
Clinical Response and Plasma Haloperidol Levels in Chronic and Subchronic Schizophrenia

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Levels of haloperidol were determined by radioimmunoassay (RIA) in 30 schizophrenic patients (diagnosed according to the criteria of DSM-III), who were treated with fixed doses of this neuroleptic for a period of 21 days. An inverted U-shaped relationship was found between the percent improvement observed in the BPRS global score and the steady state of haloperidol. The interval of effective concentration of haloperidol was set between 12.0 and 35.5 ng/ml. However, the limits of such an interval found in the subchronic schizophrenic subgroup (SS) ranged from 7.4 to 24.9 ng/ml, whereas in the chronic schizophrenic subgroup (CS), it ranged from 14.8 to 38.5 ng/ml. This finding suggests that the interval of effective concentrations may vary as a function of the number of years of evolution of the subjects' illness. This may be compatible with the development of tolerance in the mesolimbic and/or mesocortical dopaminergic systems as a response to prolonged neuroleptic treatments.

Introduction

Numerous studies have shown that there is an interval of haloperidol plasma concentrations associated with a good clinical response (Magliozzi et al. 1981; Smith et al. 1982, 1984, 1985; Extein et al. 1983; Mavroidis et al. 1983; Garver et al. 1984; Miller et al. 1984; Davis et al. 1985; Potkin et al. 1985). Yet other studies have merely been able to demonstrate the presence of a lower limit of effective plasma concentration (Mendlewicz et al. 1981; Cabranes et al. 1985; Ramos et al. 1985). Some studies could not find any relationship between these two variables (Bjornal et al. 1980; Rimon et al. 1981; Bleeker et al. 1984; Bigelow et al. 1985), although the subject samples used in these latter studies were not adequate (Bjornal et al. 1980; Rimon et al. 1981). Although the majority of these studies describe a "therapeutic window" for haloperidol, discrepancies are noted in the methods for determining these levels of the interval. Thus, it varies between 3.4 and 11 ng/ml (Garver et al. 1984), 7 and 17 ng/ml (Smith et al. 1984), 4 and 26 ng/ml (Potkin

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Received February 9, 1988; revised November 26, 1988.

et al. 1985), or 15 and 40 ng/ml (Miller et al. 1984). These discrepancies may, at least in part, be due to the use of heterogeneous samples, which have included patients in the early stages of schizophrenia, schizoaffective, and schizophreniform disorders, as well as chronic schizophrenic patients and patients belonging to other psychotic categories. Mavroidis et al. (1985) have recently suggested that different subtypes of schizophrenia may have different intervals of effective concentrations of haloperidol or other neuroleptics. They emphasized that patients with schizophreniform disorders may have a good clinical response to levels of haloperidol that are less than 2 ng/ml.

Bearing these considerations in mind, we have designed a study that attempts to establish a relationship between plasma levels of haloperidol and clinical response in a sample made up exclusively of schizophrenic patients. Patients suffering from schizoaffective or schizophreniform disorders (according to the DSM-III criteria) were excluded. Furthermore, we tried to test whether or not there are any differences between the intervals of effective concentrations of haloperidol in chronic and subchronic patients.

Methods

The sample included 36 male inpatients, all of whom were diagnosed as suffering from schizophrenia according to DSM-III diagnostic criteria. Of these initial 36 subjects, 4 dropped out of the study due to medication side effects, and 2 refused to continue. Thus, the data reported here pertain to the 30 subjects who completed the protocol. Their average age was 26.2 ± 5.5 years (range 18–41). The average duration of illness was 5.1 ± 5.4 years (range 6 months–23 years). None of the patients included in the study had been previously considered to be nonresponsive to neuroleptic treatments, and all gave written consent to participate in the study.

The subjects were classified as either chronic schizophrenic ($n = 20$) or subchronic schizophrenic ($n = 10$), based on the duration of the illness. For the subchronic schizophrenic (SS) group, the average age was 22.9 ± 4.4 (range 18–29 years). None of them had ever been hospitalized, and the average duration of illness was 0.56 ± 0.16 years (range 6–11 months). For the chronic schizophrenic (CS) group, the average age was 27.8 ± 5.4 (range 22–41 years), and the average duration of the illness was 7.3 ± 5.3 years (range 2.5–23 years). All of these patients were living in the community and were hospitalized only when decompensated. The average hospitalization of the CS group was 3.6 ± 3.1 months (range 0–14), and no patient had been hospitalized more than 5 times.

