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Neuroendocrine Tests during Treatment with Neuroleptic Drugs I. Plasma Prolactin Response to Haloperidol Challenge

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Summary: The plasma prolactin (PRL) response to haloperidol 2 or 4 mg i.m. was studied in 18 schizophrenic men during their routine treatment with neuroleptic drugs. A substantial rise of the PRL level above the treatment baseline occurred in all but four of the 20 tests showing that the PRL elevation induced by treatment was not maximal. The challenge was ineffective only in patients receiving very high daily doses of medication. The increment was inversely correlated to the daily dose of medication but unrelated to plasma haloperidol concentrations during the test. Chronic schizophrenics who were receiving long term treatment and had low basal PRL levels did not show tolerance to the prolactin stimulating effect of haloperidol. That prolactin rose during the test in patients who had improved during their current treatment indicates that the degree of dopamine receptor blockade required for therapeutic effects is below that which produces a maximal PRL response.

The functional state of the dopaminergic system in patients receiving neuroleptic treatment is interesting because of the relationship between the antipsychotic and antidopaminergic effects of these drugs. For this reason, increased levels of plasma prolactin (PRL) which reflect changes in dopamine-mediated inhibition of PRL release, have been studied extensively as an index of neuroleptic induced dopamine (DA) receptor blockade (see recent review by Rubin and Hays, 1980). However, the significance of these changes is uncertain. According to some workers, therapeutic doses of neuroleptics are equal to or greater than those that produce the maximal rise of PRL (Gruen *et al*, 1978; Ohman and Axelsson, 1978; Rubin and Hays, 1980). If this is the case, PRL levels found during treatment would represent the upper limit of the PRL response rather than the degree of DA receptor blockade. Moreover, the range of PRL response differs among patients, so that the same plasma concentrations do not necessarily correspond to the same degree of DA receptor blockade. Finally, the possibility that, after years of chronic treatment, some tolerance develops to the prolactin stimulating effect of neuroleptics (de Rivera *et al*, 1976; Laughren *et al*, 1979; Naber *et al*, 1979) makes the interpretation of the 'resting' PRL levels even more difficult.

To assess empirically the degree of DA receptor blockade during neuroleptic treatment we have tested hormonal responses to DA agonists and antagonists. In the first study (Kolakowska *et al*, 1981), plasma PRL was challenged with an additional dose of chlorpromazine 50 mg i.m. The increment of PRL levels over the treatment baseline identified eight patients (of 21) whose PRL response to their current medication was below the maximum. However in the others the ineffectiveness of this challenge was not a sufficient proof that the baseline level represented the upper limit of PRL response, for in some of these 'unresponsive' subjects, higher PRL concentrations followed chlorpromazine 100 mg i.m. or an increased daily dose of neuroleptics. Consequently, it was still not certain whether the therapeutic effect of neuroleptics requires the degree of DA receptor blockade which produces maximal PRL elevation.

The present study used a more potent challenge—haloperidol 2 or 4 mg i.m.—to identify more reliably the patients whose PRL can be raised further during neuroleptic treatment. It aims to assess: (i) the relationship between these responses and certain clinical variables, (ii) the possible significance of this test of function and (iii) the response to the haloperidol challenge of patients whose low PRL concentration during long-term treatment suggests tolerance to the PRL stimulating effects of neuroleptics. In unmedicated men, haloperidol 0.5 mg i.m. results in a definite plasma PRL rise which is repro-

TABLE I

Haloperidol test: Plasma prolactin increment (△PRL) expressed in miu/L and as percent of the baseline level (%)

Patients				Neuroleptic treatment					Haloperidol Test					
				Present					Haloperidol			Prolactin		
					Drug and dose								△PRL	
Test No.	Sex	Age	Stage of schizophrenia	Total duration (years)	Depot	mg/week	Oral	mg/day	Clinical response	Dose (mg)	Max level (ng/ml)	Baseline (miu/L)	miu/L	%
1	M	36	acute	1/12	FPT	30	—	—	poor	2	2.8	100	940	940
2	M	34	remission	4	FPT	6.6	—	—	good	2	3.8	344	1616	473
3	M	32	remission	>10	FPZ	37.5	—	—	good	2	3.35	534	1086	200
4	M	37	acute	2/12	—	—	FPZ	10	good	2	5.1	2250	1350	60
5	M	33	chronic	7	FPT	200	—	—	poor	2	1.7	1410	90	6
6	M	48	chronic	>10	FPZ	16.7	—	—	poor	2	—	336	564	168
* 7*	M	33	chronic	7	FPT	300	—	—	poor	4	3.2	1740	240	14
8	M	31	chronic	7	FPT	400	—	—	poor	4	4.0	1530	150	9
9	M	33	chronic	>10	FPT	100	—	—	poor	4	5.6	690	330	48
10	M	22	acute	2/12	FPT	80	—	—	partial	4	8.9	2100	720	34
11	M	26	chronic	8	FPZ	100	—	—	poor	4	6.8	618	712	115
12	M	48	chronic	>10	FPZ	25	—	—	poor	4	1.3	554	526	96
13	M	54	remission	>10	FPZ	25	—	—	good	4	4.05	570	440	77
14	M	63	chronic	>10	FPZ	12.5	—	—	poor	4	3.85	280	1290	461
15	M	32	acute	1/12	FPZ	25	—	—	good	4	3.4	796	1044	130
16	M	48	chronic	>10	—	—	PrCP	45	poor	4	4.3	2040	180	8
17	M	55	chronic	>10	FPT	50	CPZ	100	poor	4	4.1	318	456	143
18	M	60	chronic	>10	FPZ	25	TFP	20	poor	4	7.1	2210	800	37
19	M	32	chronic	>10	FPZ	25	PRPH	48	poor	4	10.2	460	420	89
20	M	32	acute	1	FPT	30	TFP	45	good	4	5.4	618	1272	205

