Case Report

Clozapine-induced Acute Hypertriglyceridemia

Mitesh Kumar, Ajeet Sidana

ABSTRACT

The aim of this study is to highlight the association between the use of clozapine and the early development of hypertriglyceridemia, a condition that substantially increases the risk of cardiovascular events and other medical complications. A 34-year-old female with a background history of schizophrenia presented with acute elevation of serum triglycerides and cholesterol within 2 weeks of starting clozapine. Her metabolic parameters normalized following discontinuation of clozapine. Possible hypotheses for lipid dysregulation with atypical antipsychotics include weight gain, dietary changes, and development of glucose intolerance; however, some other factors may be responsible for this rapid escalation of lipid levels. Lipid and metabolic profiles should be closely monitored in patients receiving clozapine to facilitate early detection and intervention to prevent further health complications.

Key words: Acute, clozapine, hypertriglyceridemia

INTRODUCTION

Patients with schizophrenia suffer from increased rates of multiple medical problems due to their lifestyle (high smoking prevalence, high-fat diet), inherent neglect of personal care, and barriers to treatment of physical illness.[1] A further important contributor to adverse health outcomes is the side effect profile of antipsychotic medications. Since the introduction of the second-generation or atypical antipsychotics, these agents have been widely prescribed for the management of patients with schizophrenia. Clozapine remains the most effective agent for the treatment of refractory schizophrenia; producing response in 30% of patients with treatment-resistant schizophrenia in a 6-week trial and up to 60% at 6 months.[2] The increasing use is due to their lower propensity to induce extrapyramidal symptoms and tardive dyskinesia as compared to typical antipsychotics. However, it presents with a different set of adverse effects. It causes weight gain and metabolic side effects, including alterations in glucose metabolism, elevation of blood cholesterol, and lipid levels, which increases the risk of cardiovascular events such as stroke and myocardial infarction.[3] Mean triglyceride levels have been found to double and cholesterol levels to increase by at least 10% after 5 years treatment with clozapine.[2] However, no case report is available in literature to the best of our knowledge, which showed acute development of hypertriglyceridemia without associated weight gain or glucose dysregulation. We present a unique case report highlighting development...
of hypertriglyceridemia within 2 weeks of starting clozapine therapy.

CASE REPORT

Ms. C, 35-year-old divorced woman was undergoing treatment from a tertiary care teaching hospital since November 2001 with the International Classification of Diseases-10 diagnoses of paranoid schizophrenia, characterized by auditory hallucinations and delusions of persecution and reference with impaired functioning since October 2001. Her history included multiple psychiatric admissions in the past, and her medical history included overweight. Her weight at the time of current admission on January 23, 2014, was 63 kg (body mass index [BMI] = 27.26 kg/m²). There was no history of coronary artery disease, hypertension, hypercholesterolemia, and diabetes mellitus. No history of any psychiatric or relevant medical history was present in the family. There was a history of poor response with risperidone and haloperidol given for adequate dosage and duration. Hence, the patient was started on clozapine on January 23, 2014, at dose of 25 mg/day which was increased by 25 mg/day to reach a dose of 250 mg/day by February 1, 2014.

Her baseline PANSS score was 85 and assessment of BMI, hemogram, serum electrolyte, fasting blood sugar (FBS), liver function test, lipid profile, serum prolactin, and electrocardiogram was within normal limits, except serum prolactin which was raised (77.8 ng/ml). However, on starting clozapine therapy, subsequent blood investigations done on February 6, 2014, and February 7, 2014, revealed acute dyslipidemia. Triglyceride levels increased many-fold and levels of cholesterol and low-density lipoprotein (LDL) were also raised. On the other hand, high-density lipoprotein levels had decreased. However, there was no significant increase in weight and FBS was also within normal limits. Clozapine was stopped due to acute dyslipidemia.

Her cholesterol, triglyceride, and LDL levels decreased and returned toward normality within 40 days of discontinuation of clozapine as shown in Table 1.

DISCUSSION

Across a range of antipsychotic medications, there is significant association with increased risk of hyperlipidemia. Each of the second-generation antipsychotic (SGA) medications, except aripiprazole, poses a risk of hyperlipidemia, which is significantly greater than the risk of no antipsychotic treatment. This significantly increases the risk of cardiovascular complications, and hence, monitoring of blood levels is of paramount importance.

There are numerous hypotheses for the various metabolic abnormalities. Usually, patients with schizophrenia are prone to obesity due to positive and negative symptoms and overall sedentary lifestyle. Furthermore, antipsychotic drugs result in increased appetite and excess food intake, possibly mediated through histamine H1 and serotonin 5HT2C receptor antagonist in the hypothalamus as well as alterations in hypothalamic fatty acid metabolism and neuropeptide expression. Another possible mechanisms by which clozapine produces metabolic abnormalities involve suppression of insulin release, insulin resistance, or impairment of glucose utilization.

