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Efficacy of citalopram and moclobemide in patients with social phobia: Some preliminary findings

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The efficacy of irreversible and reversible monoamine oxidase inhibitors (MAOIs) in the treatment of social phobia (SP) is well established. Recently, selective serotonin reuptake inhibitors (SSRIs) have been used more frequently. In the present study, the efficacy and side-effect profile of citalopram, an SSRI, and moclobemide, the only MAOI used in Turkey, were compared. The 71 patients diagnosed with SP according to DSM-III-R were randomly assigned to two subgroups; citalopram ($n = 36$) or moclobemide ($n = 35$). The study was an 8-week, randomized, open-label, rater-blinded, parallel-group trial. All patients were assessed by Hamilton anxiety rating (HAM-A), Liebowitz social anxiety (LSAS), clinical global impression-severity of illness (CGI-SI) and clinical global impression-improvement (CGI-I) scales. There was a similar percentage of responders (citalopram 75%, $n = 27$ and moclobemide 74.3%, $n = 26$), with a $> 50\%$ or greater reduction in LSAS total score and ratings of 'very much' or 'much improved' on the CGI-I. None of the patients withdrew from the study. The results of the present study suggest that citalopram has shown promising results in patients with SP. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — social phobia; citalopram; moclobemide; efficacy; side-effect

INTRODUCTION

Social phobia (SP) is an anxiety disorder that is characterized by the fear of being ashamed or humiliated in various social settings including performance and test situations. Several epidemiological surveys have demonstrated that SP is a common and disabling disorder (Weiller *et al.*, 1996). In a national field study, the lifetime prevalence of SP has been reported to be 13.3% (Kessler *et al.*, 1998).

Several treatment strategies are used for the treatment of SP. Although some psychotherapeutic approaches have been reported to be effective and useful, they do not seem to be widely available and accessible for the majority of the patients (Juster *et al.*, 1996; Marks and Gelder, 1996). Both irreversible monoamine oxidase inhibitors (MAOIs) such as phenelzine (Liebowitz *et al.*, 1992) and reversible MAOIs such as moclobemide and brofaromine (Versiani *et al.*, 1992; Fahlen *et al.*, 1995) have been shown to be effective in SP. However, there are some studies (Noyes *et al.*, 1997; Schneier *et al.*, 1998) indicating that moclobemide is not effective in the treatment of SP. More recently, attention has been focused on the use of selective serotonin reuptake inhibitors (SSRIs) in the treatment of SP. SSRIs such as sertraline (Katzelnick *et al.*, 1995), fluvoxamine (Van Vliet *et al.*, 1994; Stein *et al.*, 1999) and paroxetine (Stein *et al.*, 1998; Baldwin *et al.*, 1999) were reported to be effective. Citalopram selectively and strongly inhibits the neuronal reuptake of serotonin. However, the efficacy of citalopram in SP has been described only in one case report (Lepola *et al.*, 1994), a case series (Simon *et al.*, 2001) or open label studies (Bouwer and Stein, 1998; Van der Linden *et al.*, 2000).

In the present study, therefore, it was decided to compare the efficacy of citalopram with moclobemide.

METHODS

Patients

The study group consisted of patients (aged 18–49 years) who had first applied to Firat University School of Medicine Department of Psychiatry and had been

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diagnosed with generalized SP according to DSM-III-R criteria. After a complete description of the study to the subjects, written informed consent was obtained from each patient. Ethical permission was approved by the Local Ethics Committee of the Firat University School of Medicine. Exclusion criteria included the presence of a severe physical illness, the history of alcohol and substance abuse or dependence, the presence of dementia or mental retardation. A total of 71 patients was recruited to the study. After a 14-day washout period, the patients were randomized to receive 8 weeks of treatment with either citalopram ($n = 36$) or moclobemide ($n = 35$). The dose range was 20–60 mg/day in the citalopram group and 300–900 mg/day in the moclobemide group being flexible dosing according to the clinical response and side effects experienced. The mean daily dose of citalopram was 36.1 ± 12.7 mg/day and moclobemide 570.3 ± 191.8 mg/day. No behavioral therapy was allowed during the study and the use of concomitant medications was prohibited, with the exception of benzodiazepine, if judged necessary by the authors. However, no patient required additional drugs.

Each patient underwent a detailed diagnostic evaluation by one trained psychiatrist using a structured clinical interview for DSM-III-R (SCID) (Spitzer *et al.*, 1990). Patients with any kind of axis I comorbidity were excluded. In addition, the Hamilton anxiety rating scale (HAM-A) (Hamilton, 1959), clinical global impression scale-severity illness (CGI-SI) and clinical global impression scale-improvement (CGI-I) were administered.

To assess the level of phobic anxiety and avoidance behavior and to identify the situations feared and/or avoided by the patients, the Liebowitz social anxiety scale (LSAS) (Liebowitz, 1987) was used.

