Rapid Onset of Therapeutic Effect of Risperidone Versus Haloperidol in a Double-Blind Randomized Trial

Jonathan Rabinowitz, Ph.D.; Tzipi Hornik, B.A.; and Michael Davidson, M.D.

Background: Speed of onset of therapeutic effect is an important dimension of drugs employed to treat psychosis and schizophrenia. Faster onset is desirable to reduce the anguish caused by delusions and hallucinations and to protect patients and others from the consequences of poor judgment associated with psychotic exacerbation. Although sufficient studies have demonstrated that novel antipsychotics have advantages over clinically employed doses of classic drugs in terms of tolerability and aspects of efficacy, less is known about differences in speed of onset of therapeutic effect. This report consists of a post hoc subanalysis of data from a large double-blind, randomized pivotal trial in which we compared onset of therapeutic effect between risperidone and haloperidol.

Method: During an 8-week period, 227 patients with DSM-III chronic schizophrenia received 4 mg/day of risperidone and 226 patients received 10 mg/day of haloperidol. Symptoms were assessed 6 times (days 0, 7, 14, 28, 42, and 56) using the Positive and Negative Syndrome Scale (PANSS) for schizophrenia and the Clinical Global Impressions-Severity of Illness scale (CGI-S). Data were analyzed using analysis of variance for multiple dependent variables and repeated-measures multivariate analysis of variance.

Results: The analyses revealed that patients receiving risperidone improved more rapidly than those receiving haloperidol as measured by PANSS total and CGI-S scores. Differences were most pronounced during the first week of treatment.

Conclusion: Results suggest that risperidone offers a more rapid response than haloperidol, particularly during the active phase of illness when time to response can be crucial.

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Received June 16, 2000; accepted Sept. 12, 2000. *From the Department of Social Work, Bar Ilan University, Israel (Dr. Rabinowitz and Ms. Hornik); and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel (Dr. Davidson).*

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Reprint requests to: Jonathan Rabinowitz, Ph.D., Bar Ilan University, 22 Akiva St., Raanana, Israel (e-mail: rabinowz@mail.biu.ac.il).

Treatment with antipsychotic drugs is generally initiated when patients already manifest unequivocal psychotic symptoms. For patients, active psychosis generates fear and anguish and can lead to deterioration of an already weak social support network. For patients and their families, active psychosis can result in increased danger since many patients manifest poor judgment and risky behavior during psychotic exacerbations. For the treatment team, active psychosis is an increased burden, and for society, an increased expense. As a result of all of the above, increasing speed of therapeutic action in actively ill patients is crucial. Clinicians and investigators have met with little success at increasing speed of action using such strategies as "rapid neuroleptization," parenteral route of neuroleptic administration, and very large doses of neuroleptics.[1] Since classic and novel antipsychotic drugs might differ in some aspects of their therapeutic mechanisms, it would be reasonable to hypothesize that they might also differ in their onset of action.

While the advantages in terms of tolerability and efficacy of risperidone over customarily administered doses of haloperidol and other conventional antipsychotic drugs have been demonstrated,[2,3] comparatively little is known about differences in onset of therapeutic response. Studies have found that risperidone has a more rapid therapeutic response than clozapine[4] and zuclopenthixol[5]; however, clozapine and zuclopenthixol are rarely used as alternative treatments to risperidone. Using higher than currently recommended dosages, Marder et al.[6] found that 6 mg of risperidone had a faster onset of action than 20 mg of haloperidol. Perhaps more relevant to current clinical practice is the comparison presented here, between the speed of therapeutic action of haloperidol, 10 mg/day, and risperidone, 4 mg/day.

