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Effectiveness and tolerability of addition of risperidone in obsessive-compulsive disorder with poor response to serotonin reuptake inhibitors

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Introduction. The addition of typical and atypical antipsychotics in patients with obsessive-compulsive disorder (OCD) resistant to serotonin reuptake inhibitors (SRI) has been reported as a useful augmentation strategy. Although antipsychotic monotherapy has been associated with ineffectiveness and even increase of psychotic symptoms (especially in psychotic patients), antipsychotics as concomitant medications have proven to be effective in several case series and pilot clinical trials. The objective of this case series was to evaluate effectiveness of risperidone as add on therapy to current SRIs treatment in OCD refractory to treatment patients.

Material and method. Risperidone add on therapy in moderate and severe treatment resistant OCD patients was reviewed. Case reports were patients fulfilling the following criteria: *a)* treatment follow-up of at least 12 weeks; *b)* SRI adequate doses, y *c)* Y-BOCS score higher than 16 score before starting treatment. A three month follow-up period was reviewed. Risperidone starting dose was low (mean 1.5 mg/day) and was increased following clinical criteria. Therapeutic response and tolerability were evalated with the following scales: Y-BOCS, CGI of change, UKU (neurological subscale) and spontaneous reported adverse events. Response criteria were the following: at least 35% of reduction in Y-BOCS from basal score and final score less than 16 and CGI-C «much improved» or «very much improved» (score 1 or 2). Intention to treat analysis was performed (patients who reported at least one risperidone dose and effectiveness measure).

Results. 31 patients had at least one effectiveness evaluation and 21/31 patients (67.8 %) were considered treatment responders. Mean risperidone dose was 3.8 mg/day. In general, risperidone was well tolerated: serious or unexpected adverse event were not reported.

Conclusion. Risperidone as add on therapy to SRIs in moderate-severe, refractory to treatment OCD patients, may be an effective and safe strategy.

Key words:
Resistant obsessive-compulsive disorder. Risperidone. Serotonina reputake inhibitors response.

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Efectividad y tolerancia de la adición de risperidona en el trastorno obsesivo-compulsivo con mala respuesta terapéutica a inhibidores de la recaptación de serotonina

Introducción. Existen algunas series de casos publicadas que sugieren la posible efectividad de los antipsicóticos, tanto típicos como atípicos, asociados a los antidepresivos inhibidores de la recaptación de serotonina (IRS) en el tratamiento del trastorno obsesivo-compulsivo (TOC) con mala respuesta terapéutica, aunque el uso en monoterapia de estos antipsicóticos no parece eficaz o incluso puede exacerbar síntomas obsesivos, sobre todo en pacientes psicóticos. El objetivo de esta recogida de datos fue evaluar la efectividad de la adición de risperidona al tratamiento habitual con IRS en una muestra más amplia de pacientes con TOC con mala respuesta al tratamiento.

Material y métodos. Se trata de una recogida de casos en la que se describen pacientes con criterios de TOC moderado-severo y resistente al tratamiento con un IRS en los que se añadió risperidona como tratamiento concomitante. Los casos recogidos fueron pacientes con: *a)* duración del tratamiento de al menos 12 semanas; *b)* dosis adecuadas de IRS, y *c)* puntuación basal superior a 16 en la escala Y-BOCS. Se tomaron datos de la evolución durante 3 meses. La risperidona se administró inicialmente a dosis bajas (med: 1,5 mg/día) y posteriormente la dosis se ajustaba según criterios clínicos. Clínicamente se evaluó la respuesta terapéutica y la tolerancia con las siguientes medidas: Y-BOCS, ICG de cambio, escala UKU modificada y reacciones adversas comunicadas espontáneamente. Se consideraron como criterios de respuesta: descenso de un 35 % o más en la puntuación de la escala Y-BOCS respecto al inicio y

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puntuación final inferior a 16 e ICG de cambio «bastante o muy mejorado» (puntuación de 1 o 2). Se realizó un análisis por intención de tratar, incluyendo aquellos pacientes con al menos una toma de dosis y al menos una evaluación de efectividad.

Resultados. En 31 pacientes existía al menos una valoración de efectividad. Veintiún pacientes de estos 31 (67,8 %) se consideraron respondedores al tratamiento. La dosis media de risperidona usada fue de 3,8 mg/día. La tolerancia fue en general buena: no se recogieron efectos adversos graves ni inesperados.

Conclusión. La adición de risperidona al tratamiento habitual con IRS en casos de TOC moderado-severo con mala respuesta terapéutica al IRS parece una alternativa efectiva y bien tolerada.