Procedure

The patients' sociodemographic and clinical data were recorded at the first interview. All patients were evaluated by using HAM-A, CGI-SI and LSAS at 0, 2, 4, 6 and 8 weeks and CGI-I at 2, 4, 6 and 8 weeks. In addition, adverse effects were reported via a semistructured questionnaire form designed by the authors, well understood by the patients. The study was an 8-week, randomized, open-label, rater-blinded, parallel-group trial. The patients and raters were blind to drug assignment, although the prescribing physician was not. At each evaluation point, the patients were assessed via the standardized scales and semistructured side-effect instrument. Efficacy was assessed principally by the mean changes in the mean LSAS score from baseline to last assessment (50% and greater reduction in total LSAS score) and by the number of 'very much' or 'much improved' ratings on CGI-I.

Statistical analysis

Statistical analysis was performed by using a statistical package for social sciences SPSS/PC 9.05 version, 1998. To compare the values of repeated measures at the different time points within the treatment groups, repeated measures analyses of variance (ANOVA) following Bonferroni's correction test for four pairwise comparisons, and between groups *t*-test were used. The χ^2-test was used to compare side effects experienced.

RESULTS

All patients completed the study. The mean age was 29.7 (SD = 11.5) years in the citalopram group and 30.9 (SD = 13.4) years in the moclobemide group. The mean duration of illness for citalopram and moclobemide groups was 6.1 (SD = 3.6) and 5.8 (SD = 3.3) years, respectively. While the citalopram group had 20 males (55.6%) and 16 females (44.4%), the moclobemide group had 19 males (54.3%) and 16 (45.7%) females. There were no significant differences between groups from the points of the mean age, the duration of illness and female/male ratio ($p > 0.05$).

At baseline, the mean HAM-A scores were 29.1 (SD = 5.3) in the citalopram group and 28.4 (SD = 5.1) in the moclobemide group. The mean HAM-A scores at last assessment were 15.3 (SD = 2.8) in the citalopram group and 16.6 (SD = 3.1) in the moclobemide group. There was no considerable difference between groups in the mean reductions of HAM-A from baseline to last assessment ($p > 0.05$). The change in the HAM-A scores between the start of treatment and week 2, 4, 6 or 8 was not significantly different between the groups (Figure 1).

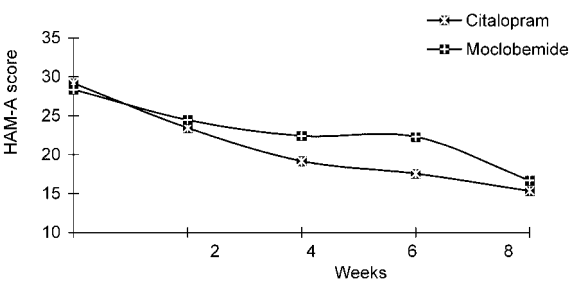

Figure 1. The mean HAM-A scores at the evaluation points in the groups, ⊠ citalopram, ⊞ moclobemide

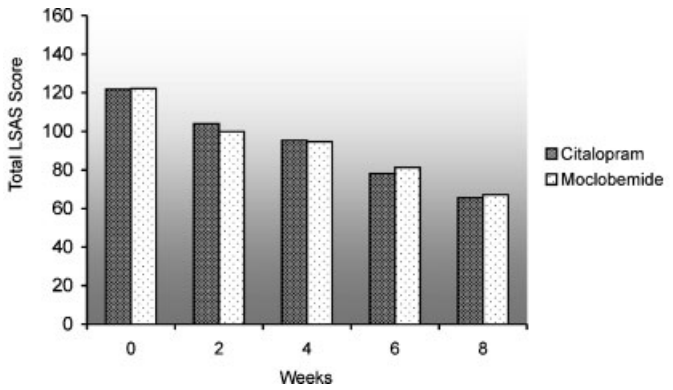

Figure 2. The mean total LSAS scores at the evaluation points in the groups, ▩ citalopram, □ moclobemide

At baseline, the mean total LSAS scores were 63.6 (SD = 11.1) for the fear subscale and 58.3 (SD = 12.4) for the avoidance subscale in the citalopram group and 60.6 (SD = 11.3) for the fear subscale and 61.6 (SD = 9.2) for the avoidance scale in the moclobemide group. No statistically significant difference was found between groups in both subscale scores ($p > 0.05$). At the final assessment, the mean LSAC-fear subscale scores were 33.6 (SD = 5.6) and 34.9 (SD = 6.3) whereas the mean LSAC-avoidance scores were 32.1 (SD = 5.1) and 34.3 (SD = 6.4) in the citalopram and moclobemide groups, respectively ($p > 0.05$). No statistically significant difference was present in regard to the change in the total LSAS scores between the start of treatment and week 2, 4, 6 or 8 between the groups (Figure 2).

The mean CGI-SI scores were 4.6 (SD = 1.3) in the citalopram group and 4.5 (SD = 1.2) in the moclobemide group at baseline ($p > 0.05$), compared with 1.3 (SD = 0.6) and 1.5 (SD = 0.7) at last assessment in the citalopram group and in the moclobemide group, respectively ($p > 0.05$). The mean CGI-I scores were 3.9 (SD = 1.3) in the citalopram group and 4.1 (SD = 1.2) in the moclobemide group at baseline ($p > 0.05$), compared with 1.4 (SD = 0.7) and 1.3 (SD = 0.6) in the citalopram and moclobemide groups at last assessment, respectively. There were no statistically significant differences between groups with respect to the reductions in CGI-SI and CGI-I scores ($p > 0.05$).

