INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int J Geriatr Psychiatry 2009; **24**: 518–522.
Published online 12 December 2008 in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/gps.2146

Amisulpride for the treatment of very-late-onset schizophrenia-like psychosis

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SUMMARY

Background Although schizophrenia affects all age groups, late or very-late-onset schizophrenia-like psychosis has not been well studied and various treatment issues remain unresolved. The objective of the present study was to evaluate the efficacy and safety of amisulpride monotherapy in a diagnostically homogeneous group of elderly patients without cognitive impairment suffering from very-late-onset schizophrenia.

Methods Twenty-six patients of mean age 76.2 ± 5.8 years, fulfilling both the recent consensus criteria for very late-onset schizophrenia-like psychosis and the DSM-IV-TR criteria for schizophrenia, were assessed by the Brief Psychiatric Rating Scale, the Clinical Global Impression Scale and the Positive and Negative Syndrome Scale at baseline and five weeks following amisulpride (50–200 mg/day) administration; also, the presence of abnormal movements was evaluated with the Simpson-Angus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale.

Results A highly significant ($p < 0.001$) improvement on all measures of psychotic symptomatology was observed in all patients. Amisulpride was very well tolerated by the patients and no clinically significant adverse effects were observed. Scores on all abnormal movement scales did not differ significantly prior to and after amisulpride treatment.

Conclusion Preliminary results indicate that amisulpride appears to be an efficacious and safe atypical antipsychotic for the treatment of very-late-onset schizophrenia-like psychosis. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — amisulpride; psychosis in the elderly; treatment; very-late-onset schizophrenia-like psychosis

INTRODUCTION

Schizophrenia typically has age of onset during late adolescence or early adulthood; yet, several patients manifest symptoms for the first time in middle or old age. These patients with late (older than 40 years) or very-late-onset schizophrenia (older than 60 years) have similar characteristics to those with early-onset schizophrenia regarding psychopathology, family history, cognitive deficits, non-specific brain imaging abnormalities, course of illness and treatment response (Howard *et al*., 2000; Jeste *et al*., 2005a). However, late or very-late-onset schizophrenia-like psychosis is more often associated with the occurrence of paranoid symptoms, less severe cognitive impairment, a markedly higher prevalence in women and a need for lower doses of antipsychotics for its treatment (Howard *et al*., 2000; Jeste *et al*., 2005a).

Since elderly psychotic patients are more sensitive to extrapyramidal side-effects, atypical antipsychotics seem to be safer in comparison to classical antipsychotics (Alexopoulos *et al*., 2004; Jeste *et al*., 2005b; Folsom *et al*., 2006). Furthermore, these patients may be more susceptible to drug interactions and metabolic changes (Katona, 2001). It is generally acknowledged that the atypical antipsychotic amisulpride has a satisfactory safety profile (among others good pharmacokinetic and cognitive-sparing profile) (Coulouvrat and Dondey-Nouvel, 1999; Ramaekers *et al*., 1999; Leucht, 2004), promotes social functioning (Saleem *et al*., 2002), and therefore seems to be a

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Received 8 May 2008
Accepted 8 September 2008

good candidate for treatment of the elderly patients (Hamon-Vilcot *et al*., 1998; Legangneux *et al*., 2000). This drug has been shown to be efficacious in dysthymic (Bellino *et al*., 1997) and psychotic (Möller *et al*., 2005) elderly patients and in the treatment of behavioural disturbances of patients with moderate to severe Alzheimer's disease (Mauri *et al*., 2006). However, in a recent study it was proposed that adverse effects offset advantages in the efficacy of atypical antipsychotics for the treatment of psychosis, aggression and agitation in patients with Alzheimer's disease (Schneider *et al*., 2006).

The objective of this 5-week open study in a naturalistic setting was to evaluate the efficacy and safety of amisulpride monotherapy in patients without cognitive impairment suffering from very-late-onset schizophrenia-like psychosis.

