International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2019): 7.583

Clozapine Intoxication with Neuroleptic Malignant Syndrome: Case Report

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Abstract: ***Background: Clozapine intoxication is defined when a person ingests clozapine which exceeds daily dose. If not treated properly, this exposure could lead into fatal complication such as neuroleptic malignant syndrome. Case report: We reported a patient, male, 37 years old, came to emergency room with a decrease of consciousness after taking 30 tablets of 25 mg clozapine, about 30 minutes before admission. Patient also developed signs of hyperthermia, tachycardia, and blood pressure rise. Subsequent examination followed and it was revealed that there was an elevation of creatinine phosphokinase levels, confirming diagnosis of neuroleptic malignant syndrome. Patient was decontaminated with gastric lavage method and trihexyphenidyl was administrated. Patient eventually regain consciousness, and made an uneventful recovery within four days. Summary: Emergency management in clozapine intoxication has an important role in preventing life threatening complication. Although the prevalence is rare, NMS must always be considered in antipsychotic intoxication case.***

Keywords: Intoxication,Clozapine, Neuroleptic Malignant Syndrome

1. Introduction

Intoxication is a condition that accompanies administration of a psychoactive substance and results in impaired awareness, cognitive, perception, judgment, affect, or behavior as well as psychophysiological function and response.[1]Intoxication is closely related to the type and dose of the drug, as well as the individual's tolerance level to a substance.[1] Intoxication can occur with substances containing psychoactive substances or substances that do not contain psychoactive substances. Intoxication of psychoactive substances could lead into a fatal outcome. One of the psychoactive substances that has a potential to develop into devastating outcome is the intoxication of the antipsychotic group.[2]

The prevalence of antipsychotic intoxication in America was estimated to be 5.21% in 2019.[2]Intoxication could occur in both typical and atypical antipsychotics. One of the antipsychotic intoxications that is very frequent is clozapine intoxication, which belongs to atypical antipsychotic class.[3] Clozapine intoxication could develop into neuroleptic malignant syndrome (NMS) which is an emergency case that needs timely intervention.[4,5]NMS is associated with the clozapine and other dopamine receptor antagonists use.[6] The incidence of NMS ranges from 0.01% - 3.2% of patients taking neuroleptic drugs.[7]NMShas mortality rate varies from 5-20%.[8] In 2011, an international consensus was made by using Delphi method, to establish a diagnosis of NMS, as listed in table.[9]Diagnosis NMS is made if it meets a cutoff score 74 out of a total of 100.[10] This case report will discuss NMS case caused by clozapine intoxication which was motived by attempted suicide.

Table 1: International Expert Consensus NMS Diagnostic Criteria.[10]

Criterion	Score
1. Exposure to dopamine antagonist or dopamine agonist withdrawal, within the past 72 h	20
2. Hyperthermia (>100.4°F or >38.0°C on at least 2 occasions, measured orally)	18
3. Rigidity	17
4. Mental status alteration (reduced or fluctuating level of consciousness)	13
5. Creatine phosphokinase (CPK) elevation	10
6. Sympathetic nervous system lability, defined as at least 2 of the following: Blood pressure elevation (systolic or diastolic ≥ 25% above baseline) Blood pressure fluctuation (≥20 mm Hg diastolic change or ≥25 mm Hg systolic change within 24 h) Diaphoresis Urinary incontinence	10
7. Hypermetabolism, defined as heart rate increase (≥25% above baseline) and respiratory rate increase (≥50% above baseline)	5
8. Negative workup for infectious, toxic, metabolic, and neurologic causes	7
Total	100

2. Case Illustration

A 37-year-old male patient, unmarried, Balinese, works as an employee, came to the emergency room on February 20, 2021 with a decreased consciousness after taking 30 tablets of clozapine 25 mg because of attempted suicide, about 20 minutes before admission to hospital. Patient regained consciousness when awakened, but mostly patient only able

to open his eyes with verbal command. When asked, patient also gave confused answer, but still able to answer questions. Patient had a history of schizoaffective disorder, with depressive type that was inconsistently controlled due to lack of motivation. Treatment history of risperidone 1x2 mg (p.o.) and clozapine 1 x 25 mg (p.o.). Physical examination revealed Glasgow Coma Scale (GCS) consciousness E3V4M6, with blood pressure 160/110 mmHg, pulse 149 beats per minute, respiratory rate 32, Oral temperature was 38,1°C, oxygen saturation 97%. On examination of the head, neck, thorax, abdomen within normal limits. The extremities felt warm and there was lead-pipe rigidityon all four extremities in the entire range of movement. Family history revealed no remarkable history.

