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Platelet Monoamine Oxidase Activity in Acute Schizophrenia: Relationship to Symptomatology and Neuroleptic Medication

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Summary: Platelet MAO activity was assessed in 35 schizophrenics during a trial of the isomers of flupenthixol. Enzyme activity was unrelated to severity of symptoms, the presence of delusions, hallucinations or thought disorder or to negative symptoms. In a few patients MAO activity fluctuated widely with time, but in the group of patients on medication there was a slow decrease in enzyme activity which was significant after 28 days of treatment. Enzyme activity after 14 days' drug treatment was still correlated with activity before treatment, but after 28 days this significant correlation disappeared. Slow effects of neuroleptic drugs on platelet MAO activity may explain previous findings of reduced activity of the enzyme in schizophrenia.

Murphy and Wyatt (1972) reported that platelet monoamine oxidase (MAO) was significantly reduced in chronic and acute schizophrenic patients compared with controls. Subsequently Wyatt and colleagues (1973) reported low platelet MAO activity in both the psychotic and non-psychotic twins of monozygotic pairs discordant for schizophrenia and suggested that low platelet MAO activity might be a genetic marker for vulnerability to schizophrenia. In the same study Wyatt *et al* found a significant inverse correlation between the severity of schizophrenic symptoms and platelet MAO activity.

These findings have become the focus of disagreement. Some workers have confirmed a reduction in platelet MAO activity in schizophrenia (Meltzer and Stahl, 1974; Nies *et al*, 1974; Zeller *et al*, 1975; Domino and Khanna, 1976; Schildkraut *et al*, 1976; Berretini *et al*, 1977; 1978; Sullivan *et al*, 1977; Orsulak *et al*, 1978) while other groups (Friedman *et al*, 1974; Carpenter *et al*, 1975; Shaskan and Becker, 1975; Belmaker *et al*, 1976; Owen *et al*, 1976; White *et al*, 1976; Becker and Shaskan, 1977) have been unable to demonstrate any differences in platelet MAO activity between schizophrenics and control subjects, sometimes in quite large samples and with strict diagnostic criteria. No group has confirmed the inverse correlation between platelet MAO activity and symptom severity although some workers have reported a relationship between low platelet MAO activity and the presence of auditory hallucinations and/or delusions (Schildkraut *et al*, 1976; Becker and Shaskan, 1977; Orsulak *et al*, 1978; Bond *et al*, 1979). Berger *et al* (1978) reported reduced platelet MAO activity in chronic schizophrenia, but failed to confirm the claim of Wyatt that within this group patients with paranoid symptoms have lower MAO activity. Friedman *et al* (1974), Shaskan and Becker (1975), Owen *et al* (1976) and Berretini *et al* (1977 and 1978) were unable to demonstrate any relationship between platelet MAO activity and symptomatology.

There is also disagreement over whether platelet MAO activity is stable in one individual over time. Murphy *et al* (1976) and Sullivan *et al* (1977) reported platelet MAO to be relatively stable whilst others (Owen *et al*, 1976) have found large fluctuations in individuals over time. Shaskan and Becker (1975) initially reported platelet MAO activity to be stable but later (Becker and Shaskan, 1977) observed considerable changes in enzyme activity in some individuals over a one month period.

Neuroleptic medication has been reported to have no effect on platelet MAO activity (Murphy and Wyatt, 1972; Wyatt and Murphy, 1976; Orsulak *et al*, 1978) and to increase enzyme activity (Owen *et al*, 1976). Takahashi *et al* (1975) reported a reduction of platelet MAO activity in schizophrenics treated with phenothiazines compared with controls but normal MAO activity in untreated patients. Friedhoff *et al* (1978) have also reported reductions in platelet MAO activity in medicated but not in unmedicated schizophrenic patients.

In the present study we have measured platelet

MAO activity over a 1-month period in a group of acute schizophrenic patients who were the subjects of a trial of the clinical efficacy of the isomers of flupenthixol. This trial provided a further opportunity not only to study the activity of platelet MAO in schizophrenia but also the relationship between symptomatology, medication and enzyme activity over a 28-day period.

