Available online at www.sciencedirect.com
ScienceDirect
Progress in Neuro-Psychopharmacology & Biological Psychiatry 30 (2006) 1291–1298
Progress In Neuro-Psychopharmacology & Biological Psychiatry
www.elsevier.com/locate/pnpbp

Effects of olanzapine on aggressiveness in heroin dependent patients

G. Gerra [g,*], G. Di Petta [a], A. D'Amore [b], P. Iannotta [b], F. Bardicchia [d], F. Falorni [d], A. Coacci [d], G. Strepparola [e], G. Campione [e], A. Lucchini [e], G. Vedda [c], G. Serio [c], E. Manzato [f], M. Antonioni [g], S. Bertacca [g], G. Moi [g], A. Zaimovic [g]

[a] *Dipartimento Dipendenze ASL Caserta, Aversa, Italy*
[b] *Dipartimento Dipendenze ASL Napoli 3, Italy*
[c] *Dipartimento Dipendenze Patologiche AUSL 6 Palermo, Italy*
[d] *Dipartimento Dipendenze ASL Grosseto, Italy*
[e] *Dipartimento Dipendenze ASL 2 Milano, Italy*
[f] *Dipartimento Dipendenze ASL Verona, Italy*
[g] *Centro Studi Farmaco-tossicodipendenze, Ser. T., AUSL Parma, Italy*

Received 28 January 2006; received in revised form 27 March 2006; accepted 20 April 2006
Available online 12 June 2006

Abstract

This study compared the anti-aggressiveness effects of the atypical anti-psychotic olanzapine with that of selective serotonin reuptake inhibitors (SSRI) and benzodiazepines (BZD) among patients with heroin dependence submitted to opioid-agonists substitution treatment. Sixty-seven (67) patients who met the DSM-IV criteria for heroin dependence and showed aggressive personality traits, not affected by comorbid schizophrenia or bipolar disorder, accepted to participate in a 12-week prospective, observational trial. Patients were included into two subgroups in relationship with treatment, for the evaluation of the endpoints at week 12: group 1: substitution treatment in combination with OLA (32 patients); group 2: substitution treatment in combination with fluoxetine/paroxetine and clonazepam (35 patients). Efficacy measures were Buss Durkee Hostility Inventory (BDHI), Symptoms Check List-90 (SCL 90) anger–hostility scores, incidence rates of aggressive incidents and attacks. The rates of patients who remained in treatment at week 12 in group 1, treated with OLA, and group 2, treated with SSRI and BDZ, were not significantly different (17=53.1% vs 16=45.7%). BDHI total, direct aggressiveness, verbal aggressiveness scores, SCL 90 aggressiveness scores and aggressive incidents rates showed a significantly more consistent decrease from baseline in group 1 than in group 2 subjects, in the patients who completed the treatment ($p<0.001$; $p<0.01$; $p<0.05$; $p<0.01$; $p<0.001$). Among the completers, 69.3% achieved early full substance abuse remission, while 30.7% achieved partial substance abuse remission, with no significant difference between 1 and 2 treatment subgroups. Although obtained by an observational–open clinical study, with multiple limitations, our findings suggest that OLA may be useful as an adjunctive agent in reducing aggressive/hostile behaviour in heroin addicted individuals during maintenance substitution treatment. Otherwise, atypical anti-psychotic OLA seems to be unable to improve the outcome in terms of addictive behavior and relapse risk in the addicted patients not affected by overt psychotic disorders.

Keywords: Aggressiveness; Clonazepam; Fluoxetine; Heroin dependence; Maintenance treatment; Olanzapine; Opioid agonists; Paroxetine

1. Introduction

Atypical anti-psychotics have been found effective for the treatment of aggressiveness in schizophrenic patients, particularly when aggression persists or is repetitive (Buckley, 1999), indicating that these drugs may have therapeutic effects on mood disorders and hostility as well as psychosis (Keck et al., 2000).

In particular olanzapine, an atypical neuroleptic drug with mood-stabilizing properties, seems to reduce hostile/aggressive behavior in schizophrenic patients (Bitter et al., 2005) and was previously shown to result in greater improvement in agitation, comprising tension, hostility, uncooperativeness and excitement, than that achieved with haloperidol (Kinon et al., 2001).

* Corresponding author. National Department on Drug Policy Via della Mercede, 9 00187 Roma, Italy. Tel.: +39 06 67796809; fax: +39 06 67796838.
E-mail address: g.gerra@palazzochigi.it (G. Gerra).

0278-5846/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2006.04.023

Nevertheless, some findings suggest that olanzapine may be more effective than traditional anti-psychotic drugs in the control of aggressive behavior also in non-schizophrenic patients, particularly in special populations such as aggressive and violent patients with brain injury, mental retardation, personality disorders (Fava et al., 1997), substance abuse disorder and senile dementia (Krishnamoorthy and King, 1998).