Laboratory test results revealed an increase in leukocyte 12.93 (4.10 – 11.00) X 10^3/µL, RBC 6.77 (4.50 – 5.90) X 10^6/µL, neutrophils absolute 10.3 (1.50 – 7.00) X 10^3/µL, monocytes 0.79 (0.00 – 0.70) X 10^3/µL and decreased MCV71 (80.0 – 100.0) fL, lymphocytes 13.8% (25.0 – 40.0) %, and eosinophils 0.2% (2.0 – 4.0). Blood chemistry examination showed elevated random blood sugar 159 (70 – 140) mg/dL and CPK 348 (<190) U/L. Electrocardiography (EKG) showed sinus tachycardia, with a pulse rate 149 beats / minute. Examination of chest x-ray and urinalysis were within normal limits.

Patient was diagnosed with: neuroleptic malignantsyndrome that was caused by clozapine intoxication, schizoaffective disorder, with depressive type, suicide attempt, sinus tachycardia, with pulse 149 beats / minute.Patientwas hospitalized, nasogastric tube was placed and gastric lavage intervention about 20 minutes after exposure to substance, administrationof Trihexyphenidyl 2x2 mg (p.o.), Nebivolol 1X5 mg (p.o.)

On February 21, 2021, patient had slurred voice, when having conversation with attending, he looked confused. He also spoke in vague words, had dysphagia and insomnia. Psychiatric assessmentrevealed a loose association with a coherent thinking process with auditory hallucinations such as hearing male and female voices whispering towards patient.Physical examination revealed compos mentis consciousness, with blood pressure 160/110 mmHg, pulse 88 beats per minute, respiratory rate 20, Oral temperature was 38,0°C, oxygen saturation 98%. All physical examination were within normal limitsand there was no rigidity. Patient was given lorazepam 1 X 2 mg at night. Trihexyphenidyl was stopped. The nasogastric tube was removed and the patient was planned to have a soft diet plan.

On February 22, 2021, there was no symptom. Blood pressure 120/70 mmHg, pulse 88 beats per minute, respiratory rate 16, Oral temperature was 36,4°C, oxygen saturation 98%. Physical examination revealed normal vital signs. All physical examination were within normal limits. The patient was discharged from the hospital and a scheduled visit to psychiatrist, internist, and cardiologist polyclinic was scheduled as a part of rehabilitation.

Image 1: Patient with flat affect

3. Discussion

In this case, patient was present with a sudden loss of consciousness after taking atypical antipsychotic drug (clozapine) for a total of 750 mg. Vital signs examination revealed febrile temperature, tachycardia and elevated blood pressure. On physical examination, there was a lead-pipe rigidity on all four extremities in the entire range of movement. Laboratory test revealed leukocytosis and hyperglycemia. Chest x-ray andurinalysis showed no abnormalities. ECG examination confirms tachycardia with pulse 149 beats / minute. CPK examination shows an increase in CPK levels. Patient was diagnosed with NMS caused by clozapine intoxication.

Clozapine is an atypicalantipsychotic used to treat refractory schizophrenia with standard daily dose of ranges from 300-600 mg/day.[11,12] Clozapine intoxication is defined as ingestion of clozapine tablets exceeding standard daily dose. In this case, patient ingested 750 mg of clozapine tablets.[12]Central nervous system depression and tachycardia were the predominant symptoms of clozapine intoxication, found in 41.2% and 33.1% cases.[13] This is consistent with findings in patient that presented to ER with decreased of consciousness and tachycardia. Central nervous system depression is mediated by the antagonistic properties of clozapine against the H_1 histamine receptor.[11] In addition, clozapine is also an antagonist to muscarinic receptors, which causes tachycardia.[11] Based on the history, physical examination, and laboratory investigations, patient can be diagnosed with clozapine intoxication, as appropriate. with literature.

