

CLOZAPINE INDUCED EXTRAPYRAMIDAL SYMPTOMS FOLLOWING ALCOHOL CONSUMPTION IN PATIENT WITH SCHIZOPHRENIA AND ALCOHOL DEPENDENCE SYNDROME: A CASE REPORT OF SIALORRHEA, ACUTE AKATHISIA AND DYSTONIA

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ABSTRACT

Clozapine (CLZ), a second-generation or atypical antipsychotic, although not recommended as the first-line drug of choice in the treatment of schizophrenia and schizoaffective disorders; however, it is recommended in the treatment of Treatment-Resistant Schizophrenia and in schizophrenic patients to decrease the recurrent risk of suicidal behavior. For the cytochrome P450 isoenzymes CYP1A2, CYP2D6, and CYP3A4, CLZ serves as a substrate. CLZ also exhibits drug-food interaction with alcohol leading to an increase in the risk of seizures and extrapyramidal symptoms. A case of a 36-year-old male patient with a known history of paranoid schizophrenia and alcohol dependence syndrome came with complaints of dystonia and hypersalivation 1 day following the consumption of alcohol after ingestion of tablet CLZ. After clinical pharmacist intervention, the doses were titrated and the patient improved gradually. With this, it can be postulated that the concomitant use of alcohol with CLZ can be a predisposing factor for drug toxicity in the patients and hence patients should be monitored and counseled to abstain from the use of alcohol while on CLZ therapy.

Keywords: Clozapine, Alcohol, Extrapyramidal symptoms, Drug toxicity, Drug-Food Interactions.

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INTRODUCTION

Antipsychotics drugs are used to treat a plethora of psychiatric ailments and are broadly classified as first-generation or typical and second-generation or atypical antipsychotics. The typical antipsychotic agents are dopamine receptor antagonists compared to the atypical antipsychotic agents that are serotonin-dopamine receptor antagonists [1]. Clozapine (CLZ) is an atypical antipsychotic medication used in treatment-resistant schizophrenia and reducing the risk of suicidal behavior in schizophrenic patients [2]. The adverse effects of CLZ range from common gastrointestinal, urogenital, pulmonary, dermatological effects and rare effects include pseudopheochromocytoma, periorbital edema, and parotitis [3]. Sialorrhea or ptyalism commonly referred to as drooling occurs when the lip margin is touched by extra saliva in the mouth. CLZ-induced sialorrhea mechanism is not clear but is attributed to muscarinic receptors M3 and M4 present in salivary gland tissue. These receptors exert opposing effects on salivation: M3 blockade and M4 stimulation enhance saliva production [4]. The sialorrhea is also linked to the α -2 antagonistic and anticholinergic activities [5].

Akathisia is intense restlessness that is marked by an inability to sit or remain still, fidgety movements, or jitteriness, as well as a subjective impression of interior restlessness, is a neuropsychiatric syndrome linked to the use of antipsychotics. As per the American Psychological Association, dystonia is described as a reduction in normal muscular tone that results in prolonged muscle contractions, aberrant posture, twisting, or repetitive movements [6,7]. For the cytochrome P450 isoenzymes CYP1A2, CYP2D6, and CYP3A4, CLZ serves as a substrate. CLZ also exhibits drug-food interaction with alcohol leading to an increase in the risk of seizures and extrapyramidal symptoms [8,9].

CASE PRESENTATION

A 36-year-old male patient with a known history of paranoid schizophrenia and alcohol dependence syndrome presented with complaints of stiffness and pain in the neck along with abnormal body movements in the right gluteal region and hypersalivation and decreased sleep for a day. The pain aggravated on trying to move and