Palabras clave:
Trastorno obsesivo compulsivo resistente. Risperidona. Inhibidores de la recaptación de la serotonina.

INTRODUCTION

Serotonin reuptake inhibitors (SRIs) are the most effective drug agents for obsessive-compulsive disorder (OCD), however 40%-60% do not have an adequate response to these[1-3]. Furthermore, the mean reduction of the symptoms range from 35%-40% measured with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[1]. The main causes of the scarce response to treatment are due to reasons beyond drug resistance and the following are the first to stand out: erroneous diagnosis, inadequate treatments, incorrect administration of the treatment by dose or insufficient time, inadequate management of comorbidity, side effects due to the dose used or treatment non-compliance[4].

Several therapeutic alternatives have been used when there is no response. Many of them have scarce empiric evidence, such as the combination of chlorimipramine with SSRI, potentiation of the SRIs with tryptophan, buspirone, lithium, fenfluramine, thyroid hormones or antipsychotics, or the alternative use of SRIs of MAOI, trazodone or nefazodone, inositol, antiandrogens or electroconvulsive therapy[5-7]. Noradrenergic antidepressants may be hardly effective and thus, desipramine added to the SRIs is not superior to the addition of the placebo[8].

Potentiation with antipsychotics is presented as an interesting alternative for these types of patients. In a double blind clinical trial in fluvoxamine refractory OCD patients, the addition of haloperidol was superior to that of the placebo to reduce the symptoms, although the effect was scarce in those patients without concomitant tics[9]. Fluvoxamine levels were not different between both groups, so that the effect was not due to pharmacokinetic interaction. This efficacy has also been demonstrated when pimozide is added to fluvoxamine in the same type of patients[10].

The new antipsychotics may have certain advantages over the classical ones for OCD patients such as their better tolerability, mainly the lower number of extrapyramidal effects and a possible greater efficacy due to their action on different serotoninergic receptors that may be implicated in OCD pathogeny. In any event, the exclusive use of these agents for OCD does not seem to be indicated. Clozapine has been associated with the appearance or exacerbation of obsessive-compulsive symptoms[11-14], it being ineffective in monotherapy for OCD[15] and leading to an improvement of symptoms in resistant OCD cases[16,17].

Risperidone as a single agent may also induce or exacerbate obsessive-compulsive symptoms, generally in psychotic patients[18-21]. However, on the contrary, there are several descriptions of OCD case series that improved when risperidone was added to treatment with a SRI[22-27].

Thus, our objectives are to assess the possible effectiveness and tolerability of risperidone associated to the usual treatment with SRI in moderate-severe OCD patients with scarce or null clinical response to the previous treatment in a larger series of cases than those previously published.

MATERIAL AND METHODS

This is based on collection of data on patients from different sites. Data were collected on patients over 18 years with OCD criteria according to the DSM-IV under treatment with SRI and without clinical improvement: *a)* moderate or severe case according to CGI baseline severity; *b)* patients currently under treatment with SRI and cognitive-behavior orientation therapy; *c)* reasonable evidence of adequate treatment compliance, and *d)* criteria of poor response (modified McDougle et al.[9], Barr et al.[8]): *1)* duration of treatment of at least 12 weeks; *2)* adequate dose of SRI according to the investigator's opinion based on response and tolerability; *3)* score greater than 16 on the Y-BOCS scale, y *4)* no more than «minimum improvement» in CGI-change with the present treatment.

The evolution data of the patients were collected and analyzed during 3 months of treatment. Treatment dose with SRI and the cognitive-behavioral therapy applied were evaluated. Administration of risperidone was initially done with a mean dose of 1.5 mg/d and then the dose was adjusted according to clinical criteria. The use of low dose benzodiazepines with anxiolytic or hypnotic purposes was recorded.

Clinically, the therapeutic response and tolerability were evaluated with the following measurements: Y-BOCS[28], with its generalized use in clinical trials in OCD patients[29]; CGI-change, modified UKU scale and the adverse reactions experienced by the patients were collected.

The following were considered as response criteria (modified McDougle et al.[9]) when the statistical analysis

was done: decrease of 35% or more on the Y-BOCS scale regarding onset and final score lower than 16 on said scale and CGI-change «quite or very improved» (score of 1 or 2).

An analysis of intention to treat was done, including those patients with at least one dose intake and at least one efficacy evaluation. Comparison of the evolution of the disorder severity during the study by the changes on the Y-BOCS and CGI scales was done with Wilcoxon text to compare two visits and the Friedman test to compare all the visits. All the hypothesis contrasts were bilateral and with 95% confidence interval. For the management of drop-outs and the lost data, the LOCF procedure was used. It consisted in carrying forward the last value available for the patients for whom there were incomplete data of their follow-up. Thus, the last data on efficacy available is inferred to the remaining visits (score on Y-BOCS and CGI scales). The McNemar test was used for the comparison of qualitative variables. The SAS/STAT statistical program was used[30].

