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Plasma Haloperidol Levels and Therapeutic Response in Acute Mania and Schizophrenia

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Summary. In an open study, 18 patients suffering from an acute episode of schizophrenia and 18 patients with severe mania were given haloperidol at different dosage levels. Haloperidol plasma concentrations were measured and the status of the patients was evaluated at intervals using the Brief Psychiatric Rating Scale (BPRS). No correlation was found between the oral dose and the plasma concentrations in the schizophrenic group, but there was a low correlation for manic patients. In both groups, however, there was a correlation between these two parameters when the drug was given intramuscularly. There was no correlation between haloperidol plasma concentrations and the BPRS scores. Of the 36 patients 28 responded well to the treatment and were discharged from hospital. A good relationship between the clinical status as observed by the clinicians and the BPRS score was found. Plasma haloperidol concentration measurement was found to be a useful tool for the detection of non-compliance or excessive plasma levels. Accordingly, the present study indicates the value of drug level monitoring as a means to improve therapy.

Key words: Haloperidol - Mania (manic depressive psychosis, manic phase) - Schizophrenia - Drug level monitoring - Therapeutic range

Introduction

Haloperidol is one of the most frequently prescribed neuroleptics. Within the last decade it has become the treatment of choice for acute psychosis, particularly for mania and acute episodes of schizophrenia. In addition to its potent antipsychotic effect, haloperidol is less sedative than other neuroleptics and has a low profile for cardiovascular side effects.

The recent introduction of therapeutic drug monitoring in psychiatry has enabled clinicians to eliminate some of the guesswork with regard to non-responders, in other words to separate out those patients who fail to respond to treatment because of non-compliance and partial compliance. Since the introduction of haloperidol, studies have been performed in order to establish which plasma concentrations are related to the best therapeutic effects (Forsman and Öhman 1977; Ericksen et al. 1978; Morselli et al. 1980 and 1981; Magliozzi et al. 1981). It has thus become possible to establish a therapeutic range of plasma levels (5-15 ng/ml). At lower levels, patients may fail to respond to treatment and at higher levels they may develop extrapyramidal side effects. Because haloperidol has no clinically significant active metabolites, it is possible to monitor the plasma levels of the parent molecule only.

The present study was undertaken in order to test whether monitoring plasma concentrations of haloperidol is, as suggested in the literature (e.g. Morselli et al. 1981), useful in the management of patients hospitalized for acute episodes of schizophrenia and mania. The study was conducted within the frame of routine clinical treatment of the patients. All subjects were hospitalized and treated independently by psychiatrists unconnected with the investigation. At the same time, the authors attempted to determine whether steady-state concentrations of the drug were achieved more rapidly and safely when administered orally or intramuscularly.

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Methods

The present investigation includes 18 patients suffering from an acute episode of schizophrenia, 14 patients with acute mania (manic-depressive psychosis, MDP) and 4 patients initially diagnosed as acutely manic who revealed a severe borderline state; all diagnoses were in conformity with the diagnostic criteria of the World Health Organization (ICD-9).

The ages of the 17 male and 19 female patients ranged from 18 to 60 years (Tables 1 and 2). All were hospitalized for an acute psychotic relapse and all were treated with haloperidol. Dosages were adjusted according to standard clinical criteria. and ranged from 5 to 30 mg per day. Haloperidol was administered intramuscularly to some patients initially, but thereafter it was given orally following adjustment for the first-pass effect. An antiparkinsonian agent (biperiden) was added as needed to control extrapyramidal side effects. Patients were evaluated by the BPRS (Overall and Gorham 1962) on admission and subsequently at 10-day intervals.

Haloperidol responders were defined as patients showing, after 20 days, a decrease of 40% of the global initial BPRS score for the patients with schizophrenia and of 30% for the patients with acute mania. This differentiation was necessary because the items (due to the intrinsic nature of the BPRS), relevant to the symptoms of schizophrenia, were more numerous than those involved by (acute) mania. As a matter of fact, the initial score was 54 points in the first group and 43 points in the second. There are different ways of expressing a reduction in BPRS scores. We chose to express our results as percentage decrease calculated on the basis of the initial scores. This procedure allows adjustment for the value of the initial score. On the contrary, the simple difference of initial and terminal

