The World Journal of Biological Psychiatry, 2007; 8(4): 256–261

ORIGINAL INVESTIGATION

Risperidone monotherapy in manic inpatients: An open label, multicentre trial

ANNA FORSTHOFF[1], HEINZ GRUNZE[1], FLORIAN SEEMÜLLER[1], ROBERT STAMPFER[1], SANDRA DITTMANN[1], BENDIKT AMANN[2], FOLKHART SCHMIDT[3], MARTIN SCHÄFER[3], LEO HERMLE[4], JÖRG WALDEN[5] & ANDREAS SCHREINER[6]

[1]*Department of Psychiatry, Ludwig-Maximilians-University, Munich, Germany,* [2]*C.A.S.M., Hospital Bennito Menni, Sant Boi de Llobregat, Barcelona, Spain,* [3]*Department of Psychiatry and Psychotherapy, Kliniken Essen-Mitte Evang, Huyssens-Stiftung, Essen, Germany,* [4]*Department of Psychiatry, Christophsbad, Göppingen, Germany,* [5]*DRV Westfalen, Wissenschaftspark, Gelsenkirchen, Germany, and* [6]*Medizin & Forschung, Janssen-Cilag GmbH, Neuss, Germany*

Abstract

Objective: The efficacy of risperidone in acute mania has been established in several controlled clinical studies. However, this may not necessarily resemble the clinical effectiveness of this treatment, as patient populations in controlled studies are considered as being not representative. This study examined risperidone monotherapy in a sample of severe manic patients in admission ward settings. *Methods:* Open label monotherapy with risperidone was examined for 3 weeks in 30 inpatients. Subjects were evaluated with structured clinical rating scales: Young Mania Rating Scale (YMRS), Clinical Global Impression, bipolar version (CGI-BP), and the Extrapyramidal Symptom Rating Scale (ESRS). In addition, the amount of concomitant use of benzodiazepines was documented. Data were analysed using a last observation carried forward method on all subjects given medication at baseline. *Results:* Significant improvement from baseline to exit was observed both for the YMRS and CGI-BP. Responder analysis revealed that two-thirds of the patients showed a reduction of $\geq$50% in the YMRS score, and 69% of the patients were rated as very much improved or much improved on the CGI-BP mania scale at study exit. Only three patients dropped out due to adverse events, in one case due to extrapyramidal symptoms. *Conclusions:* The efficacy of risperidone in the acute treatment of mania as observed in controlled studies could be replicated in this open monotherapy study in a severely manic inpatient population. Considering the mean maximal dosage of 5.5$\pm$0.9mg risperidone, the tolerability and safety profile appeared satisfactory.

Key words: *Bipolar disorder, mania, risperidone, antipsychotics, monotherapy*

Introduction

Bipolar disorder is a recurrent, devastating and life-threatening major psychiatric disorder with a prevalence rate of approximately 4% of the adult population (Hirschfeld et al. 2003). Characterized by episodes of mania and depression, the illness too often leads to long-term psychosocial disability and is associated with a high suicide risk for both phases – depression and mania (Müller-Oerlinghausen et al. 2002).

Lithium has been the standard treatment for acute mania for many years; the use of antipsychotic drugs as adjunctive treatment in the acute phase of bipolar disorder is well established, though practice varies widely (Dunner and Fieve 1974). Within the last years several studies showed acute antimanic efficacy of the atypical antipsychotic risperidone. Hirschfeld et al. (2004) showed a rapid antimanic effect of risperidone monotherapy in a larger, double-blind, placebo-controlled trial, and more recently Khanna et al. (2005) demonstrated strong efficacy of risperidone in a severely manic Indian population. In a comparative, placebo-controlled 12-week study, risperidone was as effective as haloperidol (Smulevich et al. 2005). Furthermore, Sachs et al. (2002) showed that the combination of risperidone and

Correspondence: Dr. Heinz Grunze, Department of Psychiatry, Ludwig-Maximilians-University, Nussbaumstr. 7, 80336 Munich, Germany. Tel: +49 89 5160 5335. Fax: +49 89 5160 5330. E-mail: Heinz.Grunze@med.uni-muenchen.de

(Received 20 October 2006; accepted 13 December 2006)

ISSN 1562-2975 print/ISSN 1814-1412 online
DOI: 10.1080/15622970601169766

lithium or valproate was more efficacious than a mood stabilizer alone in the treatment of acute bipolar mania.