All the patients included in the study spent at least 10 days without oral medication and 4 months without depot neuroleptics. The patients were randomly divided into three groups of 10. The first group was given 15 mg of haloperidol a day, the second group 20 mg a day, and the third group 30 mg a day. The dosage was constantly maintained for the 21 days that the study lasted and was given in 2 daily doses. During this period, the patients received no other drugs, except occasionally anticholinergic drugs (Biperidin) when severe extrapyramidal symptoms were present. Of the 12 patients who received Biperidin, 6 were in the 30-mg group, and 3 were in each of the other two groups.

Blood samples were drawn on days 4, 7, 14, and 21 for haloperidol determinations. Blood was drawn between 8:30 and 9:00 AM, approximately 12 hr after the last nightly dose. Blood samples were centrifuged and stored at -20°C until they were processed. The concentrations of haloperidol were analyzed by radioimmunoassay (RIA) using standard commercial tests (IRE, Belgium). The haloperidol antibody was administered following the procedure of Michiels et al. (1976). In order to avoid any possible interference

from the presence of haloperidol metabolites, a previous organic extraction was performed using heptane/isoamyl alcohol (9.8/1.5) in an alkaline solution (Van Den Eeckhout et al. 1980). This method has a sensitivity of 0.05 ng/ml, with intra- and interassay variation coefficients of 6.7% and 7.13%, respectively.

Brief Psychiatric Rating Scale (BPRS) ratings of the patients' clinical state were made on days 0, 4, 7, 14, and 21. Both the BPRS total score and the score from each of the five BPRS factors (Guy 1976) were taken into account. We also evaluated the psychosis factor (i.e., the sum of the scores obtained in factors 3 and 4), the "positive symptoms" (i.e., the sum of the scores obtained in factors 3, 4, and 5), and the "negative symptoms" (i.e., factor 2) (see Angrist et al. 1980). The raters were blind to plasma level data.

The clinical improvement was evaluated by means of the following formula:

$$\text{Improvement (\%)} = \frac{\text{BPRS SCORE (day 0)} - \text{BPRS score (day 21)}}{\text{BPRS score (day 0)}} \times 100$$

This percent improvement sums up in a precise manner the clinical evolution upon reduction of the variability and the correlation with the baseline scores (Overall et al. 1975). Responsive patients were defined as those who showed a percent improvement in the total score of the BPRS on day 21 that was equal to or greater than 40%, following a modification of the criteria used by Magliozzi et al. 1981.

Taking into account the pharmacokinetic characteristics of haloperidol (Forsman and Ohman 1977; Itoh et al. 1984) the mean concentrations obtained on days 7, 14, and 21 were defined as steady-state levels of haloperidol. The relation between the percent clinical improvement observed in the total score of the BPRS and its five subscales and the stable levels of haloperidol was investigated by means of linear regression analysis and second and third grade polynomial regression. In this article, we report the fit that gives the highest value of R^2 .

The lower limit of the interval of effective concentrations was calculated by finding the value of haloperidol concentration (X) that corresponds to a percent improvement in the total score of the BPRS of 40% (Y) in the regression equation obtained. Whenever an equation of second grade polynomial regression was obtained, the upper limit of the interval was determined by calculating the inflexion point of the curve that represents such equation. Comparisons between pairs of means were done by t -tests. All the statistical analyses were performed using the SYSTAT statistical package for microcomputers (Wilkinson 1986).

Results

Patients showed a total score in the BPRS on day 0 of 51 ± 11.5 . The score obtained in the positive symptoms subscale of the BPRS on day 0 was 40 ± 6.9 , which represents 66.1% of the total score obtained in the BPRS. The score obtained in the negative symptoms on day 0 was 9.9 ± 4.2 , which represents 19.4% of the total score of the BPRS.

In comparing SS and CS scores obtained on day 0 of the total BPRS and those obtained in different subscales (factors 1, 2, 3, 4, 5, psychosis, and positive symptoms), no significant differences were found between those two subgroups of subjects. Likewise, no significant differences appeared when SS and CS subjects were compared in either the dosages administered (0.31 ± 0.11 mg/kg/day versus 0.29 ± 0.11 mg/kg/day, $t_{(28)}$

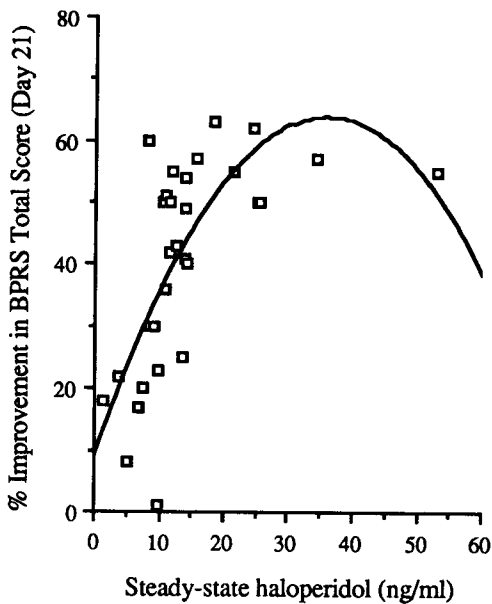


Figure 1. Relationship between haloperidol plasma levels and percent improvement in total BPRS score. The line represents best-fit curvilinear regression. Polynomial regression equation was $y = 9.1089 + 3.0738x + 0.431x^2$; $R = 0.69$.

