

Clinical implications of determination of plasma haloperidol levels

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ABSTRACT - The aim of this study was to analyze the clinical utility of monitoring plasma levels, since the utility of monitoring is not yet well established. After a washout period, 30 schizophrenic patients were given fixed doses of haloperidol for 3 weeks. A U-shaped second-grade polynomial relationship ($R = 0.69$) was found between steady state of haloperidol and percentage improvement in total score on the Brief Psychiatric Rating Scale. The interval of effective concentrations was between 12 and 59 ng/ml. Fourteen of the 15 patients who had a steady state of haloperidol within that therapeutic interval were responders: only 5 out of the 15 patients below the therapeutic interval were responders. None of the 5 patients who had concentrations below 8 ng/ml was a responder. Furthermore, responder patients showed a steady-state level of haloperidol significantly higher than that of nonresponders. These data suggest that plasma levels of haloperidol are predictors of therapeutic response in schizophrenic disorders.

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In recent years, numerous authors have suggested the existence of a relationship between plasma levels of haloperidol and clinical improvement of schizophrenic symptoms (1-10), although other authors disagree with these findings (11, 12). These authors generally observe a curvilinear relationship in the form of an inverted U, compatible with the existence of a therapeutic window (3-7, 13). However, most of the samples used were very heterogeneous, often grouping patients presenting schizophrenic symptoms for the first time with chronic schizophrenics, schizophrenic disorders or schizoaffective disorders. It is thus not unusual that there are relevant discrepancies in the limits of the supposed therapeutic window, especially since patients with schizo-

phreniform or schizoaffective disorders present favorable responses to haloperidol levels of less than 3 ng/ml. Different methods have been used to analyze plasma concentration of haloperidol such as gas chromatography (GC) (14), high pressure gas chromatography (HPGC) (12,15), gas chromatography associated with mass spectrometry (GCMS) (16), radioreceptor assay (17) and radioimmunoassay (RIA) (18, 19). Haloperidol RIA is highly sensitive, reliable and reasonable in cost. Previous extraction using heptane-isoamyl alcohol in an alkaline solution eliminates haloperidol metabolites that might interfere with binding to the specific antibody (20), yielding haloperidol concentrations similar to those obtained by gas chromatography (21).

In this study we attempted to evaluate the utility of plasma haloperidol levels as predictors of clinical response in a sample of patients strictly diagnosed as schizophrenics, from which patients with schizophreniform or schizoaffective disorders were excluded. The study was based on the methodological recommendations of May & Van Putten (22) and Meltzer et al. (23). Moreover, the sample was selected on the basis of the predominance of positive symptoms, which are linked to a state of dopaminergic hyperactivity and therefore are most likely to respond favorably to neuroleptics (24).

Material and methods

We studied 30 patients diagnosed as schizophrenics according to DSM-III criteria of the Psychiatry Department of the Hospital Clinico de Madrid. The mean age of the sample was 26.2 ± 5.5 years and the mean duration of the disease was 5.1 ± 5.4 years. No patient diagnosed as schizoaffective or schizophreniform disorder was included in the sample. Ten of the patients studied were considered to have had their first episode of schizophrenia, the duration of the disorder being over 6 months and under one year. None of the patients included in the sample was previously nonresponsive to neuroleptic treatment. All gave written consent to participate in the test. Patients received no neuroleptics for at least 10 days before the onset of the study. Patients were randomly assigned to groups of 10 patients who received the following dosages of oral haloperidol: 15 mg/day, 10 mg/day and 30 mg/day. The dosage was divided into 2 daily doses and was maintained constant for 21 days.

On days 4, 7, 14 and 21, blood was extracted for plasma haloperidol measurements at 8.30–9.00 a.m., approximately 12 h after the last nightly dose. Samples were centrifuged and stored at -20° until processing.

Haloperidol concentration was analyzed by radioimmunoassay (Irebelgium) after previous extraction with heptane-isoamyl alcohol (9.8/1.5) in an alkaline solution. The sensitivity of the method was 0.05 ng/ml. The intra- and inter-assay variation coefficients were 6.7% and 13.7%, respectively.

Clinical status was assessed on days 0, 4, 7, 14 and 21 using the Brief Psychiatric Rating Scale (BPRS) (25). We evaluated total BPRS score and itemized scores for the 5 factors described by Guy (26): I) anxiety-depression; II) anergy; III) thinking disorders; IV) activation; V) hostility-suspicion. Percentage clinical improvement at day 21 was calculated from total BPRS scores.