METHOD

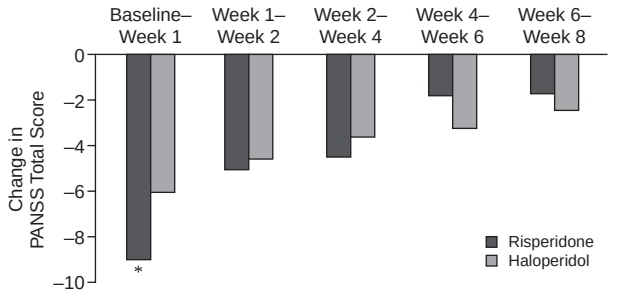
This is a post hoc subanalysis of data from a pivotal randomized controlled trial of patients with chronic schizophrenia receiving risperidone or haloperidol for 8 weeks.[7] Symptomatology and efficacy were assessed 6 times during the trial (days 0, 7, 14, 28, 42, and 56) using the Positive and Negative Syndrome Scale (PANSS)[8] for schizophrenia and the Clinical Global Impressions-Severity of Illness scale (CGI-S).[9] Patients from 15 countries were recruited into the study if they met DSM-III criteria for

Table 1. Characteristics of Patients in an 8-Week Double-Blind Trial[a]

Variable	Risperidone, 4 mg/d (N = 227)	Haloperidol, 10 mg/d (N = 226)
Male/female	152/75	150/76
Age, mean (y)	38.1	38.1
Baseline total PANSS score, mean (SE)	89.6 (1.16)	88.8 (1.10)
Baseline CGI-S score, mean (SE)	4.8 (1.06)	4.7 (1.03)
Completers, total N (%)	182 (80)	163 (72)

[a]No significant differences were found between groups.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale.

Figure 1. Changes in Positive and Negative Syndrome Scale (PANSS) Total Score



*p < .05.

chronic schizophrenia and had a total PANSS score between 60 and 120.[8] Additional details on the trial and the complete sample are presented elsewhere.[7] Data were given to the authors by Janssen Research Foundation (G. De Smedt, M.D., data on file, Janssen Pharmaceutica) upon the authors' request with no hypotheses or research questions specified.

In this subanalysis, we included all patients in the trial who had been randomly assigned to the risperidone, 4 mg/day, group (N = 227) and all of those patients randomly assigned to the 1 haloperidol (10 mg/day) group (N = 226). The risperidone, 4 mg/day, group was selected for analysis over groups receiving the other 4 dosages (1, 8, 12, and 16 mg/day) included in the study since 4 mg/day was believed to be the most clinically relevant. Dosages of 8, 12, and 16 mg/day have been shown to offer no greater symptom relief than 4 mg/day while being associated with higher risk of adverse effects,[7,10] and 1 mg/day offers inferior symptom relief compared with the other dosages.[7] In addition, recent large-scale studies of clinical practice have found that the mean dose prescribed ranges from 4 mg/day[11] to 5.3 mg/day,[12,13] which is similar to the average maintenance dose recommended by a consensus of experts (4 to 6 mg/day).[14] Characteristics of patients are presented in Table 1. There were no significant differences between the 2 groups of patients in sex and age distribution or in symptomatology at baseline.

Data Analysis

Two sets of analyses were conducted to compare speed of onset of response between patients receiving risperidone and haloperidol. The first set examined change, which was defined as difference in PANSS total and CGI-S scores, for each study week since the previous measurement. The difference in initial change, that is, from baseline to first week on treatment with study medication, was tested using analysis of variance for multiple dependent variables (MANOVA) using the general linear model. This model included both PANSS and CGI-S scores. This, and all subsequent models, included study drug and, given the differences in numbers of patients in each country, controlled for country. Results are presented as adjusted means. Since all patients were still in the trial during the first week, analyzing change over the first week enabled the inclusion of all study patients, even those who later dropped out of the trial. Change for those patients who completed the entire study (80% of risperidone patients and 72% of haloperidol patients) was compared using repeated-measures MANOVA in which the parameter of interest was the contrast of time-by-group interaction.

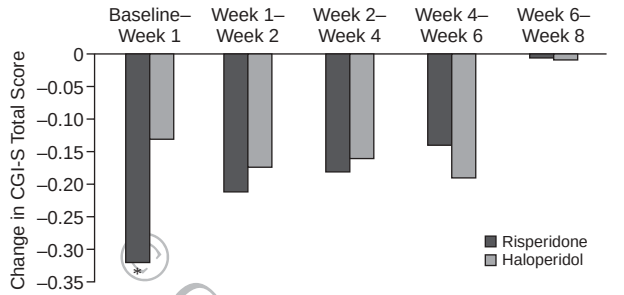
The second set of analyses focused on patients who improved during the trial and examined percentage of total change by study week. For this purpose, the total change for each patient was calculated by dividing change in each study period by the overall improvement. Thus if a patient improved 30 points on the PANSS, of which 15 points was during the first study week, they would receive a score 50% on this variable for the first interval. As in the first set of analyses, difference between treatment groups was tested using repeated-measures MANOVA.

