THE EFFECT OF PROPRANOLOL ON CSF AMINE METABOLITES IN PSYCHIATRIC PATIENTS

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- 1 In view of the central side effects of β -adrenoceptor blocking agents and their alleged antipsychotic action in the absence of DA receptor blockade, it is important to establish which neurotransmitters are likely to be involved. Previous animal and patient studies have, however, produced conflicting data on this point.
- 2 The changes in CSF HVA, 5HIAA and MHPG during treatment with propranolol (960 mg/day) in chronic schizophrenic patients were monitored on four occasions over 30 days.
- 3 Clinical changes were monitored by the Wing and Krawiecka Scales and motor activity was assessed by pedometer.
- 4 CSF HVA levels were significantly increased by propranolol and the rise continued throughout the 30 day period. There were no significant changes in the other metabolites.
- 5 There was no evidence of any therapeutic benefit from propranolol treatment in these patients.
- 6 These findings may explain the central side-effects and occasional reports of schizophreniform psychosis after propranolol, since an increase in DA turnover occurs without DA receptor blockade

Introduction

Alterations in the levels of CSF neurotransmitter metabolites produced by neuroleptics has extended our knowledge of the mode of action of antipsychotic drugs (Sedvall, 1980; Wode-Helgødt *et al.*, 1977), which in turn is the best guide we have to the underlying pathophysiology of schizophrenia (Carlsson, 1977). It now seems clear, for example, that neuroleptics increase CSF homovanillic acid (HVA) levels for about 3 weeks (Post & Goodwin, 1975; van Praag, 1977; Rùther *et al.*, 1976), whereas 5-hydroxyindoleacetic acid (5HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) levels fall (Sedvall, 1980; Wode-Helgødt *et al.*, 1977). In one study, the best correlation with clinical response was the fall in CSF MHPG at 4 weeks (Sedvall, 1980).

The possibility that propranolol might have unique antipsychotic properties (Yorkston *et al.*, 1974, 1976, 1977), unrelated to dopamine (DA) receptor blockade (Conway *et al.*, 1978), raised the important question of its similarities and differences from standard neuroleptics in its effect on these amine metabolites. Animal studies were divided in their conclusions about the effects of propranolol on DA neuronal

activity. Increased striatal tyrosine hydroxylase activity (Peters & Mazurkiewicz-Kwilecki, 1975), elevated limbic DA turnover (Fuxe *et al.*, 1976; Wiesel, 1976), elevated striatal DA (Mahon *et al.*, 1977; Morinan & Leonard, 1977), and no changes in NA, DA or 5HT turnover (Lavery & Taylor, 1968), striatal DA receptor number (Ebstein *et al.*, 1979), or DA mediated activity (Green & Grahame-Smith, 1976), following propranolol had all been reported.

Our first opportunity to look at propranolol-induced changes in CSF amine metabolites in man, during a small trial of propranolol in schizophrenia (King *et al.*, 1980), indicated that propranolol (1000 mg/day for 1–2 weeks) increased CSF HVA levels, decreased MHPG levels but produced no significant changes in 5HIAA. We felt it was important to try to replicate these findings in a larger study, and to see if it would be possible to identify the time course of these changes. Accordingly we studied a further group of chronic 'treatment resistant' schizophrenic patients treated with high doses of propranolol alone for 30 days in such a way that with three lumbar punctures from each patient we could monitor the

CSF metabolite changes at 10 day intervals for 1 month.

Methods

Thirteen chronic schizophrenic patients (eight male, five female), of mean age 42 years, who had shown a poor or marginal response to neuroleptics were selected for the study. Mean duration of illness was 16.5 years, with a range of 2 to 32 years. Clinical details are given in Table 1. A diagnosis of schizophrenia was supported by the criteria of Feighner *et al.* (1972) in all cases. All patients had rateable 'positive' and 'negative' symptoms of schizophrenia. Patients were excluded from the study if any of the following were present: heart disease, hypertension, asthma, diabetes mellitus, liver disease, or organic brain syndrome, alcoholism or drug dependence, pregnancy or a requirement for continued use of any drug other than the study medication.