According to Overall (27), this percentage improvement more precisely reflects the clinical evolution during pharmacological treatment by reducing the variability and correlation with baseline scores.

Using a modification of the criterion of Magliozzi et al. (1), we defined responders as patients who presented an improvement of 40% or more in the BPRS total score on day 21.

The evolution of plasma haloperidol concentration and clinical improvement in relationship to dosage were analyzed by an analysis of variance (ANOVA). The two means were compared using Student's *t*-test. When the variances were not homogeneous, the Welch transformation was applied. The relationship between percentage clinical improvement and plasma levels of haloperidol was analyzed by means of second- and third-grade linear and polynomial regression, although this article only gives the adjustment that produced the highest R^2 value. The lower limit of the interval of effective haloperidol concentration was calculated by finding the neuroleptic level (X) that corresponded to a 40% improvement (Y) in BPRS total score in the regression equation obtained. When a second grade polynomial relation was obtained, both haloperidol values corresponding to a percentage improvement of 40% were calculated, being considered as the limits of the therapeutic window. Likewise, the drug concentration that corresponded to the point of inflection of the curve was calculated by finding the derivation from the regression equation. All statistical analyses were performed using the SYSTAT statistical package for microcomputers (28).

Results

1. Dosage (mg/kg/day) correlated positively ($P < 0.01$) to the plasma haloperidol concentra-

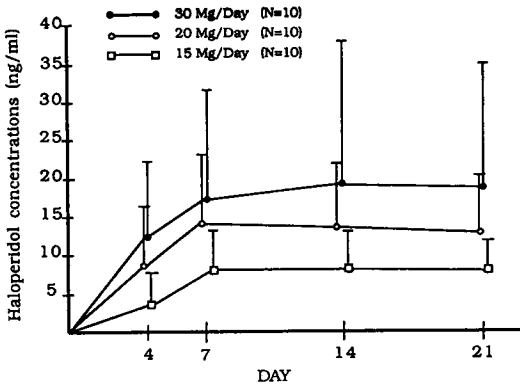


Fig. 1. Plasma haloperidol levels in relation to the range of dosages administered and time.

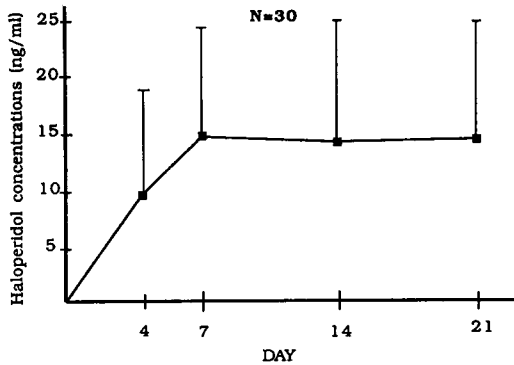


Fig. 2. Evolution of haloperidol levels during the 3 weeks of treatment in the total patient group.

tions attained on days 4 ($r = 0.53$), 7 ($r = 0.52$), 14 ($r = 0.58$) and 21 ($r = 0.48$), as well as to steady-state levels ($r = 0.59$). However, a group (3) \times time (4) ANOVA did not yield any significant differences between haloperidol concentrations attained by each of the 3 subgroups into which the sample was divided in accordance with the dosage administered (mg/day) ($F(2,27) = 2.70$, $P = 0.08$) (Fig. 1).

2. The BPRS mean score attained on day 0 was 51 ± 11.5 . The score for positive symptoms (sum of the scores obtained for factors III, IV and V) was 33.8 ± 5.8 , which represents 66% of

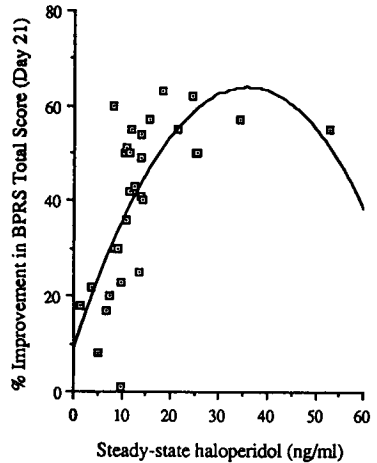


Fig. 3. Relationship between plasma haloperidol levels and percentage improvement in BPRS total score. The line represents best fit curvilinear regression. Polynomial regression equation was: $Y = 9.109 + 3.074 X + 0.431 X^2$; $R = 0.69$.

the BPRS total score. The mean score for factor II was 9.9 ± 4.2 (19%) and for factor I, 7.4 ± 2.4 (14%).