These lines of evidence suggest that risperidone has an important role in the treatment of acute mania. The receptor-binding profile is characterised by a potent antagonism of the serotonin 5-HT2A, the dopamine D2 and, the a-adrenergic 2c receptors (Leysen et al. 1994; Kalkman and Loetscher 2003) and is discussed to be relevant for the treatment of bipolar mania.

Whereas the cited studies were conducted as phase III studies for registration purposes, patients may thus not be representative for a clinical sample (Licht et al. 1997). Besides randomized controlled studies, a recent review identified six observational studies of risperidone in acute mania (Nguyen and Guthrie 2006). However, these studies are to some degree flawed by being either retrospective, small in size and/or combination treatment trials with various medications. Our prospective study focussed on the efficacy and tolerability of risperidone monotherapy in acutely manic inpatients in routine admission ward settings.

Methods

Design

This was a 3-week, open-label, multicentre trial conducted in Germany to assess the efficacy and tolerability of risperidone in the treatment of acute bipolar mania. Participating centres were the Departments of Psychiatry at the Universities of Munich, Freiburg, Münster, Tübingen, Kiel, and the Psychiatric Hospital Christophsbad Göppingen. The vast majority of patients (22/30) were recruited in Munich and Freiburg.

Subjects

The protocol was approved by the institutional review boards of all participating centres. After thorough explanation of the study, patients provided written informed consent prior to participation. Patients who met the DSM-IV criteria for bipolar disorder with a current episode of acute mania (DSM-IV: 296.4 ×) and who were able to give a written informed consent were included in the study. The patients, men and women aged between 18 and 65 years, had to have a Young Mania Rating Score (YMRS) of at least 20. All patients were voluntarily hospitalised for the treatment at the time of enrolment and throughout the study.

Patients were excluded from the study if they had a diagnosis of rapid cycling or substance-induced mania. They were also excluded if they had a history of substance dependence within the 3 months prior to the screening. Additional exclusion criteria were a known history of previously poor response to risperidone, acute medical illnesses that needed medical intervention, such as cardiac diseases, seizure disorders, or the use of depot-neuroleptics within the last 4 weeks. Concomitant therapy with antidepressants, other antipsychotics, lithium, anticonvulsant mood stabilizers, ECT, anxiolytic or sedative-hypnotic drugs was prohibited, with the exception of diazepam and lorazepam as rescue medication.

Women of childbearing age were excluded if they did not practice an acceptable method of contraception.

Efficacy

Efficacy was assessed with the following standard rating scales: the Young Mania Rating Scale (YMRS) (Young et al. 1978) and the Clinical Global Impression (CGI) severity scale, version for bipolar disorder(Spearing et al. 1997). The primary measure of efficacy was the reduction of the YMRS score. Secondary endpoints were the number of responders (defined as a 50% reduction of the YMRS), the improvement of the CGI-BP score, and the amount of concomitant benzodiazepine use.

All efficacy measures were administered at baseline (day 1), day 3,7,10, 14 and 21 (endpoint).

Dosing and titration

Study medication was proposed to be titrated from 2 to 6 mg daily, according to doctor's judgement of the clinical symptoms of the patients. The medication was given b.i.d.; if tolerability problems occurred, it could alternatively be given only at night time. During the study plasma levels of risperidone were measured twice (at day 10 and 21).

As rescue medication, the use of benzodiazepines (diazepam, maximal dose 60 mg/day, or lorazepam, maximal dose 7.5 mg/day) and biperiden (maximum dose 4 mg/day) was allowed throughout the study.

Safety

Patients were interviewed for adverse events and any complaints were well documented. Movement disorders were evaluated at every study visit using the standardized Extrapyramidal Symptom Rating Scale. Vital signs were assessed at every study visit. Weights, ECG, laboratory test, urine analysis were assessed at baseline and at the end of the study. A pregnancy test for female patients had to be negative at baseline.

