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Haloperidol plasma 'threshold' levels for relapse prevention in schizophrenia: a study with haloperidol decanoate

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Abstract

Forty-eight schizophrenic outpatients treated with flexible doses of haloperidol decanoate were followed up in a naturalistic fashion for 3 years with periodic monitoring of clinical symptoms, side effects and haloperidol plasma concentrations. There was no relationship between plasma level and clinical response, however categorical data analysis showed that patients with plasma levels over 4 ng/ml had a significantly reduced relapse rate compared with patients with plasma levels below this plasma 'threshold' level. This effect could be observed during the first, second as well as third year of treatment. The relapse rate did not change significantly in relation to time (during years 1, 2, 3), when patients with haloperidol plasma levels below and equal to or over 4 ng/ml were considered separately. In patients with haloperidol equal to or over 4 ng/ml, the variability (measured as coefficient of variation %) in the total scores of SAPS and SANS was lower, indicating a better clinical stability. These data are in fairly good agreement with other literature findings showing that an indiscriminate dose reduction strategy during long-term treatment of schizophrenic disorders with haloperidol decanoate should be discouraged, since it leads to an increase in the relapse rate. Before deciding about a dose reduction, clinicians should take into careful consideration some clinically relevant variables (i.e. frequency of previous relapses, severity of symptoms, iatrogenic depression, risk for development of extrapyramidal side effects) for each patient. A better clinical stability during treatment with haloperidol decanoate can be obtained when plasma 'threshold' levels for response are reached.

Keywords: Schizophrenia; Relapse prevention; Haloperidol decanoate; Plasma level; Long-term treatment

1. Introduction

Relapses in schizophrenic disorders are mainly responsible for further psychological and quality of life deterioration of patients and for causing particularly high social costs. Maintenance therapy with neuroleptics is a critical issue for relapse prevention, and the prophylactic efficacy of 'typical' neuroleptics like haloperidol (HL) has been widely documented in the literature.

However, since neuroleptics also produce some important unwanted effects, especially extrapyramidal ones like tardive dyskinesia, a dose reduction has been suggested in order to maintain the antipsychotic efficacy minimizing the risk for development of adverse reactions.

According to some authors the low dose vs standard or high dose of traditional neuroleptics is effective both during acute exacerbations and in maintenance treatment of stabilized schizophrenic outpatients (Schooler, 1991; Burnett et al., 1993). But there are also some studies using lower dose neuroleptics in maintenance therapy for schizophrenic outpatients showing a statistically greater chance of clinical relapse (Marder et al., 1987; Kane et al., 1994).

The aim of this naturalistic multicenter study was to ascertain (i) whether plasma concentrations of HL could influence the relapse rate in schizophrenic patients treated on a long-term basis with haloperidol

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decanoate (HL-D); (ii) if 'threshold' plasma concentrations could be envisaged for a better clinical stabilization and better relapse prevention; and finally (iii) if positive and negative schizophrenic symptoms were equally sensitive to such a 'threshold' plasma level.

2. Material and methods

Forty-eight schizophrenic outpatients, diagnosed according to DSM-IIIR criteria, of both sexes (19 females and 29 males) with ages ranging from 21 to 48 years and a mean duration of illness of 8(±5) years were followed up to 3 years in a naturalistic multicenter study, while receiving flexible monthly doses of HL-D ranging from 25 to 375 mg i.m. (mean 120.6 ± 74.8 mg for the first year of treatment; mean 138.6 ± 86.5 mg for second year of treatment; mean 174.2 ± 88.9 mg for the third year of treatment).

Clinical assessment was made on a bi-monthly basis using BPRS, SANS, SAPS and the Simpson and Angus rating scale for extrapyramidal symptoms. Relapse was defined as a deterioration of 30% or more on the previous BPRS, SAPS or SANS total scores and a DSM-IIIR diagnosis of acute schizophrenic exacerbation.

Plasma HL concentrations were determined three times per year. Blood samples were obtained in the morning, at 8 a.m. Clinicians who were in charge of the patients were not aware of the HL plasma level measurements.

The HL plasma determination was made using a gas-chromatographic method (Abernethy et al., 1984); values ranged from 0.8 to 41 ng/ml.

Statistical methods included a linear regression analysis, the categorical data analysis method as implemented in the SAS system and the cluster analysis according to the Wards method (SAS Institute Inc., 1994).