FPT = flupenthixol

FPZ = fluphenazine

PrCP = prochlorperazine

CPZ = chlorpromazine

TFP = trifluperazine

PrPH = perphenazine

* Tests 7 and 12—same subjects as tests 5 and 6 respectively.

ducible, varies among subjects and is correlated with plasma haloperidol levels (Langer *et al*, 1977; Asnis *et al*, 1979; Rubin and Hays, 1979).

Subjects and Methods

Eighteen male patients were studied during their routine treatment with neuroleptic drugs (Table I). They fulfilled the research diagnostic criteria (Spitzer *et al*, 1975) for schizophrenic or schizo-affective illness, were free of physical illness and gave informed consent to take part in the study.

On the day of the test, a butterfly needle was inserted into a forearm vein at around 9.30 a.m. and blood samples were collected for 30 min. and 15 min. before, and at the time of the administration of haloperidol 2 or 4 mg i.m. and every 30 minutes for three hours after this. In patients treated with depot preparations of neuroleptics, the test was carried out in the middle of the interval between injections.

Plasma PRL was measured by a specific double antibody radio-immunoassay (McNeilly and Hagen, 1974), with MRC preparation 750/5504 as a standard. The normal PRL range in men was 150–616 miu/L (1 ng/ml equals approximately 27.5 miu/L).

Haloperidol in plasma was measured with radio-immunoassay (Michiels *et al*, 1976). Intra- and inter-assay precision of this method (CV) was ± 10 per cent and the lower limit of detection (sensitivity) −0.2 ng/ml.

To compare patients' medication, daily doses of neuroleptics were expressed as chlorpromazine equivalents (Davis, 1976). Non-parametric statistical methods were used to examine the relationship of hormonal responses, baseline plasma PRL levels and the clinical variables.

Results

Table I shows the maximal concentrations of plasma haloperidol and the maximal increment of plasma PRL, expressed both in absolute values (△PRL) and as a percentage of the baseline (% △PRL).

Peak plasma haloperidol concentrations varied three-fold after the dose of 2 mg i.m. (from 1.3 to 5.1 ng/ml) and five-fold after 4 mg i.m. (from 2.1 to 10.2 ng/ml). Maximal levels were reached after 30 min. in six of the seven tests with 2 mg i.m.: after the higher dose, plasma drug concentration continued to rise for 60 min. or longer in nine of fifteen tests.

A sustained rise of plasma PRL was produced by haloperidol 2 mg in five of the six tests and by 4 mg in eleven of the fourteen. In these 'positive' tests, the rise in PRL began at 30 or 60 min. and the level did not return to the baseline within the period of observation. The maximal increment of PRL ranged from 330 to 1616 miu/L (34 to 940 per cent of the baseline). In the remaining four tests, plasma PRL showed only irregular fluctuations and never exceeded the baseline level by more than six to fourteen per cent (90 to 240 miu/L). The patients with 'negative' tests were