= 0.232, NS) or when compared in their respective steady states of haloperidol (15.2 ± 8.8 ng/ml versus 14.2 ± 10.9 ng/ml, $t_{(28)} = 0.244$, NS).

The steady state of haloperidol showed a second grade polynomial relation with the percent improvement observed in the total score of the BPRS ($R = 0.69$; Figure 1), with the psychosis factor ($R = 0.76$), and with the positive symptoms ($R = 0.78$; Figure 2). No other type of relationship between the percent improvement observed in factor 2 and

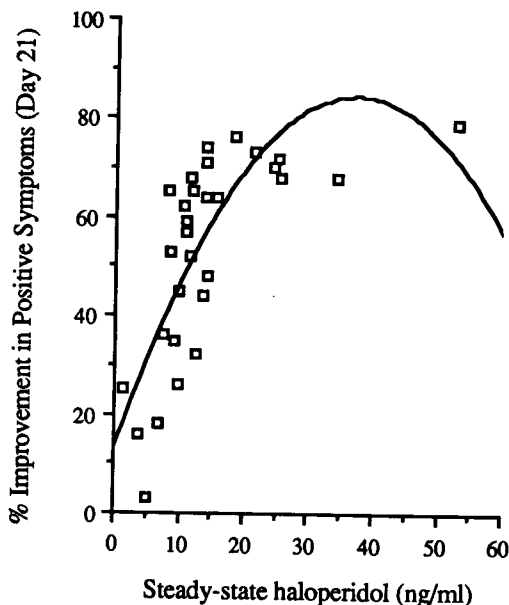


Figure 2. Relationship between haloperidol plasma levels and percent improvement in BPRS positive symptoms score. The line represents best-fit curvilinear regression. Polynomial regression equation was $y = 9.9604 + 3.8488x + 0.0518x^2$; $R = 0.78$.

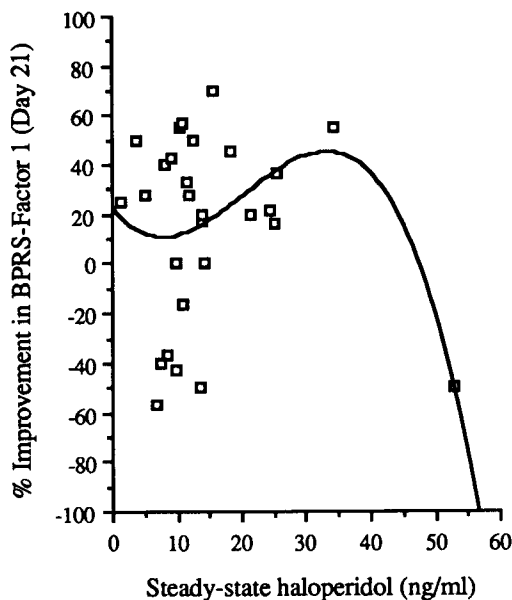


Figure 3. Relationship between haloperidol plasma levels and percent improvement in BPRS factor 1 score. The line represents best-fit curvilinear regression. Polynomial regression equation was $y = 23.0059 - 3.3284x - 0.262x^2 - 0.0043x^3$; $R = 0.43$.

the steady state of haloperidol was observed. Factor 1 (anxiety, depression) showed a third grade polynomial relationship ($R = 0.43$; Figure 3) with the steady state of haloperidol.

The lower limit of the interval of effective concentrations was 12.0 ng/ml, and the upper limit was 35.7 ng/ml (Figure 1). When the relationship between the percent improvement in the total score of the BPRS and the steady state of haloperidol in the subgroups SS and CS was studied separately, a second grade polynomial relationship was also found in both groups ($R = 0.71$ for the SS patients and $R = 0.77$ for the CS patients; see Figure 4). For the SS, the upper and lower limits of the interval of effective concentrations were from 7.4 ng/ml to 24.9 ng/ml. For the CS subjects, the limits were from 14.8 ng/ml to 38.5 ng/ml.