METHOD

Patients

A total number of 105 patients were assessed at the Psychogeriatric Outpatient Service of the Academic Department of Psychiatry, at the Eginition Hospital. All patients were physically examined and psychiatrically screened by two psychiatrists who administered the Structured Clinical Interview for DSM IV Axis I Disorders Patient's Edition to each subject and assessed cognitive function through the Mini Mental State Examination (MMSE) (Folstein *et al*., 1975). Subjects with a history of substance dependence or current abuse, or with a neurological disease were excluded from the study. Sixty-seven patients were excluded (55 suffering from dementia and 12 suffering from a neurological disease) and four were not included as they refused to provide written informed consent. From the remaining 34 patients, 26 fulfilled both recent consensus criteria for very late-onset schizophrenia-like psychosis in the elderly (Howard *et al*., 2000) and DSM-IV-TR criteria for schizophrenia (APA, 2000). All subjects gave their written informed consent before entering the study. The study was carried out in accordance with the Declaration of Helsinki and after the approval of the Ethics Committee of Eginition Hospital. The subjects presented with delusional ideas and some of them were agitated; none of them suffered from any type of psychotic symptomatology in the past. All included subjects had a MMSE score above 26 at inclusion. All 26 patients (17 women and 9 men) completed the 5-week open study. Age range was between 65–85 years (mean: 76.2 ± 5.8 years).

Treatment

Amisulpride was introduced gradually and the dosage was adjusted according to the clinical condition. The mean dose of amisulpride at baseline was 91.3 ± 33.1 mg/day (range 50–150) and at week 5 was 101 ± 38.4 mg/day (range 50–200 mg/day). Concomitant medication included antihypertensive drugs ($n = 9$), anticoagulants ($n = 3$), lorazepam ($n = 2$, range: 1–2.5 mg/day), bromazepam ($n = 1$, 1.5 mg/day), alprazolam ($n = 1$, 1.5 mg/day), antiarrhythmics ($n = 3$) and antidiabetic medication ($n = 1$).

Assessment and analysis

The Brief Psychiatric Rating Scale (BPRS) (Ventura *et al*., 1993), the Clinical Global Impression Scale (CGI) (National Institute of Mental Health, 1976a) and the Positive and Negative Syndrome Scale (PANSS) (Kay *et al*., 1987) were administered at baseline and after 5 weeks. Adverse events, routine laboratory biochemical tests results and changes in body weight were recorded. Extrapyramidal symptoms were evaluated with the Simpson–Angus Scale (Simpson and Angus, 1979), Barnes Akathisia Scale (Barnes, 1989) and the Abnormal Involuntary Movement Scale (AIMS) (National Institute of Mental Health, 1976b). Electrocardiogram (ECG), heart rate and blood pressure were also monitored during the study. For comparisons between scores at baseline and after 5 weeks of treatment, the non-parametric Wilcoxon Signed Ranks Test for two related samples was used.

RESULTS

Measures of psychopathology

Distributions of scores on the BPRS, CGI and PANSS Positive, PANSS Negative, PANSS General Psychopathology and PANSS Total Score at baseline and at 5 weeks following amisulpride treatment are presented in Figure 1.

A statistically significant improvement on BPRS, CGI, PANSS Positive, PANSS Negative, PANSS General Psychopathology and PANSS Total Scores was observed by the end of the study (Figure 1). The percentage reduction on psychopathology measures after five weeks of treatment with respect to baseline was 30% for BPRS and 49% for CGI, 38.7% for PANSS Positive score, 29% for PANSS Negative score, 26% for PANSS General Psychopathology score and 46.6% for PANSS Total Score. This considerable improvement of psychotic symptomatology, i.e. delusional ideas and agitation, was

