

DETERMINATION OF PLASMA HALOPERIDOL CONCENTRATIONS BY RADIORECEPTOR ASSAY IN SCHIZOPHRENIA: CLINICAL UTILITY

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Abstract

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1. Haloperidol concentrations were determined by radioreceptor assay (RRA) and prolactin concentrations were measured in 20 patients diagnosed as schizophrenia (DSM-III).
2. The patients were treated with a fixed dose of haloperidol for 21 days.
3. Our results suggest the existence of a curvilinear relationship, in the form of an inverted U, between stable haloperidol levels and clinical improvement assessed by total BPRS score.
4. We also found a curvilinear relationship between the improvement observed in positive symptoms and state steady levels.
5. No relationship was seen between improvement in negative symptoms and state steady levels.
6. An interval of optimal haloperidol concentration was found: 8.1 ng/ml to 19.6 ng/ml.
7. No relation was found between the dose of haloperidol administered and plasmatic concentration, nor between haloperidol and prolactin levels.
8. Our findings suggest that haloperidol concentrations determined by RRA have clinical utility as predictors of response in schizophrenia.

Keywords: clinical response, haloperidol, plasma levels, prophylaxis schizophrenia.

Abbreviations: brief psychiatric rating scale (BPRS), radioimmunoassay (RIA), radioreceptor assay (RRA), coefficient of variation (C.V.)

Introduction

Number of authors have suggested the possible utility of monitoring plasma neuroleptic levels in clinical practice (Morselli, et al.,1981; Mavroidis et al.,1983; Cabranes et al., 1985; Ramos et al.,1985). Various procedures have been described for quantifying the blood concentrations of these drugs, the most frequently used being gas chromatography (Curry et al.,1968; Forsman et al.,1974) or radioimmunoassay. These procedures have been developed for haloperidol (Michiels et al.,1975; Clarke et al., 1977) and other neuroleptics (Kawashima et al.,1975; Jorgenssn, 1978). Recently, Creese and Snyder (1977) developed a radioreceptor assay (RRA) for neuroleptics based on competition to bond dopaminergic receptors between the different substances with neuroleptic activity present in a plasma sample and tritiated spiroperidol. This technique allows determination of the concentration of any neuroleptic, or combination of neuroleptics, and all metabolites capable of binding

dopaminergic receptors. Attempts have been made to establish a relationship between neuroleptic levels determined by RRA and clinical response, but the results have been contradictory. Some authors confirm the existence of such a relationship (Tune et al., 1980, 1981; Cohen et al., 1980; Van Putten et al., 1982; Kucharski et al., 1984) while the others do not (Miller et al., 1984; Rimon et al., 1981; Smith et al., 1984, 1985). However, some of the studies have methodological defects such as absence of a fixed dose design, small samples, samples that include patients with heterogeneous diagnoses, or use different neuroleptics or combinations of neuroleptics. Thus the clinical utility of RRA has yet to be established.

On the other part, administration of neuroleptics raises circulating prolactin levels (Meltzer and Fang, 1976). This effect is linked to the blockade of tuberoinfundibular dopaminergic receptors. It is thus possible that the prolactin levels attained during neuroleptic treatment may be related to total neuroleptic activity in plasma.

In this study, the authors attempt to assess the clinical utility of determining plasma haloperidol concentrations by RRA as a predictor of clinical response in a sample of schizophrenic patients. The authors also tried to evaluate the relation between plasma neuroleptic activity and prolactin levels. The study was designed after considering a series of methodological recommendations (May and Van Putten, 1978; Meltzer et al., 1983) to avoid the design deficiencies mentioned above. Clinical improvement was quantified with the BPRS scale and two BPRS subscales, for positive symptoms (BPRS psychosis factor) and negative symptoms (factor II of the BPRS).

Methods

Subjects

Twenty male patients were studied, all of them were hospitalized with a diagnosis of schizophrenia according to DSM-III criteria. Mean age of patients was 24.9 ± 4.9 years (range: 18-41). Mean duration of the disease was 4.2 ± 4.8 years (range: 0.5-20). Nine patients were considered chronic and 11 subchronic (DSM-III). According to clinical type, 15 presented paranoid schizophrenia, 4 undifferentiated schizophrenia and 1 disorganized schizophrenia (DSM-III). None of the patients included in the sample had been previously considered unresponsive to neuroleptic treatment. All patients gave written consent to their inclusion in the study.

