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SERUM PROLACTIN LEVELS IN SCHIZOPHRENIA: EFFECTS OF NEUROLEPTIC MEDICATION – A PRELIMINARY STUDY

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Introduction

The dopamine (DA) hypothesis of schizophrenia has gained much ground in the last decade. The emphasis on DA hypothesis of schizophrenia is based on the ability of the DA releasing agent, amphetamine, to mimic the clinical picture of paranoid schizophrenia (Snyder 1972; Carlsson 1978 and Crow 1982). Catecholamine precursor L – Dopa also is known to produce symptoms of schizophrenia (Carlsson 1978). Although the role of DA in inducing schizophrenic symptoms is well accepted, there is so far no direct support for a primary causative role of DA in schizophrenia. Studies in various laboratories have not provided any conclusive evidence in this matter (Meltzer *et al* 1974, Carlsson 1978, Bird *et al*1979, Crow 1982).

The specific brain areas where dopaminergic transmission plays an important role are basal ganglia, limbic forebrain and tubero infundibular pathway terminating in hypothalamus. Many of the abnormalities in thought process and behaviour are considered to be due to abnormalities in limbic forebrain (Carlsson 1978). The tubero-infundibular dopaminergic pathway exerts an inhibitory action on prolactin release (Carlsson 1977, Johnstone *et al* 1977, Meltzer *et al* 1974, Benedetti 1984). This effect is mediated via the release of prolactin inhibitory factor into the pituitary portal vessels or through a direct action on the pituitary by the DA reaching the gland via the pituitary portal system. Thus the level of prolactin in blood can serve as an index of dopaminergic function in schizophrenia.

In schizophrenics, neuroleptics are found to produce an actual normalisation of disturbed behaviour. All known antipsychotic drugs appear to possess antidopaminergic activity (Crow *et al* 1977) and all antidopaminergic agents possess antipsychotic activity (Carlsson 1978). A rough correlation exists between DA antagonistic effects and clinical antipsychotic potency (Carlsson 1978). Neuroleptics by virtue of their DA blockade tend to enhance secretion of prolactin. Thus prolactin secretion also correlates well with the antipsychotic properties. Since both the therapeutic response and the improvement in serum prolactin levels are caused by the antidopaminergic action of the neuroleptics the view that increased prolactin secretion can be used as an index of DA receptor blockade, has emerged.

In the present study, it is envisaged to study serum prolactin levels in schizophrenics and control subjects to determine the possible correlation of dopaminergic function and schizophrenia. In addition, the possible correlation between clinical improve-

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ment and changes in central DA activity as indicated by changes in prolactin level is also to be observed. Very few studies have concentrated on prolactin levels in Indian patients with functional psychoses.

Materials and Methods

The present study included 26 patients (14 male and 12 female) who met Feighner's criteria (Feighner *et al* 1972) for the diagnosis of schizophrenia and 43 control subjects (22 male and 21 female) matched for age and sex. The study was double blind.

None of the subjects had received any psychoactive medication or hormonal preparation for a period of at least two months prior to the study (none of the patients had received depot phenothiazines) nor was any one suffering from any significant physical illness. Female subjects who were pregnant or in puerperium, were not included in this study.

Blood samples were collected from the patients at the time of diagnosis before being put on neuroleptics. The samples were collected between 9.00 and 11.00 a. m. Serum was separated and stored at −20°C until the time of analysis. Samples of blood were again collected at the end of 3 months following diagnosis when all the patients were on maintenance medication. Serum prolactin was estimated by radio immunoassay technique (Hwang *et al* 1971, Jacobs *et al*1972). The radio immunoassay kit used was Biodata Prolactin ter kit. Quantitative determination by this kit is done without any preliminary treatment of the samples, using prolactin labelled with ^{125}I as the radio active tracer.

The drugs administered were chlorpromazine (300-1200 mg.) and trifluperazine (15-45 mg.) The progress of the patients was assessed by clinical interviews, reports of the nurses and reports from the relatives of the patients. The patients were also rated on Brief Psychiatric Rating Scale once a week. None of the patients received any other antipsychotic drug or Electro-convulsive Therapy.

Results

At the end of three months all the patients showed improvement as made out by clinical interviews, nurses' report, reports from the relatives and the BPRS scores.

The prolactin levels of the control subjects and those of the unmedicated schizophrenics are shown in Table 1. It can be seen that the prolactin values do not significantly differ in these two groups.

Depending on the duration of the illness the patients were divided into two groups – one having symptoms for less than 2 years and another symptomatic for more than 2 years. The prolactin levels of the two groups are given in Table 2. It appears that these two groups differ very little as regards their serum prolactin levels.