Subjects and Methods

(i) *Acute schizophrenic patients in a trial of the isomers of flupenthixol*

The subjects were patients with acute psychotic illnesses, who conformed to the criteria for nuclear schizophrenia of the Present State Examination (Wing *et al*, 1974) and who participated in a trial of the isomers of flupenthixol (Johnstone *et al*, 1978). Forty-five patients were randomly and blindly allocated to one of three treatment groups, α-flupenthixol, β-flupenthixol or placebo. The trial lasted for four weeks. Where acute behavioural disturbance or distress made it necessary, patients were given chlorpromazine in doses of 100 mg, and the amount of chlorpromazine given in each case was recorded. Samples for MAO estimation were obtained in 35 (21 male, 14 female) of the 45 patients. The study was confined to patients with new acute schizophrenic symptoms who had either received no neuroleptic medication in the month prior to admission or who had received less than 200 mg per day chlorpromazine or equivalent for 1 week during that month. Thirty of the 35 patients in whom platelet monoamine oxidase activity was estimated had either never received neuroleptic medication or had received none in the month before admission. The remaining 5 patients had received medication within the limits described above.

The mental states of the patients were assessed before, and at weekly intervals during the study, with the rating scales for schizophrenia devised by Krawiecka *et al* (1977). This scale assesses anxiety; depression; flattening/incongruity of affect; retardation; hallucinations and delusions; incoherence of thought and poverty of speech—each on a five-point scale. In the present study the scale was modified to allow flattening and incongruity of affect to be assessed separately.

Platelet monoamine oxidase activity was measured with ^{14}C tyramine as substrate as previously described (Owen *et al*, 1976), before treatment was begun and at the end of the 4-week trial period. In most cases (n = 31) platelet MAO activity was also estimated in samples taken on day 14 of the trial.

(ii) *Chronic schizophrenic patients on neuroleptic medication*

The results of the platelet MAO determinations suggested the possibility that chlorpromazine might have a particular tendency to reduce platelet MAO activity. For this reason an additional study was carried out on 24 chronic schizophrenic patients whose illnesses conformed to the Feighner criteria for schizophrenia (Feighner *et al*, 1972). Platelet MAO activity was measured on single blood samples from these patients and the enzyme activities in the 11 patients being treated with chlorpromazine were compared with those in the 13 patients treated with other neuroleptics (thioridazine, trifluoperazine, flupenthixol or fluphenazine).

Results

(a) *Platelet MAO activity and relationship to symptomatology in acute schizophrenic patients*

In the patient group as a whole (i.e. those receiving α- or, β-flupenthixol or placebo) there was no significant change in mean platelet MAO activity over the 28-day course of treatment (Fig 1). When the three treatment groups were considered separately (Fig 2) platelet MAO was decreased by 24 per cent in patients on α-flupenthixol and by 21 per cent in patients on β-flupenthixol, although neither of these changes was separately significant (but see section (c)

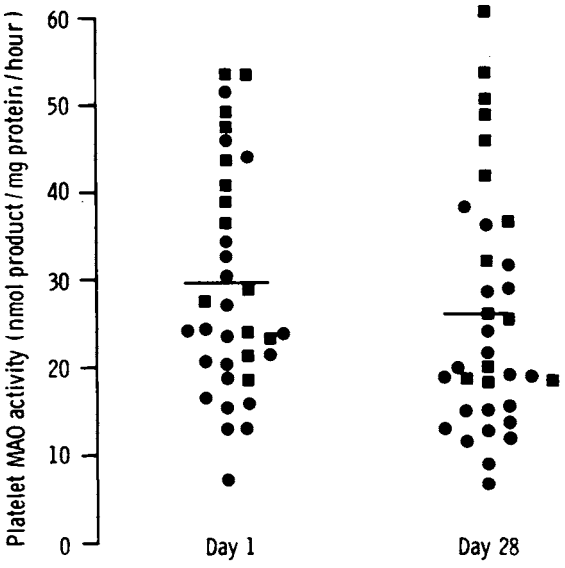

FIG 1.—Platelet MAO activity in acute schizophrenic patients at the start and after 28 days' treatment with α- or β-flupenthixol. (●) males, (■) females.