To this purpose, olanzapine was used to treat severe aggression in non-psychotic teenage boys with neuropsychiatric disorders, markedly increasing sense of well being and self-control (Soderstrom et al., 2002). Accordingly, preliminary results have been obtained in patients with Tourette's disorder, in which olanzapine was found a safe and effective treatment for aggression and tics, alternative to other anti-psychotics (Stamenkovic et al., 2000; Stephens et al., 2004). The use of atypical anti-psychotics in children and adolescents with aggressiveness has increased significantly over the past few years. Atypical anti-psychotics are associated with a more favorable side-effect profile, and growing evidence supports their efficacy for aggression in this population (Patel et al., 2005).

A retrospective, open-label, naturalistic trial showed olanzapine ability to control challenging behaviors in intellectually disabled adults with self-injurious, aggressive, and disruptive behavior (Janowsky et al., 2003). Accordingly, pervasive developmental disorder displaying aggression and/or self-mutilation or geriatric conditions such as senile dementia and aggression have been successfully treated with olanzapine by other research groups (Toren et al., 1998; Chengappa et al., 2001; Glick et al., 2001).

To increase the evidence concerning the use of olanzapine in the control of aggressiveness in non-psychotic patients, olanzapine was recently reported to significantly ameliorate chronic dysphoria and impulsive aggression in women with borderline personality disorder (Zanarini et al., 2004).

Although no conclusive evidence exists to suggest whether atypical anti-psychotics are useful means for controlling aggression, Cochrane analyses on Controlled Trials Register (2002) and Schizophrenia Group's Register (2004) did not exclude that olanzapine has some value in helping manage acute aggression or agitation, especially where it is necessary to avoid some of the older, better known treatments (Belgamwar and Fenton, 2005).

The aim of the present study was to evaluate the possible effectiveness of olanzapine, in combination with methadone or buprenorphine, in the control of aggressive behavior of non-psychotic addicted individuals. To this purpose, heroin addicted patients who were characterized by aggressive personality traits received either olanzapine (group 1) or selective serotonin reuptake inhibitors (SSRI) and benzodiazepines (group 2) as adjunctive medication, in combination with maintenance substitution treatment.

The anti-aggressive effect of olanzapine have not yet been directly demonstrated in addicted individuals in a prospective study. The data reported in this article were obtained during the conduct of a multi-centre, prospective, observational trial designed to examine the efficacy of olanzapine in combination with opioid-agonists compared with that of SSRI and BDZ.

Our hypothesis was that multi-receptor antagonists such as olanzapine (Gerlach and Peacock, 1995) may inhibit aggressive behavior in addicted individuals, as measured by rating scales and by number of defined events, reducing hostility attitude and irritability.

2. Material and methods

2.1. Subjects

Sixty-five heroin dependent subjects were selected from among outpatients participating in Caserta, Grosseto, Milan, Naples, Palermo and Parma Addiction Services Programs (Servizi Tossicodipendenze-Ser.T) of the public health system during the period July 2004–March 2005. Addiction Services in Italy provide outpatients treatment programs, with different therapeutic and rehabilitative strategies: methadone, buprenorphine and naltrexone are administered in association with possible psychosocial intervention, such as psychotherapy, family therapy, group therapy, social support and medication for dually diagnosed patients. Most of the patients in the Italian Addiction Services are seeking treatment for heroin dependence, although the same Services offer rehabilitative programs also for cannabis, cocaine and alcohol addiction. No exclusion criteria are applied to select patients in the public health system. All the patients have been routinely evaluated using a self-report and observer-rated questionnaire concerning addiction history and a psychiatric diagnostic screening. Data describing a detailed history of the patients were also obtained from previous drug addiction centers records.

Subjects eligible for this open-label study were all the heroin dependent patients entering methadone and buprenorphine long-term treatment during the 9 months between July 2004 and March 2005, who showed aggressive personality traits without a comorbid diagnosis of schizophrenia or bipolar disorder (DSM Axis I criteria). To be included in the study the patients had to score higher than 60 at BDHI baseline evaluation.

The informed consent to participate in an observational study was obtained from each patient. No one of the patients, who were not paid for their participation, refused to take part in the study.

Participants were heroin dependent for at least 5 years (mean 8.1 ± 3.0). Daily intake of heroin ranged from 1.5 to 3.0 g of street heroin, being the purity of the drug on the Italian illicit market in the range between 10% and 15% (Italian National Report 2004).

All the patients included in the study have abused alcohol or other illicit drugs occasionally. Patients with long-lasting periods (more than 3 months) of consumption of drugs other than heroin or prolonged (more than 6 months) alcohol dependence in the clinical history were excluded. Additional exclusion criteria included severe chronic liver illness (transaminases > 60 U/L and gammaglobulines > 21%), renal disease (creatinine clearance: 100–120 mg/L/min), other chronic medical disorders, recent significant weight loss or obesity, endocrinopathy or immunodeficiency.

Blood samples for the evaluation of glucose plasma levels have been collected at the beginning of the study, at week 4, 8 and 12.

2.2. Data collection strategy

The patient inclusion form requested the following information: patient identification, heroin exposure extent (years),