3. Results

Table 1 shows that patients with plasma levels of more than 4 ng/ml had a significantly reduced relapse rate compared with patients with HL plasma levels below this threshold. This effect could be observed in the first, second as well as the third study year. In fact, the categorical data analysis considering two factors in relation to the blood levels of HL and year of treatment showed that the rate of relapse was quite different in the two groups. Moreover, since there was a poor response with plasma levels lower than 4 ng/ml, clinicians tended to increase HL-D dosage (and relative plasma levels) during the second and third study years (Table 1).

The relapse rate did not change significantly in relation to time (during years 1, 2, 3) when patients with HL plasma concentrations below, equal to or over 4 ng/ml were considered separately. In patients with plasma levels equal to or over 4 ng/ml, the variability in the total scores of the rating scales BPRS, SAPS and SANS (coefficient of variation) was lower and patients with higher variability in BPRS or SAPS and SANS total scores presented more relapses compared to those with lower fluctuations.

Optimal risk-benefit ratios were observed with HL levels ranging from 4 to 8 ng/ml. Plasma levels over 8 ng/ml were associated with a higher incidence of side effects (e.g. extrapyramidal symptoms). This 'threshold' plasma concentration was seen in patients with positive rather than negative symptoms.

In fact, the variability in mean SAPS total score for each subject, measured as coefficient of variation, was inversely related to their mean HL plasma levels ($r = 0.489$; $P < 0.001$). In contrast, the coefficient of variation for SANS for each patient did not correlate with their mean plasma HL levels ($r = 0.034$; NS).

The cluster analyses further clarify this point since for SAPS there are two clusters and a negative relationship between SAPS total score (CV%) and

Table 1

HL Plasma level	<4 ng/ml			>=4 ng/ml		
YEAR	1	2	3	1	2	3
PATIENTS (N)	18	13	8	30	35	39
Relapsed	6	7	5	5	5	7
(%)	33.33	53.85	62.50	16.67	14.29	17.95

Prob Chi=0.0004
Chi Sq=12.47

Prob Chi=1.489
Chi Sq=0.475

Prob Chi=0.184
Chi Sq=0.9120

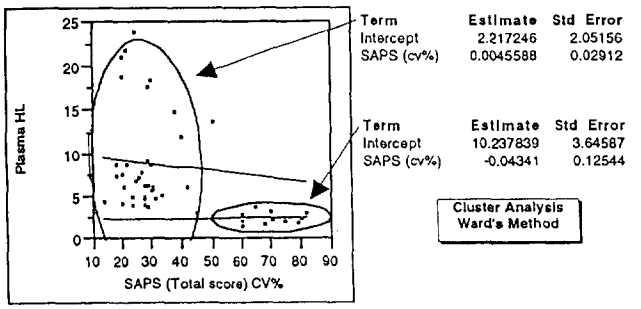

Fig. 1. Cluster analysis of positive symptoms.

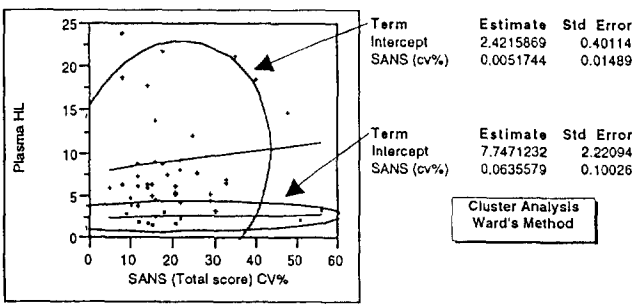

Fig. 2. Cluster analysis of negative symptoms.

mean HL plasma levels. In case of negative symptoms there is only one cluster and the relationship between SANS and HL levels is slightly positive. It means that higher HL levels lead to a lesser degree of stabilization (Figs. 1, 2).

4. Discussion

HL plasma levels equal to or over 4 ng/ml appear to be associated with a reduced relapse rate in schizophrenic patients, thus confirming previous preliminary findings (Altamura, 1992).

At variance with data about HL treatment during psychotic exacerbations, where plasma levels ranging from 5 to 12 ng/ml appeared to be particularly effective (Van Putten et al., 1992), in this study it was not possible to find any relationship between plasma level and clinical response.

Our findings, showing that higher plasma levels (and higher dosages) are more effective in preventing relapse in chronic schizophrenic patients, are also in good agreement with recent clinical data from a multicenter trial (Kane et al., 1993). They reported in a 1-year comparison of four HL-D dosages at a fixed dose of 25, 50, 100 and 200 mg that relapse rates were 63%, 25%, 23% and 15% respectively.

