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Haloperidol Plasma Levels and Clinical Response in Paranoid Schizophrenics

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Summary. The relationship between haloperidol plasma levels, plasma prolactin, and therapeutic efficacy was evaluated in 20 paranoïd schizophrenics in a fixed-dose study for 6 weeks. We found a significant intrapatient cross-correlation of therapeutic efficacy, as measured by decrease in MSS and BPRS rating scales and time-dependent haloperidol and pro lactin changes, which were tested at weekly intervals. However, no significant curvilinear relationship was present between steady-state haloperidol plasma levels and MSS and BPRS improvement scores. Our data do not furnish clear-cut evidence in favor of the existence of a therapeutic window for haloperidol plasma levels in paranoïd schizophrenia.

Key words: Haloperidol – Prolactin – 5HIAA – HVA – BPRS – MSS

Introduction

The relationship between haloperidol plasma levels and therapeutic efficacy in schizophrenic patients has been the focus of considerable controversy in recent years. A significant correlation between plasma concentration of haloperidol and improvement of schizophrenic symptomatology has been suggested by Calil et al. (1979), Tune et al. (1980), Mendlewicz et al. (1981), Magliozzi et al. (1981), and Kucharski et al. (1984). Others have failed to observe a significant relationship between plasma levels and clinical efficacy of haloperidol (Bjorndal et al. 1980; Moller et al. 1981; Rimon et al. 1981; Moulin et al. 1982; Shvartsburd et al. 1983). Some investiga tors have examined the relationship between plasma prolactin and haloperidol levels (Rama Rao et al. 1980; Gruen et al. 1978; Moller et al. 1981; Rubin et al. 1980; Bjorndal et al. 1980), as well as the ability of serum prolactin (PRL) to predict clinical response in schizophrenia, but these studies have also had conflicting results (Rotrosen et al. 1978; Gruen et al. 1978; Bjorndal et al. 1980). In the present study we assessed the relationship between haloperidol plasma levels, clinical efficacy, and prolactin secretion in a fixed-dose study of haloperidol in male and female paranoïd schizophrenic patients.

Methods

The patients included 11 males, aged 28 ± 6 years (mean ± SD, range 19–38), and 9 females, aged 36 ± 8 years (range 25–53), who had been diagnosed as paranoïd schizophrenics according to the Research Diagnostic Criteria (RDC) of Spitzer et al. (1978). Six patients were subdiagnosed as acute, 8 as subacute and 6 as subchronic. None fulfilled the chronic subtype diagnosis and no patients were included if presenting the first episode of the illness. Diagnosis was established using the RDC criteria by consensus of two of the psychiatrists participating in the study (P.L., P.H.). All patients presented a clinical state sufficiently severe to warrant hospitalization; none had received long-acting neuroleptics during a 3-month period preceding the hospitalization. All were admitted between November 1980 and March 1983 to the clinical research ward of the Erasme Academic Hospital of the University of Brussels. After informed consent was obtained, the patients underwent a drug washout placebo period of at least 8 days (only 4 mg flunitrazepam was allowed at night). Psychometric evaluations were done using the French version (Bobon and Mendlewicz 1981) of the Montgomery Subscale for Schizophrenia (MSS; Montgomery et al. 1978) and the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962). Patients were included in the study if there had not been at least a 25% improvement in the baseline MSS or BPRS scores during the washout period. All patients were in good physical health with no evidence of any organic disease. On the first day after the washout period, patients received 30 mg haloperidol orally in liquid concentrate three times a day on day 0 (at 8 a.m., 12 a.m. and 10 p.m.). MSS and BPRS ratings as well as blood sampling for determination of serum PRL were obtained before haloperidol administration. The whole protocol lasted 6 weeks. At the end of each treatment week, blood was sampled at 8 a.m. (10 h after the last drug administration) for determination of haloperidol and PRL levels. MSS and BPRS ratings were performed on the same day as blood sampling by the same rater (P.L.). The rater was unaware of the results of serum haloperidol and prolactin. An antiparkinsonian drug (50 mg orphenadrine up to 6 tablets a day) was added when necessary. Orphenadrine was chosen because it has been shown (Forssman and Ohman 1977) that it does not modify haloperidol plasma levels. Eleven patients (nos. 3–5, 7–9, 14, 16, 18, 19) were given orphenadrine (Table 1). Four patients dropped out of the study because of severe side effects (hypersedation, major extrapyramidal symptoms insufficiently corrected by orphenadrine) and were switched to a 15-mg haloperidol daily regimen. These patients were not included in the study. Flunitrazepam up to 4 mg was allowed at night when necessary. In nine patients who gave their informed consent to this procedure, lumbar puncture and CSF sampling was performed after 6 weeks of treatment for deter-

