Eur Arch Psychiatry Clin Neurosci (1995) 245:45–49

ORIGINAL PAPER

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A path-analytical approach to differentiate between direct and indirect drug effects on negative symptoms in schizophrenic patients

A re-evaluation of the North American risperidone study

Received: 14 November 1994 / Accepted: 28 November 1994

Abstract The hypothesis that differences in drug effects of risperidone and haloperidol on negative symptoms in schizophrenia are secondary to effects on positive, extrapyramidal, and depressive symptoms was investigated by means of an analysis of the data from the USA-Canada risperidone double-blind randomized clinical trial of 523 chronic schizophrenic patients. Regression analyses in the total sample and within treatment groups confirmed a strong relationship between changes in negative symptoms and the other variables studied ($R^2 = 0.50–0.51$, $p < 0.001$). Only depressive symptoms did not contribute significantly to these results ($p > 0.10$). Path analysis showed that the greater mean change ($p < 0.05$) of negative symptoms with risperidone compared to haloperidol could not be fully explained by correlations with favourable effects on positive and extrapyramidal symptoms. The relationship between shift in extrapyramidal symptoms and shift in negative symptoms failed to reach statistical significance; however, there was a clear tendency in the expected direction in both treatment groups.

Key words Neuroleptics · Negative symptoms · Risperidone · Schizophrenia · Haloperidol

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Introduction

A recent review of published studies on the efficacy of neuroleptics in treating the schizophrenic negative syndrome reveals that no definitive conclusion can be drawn as to the comparative validity of two hypotheses: whether neuroleptics exert a beneficial effect directly on negative symptoms (primary symptoms); or whether they have indirect effects on negative symptoms (secondary symptoms) through an improvement in positive symptoms and a decrease in extrapyramidal symptoms (Möller 1993). The same review suggests there is evidence that neuroleptics, or at least the putative atypical neuroleptics, can reduce negative symptoms. Atypical neuroleptics that have a lower risk of extrapyramidal side effects are often described as advantageous in the treatment of negative symptoms.

Assessing drug effects in negative symptoms has been complicated by the deficiencies of the studies reviewed. Since most of the trials in the literature reviewed were carried out in patients with mixed negative and productive (positive) symptoms during an acute episode of schizophrenia, rather than with those in a deficit state, the question arises whether negative symptoms that are not predominantly or exclusively secondary to positive symptoms can be improved. The overlap of negative symptoms of schizophrenia, extrapyramidal side effects, and depression complicates the assessment of different pharmacological treatments for negative symptoms. If one drug is found to be more effective in treating negative symptoms than another, this effect might be produced through its greater efficacy directly on negative symptoms or indirectly through a more favourable clinical profile on positive symptoms, depression, akinesia or sedation.

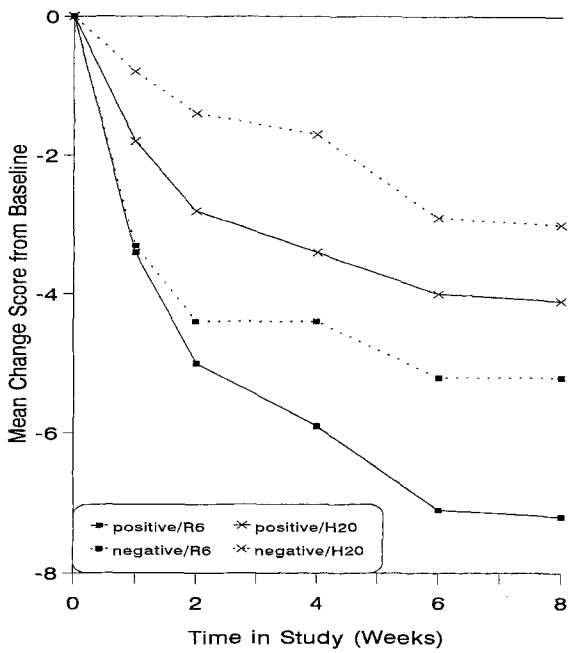
Along with the ambiguities associated with the concepts of primary and secondary negative symptoms (Carpenter et al. 1985), problems relating to the assessment of primary and secondary negative symptoms and to the differentiation of coexisting multiple forms of secondary negative symptoms render the data so far reported in the

Table 1 Suggestions of the working group on negative symptoms in schizophrenia (Möller et al. 1994)

