters, 1978). These findings suggested the possibility that platelet

aggregation responses could be used as a pharmacodynamic index of CPZ activity which could be related to clinical changes during treatment.

An attempt to replicate these findings in a separate group of chronic schizophrenic patients receiving chlorpromazine showed, however, that the incidence of enhanced platelet aggregation responses was significantly lower than that reported in earlier work (Boullin, Knox, Peters & Orr, 1978). We have therefore carried out a series of studies aimed at a critical examination of the value of platelet aggregation responses as an index of neuroleptic drug action. We sought to extend the findings with chlorpromazine to a number of other neuroleptic drugs in common clinical use. A simple expectation would have been that phenothiazine drugs other than CPZ, and possibly non-phenothiazine neuroleptics of known therapeutic value in schizophrenia would also cause en-

hanced aggregation. We have also carried out more intensive studies with individual patients in order to examine the consistency and reliability with which aggregation responses could be obtained.

Methods

Subjects

The subjects were 139 patients who were in-patients or day-patients at Littlemore Hospital, Oxford, and who were receiving one of the following neuroleptic drugs: chlorpromazine, fluphenazine, flupenthixol, haloperidol, thioridazine, trifluoperazine and the non-neuroleptic phenothiazine promethazine. Eighteen patients had been recently admitted and had not received any medication for at least 6 months; the remaining 121 were chronic schizophrenic patients on long-term medication. Twenty-seven normal controls were also tested.

In addition, four patients who had been tested in the original study in 1975 and who were still receiving chlorpromazine were studied more intensively as described below. Details of the number of patients on each drug studied are given in Table 1.

Table 1 Numbers of recently admitted patients, chronic schizophrenic patients and normal controls tested on each drug.

	Recently admitted patients	Chronic schizophrenics	Controls
Chlorpromazine	7	40	—
Fluphenazine	3	23	—
Thioridazine	—	15	—
Flupenthixol	1	20	—
Trifluoperazine	2	15	—
Haloperidol	1	8	—
Promethazine	4	—	—
No medication	—	—	27
Total	18	121	27

Measurement of platelet aggregation responses

Venous blood (20 ml) was withdrawn into 0.129 M sodium citrate and centrifuged at 100 g for 9 min. Platelet rich plasma (PRP) was then dispensed into plastic aggregometer tubes using siliconised glass pasteur pipettes and transferred to an aggregometer. Aggregation responses were then measured by observing the changes in light transmittance through the sample of the PRP induced by the addition of 200 μ mol 5-HT (Born, 1962). The magnitude of aggregation responses were represented by the total change in light transmittance in the sample of PRP and ex-

pressed as a percentage of the response induced by 20 μ mol adenosine diphosphate (ADP), as described by Orr & Boullin (1976).

Protocol

Thirteen of the eighteen recently admitted patients were studied over a period ranging from 4 to 15 weeks. Blood samples for platelet aggregation studies, plasma drug and prolactin levels were withdrawn at weekly intervals before the morning dose of medication was given, and clinical ratings using the brief psychiatric rating scale (BPRS) (Overall & Goreham, 1962) were carried out on the same day. Clinical ratings were blind to the platelet aggregation findings. One hundred and twenty-one chronic patients receiving one only of the neuroleptic drugs listed above were tested on a single occasion. Blood samples were withdrawn before the morning dose of medication was given.

Four chronic schizophrenic patients were also studied at weekly intervals for 8 weeks. Blood samples for platelet aggregation studies and plasma chlorpromazine levels were withdrawn under the same conditions each week and before the morning dose of chlorpromazine was given. Each sample was tested as often as possible on each occasion, in order to examine within-sample reliability.

Results

Figure 1 illustrates the types of platelet aggregation seen in patients receiving neuroleptic drugs. Figure 1a shows a normal reversible response; Figure 1b shows a biphasic enhanced response and Figure 1c shows markedly enhanced platelet aggregation, characterised by an increase in the initial rate of aggregation and irreversibility. Only responses similar to those shown in Figure 1c were considered to represent enhanced aggregation, as 'secondary phase' aggregation was unequivocally present.

The frequency with which enhanced responses were observed in the group of recently admitted patients, in the group of chronic patients receiving one of the drugs mentioned above and a group of normal age-matched controls is shown in Table 2.

The table shows that five of seven recently admitted patients receiving chlorpromazine showed enhancement of aggregation at some time during their treatment, and this is in keeping with our previous work (Boullin, Orr *et al.*, 1978). The number of patients in this group on other neuroleptic drugs used as a drug of first choice was too small for any trends to emerge; of the seven patients receiving fluphenazine, flupenthixol, trifluoperazine, or haloperidol, four patients showed enhanced aggregation and three showed normal reversible responses. None of the

four patients receiving the non-neuroleptic phenothiazine promethazine showed enhancement of aggregation.

Figure 1 Types of platelet aggregation responses to 5-HT seen in patients treated with neuroleptic drugs.

The frequency of enhanced platelet aggregation responses shown in chronic patients was less than that previously reported (Boullin, Orr *et al.*, 1978). Only eight of forty patients receiving chlorpromazine showed enhanced aggregation and, of sixty-six patients receiving flupenthixol, haloperidol or thioridazine, thirteen showed enhanced aggregation. None of the fifteen patients receiving trifluoperazine showed enhanced aggregation, and this confirms our findings in ten other chronic schizophrenics receiving trifluoperazine in whom enhanced aggregation responses could not be elicited. Three of the twenty four normal age-matched controls who were not receiving any medication also showed enhanced responses; the incidence in normals reported here is in line with other reported work (Besterman & Gillett, 1973).