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minations of CSF 5HIAA, HVA, and haloperidol. Plasma and CSF haloperidol were determined by a radioimmunoassay procedure (Michiels et al. 1976), using the commercially available kit (IRE, Belgium). PRL was also determined by radioimmunoassay (IRE, Belgium). HVA and 5HIAA were measured by HPLC with electrochemical detection, using an adaptation of the method of Cross and Joseph (1980).

Inter- and intra-assay coefficients of variation were 12% and 3%, respectively, for haloperidol, 8% and 8% for prolactin, 10% and 3% for HVA, and 13% and 10% for 5HIAA.

Statistical Analysis

Concomitant evolution of psychometric, pharmacologic, haloperidol and prolactin variables during the 6-week study period was assessed using time series analysis (Box and Jenkins 1976). Cross-correlations were computed using time series methods without lag and with several lags (period of 1 week) to test the influence between the delay and the measure (Dixon and Brown 1981). For each subject we computed the cross-correlation between weekly MSS, BPRS, plasma haloperidol, and prolactin values. Intergroup differences were tested through the *t*-test. Values are expressed as mean ± SD unless otherwise stated. Spearman rank correlation was used when appropriate. The relationship between mean steady-state haloperidol plasma levels and improvement scores (defined as percentage of improvement over baseline scores) were studied using quadratic regression to test a possible curvilinear "therapeutic window" (Dunn and Clark 1974). Steady-state haloperidol levels reported here for each patient are mean values calculated from blood level measurements at week 1, 2, 3, . . . 6 after the start of drug administration.

Results

1. Clinical and Pharmacologic Characteristics of the patients are illustrated in Table 1.

Haloperidol steady-states (defined as mean haloperidol plasma levels from week 1 to 6) ranged from 4.3 to 25 ng/ml for a fixed 30 mg daily dose, showing a 6-fold difference between the lowest and the highest value. All but one patient improved during the trial; improvement scores, as expressed in percentage of initial MSS values ranged from 16% to 82%. The one patient whose clinical state remained unchanged during the study also had the lowest haloperidol steady-state value (4.3 ng/ml) (patient 20). Values obtained during the whole trial at 1-week intervals were then studied according to the following procedures. First haloperidol, PRL, MSS, and BPRS values obtained at week 1, 2, 3, . . . 6 were compared in subgroups of paranoïd schizophrenic males versus females. These data are presented in Table 2. Females as a group were older (36 ± 8 versus 28 ± 5 years; $p < 0.05$), smaller (163 ± 7 versus 170 ± 5 cm; $p < 0.05$) and lighter (57 ± 8 kg versus 67 ± 8 kg; $p < 0.05$) than men.

