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Original article

A double-blind randomised comparative trial of amisulpride versus olanzapine for 2 months in the treatment of subjects with schizophrenia and comorbid depression

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Abstract

Purpose: To compare the efficacy and safety of amisulpride and olanzapine in subjects with schizophrenia and comorbid depression in a randomised double-blind trial.

Patients: Eighty-five adult patients fulfilling DSM-IV criteria for schizophrenia and presenting a depressive episode were randomised to amisulpride (200–600 mg/day) or olanzapine (5–15 mg/day) for 8 weeks. Primary efficacy variables were change in Calgary Depression Scale (CDS) score and Clinical Global Impression (CGI) of Change. Safety was monitored by adverse event reporting and determination of extrapyramidal function and metabolic variables.

Results: The mean change from baseline of CDS score was –6.84 in the amisulpride group and –7.36 in the olanzapine group. 65.9% and 61.5% of subjects, respectively, were considered "much" or "very much" improved. No significant inter-group difference in effect size was observed. The frequency of adverse events was low and emergence of extrapyramidal symptoms was not seen. Four patients in the olanzapine group developed abnormal triglyceride levels. Mean weight gain was 1.45 and 0.5 kg, respectively, in the olanzapine and amisulpride groups.

Conclusion: Amisulpride and olanzapine are effective in patients with schizophrenia and comorbid depression. Tolerance of both drugs was acceptable, although use of olanzapine was associated with a trend toward greater metabolic side-effects [19].

Keywords: Amisulpride; Olanzapine; Schizophrenia; Depression; Randomised clinical trial

1. Introduction

Depression is a common but little studied syndrome in schizophrenia. The proportion of subjects with schizophrenia who also present co-morbid depression has been variously reported in the past as being between 7% and 75%, [25,30], with the apparent discrepancies being attributed to differences in the definitions used for both schizophrenia and depression as well as differences in assessment methodology and subject status [30]. However, there is now general agreement that depressive syndromes are present in around 25% of all cases of schizophrenia [25]. The consequences of co-morbid depression in schizophrenia can be serious, as it is associated with worse outcome, impaired function, poor quality of life and higher rates of relapse and re-hospitalisation [30,31] and may also contribute to the high rates of suicide in schizophrenia (Collaborative Working Group) [30].

Depressive symptoms are relatively resistant to conventional antipsychotics such as haloperidol and, in addition, these drugs do not reduce the risk of suicide [17]. However, there is some evidence that the newer atypical antipsychotic drugs, such as amisulpride, clozapine, olanzapine and risperidone, may be more efficacious in combating depression and suicide than the conventional drugs. Clozapine has been shown to reduce the suicide attempt and completion rates in schizophrenia and schizoaffective disorder by as much as 75–85% [17] and to be more effective than olanzapine in this respect [18]. On the other hand, olanzapine has been shown to be effective in ameliorating depression associated with schi-

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zophrenia as compared to placebo or haloperidol [8,32] and risperidone to be more effective than haloperidol in patients with high anxiety/depression scores [26]. The antidepressant properties of these atypical neuroleptic drugs has been suggested to be due to their broad affinity for neurotransmitter receptors, particularly the serotonin receptor, 5-HT_2, as compared to conventional neuroleptic drugs that are relatively specific for dopamine D_2 receptors [30,32].

However, amisulpride is an atypical antipsychotic that has a selective affinity for D_2 and D_3 receptors with no relevant affinity for serotonin receptors [28]. Phase II and III studies have shown that amisulpride has at least comparable antipsychotic activity to haloperidol, α-flupenthixol, risperidone and olanzapine but with a lower risk of extrapyramidal side-effects [19]. This drug is also effective on primary negative symptoms, for which conventional antipsychotics are of limited use [15]. In addition, studies using animal models have suggested that amisulpride has antidepressant properties [24] and this has been confirmed by clinical studies where amisulpride was found to be as effective as standard antidepressants in patients with dysthymia [7,14,27]. Moreover, a pooled analysis of three clinical studies concluded that amisulpride improves depressive symptoms to a significantly greater extent than either haloperidol or risperidone in subjects with acute exacerbations of schizophrenia [25]. The advantage in favour of amisulpride was seen as soon as the second week of treatment and was particularly pronounced in severe subjects. However, although available data suggest that atypical antipsychotics such as amisulpride and olanzapine improve depressive symptoms in patients with schizophrenia, no data are available concerning their efficacy in patients fulfilling diagnostic criteria for depression. To address this issue, we have now performed a randomised clinical trial of amisulpride and olanzapine in patients with schizophrenia and comorbid depression.