RESULTS

Figure 1 shows the cumulative change in PANSS total score by study week, illustrating that through week 4 the risperidone group improved more rapidly than the haloperidol group. Specifically, the first 2 data points show that on PANSS scores, the risperidone group improved a mean ± SE of 9.02 ± 0.98 points from baseline to first week, whereas the haloperidol group improved 5.89 ± 1.31 points. This difference was statistically significant ($F = 4.2$, $df = 1, 449$; $p = .04$). When examining change across all data points for those patients who completed the trial, using repeated-measures MANOVA, we found a time-by-group interaction on the linear contrast ($F = 4.20$, $df = 1, 317$; $p = .04$). This finding suggests that the 2 treatment groups change linearly over time at a different pace, with the risperidone group improving faster than the haloperidol group.

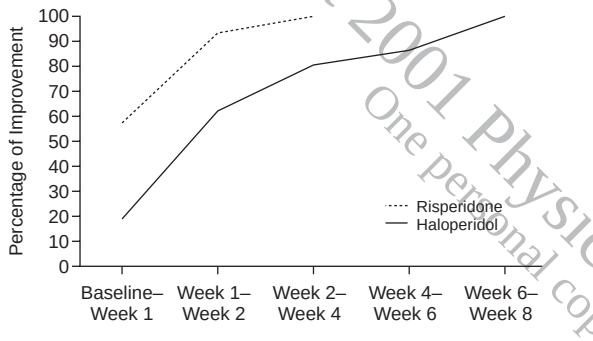
Figure 2 shows change in CGI-S score by study week. Similar to Figure 1, this graph reveals the same pattern of faster response in the risperidone group until week 4. As in

Figure 2. Changes in Clinical Global Impressions-Severity of Illness Scale (CGI-S) Total Score



*p < .05.

Figure 3. Percentage of Total Improvement in Positive and Negative Syndrome Scale Score From Baseline by Study Week[a]

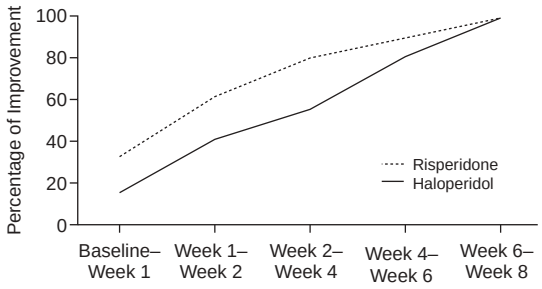


[a]Excluding patients who did not improve and those who did not complete the trial.

Figure 1, the first 2 data points show that between baseline and the first week of the trial, the risperidone group improved more on the CGI-S than did the haloperidol group (0.32 ± .05 vs. 0.13 ± .07, respectively; F = 5.6, df = 1, 449; p = .02). When examining change from baseline across all data points for those patients who completed the trial, the overall MANOVA model found a significant time-by-group interaction on the linear contrast, which suggests that the 2 treatment groups change linearly over time at a different pace (F = 9.80, df = 1, 317; p = .002), with the risperidone group improving earlier than the haloperidol group.

Focusing on those patients who improved over the 8-week trial, Figures 3 and 4 illustrate the mean percentage of improvement per study week on the PANSS and CGI-S. As seen in Figure 3, during the first study week, patients taking haloperidol (N = 140) achieved 19% of their total improvement on the PANSS, and those taking risperidone (N = 162) achieved 58% of their total improvement. Figure 4 reveals that on the CGI-S, patients taking haloperidol achieved 16% of their total improvement during the first week, whereas those taking risperidone achieved 34% of their total improvement. The MANOVA model found a

Figure 4. Percentage of Total Improvement in Clinical Global Impressions-Severity of Illness Scale Score From Baseline by Study Week[a]



[a]Excluding patients who did not improve and those who did not complete the trial.

nearly significant time-by-group interaction on the linear contrast for the PANSS (F = 3.4, df = 1, p = .07) and a significant interaction for the CGI-S (F = 6.8, df = 1, p = .01), which suggests that the patients' improvement in the 2 treatment groups was linear over time and that the groups progressed at a different pace, with the risperidone group improving earlier than the haloperidol group.