Females showed higher haloperidol plasma levels at weeks 1, 2, 3 and 6 and very significantly higher PRL levels during the whole period of the trial. No difference was observed between the two groups or between weekly mean MSS or BPRS ratings between schizophrenic males and females. Using time series analysis a cross-correlation was performed to assess the relationship between haloperidol, prolactin, MSS, and BPRS ratings during the trial (Table 3; Fig. 1). A very significant relationship was found between haloperidol plasma levels and prolactin stimulation, as well as between those two parameters and the decrease of schizophrenic symptomatology, as

Table 1. Clinical and pharmacological characteristics of the patients

	Age	Sex	HAL steady state (ng/ml)	MSS day 0	MSS week 6	MSS improvement score	BPRS day 0	BPRS week 6	BPRS improvement score	CSF HAL week 6 (ng/ml)	Plasma HAL week 6 (ng/ml)	CSF HVA week 6 (ng/ml)	CSF 5HIAA week 6 (ng/ml)	Plasma PRL week 6 μ(U/ml)
1	34	F	12.6	12	10	16	43	35	18					
2	26	M	13.6	45	19	57	81	52	36					
3	40	F	25.0	33	6	82	64	27	58	2.6	19.8	30	28	4111
4	27	M	17.2	36	12	66	61	40	34	1.5	12.4	40	21	2162
5	25	M	13.3	28	7	75	43	30	30	1.7	21.4	34	27	577
6	52	F	12.9	48	17	64	63	41	34	1.0	12.9	36	39	2518
7	48	F	8.0	38	10	73	69	38	44					
8	40	M	7.6	21	8	61	52	30	42	1.1	6.1	17	44	820
9	24	M	9.1	46	26	47	64	53	17					
10	29	F	21.9	31	14	54	65	48	26					
11	33	F	15.7	40	15	62	73	34	53	2.6	15.0	30	21	2558
12	28	F	15.6	16	8	50	38	22	42					
13	33	M	9.6	26	9	65	52	30	42					
14	28	F	14.0	37	14	62	58	37	36	1.9	14.9	36	26	3415
15	32	F	13.6	44	12	72	90	37	59					
16	33	M	10.9	34	17	50	79	49	38					
17	19	M	9.7	44	9	75	64	33	43					
18	31	M	7.3	17	14	17	53	40	24					
19	24	M	9.5	31	13	58	64	34	49	1.0	13.6	37	34	1340
20	26	M	4.3	48	48	0	67	65	3	0.8	4.2	27	19	1357

Table 2. Haloperidol, PRL, MSS, and BPRS at weekly intervals in male and female patients

	Males (ng/ml)	Females (ng/ml)	p		Males (μU/ml)	Females (μU/ml)	p
				PRL 0	208 ± 139	285 ± 170	n.s.
HAL 1	8 ± 3	14 ± 5	<0.05	PRL 1	960 ± 392	2143 ± 860	<0.005
HAL 2	9 ± 3	14 ± 5	$=0.05$	PRL 2	1005 ± 560	3471 ± 1615	<0.005
HAL 3	10 ± 2	16 ± 5	<0.025	PRL 3	904 ± 333	3393 ± 1444	<0.01
HAL 4	11 ± 5	16 ± 7	n.s.	PRL 4	1117 ± 599	3394 ± 1842	<0.01
HAL 5	11 ± 3	26 ± 7	n.s.	PRL 5	1077 ± 485	3200 ± 523	<0.001
HAL 6	8 ± 3	14 ± 4	<0.05	PRL 6	1284 ± 639	3556 ± 866	<0.01
MSS 0	34 ± 11	33 ± 12	n.s.	BPRS 0	61 ± 11	62 ± 15	n.s.
MSS 1	25 ± 13	21 ± 10	n.s.	BPRS 1	51 ± 11	46 ± 7	n.s.
MSS 2	21 ± 12	19 ± 9	n.s.	BPRS 2	47 ± 15	44 ± 2	n.s.
MSS 3	18 ± 8	16 ± 6	n.s.	BPRS 3	44 ± 13	44 ± 9	n.s.
MSS 4	17 ± 12	13 ± 4	n.s.	BPRS 4	41 ± 12	39 ± 7	n.s.
MSS 5	17 ± 13	12 ± 3	n.s.	BPRS 5	43 ± 15	36 ± 6	n.s.
MSS 6	16 ± 11	11 ± 3	n.s.	BPRS 6	41 ± 11	35 ± 7	n.s.