Statistical analysis

As this was an open study with 30 patients, statistical analysis consisted primarily of descriptive statistics and is shown in graphs.

The primary and secondary efficacy analyses were performed on the intent-to-treat (ITT) population, which included all patients who took at least one dose of study medication and who had at least a baseline YMRS assessment. A last observation carried forward (LOCF) approach was used in the primary assessment of each of the efficacy endpoints, and statistical significance was determined by the asymptotic Wilcoxon test for dependent samples; primary outcome was defined as the reduction in the YMRS. For comparison of those patients who completed the study ($n=22$), and those who dropped out earlier ($n=8$), the asymptotic Mann–Whitney *U*- test for independent sample and the Chi^2-test were used, respectively, depending on the scale level. The significance level was set at $\alpha=0.05$ for all statistical tests without adjustment for multiple testing.

Results

A total of 30 patients were included in the study. Twenty-two patients completed the study (73%). The most common reasons for discontinuation were lack of compliance with the study medication (two patients) and side effects (three patients).

Seventeen patients were male, 13 female. The mean age was 42.44 years (SD $\pm$ 13.34) (see Table I) All patients were included while in acute manic episodes. The mean severity of the YMRS at baseline was 28.83 (SD $\pm$ 6). There were no significant differences in baseline severity in the Young Mania Rating Scale between completers and those who dropped out.

The mean initial dosage of the risperidone medication was 3.53 mg (SD $\pm$ 1.74), the mean of the individual peak dosages of the single patients, achieved at any time during the study was 5.5 mg (SD $\pm$ 0.90) and the mean dosage for the last visit was 4.73 mg (SD $\pm$ 1.11). Twenty-two of the 30 patients had the maximal dose of 6 mg/day at least once during the study.

Table I. Demographic data.

Number of patients	30
Gender (m/f)	57%/43%
Mean age $\pm$ SD	42.4 $\pm$ 13.3 years
Range	19–65 years
Subtype of manic episode	
Euphoric	53.3%
Dysphoric	43.3%
mixed	3.3%
Dosage of risperidone (mg/day)	
Mean starting dose $\pm$ SD	3.5 $\pm$ 1.7
Mean maximum dose $\pm$ SD	5.5 $\pm$ 0.9
Mean dose at endpoint $\pm$ SD	4.7 $\pm$ 1.1
Concomitant medication	Diazepam 80% Lorazepam 16.7%

Efficacy measures and responders

The analysis of change from baseline for the Young Mania Rating Scale data included all 30 patients (LOCF). The mean total score of the YMRS at baseline was 28.83 (SD $\pm$ 6). As early as day 3, a significant ($P<0.0005$) reduction compared to baseline was observed which remained significant at each following time point. At the endpoint, the mean reduction of the YMRS was 16.12 (SD $\pm$ 10.94) (see Figure 1). Twenty patients (66.67%) showed a reduction of $=50\%$ in the YMRS score, and were thus classified as responders in the primary outcome criteria (see Figure 2).

The subanalysis between the groups of patients who completed the study ($n=22$), and those who dropped out earlier ($n=8$), showed that the number of responders was significantly higher in the group who completed the study (77.3 vs. 37.5%).

The results of the CGI-BP are shown in Figure 3. At endpoint, 69% of the patients showed an improvement of mania CGI-BP2- mania: 'very much improved' or 'much improved').

Safety and tolerability

The safety analysis included all 30 patients who received at least one dose of the study medication. One serious adverse event occurred, as one patient developed a delirious state. Only three patients dropped out due to adverse events. One patient had an exanthema, and risperidone had to be stopped on day 7; the second patient dropped out because of sinus tachycardia, and the third patient dropped out when developing extrapyramidal symptoms he was not willing to tolerate.