DISCUSSION

The results of this post hoc analysis suggest that patients respond more rapidly to risperidone than to haloperidol, particularly when time to response may be crucial. It would be reasonable to assume that a more rapid response reduces suffering by patients and families and the danger associated with florid psychosis, as well as treatment costs. It is also conceivable that more rapid response could be associated with greater patient compliance, since patients who experience more rapid relief from symptoms may be more likely to adhere to treatment. All of these hypotheses should be tested in prospective studies.

It is far from clear what differences in the mechanisms of action between the 2 drugs account for differences in the therapeutic effects, including the differences in the onset of action presented here. For example, the differences between the 2 drugs in their ability to produce extrapyramidal symptoms has often been attributed to differences in the ratio of dopamine-2/serotonin-2 receptor blocking, but this hypothesis has recently been challenged.[15] While dopamine receptors are blocked hours after the administration of the first dose of neuroleptic drug, it takes at least several days for the antipsychotic effect to emerge[16] and, at times, several weeks[17] or months[18] to fully manifest. Thus the puzzle associated with the mechanism of action is far from solved. It is conceivable that intracellular mechanisms beyond receptor blockade, such as second messengers or gene induction, are differentially effected by each drug, thus possibly accounting for the differences in onset of action,[15] which will have to be tested in future research.

The results of the study are consistent with previous studies, which have found that risperidone had a faster speed of response than clozapine,[4] zuclopenthixol,[5] and haloperidol.[6] The major limitation of this analysis is that it was post hoc and should thus be viewed with caution. Post hoc reanalysis of databases accumulated during large pivotal trials presents a number of risks and some benefits. First, the risks are of "piecemeal" publication by which the same data and analysis are published in different journals under different titles and authorships, or very closely related aspects of the same trial are published separately.[19] Second, post hoc, unplanned analysis of subpopulations, subscales, or other aspects of the trial raise the risk of type I errors by which multiple analyses lead to spurious statistically significant findings.[20,21]

A possible benefit of post hoc reanalysis of large databases is that it enables investigators to propose bold and original hypotheses without having to invest the resources essential for conducting adequately powered prospective clinical trials.[21] This is particularly relevant in clinical neuroscience and even more relevant in schizophrenia, for which we are still far from understanding the biological processes mediating the therapeutic effects of drugs. For example, we cannot identify a priori subpopulations of treatment-refractory or treatment-responsive patients or match a particular antipsychotic drug to a specific aspect of the illness. Hence, it is often hard to justify prospective trials targeting specific symptoms, specific aspects of the schizophrenic illness, or specific subpopulations. Any clue obtained from post hoc "effort-free" analysis can help design prospective studies whose rational is supported at least by the results of the post hoc analysis.

Given the possible benefits of post hoc reanalysis of large databases, the risk of creating the appearances of several trials by multiple or partial publication of the same trial can be contained by editorial suppression of this practice and, when justified by the richness of data accumulated during a trial, by clear and unequivocal acknowledgment of the original publication, as well as by highlighting overlapping aspects between the publications.[19] The risk of spurious findings (type I errors) associated with multiple post hoc analyses can be avoided by highlighting the exploratory nature of the results and by cautioning readers from using such results in clinical practice before the results are confirmed by a priori designed trials.[21]

Future prospective planned studies should reexamine the comparative speed of action of risperidone versus haloperidol in both chronic and early-episode long-stay patients. In addition, attention should be directed to studying patients who are neuroleptic-naive. In the current study of chronic patients, most patients had been previously treated with neuroleptics; thus, it is possible that the differences in speed of onset of therapeutic action found in this sample might not pertain to neuroleptic-naive patients. It should also be noted that the analysis conducted in this article is novel and was not a planned feature of the study, and the study groups chosen were based on evidence of clinical efficacy that emerged after the trial was designed. Given the importance of speed of action, a priori consideration should be given to analyzing it in trials of antipsychotic medications. Although it presents special methodological problems, speed of therapeutic action should also be examined in naturalistic trials.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), risperidone (Risperdal).

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