RESULTS

Data were collected and analyzed on 35 patients (table 1). Thirty of them (85.7%) had at least one follow-up of 3 months. Five other patients had not completed a 3 month treatment: the follow-up was interrupted early in two (5.7%), in 2, it was interrupted due to side effects (5.7%) and in one, it was suspended due to lack of patient collaboration (2.9%). It was considered that 28 patients (80%) had good treatment compliance (more than 80% of the medications).

Mean daily dose of risperidone of these patients was 3.8 mg (SD: 1.9). Dose of the different antidepressants used was 41.7 mg/day (SD: 18.3) of paroxetine (n=6), of 40.0 mg/d (SD: 28.2) of fluoxetine (n=2), of 175 mg/d (SD: 95.7) of sertraline (n=5), of 309 mg/d (SD: 58.4) of fluvoxamine (n=14), of 246.4 mg/d (SD: 39.3) of chlorimipramine (n=7) and 40 mg/d of citalopram (n=1).

Analysis by intention to treat was conducted for 31 patients (88.6%). Four were excluded as they had no efficacy evaluation. The Y-BOCS scale score in these patients decreased from 27.1 (SD: 6.6) in the baseline evaluation to 13.8 (SD: 8.2), three months later ($p<0.0001$) (fig. 1). CGI-severity decreased from 5.1 (SD: 0.9) to 3.4 (SD: 1.2) ($p<0.0001$) and CGI-change from 3.7 (SD: 0.5) at 15 days to 2.4 (SD: 0.8) at 3 months ($p<0.0001$).

CGI efficacy was good or excellent in 24/31 patients (77.4%). There was a decrease of at least 35% over the baseline score of Y-BOCS in 25/31 patients (80.6%). Of these 25 patients, 4 did not decrease below 16 points in the final evaluation of the Y-BOCS scale. Thus, 21 patients were considered responders (67.8%).

Table 1 Characteristics of the patients

Characteristics (mean and standard deviations or frequency [%])	Total of patients (n = 35)
Age (years)	38.54 (13.8)
Males	18/34 (52.9%)
Civil status	
Single	16 (45.7%)
Married	18 (51.4%)
Separated and/or divorced	1 (2.9%)
Study level	
Primary/basic education school graduate certificate	11 (33.3%)
High school/vocational training	14 (42.4%)
University	8 (24.3%)
Work activity (n = 34)	
Has none	4 (11.8%)
Housewife/househusband	5 (14.7%)
Liberal profession	4 (11.8%)
Self-employed	2 (5.9%)
Worker/employee	16 (47.1%)
Student	2 (5.9%)
Pensioner	1 (2.8%)
Work situation	
Active (working)	18/34 (52.9%)
Psychiatric comorbidity	20 (57.1%)
Depression	5 (14.3%)
Dysthymia	5 (14.3%)
Panic disorder	2 (5.7%)
Hypochondria	1 (2.9%)
Toxic consumption	13 (37.1%)
Tobacco	10 (28.6%)
Alcohol	3 (8.6%)
Cannabis	1 (2.9%)
Medical background	8 (22.9%)
Total score (Y-BOCS scale)	26.8 (6.3)
Disease severity (CGI scale)	5.0 (0.9)

General tolerability was good without unexpected adverse events. Seven adverse events (two patients gained weight, one had tremors, one muscle rigidity, one dysarthia, one hypokinesis and one dizziness) were collected for 4 patients of the 35 (11.4%), 6 having moderate intensity and one mild. In the subscale of extrapyramidal symptoms of the UKU, there were only differences in hypokinesis ($p<0.1$). Antiparkinsonian medication was prescribed in six patients. There were 2 patients who dropped-out of treatment early (before 3 months) due to poor tolerability (extrapyramidal effects).