Table 1

Patient no.	Age	Sex	Diagnosis (manic state)	BPRS score		Mean halop. level (ng/ml)	Anticholinergic agents
				Initial interview	Final interview (20 days)		
2	45	F	MDP circular	36	22	7.0	Akineton 6 mg/d
4[a]	48	F	MDP circular	49	37	7.9	Akineton 6 mg/d
10	54	F	MDP circular	40	18	6.0	Akineton 2 mg/d
18	52	F	MDP circular	37	19	11.3	Akineton 2 mg/d
22	36	F	MDP manic	51	28	2.1	Akineton 4 mg/d
27	60	F	MDP mixed	43	26	10.3	–
29	39	F	MDP circular	44	29	12.9	Akineton 4 mg/d
30	31	M	MDP circular	45	25	10.6	Akineton 4 mg/d
31	34	F	MDP circular	44	23	9.7	Akineton 2 mg/d
32	53	M	MDP circular	37	23	9.8	Akineton 4 mg/d
33	31	F	MDP circular	39	21	9.9	Artane 5 mg/d
36	60	M	MDP circular	42	21	6.4	Akineton 2 mg/d
7	36	F	MDP-borderline	48	28	8.7	–
11[a]	29	M	MDP-borderline	34	29	5.2	Akineton 2 mg/d
14[a]	28	F	MDP-borderline	42	37	8	Artane 4 mg/d
17	18	F	MDP-borderline	46	18	5.3	Akineton 2 mg/d
24	46	F	MDP-borderline	54	20	7.2	Akineton 2 mg/d
6[a]	53	F	Manic reaction	40	31	10	–

[a] Non-responders

Table 2

Patient no.	Age	Sex	Diagnosis (schizophrenia)	BPRS score		Mean halop. level (ng/ml)	Anticholinergic agents
				Initial interview	Final interview (20 days)		
1	34	M	Paranoid	56	25	3	Akineton 6 mg/d
3	33	F	Paranoid	63	27	6	Akineton 4 mg/d
5	26	F	Hebephrenic	57	26	11.2	Akineton 4 mg/d
8	26	M	Paranoid	57	25	5.2	Akineton 2 mg/d
9	24	M	Paranoid	61	23	8.3	Akineton 4 mg/d
12	36	F	Paranoid	59	28	11.6	–
16	37	F	Paranoid	44	23	3.9	–
19	24	M	Paranoid	47	27	7	Artane 5 mg/d
20[a]	25	M	Hebephrenic	60	42	3.5	–
25	37	M	Schizoaffective	43	23	6.3	–
23[a]	23	M	Hebephrenic	59	47	7.6	Akineton 4 mg/d
28[a]	25	M	Schizoaffective	47	34	10	–
35	21	M	Schizoaffective	52	23	12.9	Akineton 10 mg/d
37	22	M	Hebephrenic	55	33	4.5	Akineton 10 mg/d
15	39	M	Acute reactive	59	21	8.4	Akineton 10 mg/d
26	37	M	Acute reactive	54	21	8.8	Akineton 6 mg/d
34	31	M	Acute reactive	57	26	13	–
13[a]	29	F	Schizoaffective	49	30	8	Akineton 2 mg/d

[a] Non-responders

scores (e.g. a decrease of 10 points is equivalent to a positive response) does not consider the fact that the absence of symptoms (i.e. baseline value) scores 18 points. This percentage evaluation shows a good relationship to the clinical judgement. As an example, patients classified as responders quickly reach global BPRS scores between 18 and 30, which corresponds to the criteria of normalization considered from a social point of view. Blood samples for assay of steady-state plasma levels of haloperidol were drawn by venipuncture while the subjects were receiving haloperidol. Steady-state levels (Forsman and Öhmen 1977) were defined as those obtained at 8 a.m., 10 h after administration of the last dose of haloperidol, the identical dosage having been administered for at least 5 to 7 days. Plasma concentrations were determined by gas-liquid chromatography (G.L.C.) with nitrogen-phosphorus selective detection using a modification of the method of Bianchetti and Morselli (1978). The sensitivity of the method was 1 ng/ml when a 2 ml sample was used and the mean day-to-day coefficient of variation was 10%.

Results

Relation of Prescribed Dose and Measured Concentrations

As shown in Figs. 1 and 2, there was a positive correlation in both groups between steady-state concentrations of haloperidol in plasma and the doses of the medication administered by intramuscular injection (mania: $r=0.558$, $P<0.05$; schizophrenia: $r=0.701$, $P<0.01$). For the oral administration, there was a low correlation in the manic group ($r=0.499$; $P<0.01$), but there was no correlation in the schizophrenic group ($r=0.123$).