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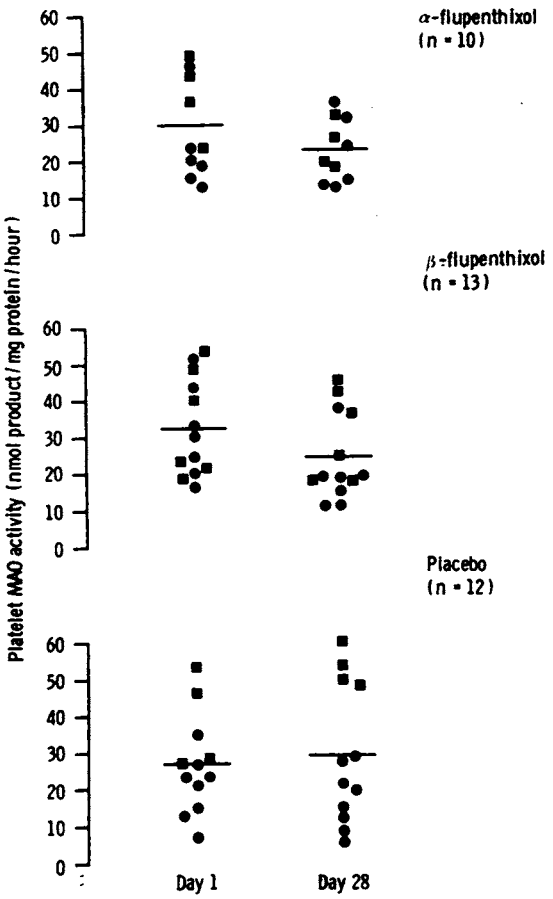

FIG 2.—Platelet MAO activity at start and after 28 days in acute schizophrenic patients receiving α-flupenthixol, β-flupenthixol or placebo. (●) males, (■) females.

below), and there was no change in patients on placebo.

Over the period of the trial there was an improvement in symptoms which was greatest in patients on α-flupenthixol (Table I). There were no significant correlations between platelet MAO activity and total rating scores on day 1 ($r = 0.15$) or on day 28 ($r = -0.10$). Neither were there any significant correlations between platelet MAO activity and positive symptoms (hallucinations, delusions and thought disorder) on day 1 ($r = -0.03$) or day 28 ($r = 0.02$), or between enzyme activity and negative symptoms on day 1 ($r = -0.14$) or day 28 ($r = 0.02$). When patients were allocated to groups with high (H) or low (L) platelet MAO activity, on the basis of whether the enzyme activity was greater than or less than the mean, there were no significant differences in mean scores between the two groups on day 1, day 14 or day 28 for any of the individual items on the Krawiecka scale. A comparison of groups with high and low platelet MAO activity with ratings for hallucinations and delusions at three points in the trial is shown in Table II—no significant differences were apparent.

The fact that the study was confined to patients with nuclear schizophrenia makes it difficult to use this sample to consider the relationship between platelet MAO activity and subtypes of schizophrenia; almost all the patients had delusions and hallucinations. An attempt was made to classify the patients as paranoid or non-paranoid on the following basis:—patients classed as paranoid had firmly held delusions in the absence of thought disorder and affective incongruity. Patients classed as non-paranoid had marked thought disorder and had affective incongruity. On this basis, 12 of the 35 patients studied could be classed as paranoid and 11 as non-paranoid, with the remainder not falling clearly into either

TABLE I

Total rating scores (Krawiecka rating scale) on day 1 and day 28 of trial of groups receiving, α- and β-flupenthixol or placebo

	Total rating scores (mean ± SD)			
	Day 1	Day 28	't'	'P'
α-flupenthixol (n = 10)	13.7±2.8	5 ±4.3	5.04	< .001
β-flupenthixol (n = 13)	12.0±3.7	8.7±5.1	1.93	NS
Placebo (n = 12)	13.2±1.8	8.8±3.7	3.35	< .01

TABLE II

Relationship between high (H) and low (L) platelet MAO activity and hallucinations and delusions on three days during the trial

		Day 1	Day 14	Day 28
Hallucinations	H	3.0±1.6	1.8±1.4	1.1±1.6
	L	3.3±1.2	1.4±1.6	1.5±1.9
Delusions	H	3.7±0.9	2.7±1.3	2.1±1.8
	L	3.9±0.5	3.1±1.1	2.4±1.6

Platelet MAO activity was described as high or low dependent on whether an individual's enzyme activity was above or below the group mean.

No significant differences.

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category. There was no significant difference in platelet MAO activity between these subgroups, with platelet MAO activities (Mean ± S.D., expressed as nanomol/mg protein/hr) of 29.0 ± 13.8 for the paranoid group and 29.3 ± 13.9 for the non-paranoid group.