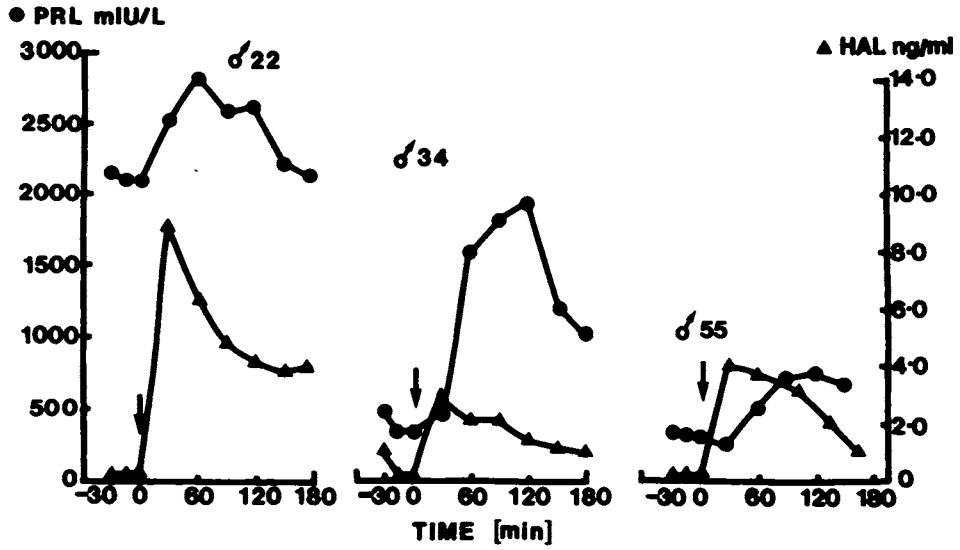

FIG 1.—Plasma prolactin (●——●) and haloperidol (▲——▲) levels following haloperidol challenge in patients No. 10 (♂ 22), 2 (♂ 34) and 17 (♂ 55).

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being treated with very large doses of neuroleptics and had high base-line plasma PRL (1410 to 2042 miu/L).

There was no correlation among subjects between the peak plasma haloperidol level and maximal PRL increment. Within individuals, the plasma PRL peak tended to be delayed by 30 to 60 min. in relation to the maximal drug concentration; PRL concentrations did not fall immediately and in some cases even showed a further rise when haloperidol levels were declining. Fig 1 illustrates this.

Among 14 patients tested with haloperidol 4 mg, the increment of PRL varied more than six-fold when expressed in miu/L (180–1290 miu/L) and more than 50-fold when expressed as a percentage of the baseline (9–461 per cent). Table II indicates that these two measures of PRL response were correlated. Both were inversely related to the daily dose of medication but only the percentage increase was also related inversely to the basal PRL concentration.

PRL increments tended to be higher in acutely psychotic patients whose treatment was of short duration than in patients with chronic illness receiving long-term medication; and higher in those with a good therapeutic response to the current medication than in the remainder. However, neither of these differences was statistically significant and both could probably be accounted for by the high daily doses of medication given to the chronic 'non-responders'.

Discussion

The haloperidol challenge produced a rise in plasma PRL over the treatment baseline in a majority of patients, showing that their PRL response to current medication had not reached its upper limit. In several patients the current treatment was effective in controlling their acute or chronic symptoms of schizophrenia even though the PRL elevation was not maximal. This indicates that 'therapeutically effective' doses do not necessarily exceed those required for maximal PRL release. Consequently, the test does not appear to be of clinical significance as a measure of DA receptor blockade induced by treatment.

Haloperidol failed to increase PRL levels further only in patients receiving very high doses of neuroleptics. The increment of PRL during the test was, overall, inversely related to the daily dose of medication but unrelated to plasma concentrations of haloperidol. This could be explained simply by the dose-response relationship: the rise in PRL depends on the relative (percentage) increase in the total level of circulating neuroleptics by the injected haloperidol —this relative increase would be great in patients treated with low daily doses but would constitute a functionally negligible fraction in those receiving very high doses. It is also possible that the PRL rise is restricted by an upper limit of the PRL response and that the higher the daily dose, the closer the basal level is to this 'ceiling'. In this case, the lack of a negative correlation between PRL increment and basal level would indicate that the absolute value of this upper limit varies widely among patients.

The test injection produced a PRL response in chronic schizophrenics who had been receiving neuroleptics for many years. A substantial PRL rise in those with relatively low basal levels during long-term medication suggests that these low levels were due to some factors other than simple tolerance to the PRL stimulating effects of neuroleptics.

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TABLE II

Intercorrelation between the daily dose of medication, baseline PRL level and PRL response to haloperidol 4 mg i.m. in 12 male patients (Spearman rho)

	PRL baseline	△ PRL in miu/L	△ PRL as % baseline
Daily dose of neuroleptics in CPZ equivalents	.503	−.643*	−.677*
PRL baseline		−.212	−.782**
△ PRL in miu/L			.675*

* $P < .05$
** $P < .01$

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II. The TRH Test

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Summary: Anterior pituitary response to TRH 200 μg i.v. was studied in ten chronic schizophrenic patients during long-term neuroleptic treatment. Nine patients had normal prolactin (PRL) response as compared with controls but in one the response was blunted; one patient had an exaggerated response. Prolactin increment was higher following TRH than haloperidol challenge. No growth hormone (GH) response to TRH was found and TSH responses were comparable to controls.

Although the acute effects of neuroleptic drugs in increasing prolactin (PRL) secretion by the anterior pituitary are well documented (e.g. Gruen *et al*, 1978), less is known of the effects of long-term neuroleptic treatment. Plasma PRL levels within the normal range have been described in schizophrenic patients on

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