European Neuropsychopharmacology (2007) 17, 138–144

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Long-term safety and tolerability of long-acting injectable risperidone in patients with schizophrenia or schizoaffective disorder

Jean-Pierre Lindenmayer [a,*], Akbar Khan [b,c], Mariëlle Eerdekens [b,c], Ilse Van Hove [b,c], Stuart Kushner [b,c]

[a] *Manhattan Psychiatric Center, New York University of Medicine, New York, NY, USA*
[b] *Johnson and Johnson Pharmaceutical Research and Development, Titusville, NJ, USA*
[c] *Beerse, Belgium*

Received 26 December 2005; received in revised form 24 July 2006; accepted 17 August 2006

KEYWORDS
Schizophrenia;
Schizoaffective disorder;
Long-acting injectable risperidone;
Effects;
Long-term

Abstract Subjects were patients with schizophrenia or schizoaffective disorder enrolled in extension studies (Study A and Study B) after participating in 12-week studies of long-acting injectable risperidone [Kane, J.M., Eerdekens, M., Lindenmayer, J.-P., Keith, S.J., Lesem, M., Karcher, K., 2003. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Am. J. Psychiatry 160, 1125-1132; Lindenmayer, J.-P., Eerdekens, L., Berry, S., Eerdekens, M., 2004. Safety and efficacy of long-acting risperidone in schizophrenia: a 12-week, multicenter, open-label study in stable patients switched from typical and atypical oral antipsychotics. J. Clin. Psychiatry 65, 1084-1089]. Twelve months of treatment were completed by 55% of Study A patients and 52% of Study B patients. The median modal dose of long-acting injectable risperidone was 50 mg/14 days in both studies. Most frequent adverse events were psychosis, headache, insomnia, agitation, and rhinitis. EPS-related adverse events were reported in 33% of patients in Study A and 22% in Study B. Patients with Clinical Global Impressions ratings of "not ill" and "mild" increased from 14% at baseline to 54% at endpoint in Study A and from 42% to 65% in Study B. It is concluded that treatment with long-acting injectable risperidone for 1 year or longer appeared to be safe and well tolerated in patients with schizophrenia or schizoaffective disorder.

1. Introduction

Since publication of the first two major trials of long-acting injectable risperidone (the 12-week double-blind study of Kane et al. (2003) and the 12-month open-label study of Fleischhacker et al. (2003), its efficacy and safety have been established in a number of further studies of patients with schizophrenia or schizoaffective disorder. The subjects in these more recent trials included inpatients (Lauriello et al., 2005), patients with schizoaffective disorder (Lasser et al., 2004a), elderly patients (Lasser et al., 2004b), and young adults (Lasser et al., 2004), and patients switched to long-

* Corresponding author. Tel.: +1646 672 6004; fax: +1646 672 6276.
E-mail address: Lindenmayer@NKI.rfmh.org (J.-P. Lindenmayer).

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doi:10.1016/j.euroneuro.2006.08.004

acting injectable risperidone from conventional and atypical oral antipsychotics (Lindenmayer et al., 2004; Turner et al., 2004; Van Os et al., 2004) as well as from conventional depot antipsychotics (Lasser et al., 2004c). In a recently published trial, a 6-month open-label European study (Möller et al., 2005), 1876 patients with schizophrenia or other psychoses who required a change in treatment were switched directly to long-acting injectable risperidone. The reasons for switching were treatment noncompliance in 38% of the patients, insufficient efficacy of their current treatment in 33%, and treatment side effects in 26%. The 6-month study was completed by 74% of the patients. Treatment with long-acting injectable risperidone was effective, as indicated by significant improvements in scores on the Positive and Negative Syndrome Scale (Kay et al., 1987) (PANSS), the Clinical Global Impressions scale (Guy, 1976) (CGI), the Global Assessment of Functioning, and the SF-36 quality of life scale, and well tolerated.

To confirm the long-term safety and tolerability of long-acting injectable risperidone, we present data from two extension studies of patients who had participated in two 12-week studies: the double-blind, placebo-controlled study of 400 patients by Kane et al. (2003) and the open-label study of 141 patients by Lindenmayer et al. (2004).