Drug Administration

All patients were at least 10 days without receiving neuroleptic treatment, or three months when a retard neuroleptic had been used. After this period, a fixed dose of haloperidol was given and maintained constant for the 21 days. This dose was fractioned into two daily dose. Ten patients were treated with 30 mg/day of haloperidol, 5 patients with 20 mg/day and 5 patients with 15 mg/day. Anticholinergic drugs were only given if severe extrapyramidal manifestations appeared. No other type of drugs was used during the trial.

Study Design

Blood samples were drawn on days 0, 4, 7, 14 and 21 in order to measure the concentrations of haloperidol and prolactin. The extractions were realized at 8.30 - 9.00 a.m., 12 hours after the last nightly dose and 1 hour after the patients awoke. To obtain blood samples a forearm vein was catheterized and maintained permeable by infusion of saline solution. Thirty and sixty minutes after insertion of the catheter, blood was drawn. The basal prolactin concentration was considered to be the arithmetic mean of the two values obtained. The blood samples were centrifuged and stored at -30°C until processing.

Haloperidol concentrations in plasma were determined by radioreceptor assay (Creese and Snyder, 1977; Ramos et al., 1985). The sensitivity of the method was 0.2 ng/ml. The intra and interassay variation coefficients were 9.25% and 14.7% respectively.

Prolactin concentrations were measured by radioimmunoassay (RIA) using a kit commercialized by Sorin Biomedica (Saluggia, Italy). The sensitivity of the method was 1.06 ng/ml and the intra- and interassay variation coefficients were 4.1% and 10% respectively.

Assessment Instruments

Clinical state was evaluated on days 0, 4, 7, 14 and 21 using the BPRS (Overall and Gorhan, 1962). The analysis was made considering the total BPRS score, the BPRS psychosis factor (sum of the scores for factors III and V) and BPRS factor II (Guy et al., 1976).

Clinical improvement was defined by the following formula:

$$\text{improvement (\%)} = \left[\frac{\text{Day 0 score} - \text{Day 21 score}}{\text{Day 0 score}} \right] \cdot 100$$

Patients who presented on day 21 an improvement in total BPRS score of 40% or more were defined as responsive, following the criterion of Magliozzi et al., (1981).

The stable haloperidol level was found by calculating the arithmetic mean of the concentrations obtained on days 7, 14 and 21, taking into consideration the characteristic pharmacokinetics of haloperidol (Forsman and Ohman, 1977; Itoh et al., 1984). Mean prolactin levels were calculated with a similar procedure.

The upper and lower limits of the interval of optimal haloperidol concentration were determined as follows: The lower limit was the calculated concentration (X) corresponding to a percentage of improvement in total BPRS (Y) of 40% in the linear regression equation $Y = aX^2 + bX + c$. The upper limit was determined by calculating the value of the haloperidol concentrations in blood (X) corresponding to the point of inflexion of the curve represented by a second degree polynomial. To obtain this value, the derivative of the regression equation was calculated by the habitual procedures.

Data Analysis

All statistical analyses were performed using a SYSTAT statistical package for microcomputers. Scatterplots, product moment correlations and linear regressions were calculated to study the relationships among measurements. Furthermore, all relations between BPRS measurements (total BPRS, BPRS psychosis factor and BPRS factor II) and steady state plasma levels were subjected to a second and third degree polynomial regression. Since these adjustments did not increase the value of R^2 , they are omitted in this paper.

Results

There was no statistically significant correlation between the dose (mg/kg/day) and the haloperidol concentrations measured on days 4, 7, 14 and 21. Nor was any correlation found between the dose and state steady haloperidol levels (Table 1). Dose (mg/kg/day) was not related either linearly or curvilinearly to clinical improvement evaluated by total BPRS, BPRS psychosis factor and BPRS factor II. Prolactin concentration did not correlate with haloperidol levels (Table 2).