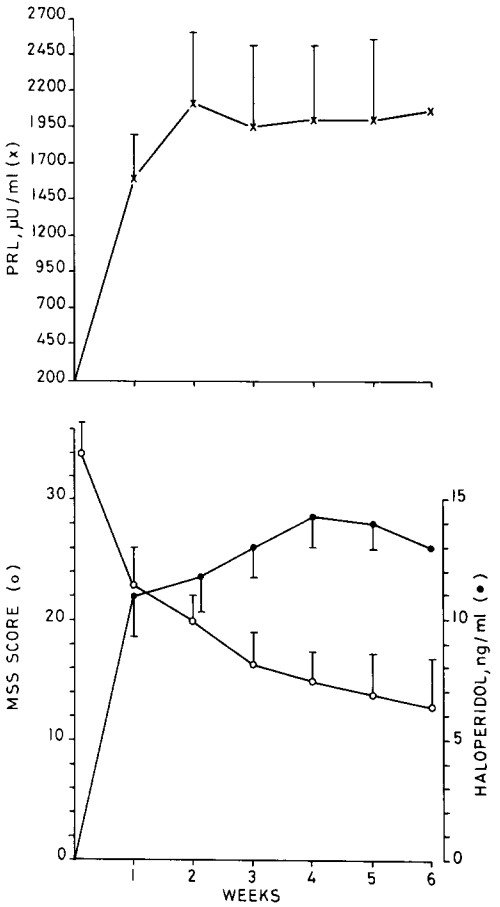

Fig. 1. Evolution of weekly plasma haloperidol, plasma prolactin and MSS ratings during the trial (mean values ± SEM)

measured by the MSS and BPRS. All significant relationships reported held true for the whole sample of schizophrenic patients, as well as for the male and female subsamples, yielding comparable coefficients and the same levels of significance for each comparison tested. Interpretation of Fig. 1 shows that increase of plasma haloperidol and prolactin is significantly

Table 3. Cross-correlations between weekly values of plasma haloperidol, prolactin, MSS and BPRS in the whole sample of schizophrenics

	Coefficient	p
Haloperidol and PRL	0.97	<0.001
Haloperidol and MSS	−0.95	<0.001
Haloperidol and BPRS	−0.96	<0.001
PRL and MSS	−0.93	<0.001
PRL and BPRS	−0.93	<0.001
MSS and BPRS	0.97	<0.001

linked to the decrease in psychotic symptomatology, measured by the MSS. Among the 20 patients, 16 showed an MSS improvement score of at least 50% at the end of the study. This 50% improvement had already been reached at week 2 in 8 of those 16 patients, showing that the therapeutic effect of haloperidol, when present, was rather precocious in our paranoïd schizophrenics.

2. Comparison of CSF, Plasmatic, and Psychometric Variables (Table 4). No significant correlation was observed between CSF HVA or 5HIAA and CSF haloperidol obtained at the end of the trial and other clinical (BPRS and MSS at week 6) and pharmacologic parameters (haloperidol levels at week 6 or mean haloperidol steady-state), with the exception of a significantly positive correlation between CSF and plasmatic (6th week) haloperidol concentrations ($r = 0.756$; $p < 0.05$, $7df$), as well as between BPRS improvement score and 5HIAA CSF values ($r = 0.826$; $p < 0.05$, $7df$).

3. Relationship Between Steady-State Haloperidol Plasma Levels and Clinical Response (Figs. 2 and 3). Quadratic polynomial regression failed to reveal a significant curvilinear correlation between plasma steady-state levels of haloperidol as measured by radioimmunoassay and clinical improvement as assessed by the MSS and BPRS scores (percent improvement on the basal scores) ($F = 3.13$, and $F = 1.84$; p = n.s.). These negative results did not provide evidence for a putative

Table 4. CSF, psychometric and pharmacological variables: correlation coefficients

