Olanzapine augmentation of paroxetine-refractory obsessive-compulsive disorder

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Abstract

The aim of the present study was to investigate the effect of adjunctive olanzapine in patients with obsessive-compulsive disorder (OCD) refractory to paroxetine. Twenty-one patients unresponsive to treatment with paroxetine, administered for at least 12 weeks at the dose of 60 mg/day, participated in a 12-week open-label, add-on trial with olanzapine (10 mg/day). The psychopathological state was evaluated by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and by Clinical Global Impression (CGI). Three patients did not complete the 12-week adjunctive treatment with olanzapine. In the 18 completers, the mean Y-BOCS score decreased significantly from 27.1 ± 4.0 at baseline to 20.1 ± 3.9 at final evaluation (P < .001). Seven patients (38.9%) were rated as responders at final evaluation. Steady-state plasma concentrations of paroxetine were not modified during olanzapine coadministration. The drug combination was generally well tolerated and initial sedation and weight gain were the most frequent unwanted effects. Our findings confirm the results of previous studies and indicate that the addition of olanzapine to ongoing treatment with serotonin reuptake inhibitors (SRI) may be beneficial in some patients unresponsive to SRI monotherapy.

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1. Introduction

Serotonin reuptake inhibitors (SRI) are the most effective agents currently available in the treatment of obsessive-compulsive disorder (OCD) (Greist et al., 1995; Piccinelli et al., 1995). Unfortunately, between 40% and 60% of patients with OCD do not respond to SRI therapy, and some patients do not experience complete remission of symptoms (Goodman, 1999). Augmentation strategies with agents enhancing serotonin function, such as lithium, buspirone and clonazepam, have yielded inconsistent results in SRI-refractory patients (McDougle, 1997). On the other hand, low doses of dopamine antagonists, such as the conventional antipsychotics haloperidol and pimozide, were found to be effective, particularly in patients who have a comorbid chronic tic disorder or schizotypal personality disorder (McDougle et al., 1990, 1994).

Over the last decade, newer antipsychotics have been introduced in clinical practice and they appear to have a better tolerability and safety profile than traditional agents. Although different reports indicate that atypical antipsychotics may induce or exacerbate OCD symptoms in schizophrenic patients (Baker et al., 1992; Kopala and Honer, 1994; Morrison et al., 1998), a growing literature suggests that some of these agents may be also beneficial in the treatment of refractory OCD (Potenza and McDougle, 1998). While available clinical data do not support the utility of clozapine in OCD (McDougle et al., 1995a), many open-label trials and one double-blind, placebo-
controlled study have documented the efficacy of adjunctive risperidone in the treatment of OCD patients non-responsive to SRI (Jacobsen, 1995; McDougle et al., 1995b, 2000; Saxena et al., 1996; Ravizza et al., 1996; Stein et al., 1997). An increasing number of open studies and case reports also support the potential benefits of other new antipsychotics, such as olanzapine (Marazziti and Pallanti, 1999; Weiss et al., 1999; Bogetto et al., 2000; Koran et al., 2000; Francobandiera, 2001) and quetiapine (Mohr et al., 2002; Atmaca et al., 2002), as adjunctive therapy for refractory OCD.

The aim of the present study was to further evaluate the efficacy and tolerability of olanzapine augmentation in patients with OCD refractory to paroxetine, a selective SRI with a documented efficacy in OCD (Zohar et al., 1996). We also investigated the effect of olanzapine on steady-state plasma concentrations of paroxetine.

2. Patients and methods

2.1. Patients

Outpatients who met DSM-IV criteria (American Psychiatric Association, 1994) for OCD, who had completed an acute phase therapy with paroxetine 60 mg/day for at least 12 weeks, and were refractory to treatment, were considered for an augmentation trial with olanzapine. According to McDougle et al. (2000), criteria for nonresponse to paroxetine included (a) less than 35% decrease on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989a,b) total score at final evaluation as compared to baseline or a final score of >16 on the Y-BOCS and (b) no better than “minimally improved” on the Clinical Global Impression (CGI) improvement item (Guy, 1976). Patients were included if they had comorbid chronic tic disorder and schizotypal personality disorder. Exclusion criteria were presence of any other primary psychiatric diagnosis, significant concurrent physical illness, alcoholism or other drug addition, pregnancy or lactation. Patients were also excluded if they received concomitant specific psychotherapies. The study was approved by the Ethical Committee of the University of Messina and all patients gave written informed consent to participate.

2.2. Drug assays

Plasma concentrations of paroxetine were measured in the week before starting treatment with olanzapine (baseline values) and at week 12 after beginning of olanzapine medication. Blood samples were drawn at about 8:00 a.m., before administration of the paroxetine morning dose. Plasma was collected after centrifugation and kept frozen at −20 °C until assayed. Steady-state plasma concentrations of paroxetine were determined by HPLC according to the method of Gupta (1994).