Table 1 Patient data

Treatment resistant patients selected and giving written informed consent:	13
Drug-free wash-out period:	1 month
Refused to cooperate further:	1
Refused further L.P. after baseline:	1
Age: Mean 42 years, range 24–64 years	
Sex: 8 males, 5 females.	
Diagnosis: Schizophrenia (Feighner Criteria)	
Length of illness: mean 16.5 years, range 2–32 years	
Positive family history of schizophrenia:	4

The study was approved by the Ethical Committee of Queen's University Faculty of Medicine. Informal patients gave informed written consent and, in the case of formal patients, the nearest relative also gave consent. All patients were drug free for a minimum of 4 weeks prior to the study, apart from occasional doses of diazepam for night sedation. Two patients had been receiving oral and three patients depot neuroleptics previously. After this drug-free washout period one patient withdrew from the study. Following the initial lumbar puncture one other patient withdrew consent for further lumbar puncture but agreed to remain in the clinical part of the study. Thus 12 patients completed the open clinical trial and 11 patients the full biochemical assessment.

The study design is illustrated in Figure 1. Following the 4 week drug-free washout period, baseline clinical ratings were performed for all patients on Day 0. These consisted of a rating of mental state using the Rating Scale devised by Krawiecka *et al.* (1977), applied by a psychiatrist and a rating of behaviour using the Wing (1961) Ward Behaviour Rating Scale, applied by a charge nurse or ward sister. In seven

patients physical activity was measured using a pedometer strapped to the left ankle. These clinical measurements were repeated at Days 10, 20 and 30. A baseline sample of CSF was collected by lumbar puncture on Day 1 and the patients were randomly divided into two groups for further CSF sampling. Group 1 had further lumbar punctures at Days 11 and 21, and Group 2 further lumbar punctures at Days 21 and 31. Thus all patients had CSF collected at Days 1 and 21, but only 4 at Day 11, and 7 at Day 31. All lumbar punctures were carried out in the left lateral decubitus position following bed rest and fasting from 22.00 h the previous night. The first 1 ml of CSF was discarded and the next 10 ml collected in a sterile container. After acidification with 0.2 ml of 6M HCl the sample was frozen to -20°C and stored for later analysis.

Propranolol was commenced on Day 2 with a 40 mg test dose. Doses were then increased up to a maximum at Day 18 of 960 mg per day, given in two equally divided doses. Eleven patients reached this dose. Pulse rate and blood pressure were monitored twice weekly.

The CSF levels of HVA, 5HIAA and MHPG were assayed by a high pressure liquid chromatography (h.p.l.c.) method with electrochemical detection (to be published) which was based on those of Kissinger *et al.* (1975), Langlais *et al.* (1980) and Cross & Joseph (1981). Using a pre-column (Co-pell ODS), 200 μl of CSF was injected directly and MHPG, 5HIAA and HVA were measured simultaneously with retention times of approximately 9, 20 and 25 min respectively. A 250 mm reverse-phase 'Hypersil' 5 ODS column was used, the mobile phase being 10% methanol: 90% 0.1 M sodium dihydrogen orthophosphate with a flow rate of 0.9 ml./min. Metabolites were identified using an LC-4A electrochemical 'Amperometric' detector (operating potential: +1.0 V) with a glassy carbon working electrode and Ag/AgCl reference electrode. Standard calibration curves for each of the metabolites were linear throughout the 10–200 ng/ml range. The limit of sensitivity was 2 ng/ml for HVA, and 1 ng/ml for 5HIAA and MHPG. Repeated estimations of the same sample were assayed with a coefficient of variation of less than 5%.

Analysis of clinical and biochemical data was by Friedman analysis of variance and, where appropriate, Wilcoxon Test for paired data. Correlation analyses were performed using the Spearman two rank correlation test.

Results

Clinical data

The results at each time of clinical rating (Days 0, 10, 20 and 30) are summarised in Table 2. Trends towards

Figure 1 Protocol for study of effect of propranolol on CSF amine metabolites in schizophrenia over 30 day period. There were four patients in Group 1 and seven in Group 2. A total of 12 patients had LP at Day 1, and 11 at Day 21.

improvement (lower scores) in some ratings and deterioration (higher scores) in others can be seen. None of these was significant at the 5% level when compared using the Friedman two-way analysis of variance for non-parametric data. Similar examination of each item of the Krawiecka scale (total of 8 items) revealed no significant changes. Three items were significantly different at Day 20 compared to Day 0 ($P < 0.05$) using the Wilcoxon test applied to all the clinical data in turn (Krawiecka 'negative symptoms' score; poverty of thought; retardation), but this is less than would be expected by chance given the numbers of tests applied. It was interesting that ratings of positive schizophrenic symptoms tended to become worse, against the trend for other symptoms, though in the absence of a placebo control little clinical significance can be attached to this.

