Metabolic Side Effects of the Rise:
The Use of Metformin to Counteract Clozapine-Induced Adverse Reactions- A Case Report.
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Introduction

Clozapine has been the most effective medication in treatment resistant schizophrenia. However, with this exceptional medication also comes with inimical side effects.

In the past decade, there has been growing concern among psychiatrists that the use of clozapine may be related to adverse metabolic effects.

For example, in the phase 3 of the CATIE schizophrenia trial, those who took prolonged periods of clozapine reported weight gain, upsurge in the blood levels of glucose, triglycerides and glycosylated hemoglobin.

We will discuss a case report of a patient taking metformin whose metabolic parameters was stabilized so patient could be maintained on clozapine.

Learning Objectives

•To understand the mechanism of action of metformin in clozapine induced weight gain
•To determine the effectiveness of metformin in negating the adverse metabolic effects

Proposed Mechanism of Action in Clozapine Induced Metabolic Side Effects

- Possible explanations for the weight gain associated with clozapine include the antagonism of hypothalamic histaminergic H1 receptors, serotoninergic 5-HT2C receptors, and/or adrenergic alpha 2 receptors.
- H1 receptors antagonism is thought by some to be the best predictor of antipsychotic-induced weight gain. Neuronal histamine has been demonstrated to suppress food intake through H1 histamine receptors in the VMH and PVN as well as regulating leptin. Clozapine have the highest affinity for H1 receptors and are associated with the greatest weight gain.
- Leptin exerts part of its effect through H1 receptor mediated pathway. Disruption of this pathway lead to leptin resistance that has been associated with obesity.
- Limited studies were available for the role of serotoninergic 5-HT2C and clozapine induced metabolic side effects. However, it was noted that those without the ~750T polymorphism of the 5-HT2C receptor had increased risk of metabolic adverse reactions.
- Activation of adrenergic system contributes to the increase of glycosogenesis, lipolysis and increased plasma glucose level. Affinity of antipsychotics for alpha 2 adrenergic receptor has been demonstrated with weight gain. This is due to self-feedback mechanism in which the release of NE is regulated by an alpha 2 receptor on the pre-synaptic axon, which inhibits NE release if activated. Clozapine has high affinity to adrenergic receptor which may contribute to increased weight gain. It was proposed that clozapine may bind to multiple receptors leading to increased weight gain and diabetes compared to other anti-psychotics.

Central Receptor Blockade by Atypical Antipsychotics in VMHN and PVN

Case Presentation

- Patient: 23-year-old African American woman with acute psychosis
- Presentation: baseline symptoms that had recently worsened, including disorganized behavior and thought, auditory hallucinations; inappropriate affect and laughter; responding to internal stimuli and thought disorder by loosening of associations.
- Medication: chlorpromazine 50 mg TID; Depakote 1250 mg q12 hours, Haldol 20 mg BID and Cogentin 2 mg q 12 hours. Decision made to give her clozapine
- Laboratory test results: Initial weight was 77.1 kg (171 lbs), BMI 29. Glucose 84 mg/dl and triglyceride was 90 mg/dl
- Treatment:
  - Clozapine was slowly titrated upward.
  - Pt gained 1.3 kg after 3 weeks from starting clozapine.
  - However, metabolic panel was WNL. HbA1c was 5.2%, glucose 80 mg/dl, and triglyceride is 52 mg/dl.
  - Metformin was increased to 850 mg BID with meals after 3 weeks. During the later 3 weeks, metformin was increased to 1000 mg BID with meals to maximize stabilization.
  - At the end of 6 weeks, her weight was 79.5 kg (175 lbs), BMI 32 and glucose 95 mg/dl. Clozapine was 150 mg q 12 hours at the end of 6 weeks.
- Results: Psychotic symptoms decreased. Pt became more logical, decreased auditory hallucinations and agitation.

Discussion

Clozapine is the most effective agent in treatment resistant schizophrenia. However, weight gain is a common side effect leading to increased risk of elevated BMI, diabetes mellitus and hyperlipidemia. Recent studies have indicated that those with severe mental illness can die up to three decade earlier than general population. Heart disease is the leading cause of death. A major risk factor for heart disease and early death is weight gain due to obesity.

Lifestyle changes have played a role in decreasing weight gain with those on clozapine. However, many patients have found it difficult to maintain their weight on lifestyle changes alone.

Metformin, which inhibits hepatic glucose production, is a well tolerated medication with minimal side effects. It plays a role by decreasing hepatic glucose production and insulin resistance. Some studies have demonstrated metformin can be weight neutral or decrease weight with those with antipsychotic-induced metabolic side effects. Studies have shown that metformin at dosage of 1000 to 2000 mg/day is effective in those diagnosed with schizophrenia lose weight. Most trials of recent weight gain found 12-16 weeks of metformin lead to loss of 50% weight gain by antipsychotic treatment. Dosages used were 750 mg daily or higher.

In this case presentation, in the initial three week period, she demonstrated slight weight gain. Metformin was increased to correct the effects of medication's side effects. Her weight continued to increase at a minimal rate until the end of 9 weeks. In a total of 6 weeks, she gained 4 pounds. Moreover, her metabolic profile continued to be WNL during the 6-week period stabilizing her metabolic effect.

One of the challenges faced by clinicians today is dealing with adverse side effects from long-term antipsychotic medications. Sustaining a healthy metabolic control becomes difficult especially on an inpatient psychiatry unit when patients have sedentary lifestyles and poor diet. Due to this growing concern, more studies are needed to establish metformin as evidence based intervention needed to fight medical complications from long-term antipsychotic side effects.

APA Guidelines

References