2.3. Study design

The augmentation trial was designed as a 12-week open-label study. Each patient gave informed consent to participate to the augmentation phase. Olanzapine was added at the initial dose of 5 mg/day and gradually increased to 10 mg/day within 2 weeks. Olanzapine was administered once daily at bedtime. Paroxetine dose, 20 mg 3 times daily, was kept constant throughout the olanzapine-addition phase. No other psychotropic medication was allowed, except for benzodiazepines in occasional cases.

2.4. Clinical assessment

The patients were rated for psychopathology at baseline and at the end of weeks 2, 4, 8 and 12 of adjunctive olanzapine by using the Y-BOCS and the CGI. Patients were classified as responders to the paroxetine–olanzapine combination if they showed (a) a 35% or greater reduction on the Y-BOCS total score at final evaluation compared to the beginning of adjunctive therapy and a final score of 16 or less and (b) a final CGI rating of “much improved” or “very much improved.”

Adverse effects, either observed or spontaneously reported, were recorded at each visit and classified in terms of onset, duration, severity, action taken and outcome. ECG and laboratory tests, including hematology, clinical chemistry and urine analysis, were performed on admission and at the end of adjunctive treatment. Blood pressure, heart rate and body weight were measured at all study visits.

2.5. Statistical analysis

Analysis of variance (ANOVA) for repeated measures was used to compare the mean Y-BOCS scores at each assessment time. Plasma concentrations of paroxetine before and after 12 weeks of olanzapine coadministration were compared by the Student’s t test for paired data. Differences in plasma paroxetine concentrations between responders and nonresponders were compared by the Student’s t test for unpaired data. Results are given in the text as means ± S.D. A P value of < .05 was regarded as statistically significant.

3. Results

Twenty-one out of 47 patients who had completed an acute 12-week treatment phase with paroxetine were refractory to SRI monotherapy and entered the open-label trial with adjunctive olanzapine. In the 26 patients who had responded to paroxetine alone, reduction of Y-BOCS score at final evaluation as compared to baseline ranged from 35% to 78% (mean reduction of 47%). The decrease in the Y-BOCS score in the 21 nonresponders ranged from 2% to 33% (mean reduction of 17%). In particular, in five of the nonresponders, the reduction was greater than 25%, which
could be defined as partial response according to the stages of response proposed by Pallanti et al. (2002).

Of the 21 patients participating to the augmentation, three subjects did not complete the study: two dropped out after 2 and 4 weeks because of adverse effects (oversedation and increased appetite with bulimic episodes, respectively) and one did not comply with the study visits. The 18 patients who completed the 12 weeks included 10 women and 8 men, with an age range of 26–62 years (42.9 ± 11.1 years). Concomitant diagnosis of chronic tic disorder and schizotypal personality disorder was present in two and three patients, respectively.

The psychopathological state, as assessed by Y-BOCS and CGI, improved significantly over the time of treatment. The mean Y-BOCS score decreased significantly from 27.1 ± 4.0 at baseline to 20.1 ± 3.9 at final evaluation (P < .001). The mean Y-BOCS scores of the 18 completers at each assessment point are shown in Fig 1. At week 12, seven patients (38.9%) were rated as responders. One subject was responder already at week 4 and three subjects at week 8. According to the stages of response proposed by Pallanti et al. (2002), all seven responders had also a remission (Y-BOCS score of 16 or less). On the other hand, none of them reached the stage of recovery (Y-BOCS value of 8 or below). Responders and nonresponders did not differ in sex, age and Y-BOCS score at baseline. One of the two patients with chronic tic disorder and one of the three with schizotypal personality disorder responded to the adjunctive treatment.

The combination paroxetine–olanzapine was generally well tolerated. The most common side effects were sedation (12 patients), weight gain up to 3 kg (8 patients), dry mouth (6 patients) and constipation (3 patients). With the exception of weight gain, these effects were generally mild and transient. No clinically significant changes in blood pressure and heart rate were recorded and no extrapyramidal symptoms occurred.

Plasma concentrations of paroxetine before and during olanzapine coadministration were available in 13 patients. In these subjects, plasma levels of paroxetine were not modified by addition of olanzapine (148 ± 68 ng/ml at baseline vs. 158 ± 70 ng/ml at week 12; NS). Moreover, there were no major differences in plasma paroxetine levels at week 12 between responders (162 ± 92 ng/ml; n = 5) and nonresponders (155 ± 58 ng/ml; n = 8). In 14 patients, classified as responders under paroxetine monotherapy, mean plasma concentration of paroxetine was 154 ± 47 ng/ml at the end of the acute 12-week treatment phase.