Discussion

In our study, the presence of an inverted U-shaped relationship between the percent improvement (measured in the BPRS total score, the psychosis factor of the BPRS, and the positive symptoms) and the steady-state levels of haloperidol stands out. These findings suggest the existence of a therapeutic window for the concentrations of haloperidol in schizophrenics. Although the percentage of the variance of the percent clinical improvement in the total score of the BPRS is moderate, as explained by the levels of haloperidol ($R^2 = 0.48$), it is possible to conclude that the monitoring of the plasma levels of haloperidol may have important clinical relevance.

If we take into account only the percent improvement observed in the psychosis factor and in the positive symptoms, it can be shown that the percentage of variance explained by the levels of haloperidol is high ($R^2 = 0.61$ for positive symptoms, $R^2 = 0.58$ for the psychosis factor). This suggests that the improvement of the positive manifestations of schizophrenic disorders is related to haloperidol concentration. No significant statistical

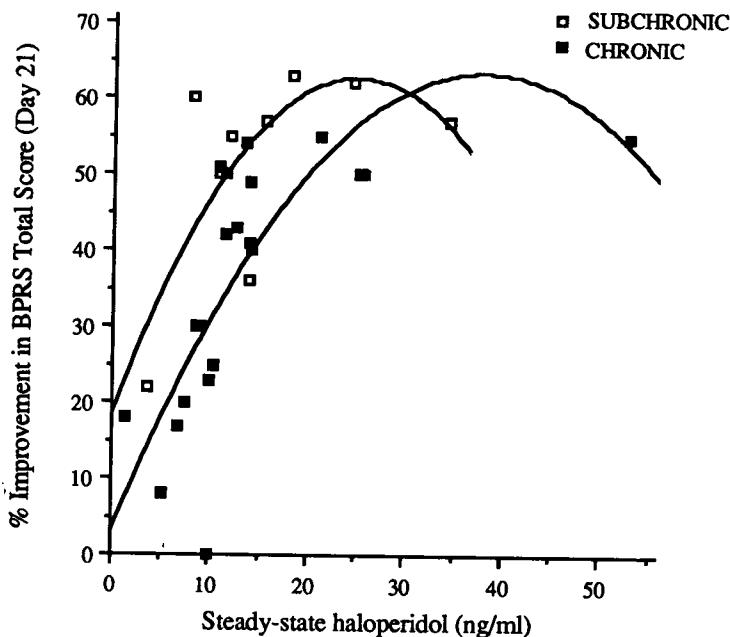


Figure 4. Relationship between haloperidol plasma levels and percent improvement in total BPRS score for chronic subjects (CS) and subchronic subjects (SS). The lines represent best-fit curvilinear regression. Polynomial regression for the CS group was $y = 3.2469 + 3.0682x + 0.0398x^2$; $R = 0.78$. Polynomial regression for the SS group was $y = 18.5846 + 3.5446x + 0.0712x^2$; $R = 0.71$.

relationship between the stable levels of haloperidol and the percent improvement observed in the negative symptoms (factor 2) could be found. This fact is compatible with hypotheses that suggest that the negative symptoms do not depend on dopaminergic hyperactivity (Crow 1980) and that such symptoms are not as sensitive to the action of neuroleptics (Angrist et al. 1980).

The relationship between the improvement observed in factor 1 (anxiety-depression) and the steady state of haloperidol suggests that concentrations above 35 ng/ml are associated with a clear worsening of the clinical manifestations measured by that factor.

The limits of the interval of effective concentrations found in our study (12–35.8 ng/ml) are higher than those described by some authors (Magliozzi et al. 1981; Extein et al. 1983; Mavroidis et al. 1983; Garver et al. 1984; Smith et al. 1984, 1985; Davis et al. 1985; Potkin et al. 1985). Although our limits are consistent with those reported by Miller et al. (1984), this study was not conducted with a fixed-dose procedure. These discrepancies may be due to the fact that these previous studies included patients with schizophreniform and schizoaffective disorders, in which low levels of haloperidol are probably adequate for a good clinical response (Mavroidis et al. 1984). These discrepancies could also be explained by variation in laboratory assay techniques.

Furthermore, our study shows that in order to get a good clinical response, SS patients need lower levels of haloperidol than CS patients do. This finding cannot be attributed to the differences in the total scores of the BPRS or in any one of its subscales at the time the study was initiated. What it may suggest is that as the illness evolves, a certain degree of resistance to the antipsychotic effects of the neuroleptics develops, which calls

for higher plasma levels to achieve a good clinical response and that lower sensitivity to the neuroleptic could depend on the development of tolerance phenomena associated with the prolonged administration of haloperidol.

The authors wish to thank Dr. Jeffrey Ring for manuscript preparation and Gloria Escudero and Dr. Francisco Angeles for their assistance in data collection.

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