Table 2 Effect of propranolol on clinical parameters

		0	10	20	30
Krawiecka (total)	(n = 12)	12.9	11.7	11.2	11.7
Krawiecka (+ve)	(n = 12)	4.1	4.3	4.5	4.7
Krawiecka (-ve)	(n = 12)	5.3	4.7	4.6	4.7
Wing (S.W.)	(n = 10)	5.5	5.2	5.1	4.5
Wing (S.E.)	(n = 10)	1.2	1.5	1.5	1.8
Activity (miles)	(n = 7)	1.6	4.6	4.6	3.5
Global rating	(n = 12)	4.9	4.7	4.7	4.8

Biochemical data

The mean levels of CSF HVA, 5HIAA and MHPG at each of the times of sampling are shown in Table 3, for the whole group of patients (Days 1 and 21 only). There is a statistically significant rise in HVA from Day 1 to Day 21 ($P < 0.05$, Wilcoxon test) for the whole group of patients (11 pairs of samples). This rise is also significant using the paired *t*-test ($P =$

0.01). The rise in 5HIAA from Day 1 to Day 21 (10 pairs of data only due to failure in biochemical analysis of one sample) is significant using the Wilcoxon test ($p < 0.05$) but not significant with the paired *t*-test. The means are in fact very similar at Days 1 and 21 and this difference between tests is probably due to the Wilcoxon being a 'ranking' test, most of the results for 5HIAA showing a slight increase over this 20 days. The sub-groups were too small to produce any significant changes at Days 11 and 31, but show interesting trends, as illustrated in Figures 2, 3 and 4.

Table 3 Effect of propranolol on CSF amine metabolites
Mean (ng/ml) $\pm$ s.e. mean (n in brackets)

Day	HVA	5-HIAA	MHPG
1	25.8 $\pm$ 3.5 (11)	17 $\pm$ 5.8 (10)	32.7 $\pm$ 9.6 (10)
21	43.3 $\pm$ 6.1* (11)	17.7 $\pm$ 5.5 (10)	38.5 $\pm$ 17.2 (10)

* $P < 0.01$

Figure 2 shows that HVA continued to rise over the whole of the 31 day period studied. There was no particular trend for the changes in CSF 5HIAA (Figure 3), but MHPG levels appeared to rise initially and then fall towards baseline values (Figure 4).

The Spearman two rank correlation test produced an expected correlation between changes in the Krawiecka 'Negative' score and the sub-item 'poverty of thought' ($r = 0.86$, $P < 0.05$) between Days 0 and 20. There also appeared to be a correlation between changes in 5HIAA and activity from Days 0 to 20 ($r = 0.86$, $P = 0.001$), but in view of the similarity in mean 5HIAA values at these times, the meaning of this is not clear. There were however no other significant correlations between the biochemical and clinical measures.

Figure 2 Histograms showing CSF HVA levels in ng/ml (mean $\pm$ s.e. mean) in the whole group of patients (▨), sub-group 1 (□) and sub-group 2 (■) at 10 day intervals. Propranolol was started on Day 2 and reached 960 mg/day at Day 18.

Discussion

Antipsychotic drugs have generally been found to cause a transient increase in CSF HVA followed by tolerance with a return to pre-treatment levels between 15 and 30 days (Post & Goodwin, 1975; van Praag, 1977; Rther *et al.*, 1976). Although Wode-Helgodt *et al.* (1977) found that CSF HVA levels were still elevated after 4 weeks on chlorpromazine there

Figure 3 Histograms showing CSF 5HIAA levels in ng/ml (means $\pm$ s.e. mean) in the whole group of patients (▨), sub-group 1 (□) and sub-group 2 (■) at 10 day intervals. Propranolol was started on Day 2 and reached 960 mg/day at Day 18.

Figure 4 Histograms showing CSF MHPG levels in ng/ml (mean $\pm$ s.e. mean) in the whole group of patients (▨) sub-group 1 (□) and sub-group 2 (■) at 10 day intervals. Propranolol was started on Day 2 and reached 960 mg/day at Day 18.

was a tendency to tolerance, whereas MHPG and 5HIAA were both decreased with no evidence of tolerance. Thus the characteristic pattern of CSF metabolite changes caused by neuroleptics seems to be a transient elevation in HVA and decreases in 5HIAA and MHPG (Sedvall, 1980; Wode-Helgodt *et al.*, 1977). In contrast to this we have found that propranolol (960 mg/day) causes an increase in DA turnover which persists for 30 days and no significant changes in either 5HIAA or MHPG. If anything, the MHPG changes were towards a transient (but non-significant) increase (see Figure 4) which might reflect central β -adrenoceptor blockade in the same way as the transient increase in HVA follows DA blockade by neuroleptics. However these MHPG results were the reverse of those found in our previous study (King *et al.*, 1980) and those reported in rat amygdaloid cortex following chronic propranolol administration by Fludder & Leonard (1979), in which a decrease in MHPG was thought to be due to pre-synaptic β -adrenoceptor blockade.

