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Original article

A naturalistic multicenter study of intramuscular olanzapine in the treatment of acutely agitated manic or schizophrenic patients

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Abstract

Background: We conducted a naturalistic, multicenter, 24-hour, nonrandomized, observational study describing for the first time the effectiveness and safety of intramuscular (IM) olanzapine to control agitation and aggression in "real world" patients with psychosis. The data thus obtained was compared with that reported from randomized double-blind clinical trials.

Method: 92 patients attending psychiatric emergency settings were enrolled. The study subjects were 44 male and 48 female patients with a mean age of 36.5 ± 12 years and DSM-IV-TR diagnoses of schizophrenia (48.9%), psychotic disorder not specified (23.9%) or bipolar disorder (27.2%). 10 mg IM olanzapine was administered to all patients. An optional second injection was permitted ≥ 2 hours later in line with hospital policy. Evaluations (PANSS-EC and CGI-S) were performed at baseline and 2 and 24 hours following the IM injection.

Results: Two hours after IM olanzapine was administered, a mean decrease of –9.6 in the PANSS-EC from a baseline score of 26.5 was recorded. At the 24-hour endpoint a statistically and clinically significant reduction in the PANSS-EC scores (11.6 ± 5.3) was observed as compared with values at study entry (26.5 ± 5.9) and at 2 hours endpoint (16.9 ± 9.3), which represent a mean decrease of –14.9 and –5.3, respectively.

Conclusion: The present naturalistic study provides naturalistic data on the effectiveness of IM olanzapine in the treatment of acute agitation in patients with schizophrenia or bipolar mania that is in line the data obtained in randomized double-blind clinical trials.

Keywords: Atypical antipsychotics; Intramuscular; Schizophrenia; Agitation; Olanzapine

1. Introduction

Agitation is common in patients with acute schizophrenia or bipolar mania [1–3]. It may also appear as a consequence of noncompliance with prophylactic antipsychotic treatment or because of lack of efficacy of antipsychotic medication [4]. The core symptoms of agitation include salient excitement, hostility, aggressive behavior, assaultiveness, violent or physical destructive behavior, verbal abuse, threatening gestures or language, extreme personal distress and vocal outbursts [5–7].

Pharmacotherapy for acute agitation includes the use of antipsychotic and benzodiazepine drugs, either alone or in combination. If treatment with oral medication is not possible, parenteral medication may be administered [8]. Until recently, only conventional antipsychotic and benzodiazepine drugs were available as intramuscular (IM) injections. Olanzapine has been one of the first atypical antipsychotics available for IM administration. Four randomized placebo and comparator controlled, double-blind clinical trials have demonstrated the efficacy of olanzapine in reducing acute agitation in approximately 1050 patients with schizophrenia, schizoaffective and

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bipolar disorder [9]. Evidence from these clinical trials has shown that IM olanzapine is associated with significantly fewer extrapyramidal system adverse effects than monotherapy with IM haloperidol [10,11].

Differences between clinical trials and utilization in real clinical practice need to be identified because of their potential clinical and economic impact. These differences include prescription of doses associated with lower efficacy or with increased risk of adverse effects, and generalization of data from the less severely ill patients recruited to clinical trials results to the more severely ill patients treated in routine practice [12]. The present study is the first description of the effectiveness and safety of intramuscular olanzapine to control agitation and aggression in "real world" patients with psychosis attending psychiatric emergency services (PES). It utilizes a naturalistic, nonrandomized, observational design. The data obtained is compared with that reported for the randomized, double-blind clinical trials.

2. Subjects and methods

2.1. Patients

Ninety-two patients attending a psychiatric emergency setting (PES) were enrolled in a multicenter 24-hour prospective, naturalistic, nonrandomized, observational study. The study subjects were 44 male and 48 female patients with a mean age of 36.5 ± 12 years (range 18–70) and DSM-IV-TR diagnoses of schizophrenia ($N = 45$; 48.9%), psychotic disorder non specified ($N = 22$; 23.9%) or bipolar disorder ($N = 25$; 27.2%). All patients were clinically agitated and appropriate candidates to receive IM treatment. Pregnant or lactating women and patients with serious medical illnesses or alcohol and other drug use (particularly sympathomimetic drugs of misuse such as cocaine, MDMA and amphetamines) in which pharmacotherapy posed a substantial clinical risk or confounded diagnosis were excluded. Urine screening drug tests were performed at study entry.