Table 1

Pearson Product Moment Correlationship between
Haloperidol Plasma Levels(ng/ml) and Haloperidol Doses(mg/kg/day)

	Haloperidol Plasma Levels				
	day 4	day 7	day 14	day 21	Steady State
Dose of Haloperidol	- 0.236	- 0.210	- 0.010	- 0.080	- 0.101

Table 2

Pearson Product Moment Correlationship between
Haloperidol Plasma Levels(ng/ml) and Prolactin Serum Levels

PROLACTIN LEVELS		HALOPERIDOL LEVELS		<u>r</u>	<u>SIGNIFICANCE</u>
Day 4	vs.	Day 4		0.246	NS
Day 7	vs.	Day 7		0.030	NS
Day 14	vs.	Day 14		- 0.079	NS
Day 21	vs.	Day 21		- 0.238	NS
Steady State	vs.	Steady State		- 0.109	NS

There was no statistically significant linear relation between state steady haloperidol levels and the percentage of improvement after 21 days of treatment in total BPRS($r=0.392$) BPRS psychosis factor ($r=0.359$) and BPRS factor II($r=0.354$). However, a second degree polynomial relation was found between state steady haloperidol concentration and the percentage if improvement was seen in total BPRS score($r=0.48$; $p < 0.05$; Fig 1) and in the score for the BPRS psychosis factor($r=0.60$; $p < 0.01$; Fig 2).

From the study of the curve in Fig 1, it can be deduced that the lower limit of the interval of optimal concentration is situated at 8.2 ng/ml of haloperidol. Likewise, concentrations superior to 19.6 ng/ml (value of the haloperidol concentration that corresponds to the point of inflexion of the curve) provide no higher therapeutic efficacy. Eighty percent (12/15) of the patients who achieved stable haloperidol concentrations of 8.2 ng/ml or more responded favorably to treatment.

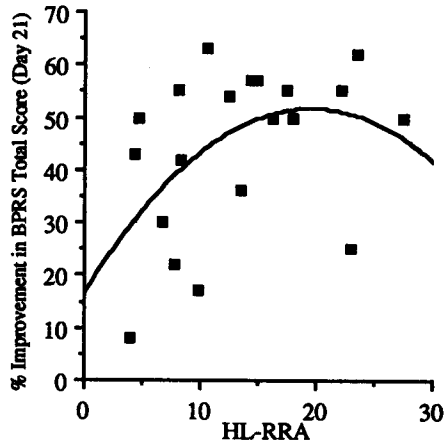


Fig 1. Relationship between haloperidol plasma levels determined by RRA and percent improvement in total BPRS score. Line represents best fit curvilinear regression. Polynomial regression equation was: $y=16.77 + 3.58x - 0.09x^2$; $R=0.47$

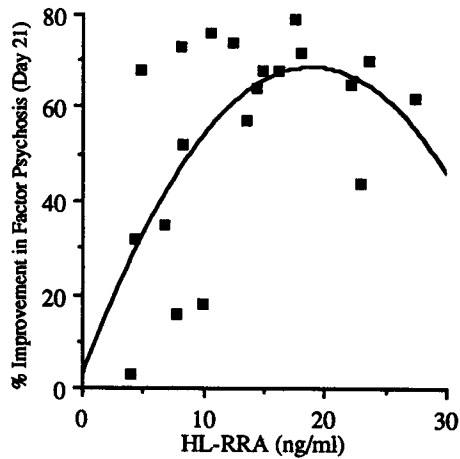


Fig 2. Relationship between plasma haloperidol levels determined by RRA and percent improvement in BPRS psychosis factor. Line represents best fit curvilinear regression. Polynomial regression equation was: $y=3.11 + 6.97x - 0.18x^2$; $R=0.60$