The management of clozapine intoxication has basic principles which include 1) emergency management, 2) clinical assessment, 3) toxin decontamination, 4) administration of antidotes, 5) supportive therapy, 6) observation and consultation, 7) rehabilitation.[13]

Emergency management is based on Decontamination, Airway, Breathing, Circulation (DABC) concept.[14] Toxin decontamination can be done by the gastric lavage.[13]Gastric lavage is effective within 30 minutes until 4 hours after

intoxication due to clozapine pharmacokinetic profile that could reach peak plasma concentration in 40 minutes.[15] Hemodialysis is rarely used because clozapine tends to bind to intravascular protein, which will reduce the benefit of hemodialysis significantly.[15]

Gastric lavage was performed in 20 minutes after the onset of intoxication and maintained every 6 hours. Airway assessment includes airway patencyand additional sounds assessment, accompanied by observation of breath muscle use.[14]Breathing assessment includes of respiration rate, cyanosis, and oxygen saturation assessment.[14] Circulation parameters including palpation of arteries carotid and if necessary, cardiac pulmonary resuscitation (CPR) can be performed on intoxicated patients.[14] In this case, intoxication emergency management was performed based on the DABC concept.

Currently there is no specific antidote for clozapine intoxication.[16] Bromocriptine is often used for antipsychotic intoxication because it has dopamine agonist component.[16]Trihexyphenidyl is also used for clozapine intoxication and extrapyramidal adverse effects caused by antipsychotics.[17] Trihexyphenidyl acts as a muscarinic receptor antagonist (M_1 antagonist).[17] Trihexyphenidyl has a half-life of 3.3-4.1 hours, and has duration of action approximately 1-12 hours.[17]The mechanism underlying trihexyphenidyl use in clozapine intoxication remains unclear.[17] Trihexyphenidyl has anticholinergic effect, providing competition with clozapine at M_1 receptors.[17]In this case patient was given 2 mg trihexyphenidyl every 12 hours for two days. Trihexyphenidyl administration at this dose has been successful in improving the clinical course of the patient and is in accordance with the literature

Patient was also given nebivolol 5 mg every 24 hours due to sinus tachycardia as part of supportive management.[18] Nebivolol is a beta-blocker class that has a rolein blocking the ß-1 receptor in the heart.[18] Classically, beta-blockers are the drug of choice for the treatment of clozapine-induced sinus tachycardia.[18] The patient was observed clinically for three days and achieved uneventful recovery. Rehabilitation cares include comprehensive outpatient consultations to psychiatrist, cardiologist, and internal medicine.

One of the serious complications of clozapine intoxication isNMS. Signs and symptoms of NMS are known as NMS tetrads which sometimes could overlap with the symptoms of clozapine intoxication, which includes: (1) mental status alteration, (2) muscle rigidity, (3) hyperthermia, (4) autonomic instability.[9] Changes in mental status occur in 82 percent of patients.[19]Muscle rigidity can be extreme and with lead-pipe characteristic.[20] Hyperthermia occurs in more than 87 percent of cases.[20] Tachycardia is in 88 percent NMS cases.[20] Based on the international consensus, patientwas exposed to dopamine antagonists within 72 hours, patient also had hyperthermia, lead-pipe rigidity in all extremities, mental status alteration, elevation CPK levels, blood pressure fluctuations, blood pressure elevation, tachycardia, and negative workup for infectious, toxic, metabolic, and neurologic causes. In this case, the diagnosis of NMS can be confirmed because it meets a total score of 100 based on the Delphi criteria.[10]

CPK is a laboratory workup that has high sensitivity in the diagnosis of NMS.[23] CPK elevation is reported to occur in 95% of cases of NMS.[23] CPK levels will increase due to rhabdomyolysis.[23] CPK is used as a biomarker for NMS because of high sensitivity in NMS cases.[23] Increase in CPK levelsis caused by changes in the central neuroregulatory mechanism and abnormal reactions of the skeletal muscles to antipsychotics.[23]

4. Conclusion

We reported patient with neuroleptic malignant syndrome which was caused by clozapine intoxication. Availability of agents like bromocriptine has important role in management of clozapine intoxication. Emergency management in clozapine intoxication has an important role in preventing life threatening complication. Although the prevalence is rare, NMS must always be considered in antipsychotic intoxication case.

