Melatonin Decreases Olanzapine Induced Metabolic Side-Effects in Adolescents with Bipolar Disorder: a Randomized Double-Blind Placebo-Controlled Trial

Ali Mostafavi, Mahmoud Solhi, Mohammad-Reza Mohammadi, Mehdi Hamedi,

Maryam Keshavarzi, and Shahin Akhondzadeh

Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran

Received: 23 Jul. 2014; Accepted: 30 Aug. 2014

Abstract- Olanzapine is the frequently prescribed drug in children and adolescents with bipolar disorder, but unfortunately it has metabolic side-effects. On the other hand, in a number of melatonin studies on sleep cycle, regulation of metabolic abnormalities has been reported. Therefore, we aimed to study effects of melatonin in reducing metabolic side-effects of olanzapine in 11-17 year-old patients with bipolar disorder. Seventy-seven 11-17 year-old outpatients entered into the study after their initial diagnosis of bipolar mood disorder by a psychiatrist. After assessing inclusion and exclusion criteria, 48 patients consented to participate in the study. Of this number, 24 patients were allocated to olanzapine, lithium carbonate, and melatonin and 24 patients were allocated to olanzapine, lithium carbonate, and placebo. Young mania rating scale was performed at baseline. Before treatment initiation and at sixth and twelfth weeks after treatment, Lipid profile, Fasting Blood Sugar (FBS), Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were measured. ANOVA with repeated measure and independent sample t-test were used for data analysis. Nineteen patients in each group completed the study and yielded data for analysis. ANOVA with repeated measure showed that FBS and Triglyceride (TG) (especially in boys) demonstrated greater increase in the placebo group compared to the melatonin group but the differences were not statistically significant. Melatonin significantly inhibited the rise in Total Cholesterol levels compared to placebo (P=0.032). Mean SBP rose more slowly in the melatonin group (1.05mmHg) compared to placebo (6.36 mmHg) (P=0.023). The trends in DBP did not show any significant pattern. Administration of melatonin along with olanzapine and lithium carbonate could significantly inhibit the rise in cholesterol level and SBP compared to placebo. The effect of melatonin on TG was more obvious in boys. Melatonin was more effective in prevention of SBP rise

© 2014 Tehran University of Medical Sciences. All rights reserved. *Acta Medica Iranica*, 2014;52(10):734-739.

Keywords: Metabolic Syndrome; Olanzapine; Melatonin; Bipolar disorder

Introduction

In the last decade, with increased use of atypical antipsychotics (AAPs) in adolescents, some concerns have been raised about safety of these drugs (1). Some studies have shown that taking AAPs are associated with metabolic abnormalities (2). The most alarming metabolic side effects that are seen with long-term intake of AAPs are considerable increases in weight, dyslipidemia, hyperglycemia, insulin resistance, and increased risk of ischemic heart disease (IHD) (3). It has been indicated that AAP intake in adults will raise serum triglyceride concentrations up to 45% (4). On the other hand, it has been found that total cholesterol (TC), LDL and HDL levels are less affected by AAPs (5). Also, some information is available on insulin resistance, glucose intolerance and diabetes in children treated with atypical antipsychotics (6). Melatonin is a hormone that is secreted from the pineal gland into the blood stream and the Cerebrospinal fluid (CSF)(7). The main role of melatonin in the body is regulation of the sleep-wake cycle (8). Melatonin also has cytoprotective, immunomodulatory and chronobiotic functions (9). The sleep-wake cycle is determined by neuroendocrine and immunological profiles and regulates metabolic homeostasis, body weight (10), and immune responses. It has been demonstrated that a disturbed sleep-wake cycle may lead to proinflammatory mechanisms and

Corresponding Author: S. Akhondzadeh

Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran

Tel: +98 21 88281866, Fax: +98 21 55419113, E-mail address: s.akhond@neda.net

metabolic syndrome (MetS) that includes obesity, diabetes and atherosclerosis. Therefore, precise assessment of metabolic syndrome and successful treatment is necessary for patients with sleep-wake cycle disorders. Melatonin is a drug that in addition to regulating the sleep-wake rhythm can antagonize MetS. Some studies have confirmed that melatonin can inhibit fat accumulation in fat tissue of obese animal models (11) The number of clinical studies on humans have supported the effectiveness of melatonin in the treatment of cardiovascular and metabolic problems (9). In one study, it was shown that melatonin can physiologically regulate metabolic activity in mammals (12). Therefore, we aimed to study effects of melatonin on reducing olanzapine metabolic side-effects in 11-17-year-old patients with bipolar disorder.