2. Methods

2.1. Two 12-week studies

In the double-blind, placebo-controlled study by Kane et al. (2003), previous medications were discontinued during a 1-week run-in period and oral risperidone was introduced at 2 mg/day and increased to 4 mg/day for at least 3 days. Previous antipsychotics received by the 400 patients included risperidone by 31%, olanzapine by 16%, and conventional antipsychotics by 19%. About 34% were receiving no antipsychotics. The patients were randomly assigned to one of four groups: placebo or 25 mg, 50 mg, or 75 mg of long-acting injectable risperidone. During weeks 1–12 of the double-blind period, the patients received six injections of placebo or long-acting risperidone, one injection every 2 weeks. Oral risperidone or oral placebo was also received during weeks 1–3 of the double-blind period.

In the open-label study by Lindenmayer et al. (2004), during a 4-week run-in period, the 141 patients continued to receive their current treatments with oral antipsychotics (olanzapine by 35%, haloperidol by 33%, and quetiapine by 32%). The patients were then switched to injections of flexible doses of 25–50 mg of long-acting injectable risperidone given every 2 weeks for 12 weeks. Oral antipsychotics were continued for 3 weeks after the first injection.

In the Kane et al. study, inclusion criteria included age 18–55 years, a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, and baseline PANSS total scores of 60–120. In the Lindenmayer et al. study, inclusion criteria included age ≥18 years, a DSM-IV diagnosis of schizophrenia, a baseline PANSS score of ≤80, and a score ≤4 on each of the following PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content.

2.2. Two extension studies

Patients who entered the extension study from Study A included those who had completed the 12-week double-blind study (Kane et al., 2003) within the previous 7 days or who had been withdrawn from the study because of safety reasons (investigators' decision) or had shown clinical deterioration (as assessed by the CGI). Due to the double-blind design of study A, the identity and dose of the study drug (placebo or long-acting injectable risperidone) were not known to the investigators at the end of the study. Therefore, at visit 1 each patient received an injection of 25 mg of long-acting injectable risperidone and was provided with 2-mg tablets of oral risperidone to be taken for 3 weeks at a dose determined by the investigator. Injections of long-acting risperidone were then given every 2 weeks at a dose of 25 mg, increasing (if clinically required) in increments of 25 mg to a maximum of 75 mg. The dose could be reduced or increased every 2 weeks in 25-mg steps by the investigator. Supplementation with oral risperidone was allowed throughout the trial. The study duration was ≥12 months (until long-acting injectable risperidone was commercially available in the United States).

In Study B, patients were enrolled in the extension study within 7 days of completing the 12-week open-label study (Lindenmayer et al., 2004). Injections of long-acting risperidone were given every 2 weeks. The starting dose was the final dose in the 12-week study. The dose could be changed in 12.5-mg increments to a maximum of 50 mg. Supplementation with oral risperidone was allowed throughout the trial. The study duration was ≥12 months (until long-acting injectable risperidone was commercially available in the United States).

Concomitant psychotropic medications in Study A included benztropine, lorazepam and hypnotics (temazepam, zolpidem). Concomitant psychotropics in Study B included benztropine, lorazepam, divalproex, and zolpidem.

2.3. Safety and efficacy assessments

Adverse events (patients' spontaneous reports) were recorded at each visit from the time of the first to the last administration of study medication. The severity of extrapyramidal symptoms was assessed by means of the Extrapyramidal Severity Rating Scale (Chouinard et al., 1980) (ESRS) at baseline, at months 3, 12, and 30, and at endpoint (last post-baseline observation carried forward) in Study A; and at baseline and then every 3 months and at endpoint (last post-baseline observation carried forward) in Study B. Treatment efficacy was assessed by means of the CGI at the same time points as above in Study B and at all time points in Study A. Weights were recorded at the same time points that treatment safety and efficacy were assessed.

2.4. Data analysis

All subjects who received at least one injection of study medication were included in the intent-to-treat analysis set. This was the primary analysis set for both safety and efficacy analyses. Changes were calculated from the initial 12-week baseline to endpoint and from the

Table 1 Patient characteristics

	Study A (N=271)	Study B (N=100)
Sex, %		
Male	72	67
Female	28	33
Age, years		
Mean ± S.D.	37.6 ± 10.0	45.4 ± 12.9
Range	18–55	18–81
Race/ethnicity, %		
White	46	48
Black	34	37
Hispanic	14	12
Other	6	3
Diagnosis, %		
Schizophrenia	92	100
Schizoaffective	8	0