ABSTRACT

Introduction: Antipsychotic medications are associated with significant weight gain, type 2 diabetes mellitus, dyslipidemia, and increased cardiovascular risk. Suggested mechanisms of weight gain from antipsychotic medication include antagonism of histamine and serotonin receptors, and effects on the hypothalamic-pituitary-adrenal axis. The objective of this study was to determine if mifepristone, a glucocorticoid receptor antagonist, could prevent olanzapine-induced weight gain. Methods: This was a randomized, double-blind trial. Fifty-seven lean, healthy men (body mass index 18-25 kg/m²) aged 19-38 years were randomized to olanzapine (7.5 mg) (n=22), olanzapine (7.5 mg) plus mifepristone (600 mg) (n=24), or mifepristone (600 mg) (n=11) daily for 2 weeks in an institutional setting. Subjects were provided food ad libitum to accentuate weight gain. Body weight was measured daily. Results: The mean change in baseline weight was +3.2±0.9 kg in subjects receiving olanzapine versus +2.0±1.2 kg in those receiving olanzapine plus mifepristone (P<0.0001). Subjects receiving mifepristone alone had a similar degree of weight gain compared to those receiving olanzapine plus mifepristone. The olanzapine group had significant increases in waist circumference when compared with the olanzapine plus mifepristone group (3.7±1.3 cm vs. 2.2±1.9 cm, respectively; P=0.006). Fasting insulin and triglycerides increased more in the olanzapine group, although differences were not statistically significant. Conclusion: Mifepristone was effective in attenuating the increase in weight associated with olanzapine treatment over a 2-week period. Longer-term studies are required to examine the durability and full magnitude of this response.

Keywords: antipsychotic; mifepristone; olanzapine; weight gain

INTRODUCTION

Second-generation antipsychotic medications have been shown to be efficacious in the treatment of severe psychiatric disorders such
as schizophrenia. These drugs have gained wide acceptance due to their lower propensity to cause movement disorders compared with older medications. The amount of weight gain associated with second-generation antipsychotics can be high but varies with the specific agent and the population under study. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study randomized 1493 subjects to olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone for up to 18 months. The amount of weight gain was highest in the olanzapine group (4.3 kg), intermediate in the quetiapine and risperidone groups, and neutral in the perphenazine and ziprasidone groups. Other reports have shown a similar profile among these drugs. Notably, 30% of subjects treated with olanzapine in CATIE gained >7% of their baseline body weight.

Antipsychotic-induced weight gain has a quick onset, occurring in the first weeks of therapy, and continues unabated for many weeks. There are data to suggest that early weight gain, occurring within the first 1-3 weeks, is a predictor of sustained weight gain through 30 months of treatment. Although patients with psychiatric disorders may have lifestyle habits that predispose them to weight gain, a low body mass index (BMI) and young age seem to be risk factors for greater weight gain.

Strategies for controlling weight gain associated with antipsychotic medication have included switching to an antipsychotic associated with less weight gain, lifestyle changes, and pharmacological therapies, all of which have had limited success. Most studies that have investigated pharmacological treatments have been in psychiatric patients. Histamine antagonists, selective serotonin reuptake inhibitors, metformin, rosiglitazone, sibutramine, phenylpropanolamine, amantadine, topiramate, modafinil, and alpha-lipoic acid have been studied in clinical trials and have shown modest to no effect on reducing weight or preventing weight gain in these studies. These pharmacological interventions have generally not been based on mechanistic considerations, which may partially underlie their lack of meaningful efficacy.

It is not yet clear by what mechanism antipsychotic medications induce weight gain. Modulation of signaling pathways that regulate body weight via antagonism of histamine (H-1) and serotonin (5HT2c) receptors, and activation of the hypothalamic-pituitary-adrenal axis have been suggested to play an important role. Reports have documented increased caloric intake associated with these drugs as a contributor to weight gain, and recent data from animal studies suggest that reductions in energy expenditure (ie, thermogenesis, physical activity) may play a role.

Reduction in insulin sensitivity may be an important component of the pathogenesis of antipsychotic medication-induced abnormalities in glucose homeostasis and the attendant dyslipidemia and increased cardiovascular risk. Patients treated with antipsychotics often have higher insulin levels and have been reported to have insulin resistance, but reports using euglycemic clamp methods in nonpsychiatric individuals receiving short courses of antipsychotics have not yielded consistent results. The effects on insulin sensitivity may be different in psychiatric patients than in subjects free from mental disorder; van Nimwegen et al. demonstrated that schizophrenic patients have hepatic insulin resistance under clamp-isotope methodology. Interestingly, Wu et al. have demonstrated that metformin, a drug that improves hepatic insulin sensitivity, prevented antipsychotic-induced weight gain in first episode schizophrenics treated with olanzapine.