(b) *Stability of platelet MAO activity over the trial period*

Although there were no significant differences in the mean platelet MAO activities between day 1, day 14 and day 28 of the trial (29.4 ± 12.9, n = 35; 30.7 ± 14.9; n = 31; 25.7 ± 13.9; n = 35, respectively), there were some individuals, of both sexes, whose platelet MAO activities varied widely over this period of time. Some extreme cases are illustrated in Fig 3.

Throughout the trial period females had consistently higher platelet MAO activities than males (Table III).

(c) *Platelet MAO activity and neuroleptic medication*

Although there was no significant difference in platelet MAO activity from day 1 to day 28 in each of the treatment groups, if patients receiving α- or β-flupenthixol were considered as one group then there was a significant reduction in platelet MAO activity ($P < .02$ paired 't' Table IV) in this group over the trial period. The fall in platelet MAO activity was most marked (24 per cent N.S.) in the patients on β-flupenthixol. Of the 13 patients in this group, 8 received chlorpromazine in addition to the trial medication. No patients receiving α-flupenthixol,

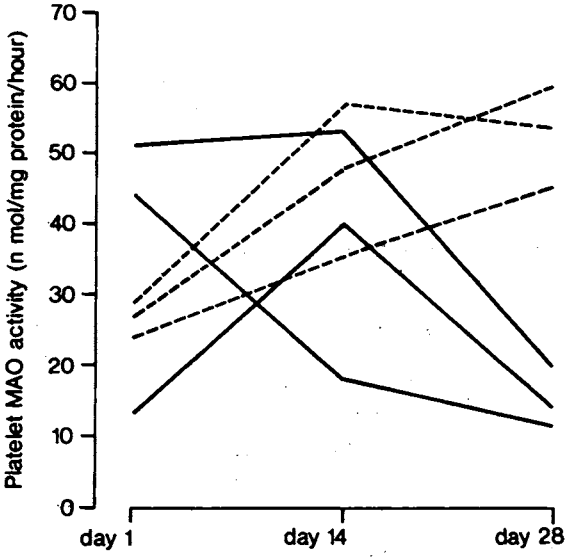

FIG 3.—Examples of large variability in platelet MAO activity over the trial period in 3 female (– – – –) and 3 male (——) patients.

TABLE III

Comparison of platelet MAO activities of male and female acute schizophrenics

	Males	Females	'P'
Day 1	24.1 ± 11.2 (n=21)	36.2 ± 12.2 (n=14)	< .02
Day 14	25.5 ± 14.5 (n=19)	39.0 ± 11.9 (n=12)	< .02
Day 28	19.4 ± 8.8 (n=21)	35.3 ± 14.9 (n=14)	< .001

Platelet MAO activity expressed as nanomoles of product formed/mg platelet protein/hr.

TABLE IV

Platelet MAO activity in groups receiving α- and β-flupenthixol and placebo over the trial period

	α, β-Flupenthixol	Placebo
Day 1	30.2 ± 12.7 (n=23)	27.0 ± 13.4 (n=12)
Day 14	30.1 ± 13.9 (n=21)	32.1 ± 17.5 (n=10)
Day 28	*23.8 ± 10.2 (n=23)	29.6 ± 19.0 (n=12)

* Significantly decreased (paired 't' = 2.5589, $P < .02$) compared with day 1.

but two patients receiving placebo, required chlorpromazine. To investigate further the possibility that chlorpromazine might have a particular tendency to reduce platelet MAO activity, enzyme activities were measured in samples from chronic schizophrenic patients (n = 11; 6F, 5M) receiving chlorpromazine and compared with those of similar patients treated with other neuroleptics (n = 13; 8F, 5M).

In chronic patients receiving chlorpromazine platelet MAO activity was 33.2 ± 13.1 nmol/mg protein/hr compared with 26.2 ± 10.5 nmol/mg protein/hr in patients receiving other neuroleptics. Thus it seemed unlikely that the decrease in platelet MAO activity over the trial period could be directly attributed to chlorpromazine.

A drug effect on platelet MAO activity was also suggested by correlations of enzyme activity on day 1 with that on day 14 and day 28 (Table V). By day 28 of the trial only the group receiving placebo had enzyme activities significantly correlated with activities on day 1 of the trial.