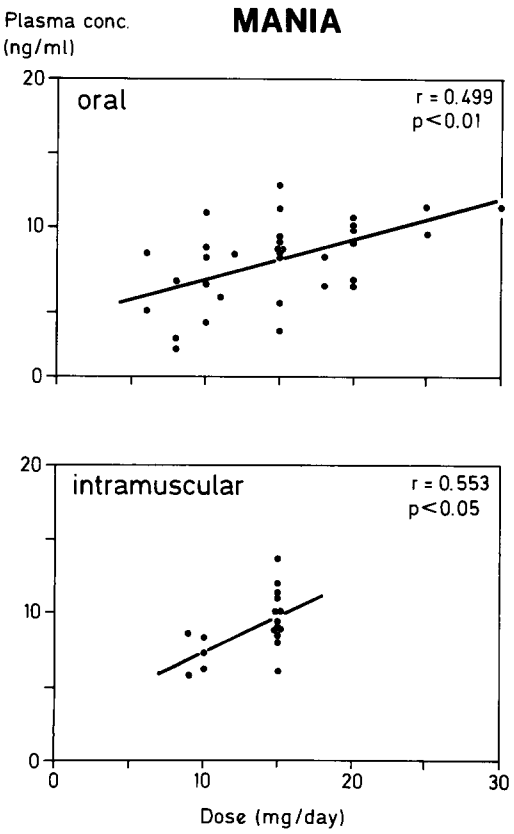

Fig. 1. Relationship between the prescribed oral dose *(upper panel)*, the administered intramuscular dose *(lower panel)* and the measured steady-state plasma concentrations in mania

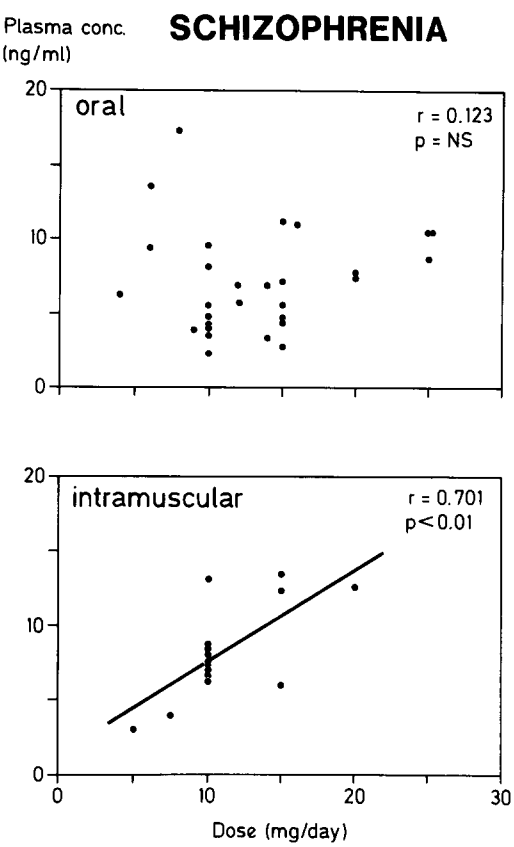

Fig. 2. Relationship between the prescribed oral dose *(upper panel)*, the administered intramuscular dose *(lower panel)* and the measured steady-state plasma concentrations in schizophrenia

Relation of Measured Concentrations and Clinical Response

When non-compliance (or partial compliance) was suspected during oral administration of the medication, monitoring provided a rational basis for reverting to intramuscular injections. Alternately, it supplied firm evidence to convince patients to comply with medical recommendations. The plasma concentrations measured during such episodes have not been included in the present analysis.

The results obtained in both groups of patients are shown in Tables 1 and 2. The mean BPRS score on admission was 43 in the manic group (range: 34 to 54) and 54 in the schizophrenic group (range: 43 to 63). The clinical course of the disease, and the analysis of the changes in BPRS scores is rapid in 8 schizophrenics and 7 manic patients. Accordingly, they were discharged from hospital after 10 days. It must be stated that these hospitalized patients were treated not only by haloperidol but that our intensive care program included complementary treatments such as ergotherapy and corporal methods.