DOI: 10.1002/gps

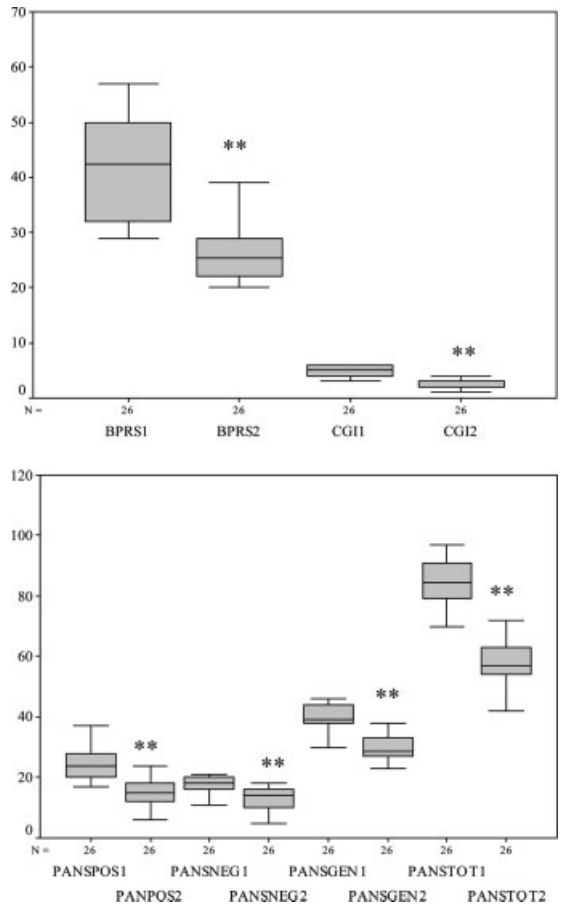

Figure 1. Boxplots of the different measures of psychopathology prior to and after amisulpride treatment. Dark line = median value; shaded box = 25th to 75th percentile of the cases; extensions (whiskers) connect the highest and lowest values that are not categorized as outliers. $^{**}p < 0.001$. 1 = baseline; 2 = after 5 weeks of amisulpride administration. BPRS = Brief Psychiatric Rating scale; CGI = Clinical Global Impression scale; PANSS GEN = PANSS General Psychopathology score; PANSS NEG = PANSS Negative score; PANSS POS = PANSS Positive score; PANSS TOT = PANSS Total score.

observed in all patients. No statistically significant change in overall cognitive function, as measured by the MMSE, was recorded. Also, no significant differences were observed between the groups of very old patients, i.e. aged ≥ 80 years, and that of patients aged 65–79 years; furthermore, no differences were observed between men and women.

Adverse effects

No significant adverse effects or abnormalities related to ECG, heart rate or blood pressure were recorded during the study; also, in the routine laboratory tests, no significant changes were observed. No sedation or sleep problems of any type were obvious after the initiation of amisulpride. At the study endpoint, the mean change in weight was 0.07 ± 0.66 kg [range (-1.5)–$(+1.2)$ kg]. Three patients (one man aged 84, and two women both aged 80) developed tremor (11.5%); in two of them the tremor completely subsided as daily dosages of amisulpride were reduced from 125 and 150 mg/day to 75 mg/day, respectively. The third patient who received 50 mg/day amisulpride, due to the amelioration of her condition, refused to reduce the dosage before the end of the five-week period.

The mean baseline Simpson–Angus score was 0.21 ± 0.14 (median = 0.2; range: 0–0.5), the mean Barnes Akathisia Scale index score was 0.038 ± 0.2 (median = 0; range: 0–1) while the mean AIMS score was 0.07 ± 0.2 (median = 0; range: 0–1). And after 5 weeks mean Simpson-Angus score was 0.22 ± 0.16 (median = 0.25; range: 0–0.6), mean Barnes Akathisia Scale index score was 0.11 ± 0.3 (median = 0; range: 0–1), and the mean AIMS score was 0.11 ± 0.3 (median = 0; range: 0–1). The scores on the Simpson-Angus scale, Barnes Akathisia Scale and AIMS increased slightly but not significantly, during the study [Simpson Agnus score ($p = 0.15$), Barnes Akathisia Scale score ($p = 0.15$) and AIMS score ($p = 0.3$)] (Table 1).

DISCUSSION

The present study demonstrated a good therapeutic response to amisulpride of patients with very-late-onset schizophrenia-like psychosis reflected in significant improvements both on the BPRS and CGI rating scales after a 5-week treatment.

To our knowledge, only a few studies have investigated to date the use of amisulpride in elderly psychiatric patients. Bellino *et al*. (1997), in a 6-month study where amisulpride (50 mg/day) was used for the treatment of dysthymia in 23 elderly patients, demonstrated its efficacy and good safety profile. In another 6-week, randomised, double-blind study (Möller *et al*., 2005) comparing amisulpride (100–400 mg/day, $n = 24$) and treatment with risperidone (1–4 mg/day, $n = 12$), both drugs were found to be suitable for the treatment of psychotic symptoms in elderly people; the sample however, consisted of a mixed group of patients with a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder or shared psychotic disorder (Möller *et al*., 2005). According to that study, by its end, PANSS total score decreased by 28%

DOI: 10.1002/gps

Table 1. Psychopathology measures and motor side-effects prior and after amisulpride treatment