Discussion

Although there were significant improvements in the mental state of most patients there were no significant changes in mean platelet MAO activity for the group as a whole over the trial period. We were

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TABLE V

Correlation of platelet MAO activity on day 1 with that on day 14 and day 28 in the three treatment groups

	Correlation coefficients	
	Day 14	Day 28
α-Flupenthixol	*0.6201 (n=10)	0.1510 (n=10)
β-Flupenthixol	*0.7101 (n=11)	0.2861 (n=13)
Placebo	0.5998 (n=10)	**0.7365 (n=12)

* $P < 0.5$ ** $P < .001$.

unable to demonstrate significant relationships between total symptom score and platelet MAO activity on the three occasions that the enzyme activity was determined. There was no relationship between positive or negative symptoms and platelet MAO activity nor any relationship between high (H) and low (L) enzyme activity and the individual items on the Krawiecka rating scales. This lack of relationship between symptomatology and platelet MAO activity is in agreement with some previous reports (Carpenter *et al*, 1975; Owen *et al*, 1976; Berretini *et al*, 1977; 1978). We were also unable to confirm the findings of Schildkraut *et al* (1976) and Orsulak *et al* (1978) that hallucinations and delusions were associated with low platelet MAO activity.

It might be argued that at the outset of the study our sample was not suitable for assessing this relationship since the method of selection meant that almost all the patients had a maximum score on delusions and hallucinations. As the study progressed, however, these features improved in some cases and persisted in others, but still no relationship between low platelet MAO activity and the psychotic phenomena emerged. In agreement with Berger *et al* (1978) but in disagreement with Wyatt we failed to find a reduction in platelet MAO activity in paranoid as opposed to non-paranoid schizophrenics.

The marked fluctuations in enzyme activity observed over the trial period in some patients agree with some (Owen *et al*, 1976; Becker and Shaskan, 1977) but not all previous reports (Shaskan and Becker, 1975; Sullivan *et al*, 1977). Domino and Gahagan (1977) studied the rate of disappearance of the MAO substrate ^{14}C tyramine in whole blood and noted significant changes in the rate of disappearance of the substrate in some individuals on re-assaying after a lapse of five months. In the present study there was some evidence that non-systematic changes in enzyme activity might, in part, be due to drug therapy; only in the group receiving placebo were enzyme activities at the end of the trial significantly correlated with activities on day 1. Such marked changes in platelet MAO activity as we observed in some individuals over relatively short periods of time (Fig 3) must cast doubt on the significance of single measurements of enzyme activity.

Throughout the trial period females had consistently higher platelet MAO activity than males. We have previously reported that female schizo-affectives have significantly higher platelet MAO activity than male schizo-affectives (Brockington *et al*, 1976). Some workers have reported platelet MAO activity to be higher in mentally normal females compared with males, but that the sex difference is no longer present in schizophrenics (Friedman *et al*, 1974; Zeller *et al*, 1975; Murphy *et al*, 1977), whilst others have found no significant sex difference in enzyme activity in either controls or schizophrenics (Meltzer and Stahl, 1974; Orsulak *et al*, 1978).

Our present finding that patients receiving α and β-flupenthixol had significantly reduced platelet MAO activity after 28 days' treatment is in contrast to our previous report (Brockington *et al*, 1976) of a small increase in activity in chronic schizophrenics after six months of depot neuroleptic medication. Our present observation of a slow reduction in platelet MAO activity in patients on neuroleptic medication is consistent with the reports of Takahashi *et al* (1975) and Friedhoff *et al* (1978) of a reduction in platelet MAO activity in chronic schizophrenic patients treated with neuroleptics for many years compared with drug-free patients.

In the present study there was no significant reduction in platelet MAO activity in patients receiving flupenthixol after 14 days' treatment (Table IV). The reduction became apparent only after 28 days. This suggests that the reduction is not due to a direct inhibitory effect of drugs on platelet MAO activity, but would be consistent with a change in platelet or enzyme synthesis. Our initial suspicion that chlorpromazine might have a particularly deleterious effect on platelet MAO activity was, however, not confirmed.

The results of the present study suggest that a detailed investigation of the short and long-term effects of various neuroleptics on platelet MAO activity may help to resolve the controversy over the activity of the enzyme in schizophrenia.

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