Aim: Evaluation of treatment effects on negative symptoms in schizophrenia
1. Patient selection: a) positive symptoms not dominating the actual clinical picture, e.g. PANSS negative type b) duration of negative symptoms > 6 months c) stable condition of the schizophrenic illness > 6 months d) flat affect and poverty of speech as core symptoms of negative symptoms e) no/low depression score
2. Design: double-blind comparison to placebo or active drug
3. Efficacy parameters: BPRS or SANS or PANSS
4. Other scales: depression scales, EPS scales
5. Statistical analyses: a) end point comparison b) interaction with productive symptoms, depression, EPS

published literature inconclusive. Consequently, the recent development of specific scales for the measurement of schizophrenic negative symptoms has been an important step forward in this field of research (Andreasen 1989; Kay et al. 1987). Another conclusion to be drawn from a review of the literature is that the design of the studies, particularly the criteria for patient selection (mostly acute schizophrencis), has been less than optimal (Möller 1993). In view of these conceptual and methodological problems, drug trials of negative symptoms do not clearly disprove either one of the competing hypotheses. A European working group, composed of clinicians and researchers from university hospitals and the pharmaceutical industry, has recently established methodological guidelines for the evaluation of drug effects in negative symptoms (Möller et al. 1994; Table 1).

One of the proposals of this working group is that direct and indirect drug effects on negative symptoms can be differentiated by advanced statistical procedures. To date, only three studies have used elementary statistics to account for potential indirect effects on negative symptoms. Meltzer (1985), employing a covariance analysis, showed that the neuroleptic effect on negative symptoms could not be explained as an effect on positive symptoms alone. Van Kammen et al. (1987), using regression analysis, described a neuroleptic effect on negative symptoms as secondary to the effect on positive symptoms. Miller et al. (1994), using Spearman correlations and multiple regression, investigated clozapine's effects on negative symptoms in 29 refractory schizophrenic patients with respect to the correlation between improvements in negative symptoms and posititve symptoms, and a decrease in both extrapyramidal symptoms (EPS) and depression. The present study is the first to apply a complex statistical model such as path analysis to differentiate between direct and indirect drug effects. The primary objective of the analysis of the data derived from the North American risperidone study (Chouinard et al. 1993; Marder and Meibach 1994) was to assess whether risperidone had a more potent direct and specific effect on negative symptoms than haloperidol.



Number of patients

Week:	1	2	4	6	8
R6:	85	81	76	61	55
H20:	85	75	66	46	41

Fig. 1 Time course of treatment with risperidone (6 mg/day) (R6) and haloperidol (20 mg/day) (H20) as measured by weekly mean change scores from baseline for the positive and negative subscales of the PANSS (combined USA-Canada study)

Methods

The data from the USA-Canada risperidone study (Chouinard et al. 1993; Marder and Meibach 1994) included 523 patients suffering from an acute episode of chronic schizophrenia according to DSM-III-R criteria (American Psychiatric Association 1987). Different daily dosages of risperidone (2 mg, 6 mg, 10 mg or 16 mg) were administered in a double-blind design and compared to 20 mg haloperidol and placebo.

Treatment effects were measured using the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987). For the present study, the subscales measuring positive, negative and depressive symptoms were relevant. Most of the items used in the depression score (somatic concern, anxiety, guilt feelings, depressive mood) are identical to the three items (anxiety, guilt feelings and depressive mood) of the anxiety-depression subscale of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1961; Overall and Klett 1972). The extrapyramidal side effects were measured on the Extrapyramidal Symptom, Rating Scale (ESRS) of Chouinard et al. (1980). In the

combined data of this 8-week trial, both drugs (haloperidol and risperidone) improved positive and negative symptoms (Janssen Research Foundation 1991). However, the 6-mg dose of risperidone produced a significantly higher reduction in positive symptoms as well as a more favorable effect in negative symptoms compared to 20 mg haloperidol as can be seen in Fig. 1 (Janssen Research Foundation 1991).

Before analysing differences in drug efficacy on negative symptoms, we tested the general hypothesis of how much improvement in negative symptoms can be explained by a reduction in positive, extrapyramidal, and depressive symptoms. This was investigated using a regression analysis with changes in negative symptoms as a dependent variable and the following four predictors: baseline values of negative symptoms, improvement in positive symptoms, changes in extrapyramidal symptoms and in depression. Changes were assessed by differences between baseline and week 8 in patients classified as completers (completers' sample, $n = 269$).

The second step was to apply a path analysis to the rating scale data (intent-to-treat sample) to determine if the greater efficacy on negative symptoms of risperidone compared to haloperidol was due to direct effects (Fig. 2).