Materials and Methods

Trial design and setting

This was a 12-week, parallel-group, randomized, double-blind, placebo-controlled trial launched at the specialty clinic for children's of Roozbeh Hospital (Tehran University of Medical Sciences, Tehran, Iran) from November 2013 to June 2014.

Participants

Seventy-seven 11-17-year-old adolescents with firsttime diagnosis of bipolar mood disorder (BMD) were referred to psychiatric outpatient clinics to be assessed for eligibility. BMD was diagnosed by a psychiatrist according to DSM-IV criteria. The patients had not received any psychiatric medications. Of the 77 patients assessed for eligibility, 29 were excluded because they did not meet the inclusion criteria or refused to participate in the study (Figure 1).



Figure 1. Flow diagram of the current study

Inclusion criteria: Demonstrating the DSM-IV diagnostic criteria for bipolar mood disorder; 11-17 years of age; weight in the normal range ($18 \le BMI \le 25$); need to medical treatment.

Exclusion criteria: Active medical conditions such as infections, seizures, liver disorders; organic brain

disorders; diabetes; risk of metabolic abnormalities; use of medicinal supplementation and appetite stimulant compounds (such as antihistamines) or appetite killers (such as derivatives of Amphetamine); BMI greater than 25; Over-use of xanthine derivatives (tea, coffee, cocoa ...); eating disorders such as Anorexia and Bulimia. The protocol was approved by the IRB of Tehran University of Medical Sciences (TUMS) (Grant No: 8144). The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions and was approved by the ethics committee at TUMS. Written informed consents were obtained from the parents of the patients before entering the trial. This trial is registered with the Iranian Clinical Trials Registry (IRCT201208071556N44; www.irct.ir)

After obtaining written consent from parents, they were entered into the trial. Forty eight patients were randomly allocated into either "olanzapine (5-10 mg/day) and lithium carbonate (3-4 mg/day) and melatonin (3mg/day)" or "placebo and lithium carbonate (3-4mg/day) and melatonin (3mg/day)" groups. The groups were concealed to patients and researcher by placebo and encoding respectively.

Demographic information was recorded. Status of the patients prior to treatment was assessed by test of Youngmania. The SBP, DBP, total cholesterol, TG, and FBS were measured at the baseline, and consecutively were repeated at sixth week and at twelfth week after beginning of the study.

Outcome

Clinical interview by a psychiatrist based on DMS-IV was used to diagnose bipolar disorder. Information about the mood of the patient was collected using the Young Mania Rating Scale that has been used in several trials in Iran (13-15) before starting the treatment.

Systolic and diastolic blood pressures were measured by a mercury barometer in the standard situation. Blood samples were gathered at baseline, 6th and 12th week by a laboratory technician and FBS, total cholesterol and TG levels were measured.

Randomization, allocation concealment and blinding

Participants were randomized to receive melatonin or placebo in 1:1 ratio using a computer-generated code. The assignments were kept in sealed, opaque envelopes until data analysis. Throughout the study, a person who administered the medications, the rater and the patients and their parents were blind to assignments. Separate persons were responsible for random allocation and interviewed the patients.

Statistical analysis

Data were analyzed using IBM SPSS Statistic 19.0.0 (IBM Corporation). Continuous and categorical variables were reported using mean (±standard deviation, SD) and number (%) respectively. Mean

differences were reported as the mean difference, MD). Two-factor repeated measure analysis of variance (ANOVA) was used to assess the effect of time and time X treatment interaction. If Mauchly's test of sphericity was significant, Greenhouse-Geisser correction for degrees of freedom was used.

Results

Thirty-eight patients (mean age \pm SD: 14.42years \pm 1.48) completed the study, 19 in each group. Mean age \pm SD in the melatonin and the placebo groups were 14.37 \pm 1.70 and 14.47 \pm 1.26 respectively (*P*=0.830). There were not also any significant differences between groups in regard of gender and Mania Rating Scale (MRS) at baseline (Table1).

