Efficacy of an Eight Week Trial of Imipramine and Citalopram in Patients with Mixed Anxiety-Depressive Disorder

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Objective: Mixed anxiety-depressive disorder (MADD) is a condition in which patients have both anxiety and depressive symptoms but do not meet the diagnostic criteria for either an anxiety disorder or a mood disorder.
The aim of this study was to compare the efficacy of imipramine and citalopram in the treatment of MADD.
Methods: Fifty one outpatients aged 18 to 55 who were diagnosed with MADD were randomly assigned to receive citalopram or imipramine for 8 weeks. Patients were assessed using Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS) at baseline, weeks 4 and 8 of the study. The mean differences in Hamilton scores from the baseline were used as the main outcome measures of response to treatment.
Results: Thirty six patients completed the study. Patients in the citalopram group (n=20) received a mean dosage of 22 mg per day during the first 4 weeks and a mean dosage of 33 mg per day during weeks 4 to 8. Subjects in the Imipramine group (n= 16) received a mean dosage of 77 mg per day during the first 4 weeks and a mean dosage of 89 mg per day during weeks 4 to 8. It was noted that the both treatments were effective on depression and anxiety at the end of the fourth and eighth weeks. However, the mean differences of HDRS and HARS scores between citalopram and imipramine groups were not significantly different at the end of weeks 4 and 8.
Conclusion: The results of this study suggest that the efficacy of regular doses of citalopram is comparable with lower range of therapeutic doses of imipramine in the treatment of MADD. A more comprehensive study is warranted to confirm the results of this study.
Key Words:
Anxiety disorder, Citalopram, Depressive disoder , Imipramine

Iran J Psychiatry 2008; 3: 16-19

Patients with mixed anxiety-depressive disorder (MADD) have both anxiety and depressive symptoms but do not meet the diagnostic criteria for either an anxiety disorder or a mood disorder (1, 2). The combination of symptoms results in a significant functional impairment in the affected person. In 1996, Dr. Gorman noted that about 85% of patients with depression suffer symptoms of anxiety (3). Recently, it has been reported that 57% of patients with major depressive disorder (MDD) also suffer a comorbid anxiety disorder (4). Patients with anxious depression" may be among one of the following 3 groups: 1) those with MDD, an anxiety disorder; 2) those with MDD and a sub-threshold anxiety symptom; and 3) patients with both sub-threshold anxiety and depressive symptoms. The latter group is considered to suffer from MADD (5).
Serotonin, norepinephrine and GABA are neurotransmitters known to be involved in Anxiety and depressive disorders (6-9). Medications affecting these neurotransmitters have been shown to be helpful in treating both anxiety and depressive disorders.
Until 1980s, tricyclic antidepressants (TCAs) were the first-line treatment for Depression. Afterwards, second generation antidepressants including specific serotonin reuptake inhibitors (SSRIs) have been used as first-line pharmacotherapy due to their more favorable side-effect profile and lower toxicity associated with overdose when compared to TCAs (10).
The effectiveness of the newer anti-depressants is frequently questioned in comparison with the more established agents. Some psychiatrists have the impression that newer anti-depressants, notably SSRIs, are clinically less effective than the TCA in treatment of depression and anxiety. Faravelli et al. reported TCAs were significantly superior over SSRIs in terms of efficacy in the treatment of both depression and anxiety in patients who had two separate episodes and were treated by a SSRI at one episode and by a TCA at the other (10). On the other hand, a review of comparative clinical trials from 1985 to 1999 in severely depressed patients that noted the effectiveness of both TCAs and SSRIs in treating severe depression

are comparable (11). A review of article by Cipriani and colleagues based on searching the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR), the Cochrane Central Register of Controlled Trials (CENTRAL), Medline (1966-2004) and Embase (1974-2004) noted statistically significant differences in efficacy and tolerability between some antidepressants and fluoxetine. This study also reported that there may be a tendency in favor of fluoxetine over citalopram in terms of the number of dropouts because of side effects. However, the authors mentioned that no definitive clinical implications can be concluded from these differences (12).

We searched the Med-line from 1990 to 2008 and could not find any article that compared the efficacy of imipramine and citalopram in the treatment of MADD.

Imipramine, a TCA, has been available much longer than citalopram, a SSRIs, for the treatment of depression. Imipramine acts by potentiating the actions of biogenic amines (noradrenaline and serotonin) in the central nervous system; it blocks histamine-1 (H1) and alpha-1 receptors and therefore may cause sedation, increase appetite, and orthostatic hypotension. This medicine may also cause anticholinergic side effects like constipation, blurred vision, and urinary retention. Imipramine has a half-life of 6 to 28 hours and is extensively metabolized through the liver; desipramine is its major active metabolite (13, 14).

Citalopram enhances serotonergic neurotransmission in the central nervous system. Its elimination half-life of 33 hours permits once daily dosing. Citalopram does not appear to be cardio-toxic, and has not been associated with seizures in humans and is relatively non-sedating. Unlike TCAs, citalopram has low anticholinergic effects. Mild and transient nausea, increased perspiration, headache, dry mouth, tremor and insomnia have been reported in patients receiving citalopram (15).

This randomized study was designed to compare the efficacy of imipramine and citalopram manufactured in Iran in the treatment of MADD.

Materials and Method

Subjects

We conducted an 8-week randomized trial at the outpatient clinic of Roozbeh psychiatric hospital in Tehran, Iran. Fifty one patients entered the study and were screened from April 2006 through September 2007. This study was approved by the Ethics Committee of Tehran University of Medical Sciences. After obtaining written informed consents and discontinuing all psychotropic medications for 2 weeks, out-patients between 18 and 55 years of age who met the criteria for MADD based on the Diagnostic and Statistical Manual of Mental Disorders, Forth edition (DSM-IV), were enrolled in the study (5). It should be noted that originally, we designed a double blind study. However, due to the limitations in appropriately manufacturing similar medications by appearance, the present study started by simple randomization of patients to receive imipramine or citalopram.