when he brought his legs down, the patient explained the movements as dance-like waves. The patient complained of hypersalivation and that his pillows used to get wet due to continuous drooling. The patient was on tablet CLZ 50 mg 1-0-1½ tablet trihexyphenidyl chloride 2 mg 1-0-0. The patient had consumed alcohol after orally administering the tablet CLZ. His symptoms were graded as 16 on the Modified Simpson-Angus Scale (MSAS) categorized as "severe degree of movement disorder" (Table 1) and score 13 on the abnormal involuntary movement scale (AIMS). The adverse reaction was graded as "Probable" using Naranjo's algorithm for causality assessment and "Severe" Level-5 adverse reaction using Hartweg's severity assessment scale. The patient was admitted to the psychiatric in-patient care and his CLZ doses were titrated to tablet CLZ ½-0-2 along with administration of tablet glycopyrrolate 2 mg 1-0-0, tablet trihexyphenidyl 2 mg 1-0-1, tablet benfotiamine 100 mg 0-1-0 and multivitamins and the patient was closely monitored. The patient's improvement was monitored using the MSAS and AIMS scale and daily mental state examinations. The patient showed significant improvement by day 5 of the treatment and reported a reduction in sialorrhea and dystonia. By day 15 of the treatment, the patient exhibited no signs of extrapyramidal symptoms and was stable and was discharged (Table 2). The patient was advised to return to the hospital for a review and follow-up after 2 weeks or sooner if there were any problems.

DISCUSSION

CLZ exerts its pharmacological effects by blockade of dopamine D_2 and serotonin 5-HT_{2A} receptors [10]. CLZ is primarily metabolized by CYP450 enzymes in the liver where the drug undergoes demethylation and oxidation. CYP3A4 and CYP1A2 are mostly involved in the metabolism along with CYP2D6 with a minor role [11]. Although CLZ is often used in clinical practice for the treatment of psychiatric disorders, the drug has the potential to cause serious adverse reactions if doses are monitored appropriately. CLZ-induced drug toxicities could be lethal if not treated on time. It is recommended to use muscarinic anticholinergic drugs for the management of sialorrhea, for mild sialorrhea use of towels is recommended for nocturnal sialorrhea [12]. CLZ-induced akathisia and dystonia are generally managed with appropriate dose titrations and also using anticholinergic drugs and pain is managed using appropriate

Table 1: Modified Simpson Angus scale

Parameter	Day-1	Day-2	Day-3
Gait	2	2	1
Arm dropping	4	3	3
Shoulder shaking	2	0	0
Elbow rigidity	1	0	0
Wrist rigidity	2	1	0
Head rotation	1	1	0
Glabella top	0	0	0
Tremor	1	0	0
Salivation	2	1	0
Akathisia	2	0	0
Total	16	8	4

Table 2: Discharge medications

T. Clozapine	50 mg	½-0-2	2 weeks
T. Trihexyphenidyl	2 mg	1-0-0	2 weeks
T. Glycopyrrolate	2 mg	1-0-0	2 weeks
T. Benfotiamine	100 mg	0-1-0	2 weeks

analgesics. It is reported that 37% of all antipsychotics experience some form of extrapyramidal symptoms during the treatment period [13]. A study conducted by Kurz *et al.* 1995 showed an akathisia incidence rate of 5.6% [14] and a study conducted by Syed *et al.* 2008 concluded that sialorrhea is a common adverse effect of CLZ with prevalence of 30–70% [15]. A study conducted by Maher *et al.* in 2016 concluded a prevalence of 7.1 % in CLZ users [16]. The concomitant use of alcohol along with CLZ is not recommended and patients are advised to refrain from alcohol use while on the medication as it can cause serious side effects including central nervous system depression [17]. There are various literature explaining the correlation between use of CLZ and development of extrapyramidal symptoms which clearly indicate that CLZ is not entirely safe for clinical use and hence must give in proper recommended doses to avoid such occurrences and the patient must be monitored closely for extrapyramidal symptoms. A cross-sectional study and meta-analysis conducted by Potvin *et al.* in 2005 and 2009 on patients with schizophrenia and comorbid substance use showed increased extrapyramidal symptoms; therefore, it is important to make patients aware of the adverse effects arising with concomitant use of alcohol with CLZ [18,19].

CONCLUSION

This case report provides evidence that the comorbid use of alcohol with CLZ aggravates the extrapyramidal symptoms. Therefore, the patients must be made aware of the effects of alcohol on antipsychotics and how it could potentially lead to fatal consequences to the patient's health. With this study, we postulate that the use of CLZ along with alcohol could be a predisposing factor for increased drug-induced toxicity in patients.

PATIENT CONSENT

The patient consent statement has been taken for publishing this article.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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