The schizophrenic subjects were also divided into a group exhibiting predominantly positive symptomatology (hallucinations, delusions, formal thought disorder, bizarre or disorganised behaviour) and another exhibiting predominantly negative symptomatology (alogia, avolition – apathy, affective flattening, anhedonia and attentional impairment). The prolactin level showed significant inverse correlation with positive symptoms, in female schizophrenic subjects. The unmedicated prolactin level was significantly less in female patients with positive symptoms when compared to female patients with negative symptoms. In male patients also there was trend in this direction but it did not reach statistical significance. The results are presented in Table 3.

The prolactin levels after medication for 3 months with neuroleptics showed

Table 1

Prolactin level in control subjects & schizophrenics

			Age – Years		Prolactin Levels ng/ml	
	Sex	No.	Range	Mean	Range	Mean
CONTROLS	Male	22	23 – 41	32 ± 1.74	2.0 – 15	8.87 ± 1.06
	Female	21	20 – 56	29.4 ± 2.25	2.1 – 25	9.80 ± 1.33
SCHIZOPHRENIA	Male	14	26 – 38	26 ± 1.43	2.4 – 20	11.61 ± 1.30
	Female	12	25 – 43	33.3 ±1.93	3.7 – 30	13.64 ± 2.26

Table 2

Correlations of duration of illness & prolactin levels

Sex	Duration of Illness	Prolactin levels ng/ml
Male	6 months to 2 years	10.61 ± 1.08
	2 years and above	10.28 ± 2.29
Female	6 months to 2 years	9.88 ± 2.09
	2 years and above	15.71 ± 2.64

Table 3

Correlation of symptomatology with prolactin levels

Sex		Nature of symptoms	Prolactin levels ng/ml
Male	6	Negative	13.30 ± 2.19
	8	Positive	10.17 ± 1.80 $p < 0.01$
Female	4	Negative	21.25 ± 2.58
	8	Positive	10.04 ± 2.19

significant elevation over the baseline in all the patients. This rise was more marked in the female subjects when compared to the male. The results are shown in Table 4. All the patients had shown marked clinical improvement at the time of the second assay. Psychotic behaviour ratings showed a decline in all the patients.

Table 4

Prolactin levels after drug therapy

	Prolactin levels ng/ml		
Sex	Predrug levels	Post drug levels	P value
Male	11.61 ± 1.30	34.09 ± 4.52	0.001
Female	13.64 ± 2.26	71.44 ± 16.94	0.01

Discussion

In this study the baseline prolactin levels in schizophrenics did not significantly differ from that of the control subjects. Hence no proof was obtained in support of the hypothesis that basal DA release from the tubero infundibular system is increased in schizophrenia as a part of the generalised hyperdopaminergic state. Other workers have also failed to find any significant difference between the serum prolactin levels of schizophrenics and controls (Cotes *et al* 1978, Johnstone *et al* 1977, Carlsson 1977 1978 and Gruen *et al* 1978). Indeed it has even been suggested that DA transmission may be reduced in some patients with chronic schizophrenia (Bowers 1974). This does not, of course, exclude the possibility that a disturbance of DA exists. The many possibilities considered in this regard are increased DA released into a small brain area, decreased transport into the sites of metabolic breakdown and receptor supersensi-

tivity, any or all of which may have escaped detection. It is also probable that the primary disturbance does not reside in the dopaminergic synapse but in a system which has intimate relationship with DA neurons (Carlsson 1977). The elevation of DA activity in a particular brain region may be due to an increased excitatory input or decreased inhibitory input. Or it may be that the dopaminergic activity is normal or even decreased but dopaminergic predominance exists because of a deficiency in a neuronal system normally serving to counterbalance or mitigate the dopaminergic influence (Carlsson 1978).

The serum prolactin levels in all the patients showed a prominent rise after antipsychotic medication. As has been mentioned earlier the tuberoinfundibular control over prolactin release is mediated by dopamine. DA receptor agonists decrease and antagonists increase prolactin levels in plasma and CSF (Carlsson 1977, Benedetti *et al* 1984, Meltzer *et al* 1976). The neuroleptic drugs by their DA receptor blockade, remove the anterior pituitary inhibition of prolactin thus enhancing the serum levels (Wheels *et al* 1980, Meltzer *et al* 1976). The antischizophrenic property of the drug is on par with its effect on the serum prolactin level. However the possibility that some part of the increase in prolactin secretion observed after neuroleptics may be a consequence of impovements in mental state rather than a direct effect of drug induced dopaminergic blockade on the tuberoinfundibular system has also to be considered (Johnstone *et al* 1977).

In our study a significant inverse correlation emerged between total positive symptoms and serum prolactin levels. Earlier studies have commented on this pattern of hormonal response (Meltzer *et al* 1976, Johnstone *et al* 1977). Increasing symptom severity and positive symptoms appear to be associated with increased DA release and decreased prolactin levels.

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