	Baseline (mean ± SE)	After 5 weeks of amisulpride therapy (mean ± SE)		
BPRS	41.5 ± 8.9 ($M = 44$; $R = 29–57$)	27.2 ± 5.8 ($M = 27$; $R = 20–39$)	$z = -4.46$	$p < 0.001$**
CGI	4.9 ± 0.97 ($M = 5$; $R = 3–6$)	2.5 ± 0.94 ($M = 2$; $R = 1–4$)	$z = -4.54$	$p < 0.001$**
PANSS POS	26 ± 7.1 ($M = 24$; $R = 17–45$)	15.9 ± 5.3 ($M = 15$; $R = 6–30$)	$z = -4.46$	$p < 0.001$**
PANSS NEG	16.9 ± 3.8 ($M = 18$; $R = 7–21$)	12.7 ± 4.1 ($M = 14$; $R = 5–18$)	$z = -4.47$	$p < 0.001$**
PANSS GEN	39.7 ± 4.3 ($M = 39$; $R = 30–46$)	29.4 ± 4.2 ($M = 28.5$; $R = 23–38$)	$z = -4.46$	$p < 0.001$**
PANSS TOT	83.5 ± 9.1 ($M = 84.5$; R = 60–97)	56.9 ± 9.5 ($M = 57$; $R = 26–72$)	$z = -4.45$	$p < 0.001$**
Simpson –Agnus scale score	0.21 ± 0.14 ($M = 0.2$; $R = 0–0.5$)	0.22 ± 0.16 ($M = 0.25$; $R = 0–0.6$)	$z = -1.4$	$p = 0.15$
Barnes Akathisia scale index	0.038 ± 0.2 ($M = 0$; $R = 0–1$)	0.11 ± 0.3 ($M = 0$; $R = 0–1$)	$z = -1.4$	$p = 0.15$
AIMS score	0.07 ± 0.2 ($M = 0$; $R = 0–1$)	0.11 ± 0.3 ($M = 0$; $R = 0–1$)	$z = -1$	$p = 0.3$

AIMS = Abnormal Involuntary Movement scale; BPRS = Brief Psychiatric Rating scale; CGI = Clinical Global Impression scale; M = median; PANSS GEN = PANSS General Psychopathology score; PANSS NEG = PANSS Negative score; PANSS POS = PANSS Positive score; PANSS TOT = PANSS Total score; R = range; SE = Standard Error.
**statistically significant for $p < 0.001$ (Wilcoxon Signed Ranks Test for two related samples).

in the amisulpride group compared to 29% in the risperidone group. An analogous reduction by 29% and 30% was observed on the BPRS score after amisulpride and risperidone treatment, respectively; various adverse effects were experienced by ten patients in the amisulpride group and one of them discontinued treatment due to the emergence of a movement disorder (Möller *et al*., 2005). No changes in cognitive function were observed using the MMSE. In a third study (Mauri *et al*., 2006), patients with moderate to severe Alzheimer's disease ($n = 18$) who were treated with amisulpride (200 mg/day), showed a remarkable decrease in the Neuropsychiatric Inventory (NPI) total scores, particularly on the sub-item of agitation; cognitive and motor symptoms did not worsen significantly over the 12-week period of the study. This is in accordance with our findings, in a population without cognitive impairment, where a considerable amelioration of agitation was observed. However, it is difficult to compare our findings with those of the other three studies (Bellino *et al*., 1997; Möller *et al*., 2005; Mauri *et al*., 2006) because patients with different psychopathological characteristics were included, conversely to our study which comprised exclusively very-late onset schizophrenia-like psychosis patients.

As far as abnormal movements concern, in our sample only three very old patients (aged ≥ 80 years) presented with tremor; this may be due to a greater susceptibility of very old individuals to develop extrapyramidal symptoms. Moreover, although there are reports that some amisulpride-treated elderly patients may present sedation and/or hypotension (Lecrubier *et al*., 2001) these side effects were not observed in any of our patients. Finally, regarding improvement of psychopathology, no significant differences were observed between very old patients aged ≥ 80 years and patients aged 65–79 years; furthermore, no differences were observed between men and women.

In conclusion, although our findings should be considered preliminary due to the limitations of a small sample size ($n = 26$), the short duration of the trial and the lack of a control group, our study conducted in a diagnostically homogeneous group without cognitive impairment showed that amisulpride monotherapy (50–200 mg/day) seems to be safe and effective for the treatment of elderly patients with very-late-onset schizophrenia-like psychosis.

CONFLICT OF INTEREST

None known

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DOI: 10.1002/gps

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