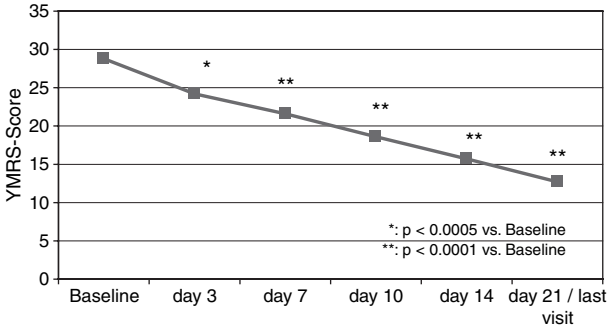

Figure 1. YMRS improvement from baseline to day 21/last visit (ITT analysis, LOCF).

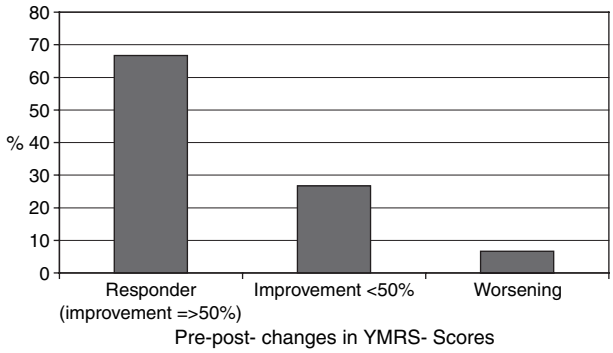

Figure 2. Pre-post changes in YMRS scores with 'Response' defined as a $\geq$50% reduction of YMRS.

Adverse events (AE) occurred in 15 of 30 patients, and 23 single adverse events were documented, 20 of them classified as mild or moderate. The majority, 14/23, occurred with 6 mg/day risperidone. Eighteen AEs were completely reversible during the study period, either with dose reduction, addition of rescue medication or spontaneously. Only three patients terminated the study early due to AEs.

The severity of extrapyramidal symptoms was assessed using the Extrapyramidal Rating Scale at every study visit and was mild at baseline (mean score 0.08) and the mean worst score during the study was 0.3 (mild to moderate). Six AEs were classified as EPS, four as akathisia, and two as rigor.

No clinically meaningful differences were found in a pre–post analysis concerning vital signs and ECG results. The mean weight was 79.01 $\pm$ 17.56 kg at baseline, but increased significantly to 80.26 $\pm$ 17.16 kg at the final visit (mean weight change: 1.25 $\pm$ 2.93 kg). However, this weight gain was not considered as clinically meaningful as only 6.67% (2/30) of patients gained more than 7% of their original weight.

Use of rescue medication

Ninety percent of patients had at least one diazepam and/or lorazepam comedication. The mean dose ($\pm$SD) of benzodiazepines (expressed as diazepam equivalents) was 15.53 $\pm$ 15.58 at day 1, 14.24 $\pm$ 12.26 between days 1 and 3, 14.57 $\pm$ 12.11 between days 4 and 7, 12.21 $\pm$ 11.92 between days 8 and 10, 11.83 $\pm$ 11.85 between days 11 and 14, 10.67 $\pm$ 12.17 between day 15 and the last day. A total of 43.3% of patients needed at least one dose of biperiden (mean dose at day 1, 0.53 $\pm$ 1.38, mean dose between day 15 and last day, 1.73 $\pm$ 2.02) for emerging extrapyramidal symptoms.

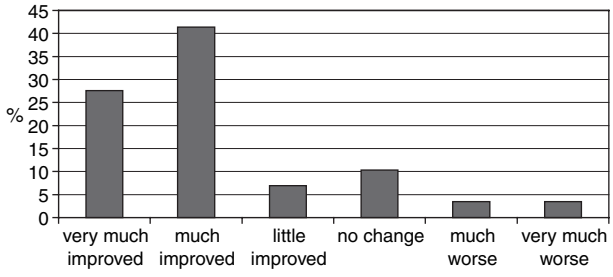

Figure 3. Physician's assessment of change in the severity of mania (CGI-BP2) comparing last observation to baseline. Data were analysed from 29/30 patients (missing data in one patient).

Correlation of risperidone plasma levels to outcome

Combined plasma levels of risperidone and its active metabolite 9-hydroxyrisperidone were 36.70 ng/ml at day 10 and 31.95 ng/ml at study end in the ITT population, supportive of a reasonably good compliance. In 15 patients, plasma levels were available both at day 10 and at completion of the study at day 21. Mean plasma levels in this sample were 39.79 ng/ml at day 10 and 33.08 ng/ml at day 21. The following analyses were therefore conducted in this sample of 15 patients who finished the study at day 21 and had plasma levels measured both at days 10 and 21.