	BPRS 6th week	MSS 6th week	Plasma haloperidol 6th week (ng/ml)	MSS improvement score	BPRS improvement score	CSF haloperidol 6th week (ng/ml)	Steady state haloperidol (ng/ml)	PRL 6th week (μU/ml)
HVA	0.292	0.017	0.143	−0.017	0.084	−0.047	0.353	0.01
5HIAA	−0.451	−0.377	0.050	0.612	0.828[a]	−0.131	−0.209	−0.218
CSF haloperidol (ng/ml)	−0.610	−0.496	0.756[a]	0.394	0.109	1	0.832[a]	0.546

[a] $p < 0.05$

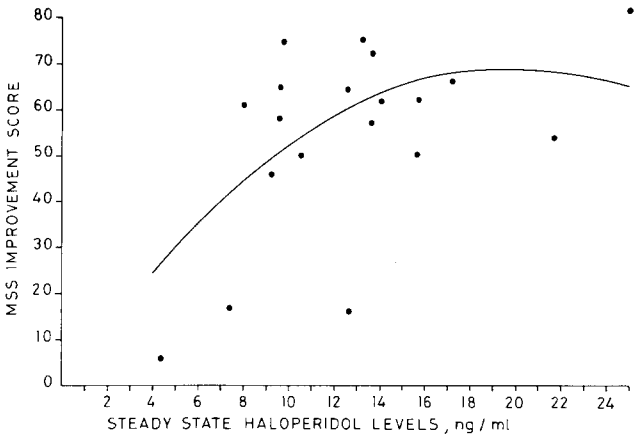

Fig. 2. Relationship between steady-state plasma haloperidol levels and MSS improvement score (curvilinear regression $y = 0.25 + 6.79, x - 0.16\,x^2$, $F = 3.13$, p = n.s.)

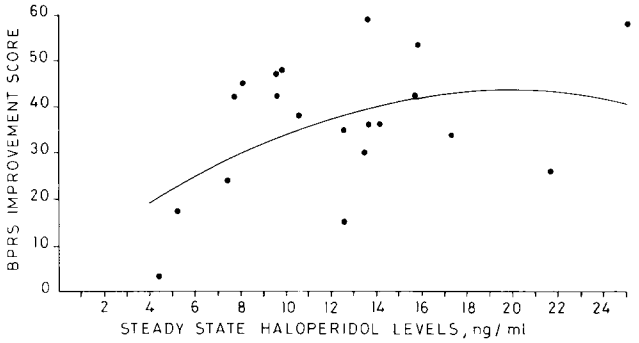

Fig. 3. Relationship between steady-state plasma haloperidol levels and BPRS improvement scores (curvilinear regression $y = 7.48 + 3.55, x - 0.8\,x^2$, $F = 1.84$, p = n.s.)

therapeutic window for haloperidol which would support better improvements at intermediate neuroleptic levels.

Discussion

To date controversial results have been reported about the relationships between haloperidol plasma levels and schizophrenia, but this may have been the result of several methodological drawbacks that were carefully controlled in this study. The discrepancies observed could be partly related to such factors as:

a) Non-fixed-dose regimens
b) Heterogeneous ascertainment of schizophrenic patients (Crow 1980), paranoïd schizophrenics presenting with a better response to treatment than hebephrenics
c) Grouping acutely ill and chronic patients
d) Sex differences (Meltzer et al. 1983)
e) Differences in assay methods (Rimon et al. 1981).