All above are plausible mechanisms to explain metabolic complications over a period. However, these mechanisms cannot explain the acute development of hypertriglyceridemia as highlighted in our case report.

In addition, recent findings indicate that some antipsychotic-induced metabolic adverse effects occur independently of weight gain. Some authors believe that the changes in serum lipid concentrations; as seen in this case, it reflects naturally occurring intra-individual biological variations. It is well-known that serum lipid concentrations fluctuate considerably within

| Date                  | January 23, 2014 (starting of clozapine) | February 6, 2014 (clozapine was stopped) | February 7, 2014 | March 19, 2014 (40 days after discontinuation of clozapine therapy) |
|-----------------------|----------------------------------------|----------------------------------------|------------------|---------------------------------------------------------------|
| Clozapine dose (mg/day) | 25                                    | 250                                    | -                | -                                                            |
| Cholesterol (mg/dl)    | 146                                    | 223                                    | 239              | 197                                                          |
| Triglyceride level (mg/dl) | 69                                   | 458                                    | 464              | 235                                                          |
| HDL (mg/dl)            | 38                                     | 29                                     | 28               | 27                                                           |
| LDL (mg/dl)            | 94                                     | 140                                    | 154              | 123                                                          |
| VLDL (mg/dl)           | 14                                     | 18                                     | 18               | 47                                                           |
| FBS (mg/dl)            | 90                                     | 88                                     | 95               | 93                                                           |
| Weight (kg)            | 63.0                                   | 63.1                                   | 63.1             | 63.0                                                         |

VLDL – Very low-density lipoprotein; LDL – Low-density lipoprotein; HDL – High-density lipoprotein; FBS – Fasting blood sugar
individuals over relatively short periods. Attributed variables include intrinsic factors (i.e., hormonal variation and illness), extrinsic factors (i.e., diet), and biological factors. The mechanisms explaining this rapid variation in serum lipid concentrations lies in intrinsic factors related to their biosynthesis and tissue use as regulated by genetic factors and their interactions with extrinsic factors.\(^9\)

To explore whether antipsychotics exert acute effects on lipid levels and other metabolic profile, a study had been conducted on mice where an intraperitoneal injection of clozapine was given. Clozapine administration rapidly induced direct transcriptional effects in the liver through genes directly controlling transcription factors, sterol regulatory element-binding protein transcription factors, peroxisome proliferator-activated receptor, and liver X receptors. This facilitated hepatic lipid deposition by upregulating lipogenesis as these genes are involved in fatty acid biosynthesis, independent of food intake and weight gain. This resulted in increase in levels of triglycerides, phospholipids, and cholesterol within 48 h.\(^{10}\)

However, no such human results are available.

**CONCLUSION**

Primary prevention of the metabolic syndrome and cardiovascular disease is an important aspect of care for severe mental disorders. According to the guidelines, patients taking SGAs should receive appropriate baseline screening and ongoing monitoring of personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease, weight and height (BMI), waist circumference (at the level of the umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile.

Hence, in the light of current case report, we suggest for more stringent and rapid monitoring of lipid levels to prevent the metabolic syndrome.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Sartorius N. Physical illness in people with mental disorders. World Psychiatry 2007;6:3-4.
2. Henderson DC, Caglierio E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: A five-year naturalistic study. Am J Psychiatry 2000;157:975-81.
3. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: A systematic review and meta-analysis. Schizophr Res 2010;123:225-33.
4. Olsson M, Marcus SC, Corey-Lisle P, Tuomari AV, Hines P, Gilbert AS, et al. Hyperlipidemia following treatment with antipsychotic medications. Am J Psychiatry 2006;163:1821-5.
5. Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology 2003;28:519-26.
6. Wirshing DA, Spellberg BJ, Erhart SM, Marder SR, Wirshing WC. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998;44:778-83.
7. Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: Insights from receptor-binding profiles. Mol Psychiatry 2008;13:27-35.
8. Fernø J, Vik-Mo AO, Jassim G, Håvik B, Berge K, Skrede S, et al. Acute clozapine exposure in vivo induces lipid accumulation and marked sequential changes in the expression of SREBP, PPAR, and LXR target genes in rat liver. Psychopharmacology (Berl) 2009;203:73-84.
9. Procysyn RM, Wasan KM, Thornton AE, Barr AM, Chen EY, Pomarol-Clotet E, et al. Changes in serum lipids, independent of weight, are associated with changes in symptoms during long-term clozapine treatment. J Psychiatry Neurosci 2007;32:331-8.
10. Birkenaes AB, Birkeland KI, Engh JA, Faerden A, Jonsdottir H, Ringen PA, et al. Dyslipidemia independent of body mass in antipsychotic-treated patients under real-life conditions. J Clin Psychopharmacol 2008;28:132-7.