References

[1] World Health Organization (WHO). Acute Intoxication. Available at https://www.who.int/substance_abuse/terminology/acute_intox/en/#:~:text=Definition,other%20psychophysiological%20functions%20and%20responses.
[2] Gummin DD, Mowry JB, Beuhler MC, Spyker DA, Brooks DE, Dibert KW, et al. 2019 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 37th Annual Report. Clin Toxicol (Phila). 2020;58(12):1360–541.
[3] Rasimas JJ, Liebelt EL. Adverse Effects and Toxicity of the Atypical Antipsychotics: What Is Important for the Pediatric Emergency Medicine Practitioner? Clin Pediatr Emerg Med [Internet]. 2012;13(4):300–10. Available from: http://dx.doi.org/10.1016/j.cpem.2012.09.005
[4] Mijovic A. Clozapine-induced agranulocytosis. Annals of Hematology Springer [Internet].2020. Available from: https://doi.org/10.1007/s00277-020-04215-y.
[5] Cheng M, Gu H, Zheng L, Wang H, Zhong Z, Wen S. Neuroleptic malignant syndrome and subsequent clozapine-withdrawal effects in a patient with refractory schizophrenia. Neuropsychiatr Dis Treat. 2016;12:695–7.
[6] Kembuan MAHN. Sidroma neuroleptik maligna patofisiologi, diagnosis, dan terapi. J Biomedik. 2016;8(2).
[7] Berman BD. Neuroleptic malignant syndrome: A review for neurohospitalists. Neurohospitalist. 2011;1(1):41-7.
[8] Tsai MC, Huang TL. Severe neuroleptic malignant syndrome: Successful treatment with high-dose lorazepam and diazepam: A case report. Chang Guang Med J. 2010; 33(5):9.
[9] Indera, Nuradyo D, Subagya. Sindrom Neuroleptik MalignaAspek Diagnosis dan Penatalaksanaan. Berk Neurosains. 2018; 17(3):152–61.
[10] Gurrera RJ, Mortillaro G, Velamoor V, Caroff SN. A Validation Study of the International Consensus Diagnostic Criteria for Neuroleptic Malignant Syndrome. J Clin Psychopharmacol. 2017

Feb;37(1):67-71. doi: 10.1097/JCP.0000000000000640. PMID: 28027111.
[11] Lebin J, Villarreal J, Chen B, Hall K. Clozapine Intoxication Mimicking Acute Stroke. Clin Pract Cases Emerg Med. 2018;2(2):155–7.
[12] Subramanian S, Völlm BA, Huband N. Clozapine dose for schizophrenia. Cochrane Database Syst Rev. 2017;2017(6).
[13] Broich K, Heinrich S, Marneros A. Acute clozapine overdose: Plasma concentration and outcome. Pharmacopsychiatry. 1998;31(4):149–51.
[14] Sukmana N. buku ajar ilmupenyakitdalamjilid I. VI. Jakarta: InternaPublishing; 2014:1054-55.
[15] Stark A, Scott J. A review of the use of clozapine levels to guide treatment and determine cause of death. Aust N Z J Psychiatry. 2012;46(9):816–25.
[16] Cheng M, Gu H, Zheng L, Wang H, Zhong Z, Wen S. Neuroleptic malignant syndrome and subsequent clozapine-withdrawal effects in a patient with refractory schizophrenia. Neuropsychiatr Dis Treat. 2016;12:695–7.
[17] Jilani TN, Sabir S, Sharma S. Trihexyphenidyl. [Updated 2020 Dec 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519488/
[18] Lally J, Brook J, Dixon T, et al. Ivabradine, a novel treatment for clozapine-induced sinus tachycardia: a case series. Ther Adv Psychopharmacol. 2014;4(3):117-122. doi:10.1177/2045125313512325
[19] Velamoor VR, Norman RM, Caroff SN, Mann SC, Sullivan KA, Antelo RE. Progression of symptoms in neuroleptic malignant syndrome. J Nerv Ment Dis. 1994 Mar;182(3):168-73. doi: 10.1097/00005053-199403000-00007. PMID: 7906709.
[20] Caroff SN, Mann SC. Neuroleptic malignant syndrome. Med Clin North Am. 1993 Jan;77(1):185-202. doi: 10.1016/s0025-7125(16)30278-4. PMID: 8093494.
[21] Sarkar S, Gupta N. Drug information update. Atypical antipsychotics and neuroleptic malignant syndrome: nuances and pragmatics of the association. BJPsych Bull. 2017 Aug;41(4):211-216. doi: 10.1192/pb.bp.116.053736. PMID: 28811916; PMCID: PMC5537576.
[22] Rosebush P, Stewart T. A prospective analysis of 24 episodes of neuroleptic malignant syndrome. Am J Psychiatry. 1989 Jun;146(6):717-25. doi: 10.1176/ajp.146.6.717. PMID: 2567121.
[23] Annamalai A. Medical management of psychotropic side effects. Med Manag Psychotr Side Eff. 2017;1–304.