Heterogeneity in the ascertainment of patients was reduced in our study by selecting paranoïd schizophrenics corresponding to Crow's type I schizophrenia (Crow 1980), putatively considered neuroleptic responders according to other studies (Johnstone et al. 1978; Angrist et al. 1980). Fixed-dose regimens and the 6-week duration of the study ensured intrapatient stability of steady-states and sufficient time for sequential clinical assessment. Finally, using Morselli's recommendations, the possible existence of relationships between clinical and pharmacologic variables was assessed among patients but also longitudinally in each individual schizophrenic at regular intervals using cross-correlation methods (Morselli 1976; Morselli and Zarifian 1980). Our results do not substantiate a therapeutic window for haloperidol levels in paranoïd schizophrenia by means of testing a possible curvilinear relationship between clinical improvement, as measured by specific psychometric scales, and haloperidol mean steady-state levels. However, this negative observation should be tempered by the fact that although all but one patient improved during the trial, the sole nonresponder also presented with the lowest haloperidol plasma levels, suggesting that, as previously reported (Mendlewicz et al. 1981), an inferior therapeutic threshold of at least 5 ng/ml is mandatory for clinical improvement. Furthermore, as the highest haloperidol levels observed reached 25 ng/ml, no firm conclusion can be reached if patients presenting with very high haloperidol plasma levels (i.e. higher than 30 ng/ml) get worse. Improvement, when observed, was reached rapidly (within 2 weeks) after the beginning of the trial, supporting previous observations (Magliozzi et al. 1981; Neborsky et al. 1981; Mavroidis et al. 1983). As there was no placebo-treated control group in this study, it is not possible to determine how many haloperidol responders would have responded to placebo alone. However, we selected for this study only those patients who did not show an improvement during a 1-week placebo washout period. Furthermore, in their placebo-controlled studies, Reschke (1974) and Gottschalk et al. (1975) showed little decrease in the average psychosis ratings in schizophrenics given placebo when compared to a neuroleptic-treated group. Nevertheless, some investigators have reported that a significant percentage (less than 25%) of acute schizophrenics do remit without receiving neuroleptic treatment (NIMH Collaborative Study 1960; Davis 1976). In agreement with previous reports from the literature, we observed a wide (six fold) range of plasma levels for a fixed oral dose of haloperidol (Forssman and Ohman 1977; Morselli 1978; Mendlewicz et al. 1981), as well as a significant correlation between

CSF and plasma levels of haloperidol (Forssman and Ohman 1977; Rimon 1981). In our patients, CSF 5HIAA was significantly and positively correlated with clinical improvement, as measured with the BPRS, lending support to a previous observation of Wode-Helgodt (1978), who reported similar observations in chlorpromazine-treated psychotic patients. We also report that measurement of prolactin profiles might be a good index of therapeutic improvement in individual patients. Although therapeutic doses of neuroleptic drugs seem to be much greater than those required for maximum stimulation of PRL (Langer et al. 1977), Ohman and Axelson (1978) have also reported significant correlations within subjects across time between the PRL responses and the therapeutic responses to thioridazine, suggesting that the time course of PRL response to neuroleptic treatment might be related to the time course of improvement in psychotic behavior. This has also been suggested by the study of Cookson et al. (1983) on haloperidol in manic patients. Higher prolactin levels in females observed in our study are in good correspondence with previous reports (Meltzer and Fang, 1976; Wode-Helgodt 1978; Meltzer et al. 1983) that females develop higher serum PRL levels than males on the same dose of neuroleptics. Significant intergroup differences in mean weekly haloperidol levels between males and females should be related to weight differences, as previously noted (Meltzer et al. 1983). A major and original finding in this study is the observation of a strong and very significant intrapatient cross-correlation of therapeutic efficacy, as measured by specific rating scales and time-dependent haloperidol and prolactin changes tested at weekly intervals. Although wide variability was observed in weekly psychometric, haloperidol and prolactin values within our patient group, excellent intraindividual correlations between the three variables were observed in each patient during the trial. Finally, in view of the hypothesis that schizophrenia is related to an overactive dopaminergic system (Snyder et al. 1974; Crow et al. 1976) and that the therapeutic effect of antipsychotic drugs is related to dopamine receptor blockade (Carlsson 1978), one could speculate that there are interindividual and time-dependent differences in degrees of dopaminergic overstimulation in schizophrenic paranoïd patients. Although the data presented in this study are entirely consistent with the above hypothesis, our results do not furnish clear-cut evidence in favor of the existence of a therapeutic window for haloperidol plasma concentrations. However, determination of haloperidol plasma levels could still have some clinical relevance with regard to therapeutic response at very high or very low plasma levels, particularly in neuroleptic-resistant schizophrenics.

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