Patients with a history of other psychiatric disorders, organic brain syndrome, serious neurological disorders, and unstable medical disorders including cardiovascular, hepatic, renal, endocrine or hematological illnesses, alcohol or drug dependency, suicidal idea as well as pregnant and lactating women were excluded from this study. Additionally, patients on other medications that could affect depression or anxiety were excluded.

Patient were assessed using a standardized 21 item scale for HDRS and HARS at the baseline, 4 and 8 weeks after medication started (16). The mean differences in HDRS and HARS scores from baseline were used as the main outcome measures of response to treatment.

To analyze the data, a two-way repeated measure ANOVA was used. In addition, a one-way repeated measure ANOVA with a two-tailed post hoc Tukey mean comparison test were performed on the change in HDRS and HARS Rating Scale scores from the baseline. An unpaired two-sided Student's t-test was used to compare the reduction in the HDRS and HARS Rating Scale scores at the end of treatment compared with baseline. Results are presented as mean ± SEM differences and were considered significant with $P<0.05$.

Results

Thirty six patients completed this randomized study (20 patients in citalopram group and 16 patients in Imipramine group). Patients in the citalopram group received a mean dosage of citalopram 22 mg/day during the first 4 weeks and a mean dosage of 33 mg/day during weeks 4 to 8. Subjects in the imipramine group received a mean dosage of imipramine 77mg/day during the first 4 weeks and a mean dosage of 89mg/day during weeks 4 to 8. It was noted that the both treatments were effective on depression and anxiety at the end of fourth and eighth weeks. HDRS scores for citalopram and imipramine groups were 18.35 and 18.12 at baseline; 13.95 and 13.75 at week 4; and 10.40 and 10.06 at week 8 respectively. HARS scores for citalopram and imipramine groups were 23.20 and 23.81 at baseline; 18.15 and 17.25 at week 4; and 14.20 and 13.62 at week 8 respectively. Therefore, the mean differences of HDRS scores between the baseline and weeks 4 and 8 in the Citalopram group were 4.40 ($p<0.001$) and 7.95 ($p<0.001$) and the mean differences of HARS in this group were 5.05 ($p<0.001$) and 9.00 ($p<0.001$) respectively. The mean differences of HDRS and HARS between citalopram and imipramine groups were not significantly different at the end of weeks 4 and 8. Therefore, this study did not show any significant differences between the two treatments in patients with MADD.

Fifteen patients dropped out of the trial before week 4 due to non- compliance with regard to taking medications or not showing up at their follow up visits. No significant differences were observed between dropout rates in the two groups.

Table 1 compares the baseline demographic and clinical characteristics of the patients in citalopram and the imipramine groups. The patients were matched by age, gender and the baseline HDRS and HARS scores. No significant differences were identified between patients in the two groups with regards to basic demographic data including age and gender.

The mean ± SEM scores of the two groups of patients during the 8 weeks are shown in Figures 1 and 2. There were no significant differences in the scores of HDRS and HARS rating scales between the two groups in week 0 (baseline).

One-way repeated measures ANOVA on mean differences for the HDRS and HARS scales between the 4th week and the baseline and between the 8th week and the baseline did not show significant differences between the two treatment groups. The differences between the two treatment groups were not significant at the endpoint (week 8). The improvement, however, was similar at the end of the fourth and eighth weeks. Both groups showed similar improvements in mean scores of HDRS and HARS at the end of the 4th and 8th weeks.

Discussion

The link between anxiety and depression is unclear. Recent estimates show that more than 55% of patients with MDD also suffer an anxiety disorder (4). Patients with MADD have a combination of depressive and anxiety symptoms that result in a significant functional impairment. There have been several studies that compared the efficacy of SSRIs with TCAs. A 12-week, double blind study compared paroxetine with clomipramine in 1002 outpatients with depression associated with anxiety. Both drugs effectively treated both depression and anxiety symptoms (17). Another double-blind study compared the effects of fluoxetine and amitriptyline in 142 anxious-agitated patients with major depressive disorder for 10 weeks. Both fluoxetine and amitriptyline resulted in a significant reduction of depression and anxiety without significant differences in treatment effects (18). Similarly, in another double-blind study, fluoxetine and amitriptyline were compared in patients with major depressive disorder associated with anxiety for 8 weeks. Again, no differences were seen in the effects of these antidepressants in the treatment of the patients (19). The present study noted that both citalopram and imipramine had similar efficacy in the treatment of MADD at the end of weeks 4 and 8. Interestingly, in this study, patients were treated with lower range of therapeutic doses of imipramine and a therapeutic dose of citalopram. Due to the fact that imipramine results in more anticholinergic and cardiovascular side effects when compared with citalopram, the latter drug may be preferred in reduction of anxiety and depressive symptoms in patients who are suffering from mood and anxiety disorders. Due to small number of patients in this study and due to the fact that many patients did not show up for a follow-up visit, we suggest that larger studies with greater number of patients and preferably with a double-blind design to be accomplished to confirm the results of this study.

Acknowledgements

This research was a part of Dr. H. khoonsari's pharmacy thesis project and was supported by Psychiatry and Psychology Research Center affiliated by Tehran University of Medical Sciences and Health Services .

The authors would like to thank Dr. S. Akhondzadeh, Dr. F. Raisi, Dr. V. sharifi , Dr. Arghavan Sadeghi zangeneh, Dr. Iravani , Miss H. Jalaeyan and Mr. A. Kamalipour. We would also like to thank the staff of Roozbeh hospital pharmacy, nursing and laboratory.

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