

Acute onset clozapine-induced hyperglycaemia: A case report

Pradeep Kumar,¹ Dheerendra Kumar Mishra,¹ Nimisha Mishra,¹ Sunil Ahuja,¹ Gyanendra Raghuvanshi,¹ Vijay Niranjana²

To cite: Kumar P, Mishra DK, Mishra N, *et al.* Acute onset clozapine-induced hyperglycaemia: A case report. *General Psychiatry* 2019;**32**:e100045. doi:10.1136/gpsych-2018-100045

Received 26 December 2018
Revised 06 February 2019
Accepted 10 February 2019

ABSTRACT

Clozapine is an atypical antipsychotic which is described to have higher efficacy among all available antipsychotic medications. Clozapine is reserved especially for resistant schizophrenia due to its side effects. Clozapine-induced metabolic syndrome and hyperglycaemia are common long-term side effects and are responsible for increased mortality in patients with schizophrenia. In this case, a patient with resistant schizophrenia was presented with acute-onset hyperglycaemia and delirium with the use of clozapine within a week. Withdrawal of clozapine in the patient led to the improvement in delirium and hyperglycaemia without the use of any hypoglycaemic agent. This case supports the notion that in certain cases clozapine can induce hyperglycaemia through possible direct pathophysiological mechanisms within a shorter time frame.

INTRODUCTION

Clozapine is a serotonin-dopamine antagonist (SDA) antipsychotic, but it differs from other SDA antipsychotics in terms of binding to dopamine and serotonin receptors, therapeutic efficacy and side effect profile.¹ In clinical practice, the use of clozapine is usually reserved for those patients who do not respond adequately to previous trials of other antipsychotic medications.² The therapeutic efficacy of clozapine is reported to be higher than that of other antipsychotics and the side effects reported are also higher.³ Various studies showed that the prevalence of metabolic syndrome among subjects taking clozapine was much higher than that of the subjects taking other antipsychotics.⁴ For the metabolic syndrome, the impaired blood glucose level is an important parameter which leads to the development of type II diabetes mellitus.⁵ A study reported that more than one-third of the subjects were diagnosed with diabetes mellitus during 5 years of follow-up therapy with clozapine.⁶ The development of clozapine-induced diabetes is commonly considered to arise as part of a metabolic syndrome evolving slowly. Therefore, monitoring fasting blood glucose at baseline, after one-month treatment and then every 4 to 6 months during clozapine therapy is recommended.⁷ Some case reports described

an onset of hyperglycaemia immediately after starting clozapine with controlled diabetes subjects,⁸ but there were no reports of clozapine-induced acute-onset hyperglycaemia in the literature. Hereby, we report a case of previously euglycaemic patient with schizophrenia who developed acute-onset hyperglycaemia within the first few days after starting clozapine therapy.

CASE HISTORY

A 37-year-old married man with a nil significant past and family history of psychiatric illness was admitted in the psychiatry ward. The total duration of illness was 5 years, and at admission, symptoms were characterised by muttering to self, third person auditory hallucinations, apathy, restricted affect and absent insight. The patient previously received trials of olanzapine and risperidone for adequate dose and duration but with inadequate response, and currently, he was off treatment since last 2 months as he was refusing to take medicines at home given by family members. So in this hospitalisation after the detailed assessment, the subject was labelled as having treatment-resistant schizophrenia and started with clozapine with a dose of 25 mg/day orally at night time and injectable haloperidol 5 mg on a pro re nata basis to manage aggression of the patient. Before initiation of clozapine, a complete physical assessment was performed. His body mass index was 26 with little abdominal obesity. Fasting blood sugar, lipid profile and ECG did not show any abnormality. Clozapine was uptitrated gradually, and the improvement in biological function like maintenance of sleep and adequate appetite was noticed along with decreased aggression and reduced gesticulating behaviour. However, on the 10th day, when the dose of clozapine reached up to 200 mg/day, patient started being delirious during the nights characterised by fluctuating altered sensorium worsening at night time along with increased psychomotor activity, decreased attentiveness and so forth. Due to these symptoms, his blood investigations were again performed and it



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Department of Psychiatry, Shyam Shah Medical College Rewa, Rewa, India

²Department of Psychiatry, Mahatma Gandhi Memorial Medical College, Indore, India

Correspondence to

Dr Dheerendra Kumar Mishra; mdheerendra.ssmc@gmail.com

was found that his fasting blood sugar was raised up to 234 mg/dL and postprandial blood sugar was 350 mg/dL. The test was repeated again the next day. Similarly, raised blood sugar levels were found. The rest of the blood parameters like kidney function test, liver function test, serum electrolytes were within normal limits. Although the tests for glycated haemoglobin and plasma level of clozapine were not performed due to the unavailability of these tests in our setup, it was decided to stop clozapine in view of possible drug-induced adverse drug reaction. After the second day of stopping clozapine, delirium in the subject improved, and over the next week his hyperglycaemia was also improved and values came within range without the use of any hypoglycaemic agents.