Discussion

Dose of haloperidol vs. plasma concentrations

On the basis of these results, no relation can be established between the dose administered (mg/kg/day) and stable haloperidol levels or daily blood concentrations. Other authors, who have used RRA (Lindemayer et al., 1984; Ravichandran et al., 1984), also found no relation between these parameters. Haloperidol concentrations determined by RIA (Bjornal et al., 1980; Itoh et al., 1984) or chromatographic methods (Forsham and Ohman, 1977; Miller et al., 1984) are usually dose-related. These findings suggest that plasmatic neuroleptic activity determined by RRA depends on factors other than dose, such as the concentration of haloperidol metabolites capable of binding dopaminergic receptors or serum factors that could produce artifacts in the results. It must be kept in mind that when RRA is used to quantify haloperidol, it measures the neuroleptic activity of haloperidol itself and that of its metabolite, reduced haloperidol. Furthermore, that metabolite is present in significant amounts in the plasma of patients treated with this drug (Ereshetsky et al., 1984) and shows discrete antidopaminergic activity (Korpi et al., 1984). It should also be remembered that some serum proteins exercise a nonspecific effect on the binding of neuroleptics to dopaminergic receptors. It is likely that realization of a prior extraction would at least partially solve these problems, although it would greatly diminish the simplicity of the method.

Haloperidol plasma concentrations vs. PRL concentrations

Prolactin concentration was unrelated to haloperidol levels as has been reported by other groups that have used RRA (Smith et al., 1984; Ravichandran et al., 1984). Neuroleptic plasma activity thus does not seem to be related to the dopaminergic blocking produced by haloperidol in the tuberoinfundibular dopaminergic system.

Haloperidol concentrations and clinical improvement

Our results show that the dose administered does not serve to predict clinical response. However, we found a curvilinear relation, in the form of an "inverted U", between stable haloperidol levels and the percentage of improvement observed in BPRS and the BPRS psychosis factor. The characteristics of the curve that represents the relation between these two variables are compatible with the existence of an interval of haloperidol concentration associated with maximum therapeutic efficacy. The lower limit of the interval would be about 8.2 ng/ml and our data suggest that at concentrations above 19.1 ng/ml no greater clinical response is obtained. These findings are similar to those seen with other techniques for quantifying plasmatic haloperidol concentration, such as RIA (Mendlewicz et al., 1981; Potkin et al., 1984; Van Putten et al., 1985) or gas chromatography (Mavroidis et al., 1983; Smith et al., 1984 and 1985). With RRA, a wide range of effective concentrations have been encountered, 11-115 ng/ml for haloperidol (Kucharski et al., 1984), 2000-3000 nM for thioridazine (Cohen et al., 1980) and 50-200 ng/ml of chlorpromazine equivalent for combinations of neuroleptics (Tune et al., 1980). These studies have been criticized because of small sample size (Cohen et al., 1980), use of combinations of neuroleptics (Tune et al., 1980; Kucharski et al., 1984), lack of diagnostic homogeneity in the sample (Cohen et al., 1980; Kucharski et al., 1984), and generally, because of the absence of

"fixed dose design". Other investigators (Rimon et al., 1981; Miller et al., 1984; Smith et al., 1984,1985) found no relation between stable haloperidol levels and improvement in BPRS scores, although some of these studies also have methodological deficiencies, like inclusion in the study sample of patients previously considered resistant to treatment or the absence of a fixed dose design (Miller et al., 1984). Only Smith et al., (1984 and 1985) base their results on a strictly designed study. However, in our study, for which the methodological faults mentioned above were taken into consideration, the conclusions differ from those reported by Smith's group. Moreover, the largest variation coefficient we obtained was insufficient to justify this discrepancy.

The C.V. of the RRA we used was comparable to that found by other authors (Lindemayer et al., 1984).

When clinical improvement was evaluated by a BPRS subscale (psychosis factor), there was strong relation, appreciable greater than that obtained with total BPRS score. Improvement in negative symptoms (BPRS factor II) was unrelated to stable haloperidol levels. We thus propose that the improvement in the symptoms associated with hyperactivity of the dopaminergic pathways could be related to neuroleptic activity in plasma. On the contrary, improvement in the negative symptoms, which are probably not associated with dopaminergic hyperactivity, is unrelated to plasmatic neuroleptic activity.

Conclusion

Our results confirm the utility of monitoring plasmatic haloperidol concentration as a predictor of response to neuroleptic treatment in schizophrenic patients. They also support the utility of RRA in clinical practice, as a simple, reliable and inexpensive technique that provides relevant information for the management of neuroleptic administration. Nonetheless, further studies of larger and more homogeneous samples are needed to clarify the discrepancies observed and define more precisely the effective intervals of concentration.

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