4. Discussion

4.1. Efficacy of olanzapine augmentation

The results of the present investigation indicate that addition of olanzapine to ongoing paroxetine treatment may be effective in some patients with OCD unresponsive to paroxetine monotherapy. A mean 25.8% decrease in the Y-BOCS was observed at the end of 12 weeks of adjunctive paroxetine. Our findings are in agreement with the results of previous augmentation trials with olanzapine in patients refractory to SRI (Marazziti and Pallanti, 1999; Weiss et al., 1999; Bogetto et al., 2000; Koran et al., 2000; Franco-bandiera, 2001). The rate of responders in our sample was 38.9%. This is slightly lower than that observed in the study by Bogetto et al. (2000), in which a lower dose of olanzapine (5 mg/day) was added to fluvoxamine. However, fluvoxamine is a potent inhibitor of the cytochrome P450 isoenzyme (CYP1A2, one of the major isoforms responsible for olanzapine metabolism, and has been associated with up to 100% increase in plasma olanzapine concentrations (De Jong et al., 2001). On the contrary, paroxetine is only a weak inhibitor of CYP1A2, while it is a potent inhibitor of CYP2D6 whose contribution to olanzapine biotransformation is marginal (Spina and Scordo, 2002). Therefore, paroxetine is not expected to cause a significant elevation of plasma olanzapine levels. In this respect, fluoxetine, another potent inhibitor of CYP2D6, was found to have a minimal effect on olanzapine concentrations (Callaghan et al., 1999).

It has been suggested that comorbid tic disorder and schizotypal personality disorder are associated with a better response to antipsychotic augmentation of SRI-refractory OCD (McDougle et al., 1990, 1994). Due to the limited number of patients with such comorbidities in our sample, it is not possible to draw definite conclusions on this topic.

4.2. Possible mechanism for the beneficial effect of olanzapine augmentation

The beneficial effect of olanzapine augmentation in paroxetine-refractory OCD patients may be explained by a pharmacokinetic or pharmacodynamic mechanism. As plasma levels of paroxetine were not modified during coadministration with olanzapine, the possibility of a pharmacokinetic interaction with paroxetine can be reasonably
excluded. With regard to this, olanzapine is a weak inhibitor of CYP isoenzymes (Ring et al., 1996) and, accordingly, has not been reported to affect plasma concentrations of any coadministered drug (Spina and Scordo, 2001). In addition, in our patients, plasma levels of paroxetine did not differ between responders and nonresponders to adjunctive olanzapine and were similar to values in responders under paroxetine alone. Therefore, it is likely that the favorable effects of olanzapine, as well as other atypical antipsychotics, may be attributable to a direct pharmacodynamic action. However, the underlying mechanisms are yet unidentified. The observation that antipsychotics may be useful in patients with refractory OCD is consistent with preclinical evidence suggesting significant interactions between serotonin and dopamine systems in mediating OCD symptoms (Goodman et al., 1996). As compared to traditional antipsychotics, atypical agents have a greater affinity for serotonin receptors than dopamine receptors. It has been suggested that the antiserotonoergic properties of atypical antipsychotics may explain the emergence or exacerbation of OCD symptoms in some patients (Potenza and McDougle, 1998). With regard to this, in our series, olanzapine did not worsen OCD symptoms.

Admittedly, the study cannot exclude the possibility that treatment response was due to a longer duration of paroxetine administration. However, in the double-blind, placebo-controlled study by McDougle et al. (2000) documenting the efficacy of adjunctive risperidone in the treatment of OCD patients nonresponsive to SRI, none of the 15 placebo-treated patients responded during the add-on phase.

4.3 Tolerability of olanzapine augmentation

The potential advantages of adjunctive olanzapine should be weighed against the risk of unwanted effects. In the present study, addition of olanzapine to paroxetine medication was generally well tolerated. However, apart from mild and transient olanzapine side effects, such as sedation and anticholinergic effects, two subjects dropped out for adverse effects and some patients experienced a clinically significant body weight gain.

5. Conclusions

Our findings provide further evidence that the addition of olanzapine to ongoing treatment with SRI may be beneficial in some patients unresponsive to SRI monotherapy. These results should be interpreted with caution due to the small sample size and the open-label design. Double-blind, placebo-controlled trials in a larger number of patients, along with trials comparing olanzapine with risperidone or quetiapine, are required to evaluate the therapeutic potential of olanzapine augmentation of SRI-refractory OCD, including determination of optimal dosage and a better definition of patients more likely to benefit from this combination.

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References