DISCUSSION

The use of clozapine that can result in impaired glycaemic control is a well-established fact and various factors are postulated to be contributory, such as increased appetite, weight gain and insulin resistance.⁹ However, clozapine-induced acute-onset hyperglycaemia within a short time is not better explained by these factors as they should result in relatively slowly evolving hyperglycaemia. In our report, the patient developed hyperglycaemia during dose increment of clozapine and it was acute in onset. Along with hyperglycaemia, the patient also developed delirium. Furthermore, when clozapine was stopped, his delirium improved within 48 hours and he was euglycaemic within a week in the absence of any hypoglycaemic agents. Clozapine has high affinity for muscarinic M2 and M3 receptors. M2 and M3 receptors are also present over pancreatic β cells.¹⁰ As per previous research, M3 receptors control cholinergic-dependent insulin release and have a role in maintaining glucose homeostasis. Previous research has also described that M3 antagonism can result in pancreatic beta cell dysfunction.¹¹ In addition, strong central anticholinergic activity of clozapine is proposed to be associated with the incidence of delirium.¹² Thus, this strong anticholinergic activity of clozapine may be a common link responsible for causing both acute-onset hyperglycaemia and delirium. Some researchers have also proposed another contributory mechanism for hyperglycaemia like mitochondrial damage to insulin responsive cells and increased glucagon secretion with the use of clozapine.¹³ However, further research is warranted to explore the underlying pathophysiological mechanisms, and meanwhile, clinicians need to be aware about the possibility of impaired glycaemic control in a relatively short time

frame with the use of clozapine in certain cases and should manage accordingly.

Contributors PK and DM contributed to the observations and conceptualise the case. NM, SA and GR contributed to the detailed assessment, evaluation and conclude the case. DM and VN contributed to the manuscript writing, proof reading and literature review.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0>

REFERENCES

1. Stroup TS, Lieberman JA, McEvoy JP, et al. Results of phase 3 of the CATIE schizophrenia trial. *Schizophr Res* 2009;107:1–12.
2. Lally J, Gaughran F, Timms P, et al. Treatment-resistant schizophrenia: current insights on the pharmacogenomics of antipsychotics. *Pharmgenomics Pers Med* 2016;9:117–29.
3. McIlwain ME, Harrison J, Wheeler AJ, et al. Pharmacotherapy for treatment-resistant schizophrenia. *Neuropsychiatr Dis Treat* 2011;7:135–49.
4. Chadda RK, Ramshankar P, Deb KS, et al. Metabolic syndrome in schizophrenia: differences between antipsychotic-naïve and treated patients. *J Pharmacol Pharmacotherap* 2013;4:176–86.
5. Cohen D. Atypical antipsychotics and new onset diabetes mellitus. An overview of the literature. *Pharmacopsychiatry* 2004;37:1–11.
6. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry* 2000;157:975–81.
7. Kar N, Barreto S, Chandavarkar R. Clozapine monitoring in clinical practice: beyond the mandatory requirement. *Clin Psychopharmacol Neurosci* 2016;14:323–9.
8. Porras-Segovia A, Krivoy A, Horowitz M, et al. Rapid-onset clozapine-induced loss of glycaemic control: case report. *BJPsych Open* 2017;3:138–40.
9. Coccarello R, Moles A. Potential mechanisms of atypical antipsychotic-induced metabolic derangement: clues for understanding obesity and novel drug design. *Pharmacol Ther* 2010;127:210–51.
10. Reynolds GP, Kirk SL. Metabolic side effects of antipsychotic drug treatment – pharmacological mechanisms. *Pharmacol Ther* 2010;125:169–79.
11. Silvestre JS, Prous J. Research on adverse drug events. I. muscarinic M3 receptor binding affinity could predict the risk of antipsychotics to induce type 2 diabetes. *Methods Find Exp Clin Pharmacol* 2005;27:289–304.
12. Centorrino F, Albert MJ, Drago-Ferrante G, et al. Delirium during clozapine treatment: incidence and associated risk factors. *Pharmacopsychiatry* 2003;36:156–60.
13. Contreras-Shannon V, Heart DL, Paredes RM, et al. Clozapine-induced mitochondria alterations and inflammation in brain and insulin-responsive cells. *PLoS One* 2013;8(suppl 3):e59012.



Dheerendra Kumar Mishra graduated with M.B.B.S. and M.P. from Shyam Shaha Medical College Rewa in India, and completed his postgraduate degree (M.D. Psychiatry) in June 2017. He also received Diplomate of National Board (Psychiatry) from the National Board of Examination. He is currently working as an assistant professor in the department of psychiatry. His research interests include advance in psychiatric treatment, mood disorder, psychopharmacology and geriatric psychiatry.