The only other comparable study in man (Belmaker *et al.*, 1979) failed to detect significant changes in any of these metabolites, but neuroleptics had only been discontinued for 9 days and the effects of neuroleptic withdrawal may have masked the effect of propranolol. All our patients had been drug-free for at least 4 weeks, and although three of them had been on dept neuroleptics, the changes in blood levels following discontinuation of these is very gradual (Kolakowska & Wiles, 1981; Wistedt *et al.*, 1981).

Further evidence of increased DA activity following β -adrenoceptor blockers is provided by animal studies showing increased amphetamine-induced turning behaviour after propranolol (Fuxe *et al.*, 1976) and increased amphetamine-induced hyperactivity after alprenolol (Herman *et al.*, 1971). One might then expect that propranolol would reduce rather than increase prolactin levels, and although in our previous study (King *et al.*, 1980; Wilson *et al.*, 1979) we found no significant effect on basal prolactin levels, there was a slight decrease in mean values, in keeping with a number of other reports (Belmaker *et al.*, 1979; Dart *et al.*, 1981; Hanssen *et al.*, 1978).

The change in DA activity might be secondary to central 5HT receptor blockade since propranolol binds to central 5HT receptors (Middlemiss *et al.*, 1977), and inhibits a number of 5HT mediated behaviours in animals (Green & Grahame-Smith, 1976; Weinstock & Schechter, 1975; Weinstock *et al.*, 1977). However no consistent effect of 5HT receptor antagonists on 5-HT turnover has been reported. While Invernizzi & Samanin (1981) found that both metergoline and methiotepin increased brain 5HIAA levels in rat brain, Green *et al.* (1981) reported a decreased rate of 5HT synthesis after these antagonists and no change after propranolol. It appears that some 5HT receptor antagonists may have agonist actions particularly on pre-synaptic receptors leading to a decrease in 5HT synthesis, depending on the doses used, relative receptor affinities and times after injection (Bourgoin *et al.*, 1978; Invernizzi & Samanin, 1981; Green *et al.*, 1981). Thus our failure to find any significant change in CSF 5HIAA is consistent with the animal literature (Green *et al.*, 1981) and still compatible with central 5-HT antagonism.

In the absence of DA receptor blockade an increase in DA turnover might be expected to cause a worsening rather than any improvement in psychotic symptoms. In this connection it is of considerable interest that in addition to the well-known central side-effects of propranolol such as nightmares and

hallucinations (Fleminger, 1978; Greenblatt *et al.*, 1976; Shopsin *et al.*, 1975; Stephen, 1966), three cases of schizophreniform psychoses in clear consciousness following treatment with β -adrenoceptor blockers have also been reported (Koehler & Guth, 1977; Steinert and Pugh, 1979). In this present study we found no evidence of any improvement with propranolol and some positive symptoms did in fact increase (see Table 2). However, we did not show any significant negative correlation between the clinical and biochemical changes.

Propranolol has only been found to be effective in schizophrenia in one placebo-controlled study (Yorkston *et al.*, 1977) in which it was given as an adjunct to standard neuroleptic treatment. Myers *et al.* (1981), however, failed to find any significant beneficial effect in a similar study. It has been shown to have no value when given alone in a double-blind controlled study of placebo, chlorpromazine or propranolol in 53 chronic schizophrenics (Peet *et al.*, 1981a). Peet *et al.* (1980, 1981b) have further shown that any beneficial effect of propranolol/neuroleptic combinations can be accounted for by a pharmacokinetic interaction leading to elevated neuroleptic plasma levels.

In conclusion, therefore, there appears to be no similarity between propranolol and neuroleptic drugs in their clinical, endocrinological or biochemical effects. Propranolol does not have any anti-psychotic effect when used alone and its adjunctive value when used with neuroleptics seems to be due to a pharmacokinetic interaction. It does not increase prolactin levels and the pattern of its effects on CSF amine metabolites differs from that of neuroleptics and perhaps accounts for the production of central side-effects in certain individuals.

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