In our sample, apart from a reduced relapse rate, patients with higher HL plasma levels showed a less important variability in SAPS total scores, compared to those with lower ones. It means that a significantly better clinical stability can be achieved when plasma levels are kept over a certain critical or 'threshold' value, as is demonstrated by the categorical data analysis for the relapse rate. However, it seems important to stress that a good negative relashionship between reduced clinical variability and HL plasma levels has been observed only for SAPS and not for SANS total scores.

Furthermore, the cluster analyses show that there are two distinct populations only for positive symptoms, and not in the case of negative ones: in the latter the relationship with HL plasma levels tends to be positive. It means that negative symptoms are less sensitive to plasma HL concentrations and in some ways they behave in an opposite way in comparison to positive ones since they tend to be less stable with higher HL levels. These findings can be explained on the basis of specific D_2 dopamine receptors blocking the activity of HL, which seems to be crucial for controlling mainly the positive symptoms (dopaminergic hyperactivity).

Using PET equipment it has been reported that low doses of HL seem to be associated in human brain with a D_2 dopamine receptor occupancy higher than 80% (Farde et al., 1988), and more recent findings show that plasma concentrations as low as about 4 nmol/l produce a D_2 receptor occupancy of nearly 75% (Nyberg et al., 1995). Moreover, Nordstrom et al. (1993) showed a good relationship between D_2 dopamine receptor occupancy, antipsychotic activity ($P < 0.05$) and the occurrence of extrapyramidal side effects.

Interestingly in the case of raclopride, a threshold in the higher range of D_2 dopamine receptor occupancy was found for the antipsychotic effects rather than a response that is continuous from 0% occupancy. At this point, it seems important to recall that there is a hyperbolic correlation between HL plasma concentrations and D_2 dopamine receptor occupancy (Wolkin et al., 1989). In other words, plasma HL concentrations exceeding the therapeutic range (5–15 ng/ml) seem unlikely to produce any additional antipsychotic effects but only extrapyramidal effects; this is compatible with the PET studies showing that 4–5 ng/ml can give rise to relatively high D_2 occupancy in the brain. In our population these plasma levels were reached with the administration of monthly doses ranging from 50 to 100 mg. However, patients with a longer duration of illness (likely to be associated with liver enzyme induction) needed higher doses to achieve 'threshold' levels, in agreement with previously reported data (Altamura et al., 1990).

In contrast, because of the complexity of the pathophysiology of negative symptoms involving other

dopamine receptors and/or neurotransmitters, HL plasma levels did not seem to influence their time course, since the CV of SANS was not related to HL plasma concentrations. Thus, a HL plasma 'threshold' for response is less likely to be found in patients showing prominently or exclusively negative features: consequently, in this case a categorical approach does not seem to be so advantageous as for positive symptoms.

In general, it seems that a categorical model rather than a correlational one could fit better with the heterogeneity of schizophrenic syndromes as reported also for clozapine (Hasegawa et al., 1993). This categorical approach seems more promising in the case of patients showing prominent positive symptomatology, and can be particularly exploited in the so-called stabilization phase of treatment which starts after the remission of an acute psychotic exacerbation and is characterized by a further psychopathological amelioration, particularly in patients with a shorter duration of illness (Altamura et al., 1990).

On the other hand, the ratio between the HL plasma levels and the administered dose (L/D ratio) tends to increase progressively in the first 4–5 months after implementation of the depot neuroleptic therapy, thus indicating that patients can be initially undertreated although using standard monthly doses of HL-D (Altamura, 1990). This can explain the particularly high relapse rate seen in the first months after hospital discharge when shifting from a conventional to a long-acting HL: particularly in this period a dose reduction can significantly increase the risk of an early relapse.

In conclusion, an indiscriminate dose reduction strategy of depot (and conventional) neuroleptics during the maintenance phase of treatment (particularly in the first 6 months), without taking into consideration important variables such as the frequency of relapses, the severity of symptoms, the risk of developing relevant side effects (particularly extrapyramidal effects), should be highly discouraged.

In our experience and on the basis of these and other literature data (Kane et al., 1994), a dose reduction of the depot formulation could be cautiously envisaged only in selected cases (i.e. patients with a low relapse frequency, or developing an iatrogenic depressive state, or with a poor tolerance of unwanted side effects of HL), and only after satisfactory clinical stabilization has been reached.

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