 Table 1. Distribution of gender, age, and Mania Rating
 Scale (MRS) between groups

	Melatonin	Placebo	P. value
Gender			0.516 [‡]
Male(N)	11	9	
Female (N)	8	10	
Age (Mean ± SD)	14.37 ± 1.70	14.47±1.26	0.830^{\dagger}
MRS (Mean ± SD)	39.42±2.21	39.44±2.17	0.974^{\dagger}
: Pearson Chi-Square test; †: Independent sample t-test			

ANOVA with repeated measure showed that fasting blood sugar showed a greater increase in the placebo group compared to the melatonin group, but the difference between groups was not statistically significant (Figure 2).



Figure 2. Estimated means of Fasting Blood Sugar (FBS) levels (mg/dl) in the melatonin group compared to placebo using ANOVA with repeated measure

Mean triglyceride (TG) levels showed a greater increase in the placebo group compared to the melatonin group (mean increment: 26.47 vs. 22.10), but the difference was not statistically significant (P=0.723). When categorizing the subjects based on gender, mean TG difference (Figure 3) was more visible in boys (40mg/dl in placebo treated boys, n=11boys vs. 24.1mg/dl in melatonin treated boys, n=9boys), but the difference between groups was still not statistically significant by independent sample t-test (P=0.3). ANOVA with repeated measure also did not show any significant difference between groups and across study duration.

Mean cholesterol increased by 24.26 mg/dl in the placebo group compared to 6.84 mg/dl in the melatonin group. Independent sample t-test showed marginally significant difference between groups in regards to cholesterol rise (F: 0.804; df: 36; P=0.061). ANOVA with repeated measure also showed a significant difference between groups and across time (P=0.032) (Figure 4).

Mean Systolic Blood Pressure (SBP) increased more slowly in the melatonin group compared with the placebo group (1.05mmHg vs. 6.36 mmHg) (F: 2.32; df: 36; P=0.023). ANOVA with repeated measure also showed a significant difference between groups and across time in regard with SBP (P=0.018) (Figure 5). But Diastolic Blood Pressure (DBP) did not show any significant trends in ANOVA with repeated measure and t-test analyses.



Figure 3. Meanof Triglyceride (TG) levels (mg/dl) in boys with bipolar disorder taking melatonin compared to placebo using ANOVA with repeated measure







Figure 5. Estimated means of Systolic Blood Presure (SBP) levels (mmHg) in the melatonin group compared to placebo using ANOVA with repeated measure

Discussion

Modabbernia *et al.*, (16) administered 3mg melatonin along with olanzapine in 36 schizophrenia patients for eight weeks and compared its effects with placebo. They found that the mean difference between baseline and 8th week was not significant in regards to cholesterol and fasting blood sugar. In our study administration of melatonin with olanzapine and lithium carbonate could significantly inhibit the increase in total cholesterol levels compared with placebo. This might have been due to longer duration of our study (12 weeks in this study versus 8 weeks in the Modabbernia study). We also found that in spite of lower increases in FBS

concentrations in the melatonin group, the difference between groups was not statistically significant. This finding was similar to the Modabbernia *et al.*, study and may show that melatonin has minimal effect on insulin resistance and FBS concentration.

Change in triglyceride between groups was marginally significant in the study by Modabbernia et al., which is similar to our findings. When we categorized our subjects based on gender, the trend in TG increase following olanzapine and lithium intake was different in males. As it is obvious in Figure 3, olanzapine plus lithium raised TG levels in boys by 40mg/dl in the placebo group (n=11boys) but this rise was as little as 24.1mg/dl in the melatonin group boys (n=9). So, addition of melatonin could sharply inhibit the rise in TG levels in boys with bipolar disorder, however, the difference between groups was not statistically significant. Clinically it is important to note this outcome because participation of a larger sample of boys might have yielded statistically significant results for difference between groups in boys.

Prevalence of the metabolic syndrome and obesity is high in patients who are taking AAPs. One reason for dyslipidemia following olanzapine intake is that metabolic effects of olanzapine were mostly identified to be related to decreased fatty acid oxidation (17). Melatonin may regulate metabolic pathways of fatty acid oxidation. Kozirog et al., in a study of 33 subjects with metabolic syndrome who had not responded to lifestyle modifications, treated subjects 2 hours before bed time with 5mg/day melatonin for 2 months, taken. After 2 months of treatment, systolic blood pressure in the melatonin group compared with controls decreased by 12.3mmHg and the diastolic blood pressure decreased by 6.7 mmHg. LDL was also reduced by 9.8 mg/dl (P<0.05) (18). Our findings on effects of melatonin on systolic and diastolic blood pressure in bipolar patients were similar to findings of Kozirog et al. Based on these findings; melatonin seems to be more effective in preventing the rise in SBP.