Immediately prior to study entry 32.6% of patients were taking prescribed antipsychotic medication (18 olanzapine, 9 risperidone and 3 haloperidol), while 67.4% of patients were not complying with prescribed antipsychotic medication. Concerning other medications, 15.2% of the patients were taking benzodiazepines, 7.6% lithium, 4.3% anticholinergic medication and 2.2% topiramate.

2.2. Interventions

In keeping with good clinical practice IM olanzapine 10 mg was administered at study entry to all patients after they had been offered, and had refused, oral medication [13]. Optional second injections were permitted ≥ 2 hours after the first injection, based on clinical judgment and in line with hospital policy. In order to avoid pharmacological interferences with IM olanzapine, no additional psychotropic drug was administered during the 24 hour observational period.

The excited component of the positive and negative syndrome scale (tension, uncooperativeness, hostility, poor impulse control, and excitement) (PANSS-EC) was utilized to measure agitation [14]. The Clinical Global Impression-Severity (CGI-S) of Illness instrument was used to record the severity of illness [15]. The PANS-EC and CGI-S were administered immediately before, and 2 and 24 hours after, administration of the IM injection. Safety was assessed by recording treatment-emergent adverse events, and changes in vital signs (blood pressure, pulse rate).

The study was conducted at five sites (four general hospitals and one psychiatric hospital) from Barcelona, Burgos and San Sebastian (Spain). The study protocol was approved by the local ethical committees. Following the recommendations of the Ethical Committee and given that all patients were treated in line with hospital policy and standard practice, retrospective written informed consent to utilize data was obtained 24–48 hours after completion of the study procedures.

Student's *t*-test for paired samples was used to compare changes in the PANSS-EC and CGI-S scores from baseline to endpoint at 2 hours after the first injection. Student's *t*-test for unpaired samples was used to assess differences between men and women. ANOVA tests were performed to compare the dependent variable (basal PANSS-EC and CGI scores) between the diagnostic groups. General Linear Model (repeated measures) was used to assess differences between baseline and endpoints at 2 and 24 hours post injection.

3. Results

The mean baseline PANSS-EC score of the enrolled patients was 26.5 ± 5.9 (range = 13–35), with the mean baseline score for each PANSS-EC item being: Poor impulse control = 5.03 ± 1.4; tension = 5.6 ± 1.1; hostility = 5.1 ± 1.6; uncooperativeness = 5.3 ± 1.5; and excitement = 5.4 ± 1.3. Women showed significantly increased baseline PANSS-EC scores than men (27.8 ± 6.1 versus 25 ± 5.4; $t = –2.3$; $P = 0.021$), and therefore sex was used as covariate in the statistical model. Age was significantly correlated neither with the PANSS-EC score nor with any of the individual PANSS-EC items (data not shown).

When age and sex were used as covariates and the psychiatric diagnoses the fixed effect factor, no significant differences were noted in the PANSS-EC scores between the diagnostic groups ($F = 1.9$; $P = 0.10$ for the corrected ANOVA test), with sex showing a statistically significant effect ($F = 4.9$; $P = 0.02$). The baseline Clinical Global Impression-Severity was moderately ill in 17.4% of the patients, markedly ill in 29.3%, severely ill in 39.1%, and among the most severely ill in 14.1%, with a mean score of 5.5 ± 0.9. After correcting for age, sex and diagnoses, no statistically significant differences were noted in the CGI scores among the three diagnostic groups, ($F = 1.8$; $P = 0.12$; ANOVA test), with only sex having a significant effect on the model ($F = 7.1$; $P = 0.009$). Due to the severity of the agitation, physical restraint ordered by the psychiatrist and performed by trained staff was necessary in 68.5% of the included patients.