The primary objective of this double-blind, parallel-group, randomised clinical trial was to compare the efficacy of treatment for 8 weeks with amisulpride and olanzapine in subjects with a diagnosis of schizophrenia and a major or minor depressive episode as defined in the DSM-IV. A secondary objective was to evaluate the safety of the two treatments in terms of incidence of adverse events and metabolic control.

2. Methods

This randomised, double-blind study was performed in 17 centres in France, Italy and Tunisia. The initial target sample size was 100 subjects. Inclusion started in February 2002 and the last subject completed the 8-week treatment period in September 2003.

1.1. Subjects

Preliminary statistical power calculations (see below) required at least 50 subjects per treatment arm to be included. The study included adult subjects aged 18–65 years of either sex with a diagnosis of schizophrenia (paranoid, disorganised or undifferentiated type) and presenting a major or minor depressive episode according to the DSM-IV criteria [4]. Inclusion criteria included a score on the Calgary Depression Scale (CDS) [1,2] of at least six and with less than three items of the positive symptoms subscale of the Positive and Negative Syndrome Scale (PANSS) [11] having a score superior to four at inclusion, and with a mental state necessitating modification of treatment. Psychotic symptomatology was required to have been stable over the month preceding inclusion into the study. Exclusion criteria related to comorbid pathologies and previous or concomitant medication use, and also extended to pregnant and lactating women, and those women of childbearing age not using an adequate means of contraception. Comorbid pathologies incompatible with the entry criteria were severe somatic disease, recent or ongoing alcohol or substance abuse, Parkinson's disease, a history of seizures, prostatic hypertrophy, paralytic ileus, phaeochromocytoma, bradycardia < 55 bpm, known hyperkalaemia, congenital prolongation of the QT interval and known risk for narrow-angle glaucoma. Forbidden concomitant medications included class Ia or III anti-arrhythmic drugs, medications known to be associated with *torsades de pointe* or to cause bradycardia and lithium within 10 days of the screening visit. Concomitant psychotropic medication, notably antidepressants, was not permitted throughout the study, with the exception of benzodiazepines either prescribed before D-6, or prescribe to during the study control agitation or insomnia. In this latest case, only benzodiazepine at doses ≤ 30 mg/day were permitted during a period not longer than 4 weeks.

Subjects currently treated with amisulpride or olanzapine or previously treated with one of these drugs without clinical response, unresponsive to two other antipsychotics of different pharmacological classes, or treated with depot antipsychotic medication within an interval corresponding to two injection periods were also excluded. Finally, subjects with a known allergy to olanzapine, amisulpride or any of their excipients were excluded. Although both in- and out-patients were eligible for inclusion in the study, it was recommended that subjects be hospitalised for the initial wash-out period.

1.2. Study procedure and treatments

At an initial screening visit, a thorough clinical and psychiatric examination was performed on subjects meeting the entry criteria. Psychotic symptoms were evaluated with the PANSS [11], depression with the CDS [1,2] and extrapyramidal symptoms with the Abnormal Involuntary Movement Scale (AIMS) [21]. At this time, a single-blind placebo wash-out period of 3–6 days was initiated and an electrocardiogram and blood test programmed.

On day zero, subjects returned for the baseline visit and the entry criteria were again verified. The state of the subjects was evaluated with the PANSS, the CDS, the AIMS, the Clinical Global Impression (CGI) [22], the Simpson–Angus Scale [29] and the Barnes Akathisia Index [5]. Subjects whose total score on the PANSS had increased by more than 20% since the