Spearman rank test correlations between plasma levels (ng/ml) and scores on the different ratings scales on day 21 revealed virtually no correlation with the absolute YMRS score ($r = 0.020$); however, higher improvement on the YMRS from baseline to endpoint appears to be correlated to higher plasma levels ($r = 0.209$). For the CGI-BP, the absolute score at study end correlates with the plasma levels ($r = 0.320$ for mania, 0.574 for depression ($P < 0.001$), and 0.367 for BP overall), suggesting that more severely ill patients also received more risperidone. In addition, improvement on the CGI-BP between baseline and endpoint is also correlated with plasma levels ($r = 0.277$ for mania, 0.489 for depression and 0.413 for bipolar overall, respectively.) As expected, both EPS scores at study end ($r = 0.403$) and increase of EPS scores during the study ($r = 0.415$) correlate with plasma levels. However, due to small sample size, all statistics are descriptive except the correlation of plasma levels and CGI-BP Depression which reached statistical significance on a $P < 0.001$ level.

Discussion

The results of this open study confirm the clinical effectiveness of risperidone in the treatment of acute mania as previously observed in controlled studies. Treatment with risperidone led to a statistically significant reduction both of the primary outcome measure, the Young Mania Rating Scale (YMRS) as well as the secondary outcome, as the CIG-BP mania. Two-thirds of the patients were classified as

responders at study exit, defined as an at least 50% improvement in the YMRS. Efficacy of risperidone was seen as early as day 3. From there on, continuous improvement was observed until study endpoint at week 3. The safety profile of risperidone was considered as generally good; however, with a mean maximal dose of 5.5 ± 0.9 mg EPS were not uncommon, but could be sufficiently controlled with biperiden.

The study examined a typical population of acutely manic patients hospitalised at admission wards. Thus, as a strength of the study, this patient population may resemble a clinically relevant population in contrast to patients in randomised, placebo-controlled studies. The efficacy of risperidone in this group of patient was not only statistically, but also clinically significant with a mean reduction of 16 points on the Young Mania Rating Scale. In addition, an improvement was observed as early as day 3, which is also of highest importance for the clinical usefulness of any given antimanic drug.

Limitations of this trial are clearly its open design, the lack of both a placebo and a comparator control group and the relatively small sample size. However, with placebo and comparator-controlled studies already existing, it was not the primary aim of the study to prove methodologically unambiguous efficacy, but to test risperidone treatment of acute mania in a real world setting. Part of this real world setting was the fact that benzodiazepines were allowed as a concomitant add-on treatment for control of agitation and sleeplessness, as this is established clinical practice. Epidemiological data demonstrate that only about 10% of acutely manic patients are treated with monotherapy in acute hospital settings (Grunze and Dobmeier 2002). With the use of risperidone, however, a continuous decrease of concomitant benzodiazepines was observed over time.

It can be argued that restricting the comedication only to benzodiazepines also limits the transferability of these study results to acute manic inpatients in general. In a recent European cross-sectional study, polypharmacy was a common phenomenon: patients with euphoric mania were treated with a mean number of 2.9 ± 1.2 psychotropic agents, and patients with mixed-state mania with 3.3 ± 1.5 psychotropic agents (Wolfsperger et al. 2006). However, with the relatively small number of patients ($n = 30$), we felt when designing this effectiveness study that it was necessary to concentrate on a well-described sample and treatment plan in order not to obscure results by the diversity of the sample or comedications.

Another point of notice is the relatively high incidence of EPS which led to the use of biperiden in a considerable number of patients. This was likely caused by a relatively rapid dosage increase with a mean starting dose of 3.5 mg of risperidone and a mean maximum daily dosage (mean of the individual peak dosages of the single patients, achieved at any time during the study) of 5.5 mg. These higher dosages of risperidone, compared to what was commonly used in the placebo-controlled studies, may reflect the greater severity of mania in our patient population. However, only one patient discontinued the study due to EPS, which were otherwise rated as mild to mild moderate. It is known from another study in a more severely ill patient population that EPS may occur frequently with high doses of risperidone, but they rarely caused study discontinuation (Khanna et al. 2005). However, continuous use of anticholinergics together with risperidone may also be critical, as case reports link it to an increased risk of developing tardive dyskinesias (Suzuki et al. 2002).