3. The percentage improvement obtained in the BPRS total score was independent of dosage range administered (mg/day) ($F(2,27) = 1.75$, n.s.). Likewise, dosage (mg/kg/day) did not significantly correlate, either linearly ($r = 0.23$) or curvilinearly ($r = 0.24$), to the percentage improvement in BPRS.

4. Of the 30 patients studied, 19 were considered responders at the end of the third week of treatment. No significant differences were found between responders and nonresponders at the onset of the trial in BPRS total score or in subscale scores. Likewise, no differences were observed between them in age, duration of disease or dosage (Table 1).

5. The group (3) \times time (4) ANOVA for patients' plasma haloperidol concentrations yielded a significant main effect for time. Since this ANOVA did not reveal any other significant effect, the means of these groups were collapsed. A post-hoc Tukey test for time did show that ha-

Table 1
Comparison of variables in schizophrenics who are responders and nonresponders to haloperidol treatment

	Responders (n = 19)	Nonresponders (n = 11)	t	P
Age	25.4±4.7	27.5±6.8	0.96	n.s.
Mean duration of the disease (years)	4.2±4.8	6.5±6.2	1.13	n.s.
Dosage (mg/kg/day)	0.31±0.11	0.29±0.11	0.23	n.s.
BPRS scores at baseline				
Total score	52.4±11.4	48.6±11.9	0.84	n.s.
Factor I	7.7±2.8	6.8±1.5	0.96*	n.s.
Factor II	9.1±4.5	10.5±4.1	0.62	n.s.
Factor III	14.8±5.0	17.1±6.5	1.32	n.s.
Factor IV	7.9±4.9	9.5±3.2	1.98*	n.s.
Factor V	12.7±6.2	12.2±6.9	0.42	n.s.
Steady-state haloperidol	18.4±10.7	8.0±3.6	3.06*	< 0.01

*With Welch transformation for homogeneity of variances.

haloperidol concentrations on day 4 were significantly lower than those encountered on days 7, 14 and 21 ($P < 0.01$). No significant differences were found in the concentrations measured on days 7, 14 and 21 (Fig. 2).

6. A second-grade polynomial relation was found, in the form of an inverted U, between the percentage improvement in BPRS total score and steady-state plasma levels of haloperidol ($R = 0.69$, $P < 0.001$) (Fig. 3). Even when we eliminated the most extreme point on the plot (steady-state haloperidol = 58.5 ng/ml), both the curvilinear relationship and the R-value remained the same.

7. The lower and upper limits of the therapeutic window of haloperidol concentration were 12 ng/ml and 59.4 ng/ml. The neuroleptic concentration that corresponded to the point of inflection of the curve was 35.7 ng/ml.

8. Of the total sample, 15 presented haloperidol levels of 12–59.4 ng/ml. Of these, 14 were responders. Five of the 15 patients with levels outside the therapeutic window were responders and 10 were nonresponders. None of the 5 patients with concentrations under 8 ng/ml were responders. Ten patients had levels of 8–12 ng/ml, of which 5 were responders (Table 2).

9. Responders presented significantly higher

Table 2
Responders and nonresponders (n) to haloperidol treatment correlated with steady state attained

	Levels of haloperidol	
	X ≥ 12 ng/ml	X < 12 ng/ml
Responders	14	5
Nonresponders	1	10
Total	15	15
	X ≥ 8 ng/ml	X < 8 ng/ml
	Responders	19
Nonresponders	6	5
Total	25	5
	8 ng/ml ≤ X ≤ 12 ng/ml	
	Responders	5
Nonresponders	5	
Total	10	

mean steady-state plasma concentrations of haloperidol than nonresponders ($P < 0.01$) (Table 1).

10. Patients with plasma haloperidol levels of 12–59.4 ng/ml presented better percentages of improvement in BPRS total scores and in the scores for factors III, IV and V ($P < 0.01$) and also for positive symptoms ($P < 0.001$). However, no significant differences were found in the percentages of improvement encountered for factors I and II (Table 3).

Table 3

Comparison of the clinical course (according to total BPRS) and the different subscales in patients with haloperidol steady state inside and outside of the therapeutic window

Percentage improvement	Levels of haloperidol		<i>t</i>	<i>P</i>
	12 ≤ X ≤ 59.4 ng/ml	12 > X or X > 59.4 ng/ml		
BPRS total score	50.4±9.8	30.5±14.4	3.73*	< 0.01
Factor I	20.0±33.6	11.4±39.8	0.62	n.s.
Factor II	16.2±16.1	16.6±21.9	0.09	n.s.
Factor III	58.3±16.3	38.4±21.9	2.73	< 0.05
Factor IV	50.0±22.8	21.5±21.6	3.47	< 0.01
Factor V	65.5±17.9	44.4±20.3	2.92	< 0.01
Positive symptoms	62.7±11.1	36.9±18.7	4.44*	< 0.01

* With Welch transformation for homogeneity of variances.