Besides the treatment variable, all variables denote differences between last observation (LOCF) and baseline (intent-to-treat endpoint analysis). We propose that a "direct effect" of the drug treatment on negative symptoms can be assumed if the treatment effect on negative symptoms cannot be "explained" statistically by changes in positive and/or extrapyramidal symptoms. This method of differentiating between primary and secondary negative symptoms is similar to the approach of Carpenter et al. (1985) who propose that "the conclusion on primary negative symptoms is based on the exclusion of secondary negative symptoms". However, there are differences in how each understands what is meant by "exclusion". If negative symptoms fail to improve when positive symptoms of schizophrenia or negative symptoms such as akinesia are treated, then Carpenter et al. (1985) assume these are primary negative symptoms and core features of the illness. In contrast, we assume primary negative symptoms and direct effects if changes in positive and extrapyramidal symptoms do not adequately predict different shifts in negative symptoms in different treatment groups. Not all arrows in Fig. 2 should be interpreted as causal influences which hold at all times for all patients: the arrow from "extrapyramidal symptoms" to "negative symptoms" indicates one indirect route by which effects may be potentially, but not necessarily, exerted on negative symptoms. It reminds us of the possible confusion between primary and secondary negative symptoms which leads to diagnostical difficulties in clinical assessments. The results of the regression analysis in the total sample showed that the overlap of depressive and negative symptoms was not relevant for the analysis. In principle, it would be possible to include other variables (i.e. depression) in the regression analysis; however, for reasons of simplicity we decided to omit them. As in our first analyses, the baseline values of negative symptoms were included as an additional predictor.

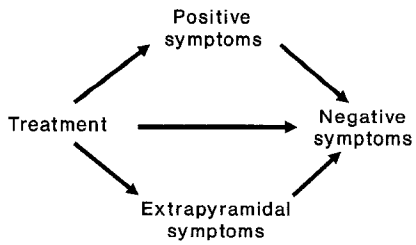


Fig. 2 Path model describing the proposed relationships between treatment, positive, extrapyramidal, and negative symptoms

If we transfer this to formulae, the following regression equations result:

$$(1)\ \text{POS (e–b)} = k_1 + a_1 \text{*POS (b)} + d_1 \text{*T};$$

$$(2)\ \text{ESRS (e–b)} = k_2 + a_2 \text{*ESRS (b)} + d_2 \text{*T};$$

$$(3)\ \text{NEG (e–b)} = k_3 + a_3 \text{*NEG (b)} + b_3 \text{*POS (e–b)} + c_3 \text{*ESRS (e–b)} + d_3\text{T}.$$

POS (e–b) is the difference in positive scores between last observation (endpoint) and baseline, and POS (b) is the baseline score of the positive subscale of the PANSS; ESRS denotes the ESRS total score (physician's examination of parkinsonism, dystonia and dyskinesia total), and NEG the score of the negative subscale of the PANSS; T denotes a dummy variable for the treatment which has the value 0 in the haloperidol group and the value 1 in the risperidone group; the parameters *k, a, b, c* and *d* are estimated in the regression analyses.

All three equations account for the baseline values of the respective variables. The third equation also accounts for the changes in positive and extrapyramidal symptoms: the treatment effect d_3 in this equation estimates the difference in shift of negative symptoms between the haloperidol and risperidone groups, if baseline values of negative symptoms, shift in positive, and shift in extrapyramidal symptoms are controlled statistically.

Results

The first regression model yielded a strong and significant prediction of improvement in negative symptoms by baseline values of negative symptoms, shift in positive symptoms, shift in extrapyramidal symptoms, and shift in depression ($n = 269$; $R^2 = 0.50$, $p < 0.001$). All predictors contributed significantly to this result (t-test, $p < 0.001$) with the exception of the change in depressive symptoms ($p = 0.11$). Changes in depressive symptoms appear to have a negligible effect in the more detailed analyses of treatment effects on negative symptoms; consequently, we did not include depressive symptoms in the path model.

The estimation of the path model (Fig. 3) shows that even after statistical control of indirect effects on secondary negative symptoms, negative symptoms were more improved with risperidone than with haloperidol. The esti-

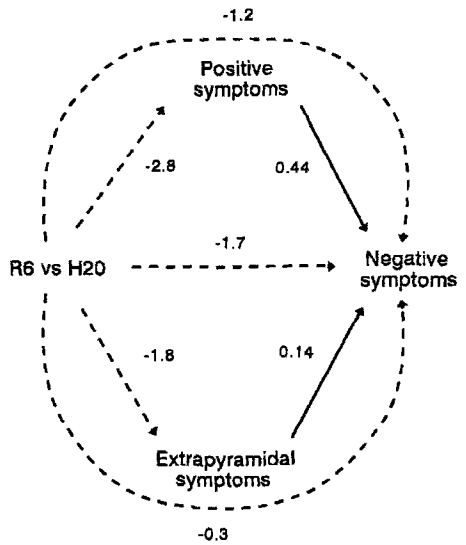


Fig. 3 Estimated path coefficients for the comparison of 6 mg risperidone (R6) (n = 85) and 20 mg haloperidol (H20) (n = 85). *Continuous lines* denote equally directed relationships, *dashed lines* inverse relationships; the *semicircles* represent the indirect effects of the treatment; all parameters are significant ($p < 0.05$)