The relationship between changes in platelet aggregation and changes in rating scale scores in the group of recently admitted patients was a variable one. Table 3 shows that six of the nine patients who had improved during treatment showed a reduction in rating scale scores and enhanced platelet aggregation. Two patients who also showed enhanced platelet aggregation did not improve. Of the five patients with normal reversible responses, three improved and two did not. It is not possible to draw any conclusions from these results as, in five of the eight patients who showed enhanced aggregation, responses varied in an apparently random manner, being enhanced one week and not enhanced the next. This variability did not seem to bear any relationship to the drug being used or to any changes in medication. Figure 2 illustrates the pattern of changes in measures of platelet aggregation and in rating scale scores over the initial period of treatment in four of the patients and shows that, while enhanced aggregation can occur soon after treatment with a neuroleptic drug is started, the consistency with which enhanced responses can be

Table 2 Frequency of enhanced and non-enhanced 5-HT induced platelet aggregation responses in recently admitted patients, chronic schizophrenic patients and normal unmedicated controls.

	Enhanced			Not enhanced		
	Recently admitted	Chronic	Controls	Recently admitted	Chronic	Controls
Chlorpromazine	5	8	—	2	32	—
Fluphenazine	1	4	—	2	19	—
Thioridazine	—	4	—	—	11	—
Flupenthixol	1	3	—	0	17	—
Trifluoperazine	1	0	—	1	15	—
Haloperidol	1	2	—	0	6	—
Promethazine	0	—	—	4	—	—
No medication	—	—	3	—	—	24

Table 3 Frequency of enhanced platelet aggregation responses in recently admitted patients treated with each drug who improved and who did not improve.

	<i>Improved</i>		<i>Not improved</i>	
	<i>Enhanced</i>	<i>Not enhanced</i>	<i>Enhanced</i>	<i>Not enhanced</i>
Chlorpromazine	3	1	2	1
Fluphenazine	1	2	—	—
Flupenthixol	1	—	—	—
Trifluoperazine	1	—	—	1

Figure 2 Changes in the brief psychiatric rating scale (BPRS) scores and in 5-HT induced platelet aggregation responses in four schizophrenic patients treated with chlorpromazine.

obtained varies from patient to patient in an unpredictable way.

The four chronic schizophrenic patients who were studied at regular intervals showed a similar variability. In these patients significant variation in platelet aggregation responses from one week to the next were observed so that enhanced aggregation on one week was not necessarily predictive of a similar response a week later. There was some suggestion that changes in drug level might have contributed to the variation in aggregation responses as plasma concentrations

were lower when normal reversible responses were seen and higher with enhanced responses. There did not seem, however, to be a critical plasma concentration below which enhanced responses would become non-enhanced.

Discussion

The rationale for using the human platelet as a biochemical index of drug action on the central nervous

system is based on the suggestion that platelets could be used as a partial model for the CNS neurone (Paasonen, 1965). There is some evidence for a measure of biochemical common ground between neuronal and platelet mechanisms (Boullin, Orr *et al.*, 1978), and the findings reported here allow some conclusions to be drawn with regard to the relevance of this common ground.

The original work showing enhanced aggregation in a high percentage of chronic schizophrenic patients receiving chlorpromazine (Boullin *et al.*, 1975; Boullin, Orr *et al.*, 1978) has not been replicated in this study. Boullin, Knox *et al.* (1978) have also reported that enhanced aggregation responses were seen in only two of thirteen chronic schizophrenic patients receiving chlorpromazine and they discussed possible factors which could account for the discrepancy with earlier work. We have confirmed that the incidence of enhanced aggregation responses in chronic patients receiving chlorpromazine and other neuroleptic drugs is lower than would have been predicted from earlier work, and we have also shown that platelet aggregation responses in patients receiving chlorpromazine are variable and do not generalise readily to other neuroleptic drugs which are also particularly effective in schizophrenia.

Enhanced aggregation responses could be demonstrated more readily in recently admitted patients receiving a neuroleptic drug for the first time. They

did not, however, occur with a reliable degree of consistency and the value of monitoring such responses as a guide to treatment is therefore open to question. We will be reporting in a separate communication a series of experiments aimed at identifying any possible technical factors which could account for the variability in platelet aggregation responses shown in this study. Another possible approach would be to investigate further the mechanism whereby enhancement of platelet aggregation occurs. Baldacci, Baldacci, Bergel & Hickman (1980) have demonstrated increases in 5-HT induced platelet aggregation rates and 5-HT uptake in rabbits treated with chlorpromazine. They suggested that enhanced responses could be due to an increase in the number of 5-HT or other receptor which, together with calcium and fibrinogen, are essential mediators of aggregation.

In view of the clinical findings reported above, it is suggested that enhanced platelet aggregation in patients receiving neuroleptic drugs, while an interesting and intriguing pharmacological phenomenon in itself, is unlikely to be of value as an empirical guide to treatment. Further work concerned with the mechanisms whereby platelet aggregation enhancement occurs may, however, be of value in clarifying some of the problems raised in these clinical studies.

This research was supported by MRC grant G977/879.

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(Received May 30, 1980)