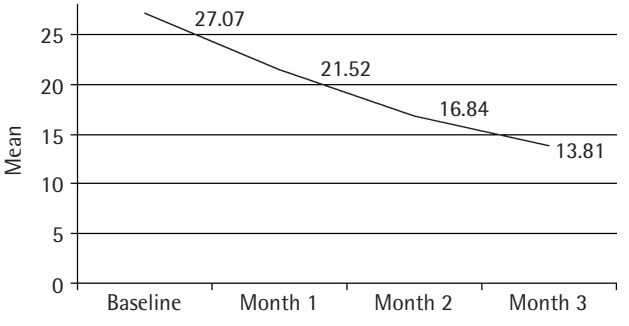

Figure 1 *Evolution of the total score on the Y-BOCS scale. By the Wilcoxon test (comparison of two visits) and the Friedman test (comparison of more than two visits), it is observed that there is a significant difference ($p < 0.0001$) in the total score of the Y-BOCS scale during the follow-up period.*

DISCUSSION

The obsessive-compulsive disorder (OCD) has an elevated percentage of cases resistant to the usual treatment. Under these situations, different drug alternatives are recommended. However, in generally, they have scarce empiric evidence of efficacy. Atypical antipsychotics are presented as a promising alternative for moderate-severe pictures, given the high index of response to these drugs when they are associated to the usual treatment, adequate tolerability profile and consistence in the results between the different studies.

There are many open studies that suggest the possible effectiveness of adding an atypical antipsychotic such as risperidone, olanzapine or quetiapine to treatment with SRI[5,21-27,31-34]. Furthermore, discontinuation of the antipsychotic may worsen the OCD clinical picture[35]. In general, the series of cases published on the use of risperidone have been on a small sample size (5 to 21 patients), but with a percentage of responses, using criteria in agreement with ours, that are similar to those observed by us (37.5% to 67%)[23-25,27]. In our case, we obtained a response in 67.8% of the cases with a larger sample size.

The randomized and placebo controlled clinical trials published recently have some data that agree with those previously mentioned. Adding low doses of risperidone in SRI refractory OCD patients in a sample of 36 patients, 20 of whom received risperidone, increases the percentage of responders regarding the SRI plus placebo group. Efficacy criteria were similar to ours and they found 50% responders with risperidone versus 0% with placebo[36]. Another clinical trial in a small sample (16 patients) obtained similar results[37].

A recent placebo controlled clinical trial with another atypical antipsychotic, quetiapine, supports that other antipsychotics may be effective, describing 64.4% response to the combination of quetiapine with a SRI[38]. We are unaware of the existence of clinical trials with other atypical antipsychotics.

Thus, potentiation with antipsychotics is presented as an interesting alternative for these types of patients. In any event, the possibility that some cases of improvement mentioned may be due to diagnostic errors, secondary obsessive symptoms, presence of schizotypal personality or changes of symptoms such as anxiety, insomnia or aggressiveness that improve with the use of antipsychotics must be pointed out.

The efficacy action mechanism of risperidone in resistant OCD is unknown. Risperidone is a benzisoxazole derivative with 5-HT2 and D2 receptor blocker action, without anticholinergic activity nor interactions with opioid, GABAergics or P substance[39,40]. Once an error in the differential diagnosis between OCD and obsessive-like symptoms secondary to schizophrenia is ruled out (6), efficacy may be due to a potentiation of the effect of SRI in the blockage of different serotoninergic receptors (5-HT1A, 5-HT1D, 5-HT2A, 5-HT2C, 5-HT7)[23] or to decreasing a possible dopaminergic hyperactivity[26]. It has been suggested that there may be a subtype of OCD with a DA/5-HT disequilibrium, since the basal ganglia receive extensive serotoninergic innervation and the serotoninergic pathways exert a tonic inhibition of the dopaminergic function[41]. It seems to be ruled out that it is due to a pharmacokinetic interaction with SRI or to increasing treatment time with SRI[9,36]. Furthermore, although it cannot be ruled out that it is an exclusive effect of risperidone, it seems unlikely by the description of cases of worsening of obsessive-compulsive symptoms with risperidone alone, generally in psychotic patients[19,20,42], or the lack of efficacy of monotherapy with clozapine in refractory OCD[15]. Thus, the most likely alternative is that of an interactive effect on the pharmacodynamic level with the SRI.

Tolerability was considered good, in agreement with other studies[25,36].

It seems to be recommendable to initiate with low doses of risperidone, given that there may be pharmacokinetic interactions between risperidone and some SRIs that cause an initial increase of the adverse events and cause clinical deterioration[43]. The maintenance dose seems to be located at around 3 mg daily. In our case, 3.8 mg/day were used and this ranged from 1 to 3.6 mg in other studies[23,25,27,35]. In addition, the antiobsessive effect of risperidone may be dose-dependent[44].

Thus, these data support the current data on effectiveness of the combined treatment (SRI and risperidone) in patients with moderate-severe OCD refractory to exclusive treatment with SRI. More studies are necessary, including clinical trials with larger sample sizes, which confirm the promising findings observed up to now.

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