mated difference, which cannot be explained by baseline values and changes in positive or extrapyramidal symptoms, amounts to 1.7 points on the negative subscale of the PANSS. The estimated model explains 41% of the variance ($P < 0.001$) in the reduction of negative symptoms, and all parameters are significant. For simplicity, the statistical effects of baseline values were ignored in Fig. 3; these "effects" were to be expected for methodological reasons alone. The baseline values were used to compute the criterion variable, the difference between last observation and baseline.

One objection to our approach could be that treatment effects on positive, extrapyramidal, and negative symptoms might induce spurious correlations between improvement scores. This argument can be refuted if the relationships between positive, extrapyramidal, and negative symptoms are also observable within treatment groups (Table 2).

Table 2 shows that the relationship between shift in positive symptoms and shift in negative symptoms is clearly confirmed within treatment groups. Although the relationship between shift in EPS and shift in negative symptoms did not achieve statistical significance, there was a clear tendency in the expected direction in both drug groups. Since the t-tests were two-sided and EPS could be treated pharmacologically, we interpreted the results as confirming the weak influence of EPS on negative symptoms compared to the influence of positive symptoms.

Discussion

A path analysis was used to differentiate between "direct" and "indirect" effects on negative symptoms in the analysis derived from the USA-Canada risperidone study. Focusing on the most appropriate dosage of risperidone (6 mg) and an intent-to-treat approach, the hypothesis that risperidone has a more potent direct effect on negative symptoms compared to haloperidol (20 mg) (Chouinard et al. 1993; Marder and Meibach 1994) was confirmed by this analysis.

Some comments concerning path analysis are necessary. The primary limitation of path analysis, which is based on correlation calculations, is that a causal relation between two variables cannot be inferred. We only know that there are correlations; these correlations can be interpreted in different ways. In this study, other interpretations than those we have made are possible. For example, it might be proposed that positive and negative symptoms may even depend on primary negative symptoms. However, our conclusion that the reduction of positive symptoms leads to a reduction of negative symptoms is more plausible, especially in view of the concept of secondary negative symptoms. In the present study, the hypothesis of a correlation between the severity of EPS and an increase in negative symptoms is less probable even though drug-induced parkinsonism can lead to apparent negative symptoms. There is an overlap at the phenomenological level between parkinsonian symptoms and negative symptoms (Hoffman et al. 1987; Prosser et al. 1987).

A potential problem with path analysis is the assumption of a linear relationship among variables. However, in-

Table 2 Relationship of changes in negative symptoms and changes in positive and extrapyramidal symptoms within each treatment group (completers' analysis)

	Shift in positive symptoms		Shift in extrapyramidal symptoms		Model[a]	
	regression	P (t-test)	regression	P (t-test)	P (F-test)	R^2
Risperidone (6 mg) n = 55	0.51	< 0.01	0.19	0.09	< 0.001	0.51
Haloperidol (20 mg) n = 41	0.45	< 0.01	0.19	0.13	< 0.001	0.50

[a] The regression model also included both baseline values of negative symptoms and changes in depressive symptoms; the latter were clearly not significant ($p = 0.91$ and $P = 0.43$) and the former were omitted for reasons of simplicity ($P = 0.02$ and $P < 0.01$)

spection of several scatter diagrams shows that the hypothesis of a linear relationship between the variables is in fact a reasonable assumption. Another limitation of the path model is the problem of multicollinearity. The significance of single coefficients in a regression model will be less precisely estimated if some predictors are highly correlated. The significance of this problem was checked against "tolerance" statistics which reflect the amount of multicollinearity in the predictors. There was little evidence that this statistical problem had a significant influence on our results.

Finally, the heterogeneous etiology of negative symptoms must be considered in all hypotheses about drug efficacy. Data derived from patients suffering from an acute schizophrenic episode (Miller et al. 1994) must be carefully interpreted as to its phase-significance. It does not necessarily follow that a neuroleptic which demonstrates an effect on negative symptoms in acute schizophrenic patients will also be helpful in negative symptoms of a chronic deficit schizophrenic state (Carpenter et al. 1988; Breier et al. 1994). Nevertheless, the extrapolation of a direct therapeutic effect on negative symptoms in schizophrenics with a mixed positive-negative syndrome to potential beneficial effects on the deficit syndrome of chronic schizophrenics seems more logical than an extrapolation without differentiation between direct and indirect effects.

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