In summary, this study supports the previously reported efficacy of risperidone in placebo-controlled studies under the conditions of daily clinical practice and demonstrates the clinical usefulness and effectiveness of this medication. For short-term treatment of mania, the safety and adverse effect profile of risperidone appears acceptable. However, lasting efficacy and long-term safety and tolerability have yet to be shown in maintenance studies of adequate duration.

Acknowledgements

We express our gratitude to the Stanley Foundation. At the time when the study was conducted, the contributing authors Florian Seemüller, Sandra Dittmann and Folkhart Schmidt were employed through an International Centre Grant of the Theodor and Vada Stanley Foundation.

Statement of interest

This study has been supported by Janssen-Cilag GmbH, Germany. Andreas Schreiner is a full-time employee of Janssen-Cilag. Heinz Grunze and Jörg Walden have served as consultant and speaker for Johnson & Johnson on several occasions. Results of this study have been previously presented at two conferences by Anna Forsthoff who received travel support from Janssen Cilag. None of the other authors have any conflict of interest with a commercial or other association in connection with the submitted article.

References

Dunner DL, Fieve RR. 1974. Clinical factors in lithium carbonate prophylaxis failure. Arch Gen Psychiatry 30:229–233.

Grunze H, Dobmeier M. 2002. Modul Therapie akuter Episoden. In: Deutsche Gesellschaft für Bipolare Störungen e.V. (DGBS e.V.), editors. Weissbuch Bipolare Störungen in Deutschland. Hamburg: CP Verlag. p 57–66.

Hirschfeld RM, Calabrese JR, Weissman MM, et al. 2003. Screening for bipolar disorder in the community. J Clin Psychiatry 64:53–59.

Hirschfeld RM, Keck PE Jr, Kramer M, et al. 2004. Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. Am J Psychiatry 161:1057–1065.

Kalkman HO, Loetscher E. 2003. alpha2C-Adrenoceptor blockade by clozapine and other antipsychotic drugs. Eur J Pharmacol 462:33–40.

Khanna S, Vieta E, Lyons B, Grossman F, Eerdekens M, Kramer M. 2005. Risperidone in the treatment of acute mania: a double-blind, placebo-controlled study of 290 patients. Br J Psychiatry 187:229–234.

Leysen JE, Janssen PM, Megens AA, Schotte A. 1994. Risperidone: a novel antipsychotic with balanced serotonin-dopamine antagonism, receptor occupancy profile, and pharmacologic activity. J Clin Psychiatry 55(Suppl 5):5–12.

Licht RW, Gouliaev G, Vestergaard P, Frydenberg M. 1997. Generalisability of results from randomised drug trials. A trial on antimanic treatment. Br J Psychiatry 170:264–267.

Müller-Oerlinghausen B, Berghofer A, Bauer M. 2002. Bipolar disorder. Lancet 359:241–247.

Nguyen LN, Guthrie SK. 2006. Risperidone treatment of bipolar mania. Ann Pharmacother 40:674–682.

Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL. 2002. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. Am J Psychiatry 159:1146–1154.

Smulevich AB, Khanna S, Eerdekens M, Karcher K, Kramer M, Grossman F. 2005. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. Eur Neuropsychopharmacol 15:75–84.

Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. 1997. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 73:159–171.

Suzuki E, Obata M, Yoshida Y, Miyaoka H. 2002. Tardive dyskinesia with risperidone and anticholinergics. Am J Psychiatry 159:1948.

Wolfsperger M, Greil W, Rossler W, Grohmann R. 2006. Pharmacological treatment of acute mania in psychiatric inpatients between 1994 and 2004. J Affect Disord in press.

Young RC, Biggs JT, Ziegler VE, Meyer DA. 1978. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 133:429–435.