Administration of melatonin with olanzapine and lithium carbonate could significantly inhibit the rise in total cholesterol levels and SBP compared to placebo. Effect of melatonin on TG was more obvious in boys. Melatonin was more effective on preventing the rise in SBP.

Acknowledgment

This study was Dr. Mahmoud Solhei's postgraduate thesis toward the Iranian Board of Psychiatry. This study

was supported by a grant from Tehran University of Medical Sciences to Prof. Shahin Akhondzadeh (Grant No: 18139).

References

- Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J Am Acad Child Adolesc Psychiatry 2006;45(7):771-91.
- Calarge CA, Acion L, Kuperman S, et al. Weight gain and metabolic abnormalities during extended risperidone treatment in children and adolescents. J Child Adolesc Psychopharmacol 2009;19(2):101-9.
- 3. Daniels SR, Arnett DK, Eckel RH, et al. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. Circulation 2005;111(15):1999-2012.
- Newcomer JW, Haupt DW. The metabolic effects of antipsychotic medications. Can J Psychiatry 2006; 51(8):480-91.
- Meyer JM, Koro CE. The effects of antipsychotic therapy on serum lipids: a comprehensive review. Schizophr Res 2004;70(1):1-17.
- 6. Laita P, Cifuentes A, Doll A, et al. Antipsychotic-related abnormal involuntary movements and metabolic and endocrine side effects in children and adolescents. J Child Adolesc Psychopharmacol 2007;17(4):487-502.
- Cagnacci A. Melatonin in relation to physiology in adult humans. J Pineal Res 1996;21(4):200-13.
- Mohammadi MR, Mostafavi SA, Keshavarz SA, et al. Melatonin effects in methylphenidate treated children with attention deficit hyperactivity disorder: a randomized double blind clinical trial. Iranian J Psychiatry 2012;7(2):87-92.
- Cardinali DP, Cano P, Jimenez-Ortega V, et al. Melatonin and the metabolic syndrome: physiopathologic and therapeutical implications. Neuroendocrinology 2011;93(3):133-42.
- 10. Mostafavi SA, Mohammadi MR, Hosseinzadeh P, et al. Dietary intake, growth and development of children with ADHD in a randomized clinical trial of Ritalin and Melatonin co-administration: Through circadian cycle modification or appetite enhancement? Iranian J psychiatry 2012;7(3):114-9.
- Cardinali DP, Pagano ES, Scacchi Bernasconi PA, et al. Disrupted chronobiology of sleep and cytoprotection in obesity: possible therapeutic value of melatonin. Neuro Endocrinol Lett 2011;32(5):588-606.
- 12. Tan DX, Manchester LC, Fuentes-Broto L, et al. Significance and application of melatonin in the regulation

of brown adipose tissue metabolism: relation to human obesity. Obes Rev 2011;12(3):167-88.

- Akhondzadeh S, Milajerdi MR, Amini H, et al. Allopurinol as an adjunct to lithium and haloperidol for treatment of patients with acute mania: a double-blind, randomized, placebo-controlled trial. Bipolar Disord 2006;8(5 Pt 1):485-9.
- Amrollahi Z, Rezaei F, Salehi B, et al. Double-blind, randomized, placebo-controlled 6-week study on the efficacy and safety of the tamoxifen adjunctive to lithium in acute bipolar mania. J Affect Disord 2011;129(1-3):327-31.
- 15. Saroukhani S, Emami-Parsa M, Modabbernia A, et al. Aspirin for treatment of lithium-associated sexual dysfunction in men: randomized double-blind placebo-

ine

r CNV

controlled study. Bipolar Disord 2013;15(6):650-6.

- 16. Modabbernia A, Heidari P, Soleimani R, et al. Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: randomized double-blind placebo-controlled study. J Psychiatric Res 2014;53:133-40.
- Raskind MA, Burke BL, Crites NJ, et al. Olanzapineinduced weight gain and increased visceral adiposity is blocked by melatonin replacement therapy in rats. Neuropsychopharmacology 2007;32(2):284-8.
- Kozirog M, Poliwczak AR, Duchnowicz P, et al. Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. J Pineal Res 2011;50(3):261-6.

Acta Medica Iranica, Vol. 52, No. 10 (2014) 739