Discussion

Our results suggest the existence of a curvilinear relation in the form of an inverted U between the percentage improvement observed in global BPRS score and steady-state plasma haloperidol. This relationship was also found by other authors for haloperidol (4, 6–8) and other neuroleptics (29–30). The curvilinear relationship suggests the existence of a therapeutic window for haloperidol concentration. In our study, the limits of this window were 12 ng/ml and 59.1 ng/ml of plasma haloperidol. Although the window was calculated mathematically, none of our patients fell above its upper limit. More subjects with higher levels of haloperidol should be studied to empirically validate that limit. Nevertheless, it should be emphasized that maximum therapeutic efficacy was attained with concentrations of about 35.7 ng/ml.

Higher levels were not associated with a higher percentage of clinical improvement and entailed greater risks of severe side effects. The limits of the therapeutic window encountered in our study differ slightly from those reported by other authors, which were lower for both upper and lower limits (4–6, 13). This discrepancy may arise because these authors use heterogeneous samples including patients with schizoaffective and schizophreniform disorders. The latter disturbances sometimes require less than 2 ng/ml to attain a satisfactory clinical response (31). This lack of sample homogeneity can produce distur-

tions that would decrease the limits of the therapeutic window. Our study sample included only schizophrenics, which probably accounts for the higher limits we found. Moreover, our patients presented high scores for both total BPRS and for subscales measuring positive symptoms. It was thus an appropriate sample to establish the relationship between plasma haloperidol levels and clinical response (23). Some patients presented a good clinical response with concentrations of less than 12 ng/ml. Thus, there may be a threshold of haloperidol concentration (12 ng/ml) above which there is a high probability of obtaining a good clinical response, while this probability is lower at concentrations of 8 to 12 ng/ml. Finally, concentrations of less than 8 ng/ml are ineffective. It is possible that the patients who respond to concentrations of less than 12 ng/ml are for the most part subchronic, since these patients may require lower concentrations than chronic schizophrenics (32).

Fourteen of the 15 patients who attained a steady-state haloperidol concentration within the limits of the therapeutic window responded favorably vs. only 5 of the 15 who presented steady-state haloperidol concentrations outside the limits of the window. Other authors found that 92% (7) or 100% (33) of patients who had plasma levels within the defined therapeutic range responded favorably. In these studies, however, 40–55% of the patients with plasma concentrations outside the therapeutic range were responders (7, 33). Available data thus seem to

indicate that plasma haloperidol concentrations are good predictors of clinical response in schizophrenics. In contrast, dosage administered had no value as a predictor of response, which underlines the utility of determining plasma concentration of haloperidol in clinical practice.

Patients who presented steady-state concentrations of haloperidol within the limits of the therapeutic window showed significantly greater improvement in the scores for BPRS total and for the subscales measuring positive symptoms than the patients whose haloperidol steady state was outside the range of the therapeutic window. There were no differences between these groups in the improvement observed in negative symptoms, however, perhaps because only positive symptoms are sensitive to the effect of neuroleptics (24, 34). Recent studies confirm that the positive manifestations of schizophrenia are dependent on dopaminergic hyperactivity in limbic structures, while negative symptoms are dependent on dopaminergic hypoactivity in the frontal cortex (35, 36), which would account for their resistance to the action of neuroleptics.

On the other hand, in our study plasma haloperidol concentrations were significantly related to the haloperidol dosage administered, in mg/kg/day, as has previously been reported (37). The percentage of variance of plasma concentration of haloperidol caused by dosage administered is very low, however ($R^2 = 0.35$). Therefore, dosage administered has only limited value as a predictor of the haloperidol levels attained.

Likewise, it was observed that steady-state concentration of plasma haloperidol was not achieved until day 7 of treatment, a finding similar to that encountered by other authors (36-38). It is thus only after one week of administering a constant dosage that plasma haloperidol determination acquires value as a predictor of response.

In summary, our study confirms the usefulness of plasma concentration of haloperidol as a predictor of clinical response in schizophrenic patients. Monitoring the plasma concentration of haloperidol, and probably of other neuroleptics, is not a pursuit that merely satisfies scientific curiosity, but can very helpful to the clinical psychiatrist.

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