A similar percentage of patients responded in the citalopram (75%, $n = 27$) and moclobemide group (74.3%, $n = 26$), with both > 50% or greater reduction in LSAS total score and having 'very much' or 'much improved' ratings on CGI-I. There was no statistically significant difference between groups with respect to the rate of responders ($p > 0.05$).

Both drugs were well tolerated. There were 53 reports of newly observed adverse events. Of them, 28 were from 11 patients in the citalopram group and 25 were from 9 patients of the moclobemide group ($p > 0.05$). Most frequently reported side effects in the citalopram group were the decreased libido ($n = 5$), retarded ejaculation ($n = 4$) and insomnia ($n = 4$) whereas those in the moclobemide group were weakness ($n = 5$) and insomnia ($n = 4$).

DISCUSSION

This 8-week trial showed that both citalopram and moclobemide were efficacious and well tolerated in the treatment of SP.

Non-selective MAOIs (phenelzine and tranylcypromine) have been widely used in the treatment of SP (Liebowitz *et al.*, 1992; Versiani *et al.*, 1992), but have limited use because of necessary dietary restrictions. When these drugs are ingested with foods containing tyramine, hypertensive crises may occur. Therefore, reversible and selective MAOIs such as brofaromine, and especially moclobemide, which do not require dietary restriction at a standard dose range are now used. Brofaromine has been demonstrated to be effective in patients with SP (Fahlen *et al.*, 1995; Lott *et al.*, 1997). Moclobemide when compared with brofaromine has been studied in more detail and it has been found to be effective in some long-term studies (Versiani *et al.*, 1992, 1996, 1997; The International Multicenter Clinical Trial Group on Moclobemide in Social Phobia, 1997), but not in others (Noyes *et al.*, 1997; Schneier *et al.*, 1998). The present study determined that dosing with moclobemide resulted in a significant improvement on both LSAS and HAM-A and was efficacious for the treatment of SP.

There is as yet no clearly defined biological abnormality, though many studies appear to suggest that SP lies somewhere between normal controls and the patients with panic disorder (Bell *et al.*, 1999). There are some data to demonstrate that benzodiazepines are useful in patients with SP, supposing that GABA may be involved in SP (Kalueff and Nutt, 1997). Some researchers have proposed that SP may be characterized by low dopaminergic function, based on the evidence that MAOIs and bupropion enhance dopaminergic function (Emmanuel *et al.*, 1991). On the other hand, a role for serotonin in SP is suggested clinically by the efficacy of MAOIs, reversible inhibitors of MAO-A (RIMAs) and more recently SSRIs which all have considerable effects on serotonin. In open-label trials using fluoxetine (Schneier *et al.*, 1992; Van Ameringen *et al.*, 1993) and double-blind studies using fluvoxamine, paroxetine and sertraline (Van Vliet *et al.*, 1994; Katzelnick *et al.*, 1995; Stein *et al.*, 1996), SSRIs have been shown to be efficacious. Studies on the efficacy of citalopram are limited: a case report (Lepola *et al.*, 1994), a case series (Simon *et al.*, 2001) and open label studies with a response rate of 60% (Van der Linden *et al.*, 2000) and 86% (Bouwer and Stein, 1998). The response rate of the present study is comparable to that of these open label studies. On the other hand, citalopram was reported to be effective in a case with obsessive compulsive disorder and comorbid elective mutism, accepted as a variant of SP (Thomsen *et al.*, 1999). In the present study, both citalopram and moclobemide had high response rates, and it is possible that these high rates may be associated with the absence of a placebo-control group.

In the present study, with respect to tolerability, the results showed that both drugs were well tolerated. The obvious side effects related to citalopram use were sexual ones. Serotonin seems to play an important role in the development of sexual dysfunctions by inhibiting libido and ejaculation, and by delaying orgasm. This influence can be explained by evidence that serotonin causes a decrease in dopamine which is a neurotransmitter enhancing sexual performance in the central nervous system of laboratory animals (Remy, 1986; Baldesarani and Mars, 1990). Although the actual mechanism is somewhat obscure, there is clear evidence that SSRIs, owing to serotonergic neurotransmission, affect sexual performance in humans, especially libido and orgasm (Rosen *et al.*, 2001) and as found in the present study.

These preliminary observations should be interpreted with caution owing to some methodological limitations: the lack of a placebo-control group and the short duration of the study. Certainly, confirmatory double-blind placebo-controlled studies which capture a lengthy perspective of the course of the disease are required. In conclusion, the results of the present study suggest that citalopram has shown promising effects in patients with SP and that both drugs are well tolerated. Further placebo-controlled studies with large numbers of patients are needed to confirm the efficacy of citalopram in SP.

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