If we consider all the responding patients (i.e. 28; 14 schizophrenics and 14 manics) the duration of hospitalization ranged from 10 days to 4 weeks. The decision to discharge a patient was made on the basis of clinical judgement. Factors such as the possibility of establishing an interpersonal relationship, the stabilization of behavioural modes or the degree of excitation were among the criteria used. In addition, we always considered the social and family context of our patients

before taking such a decision. The fact that our psychiatry system is based on a "sectorial organization", in which inpatient and outpatient care are clearly integrated, influences (to some degree) the appreciation of the degree of response of a given therapy.

Overall, the combination of the above mentioned clinical criteria and the BPRS scores allow an evaluation of the course of acute episodes of schizophrenia and mania, even if the BPRS scale is less adequate in manic states and shows little sensitivity to personality disorders. For example, when a manic state is associated with an underlying neurosis, personality disorder or borderline state, the BPRS score only partially captures the therapeutic effect of the mood disorders. It must be stated, however, that it was not possible to detect a correlation between any of the sequential BPRS ratings and the mean steady-state haloperidol concentrations. This confirms results obtained by others (e.g. Extein et al. 1982).

Among the 8 patients who were considered as non-responders, 2 showed manic reactions on a borderline state, 1 manic state on an underlying neurosis, 1 manic state on a circular MDP, 2 schizoaffective schizophrenics and 2 hebephrenics. In the group of nonresponders, 5 patients presented personality disorders associated with the diagnosis of schizophrenia or MDP (in the sense of explosive personality disorder, personality disorder with predominantly sociopathic manifestation of ICD 9, 301.3-301.7).

These special personalities appear as a trend to conflict and impulsive actions even in a period of clinical remission. All these patients showed haloperidol plasma concentrations between 3.5 and 10 ng/ml.

Discussion

As suggested by Magliozzi et al. (1978), the practice of varying dosage according to clinical judgement usually does not offer a sound basis for establishing a "therapeutic range" because extremes such as non-responders, toxic or non-compliant patients are excluded from the analysis. This is even more the case, as in our study, in which dosage and compliance are feedback controlled by the measurement of plasma concentrations. Accordingly, it is not possible to ascertain on the basis of the present data, for example, whether a concentration range of 5 to 15 ng/ml (Morselli et al. 1981) is more appropriate than 8 to 18 ng/ml (Magliozzi et al. 1981). It is possible, however, to conclude that aiming at haloperidol concentrations of this magnitude will enable rapid detection of non-responding and non-compliant patients, and will insure a high rate of therapeutic success in adequately chosen patients suffering from an acute episode of mania or schizophrenia.

The next question that arises concerns the usefulness of plasma levels measurement instead of monitoring the prescribed dose. Clearly, the answer is "yes" if compliance is a problem. From the present data, it also appears that although there is a relation between the prescribed dose and the measured steady-state concentrations, the relation is too low to serve as a reliable guide to therapy, whether for oral or intramuscular administration. Of interest is the finding that there was no correlation between the prescribed oral dose of haloperidol and the plasma concentrations in the schizophrenic group, whereas a correlation was found in the manic group (Figs. 1 and 2). This finding is probably related to a different degree of partial compliance in the two types of patients, although such a supposition demands careful demonstration before definite conclusions can be drawn.

As far as clinical practice is concerned, we recommend intramuscular injection of haloperidol as the administration mode of choice in the initial phases of treatment. Once adequate steady-state concentrations have been reached and symptoms begin to regress, the medication may be administered orally for the convenience of the patient, although it should not be forgotten that on the average approximately 30% of the drug is metabolized during the first-pass through the liver when it is taken orally.

Last but not least, haloperidol concentration monitoring may influence the behaviour of the team in charge of the hospitalized patient. The security given by the detection of abnormally high drug concentrations, or the possibility of detecting non-compliance is certainly a positive factor which influences the attitude of both doctors and nurses when they use this "incisive neuroleptic". The fact that after discharge from hospital patients will be under the supervision of an outpatient system, which would also use the facilities of drug concentration monitoring, is considered a factor that may contribute to a reduction of the time spent by the patient in the psychiatric hospital.

Conclusions

From our results, it appears that haloperidol plasma concentration monitoring is a means to safe, effective treatment in a majority of patients suffering from an acute episode of mania or schizophrenia.

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