PBR
Pharmaceutical & Biomedical Research

December 2024. Volume 10. Number 4

Case Report

Investigating Clozapine-induced Sialorrhea Improvement in Highland Climate Area: A Case Study

Amir Asadi[1, 2], **Mahdi Salehi**[3], **Seyed Hamzeh Hosseini**[4*]

1. Department of Psychiatry, School of Medicine, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran.
2. Psychiatry and Behavioral Sciences Research Center, Mazandaran University of Medical Sciences, Sari, Iran.
3. Student Research Committee, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran.
4. Department of Psychiatry, Psychosomatic Research Center, School of Medicine, Sari Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Sari, Iran.

*** Corresponding Author:**
Seyed Hamzeh Hosseini, Professor.
Address: Department of Psychiatry, Psychosomatic Research Center, School of Medicine, Sari Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Sari, Iran.
Phone: +98 (911) 1242487
E-mail: hosseinish20@gmail.com

Article info:
Received: 19 Aug 2024
Accepted: 06 Sep 2024

Keywords:
Sialorrhea, Schizophrenia, Clozapine, Climate

ABSTRACT

Background: This case report describes the elimination of clozapine-induced sialorrhea through a change in residence, highlighting how environmental factors can influence medication side effects.

Case Report: The subject was a 39-year-old woman diagnosed with schizophrenia, who had been experiencing significant sialorrhea as a side effect of clozapine treatment. After relocating to a highland climate, the patient's excessive salivation was significantly resolved. Importantly, this change occurred without the need for any adjunctive medications, such as atropine, which are commonly prescribed to manage this side effect.

Conclusion: This case underscores the importance of considering environmental factors when evaluating drug effects in patients. It serves as a reminder to healthcare providers to be aware of how changes in a patient's residence may impact the pharmacodynamics of medications, such as clozapine. Understanding these dynamics can lead to more personalized treatment approaches and improved patient outcomes, emphasizing the need for further investigation into the relationship between climate and medication side effects.

Citation Asadi A, Salehi M, Hosseini SH. Investigating Clozapine-induced Sialorrhea Improvement in Highland Climate Area: A Case Study. Pharmaceutical and Biomedical Research. 2024; 10(4):367-370. http://dx.doi.org/10.32598/PBR.10.4.1312.1

http://dx.doi.org/10.32598/PBR.10.4.1312.1

PBR
Pharmaceutical & Biomedical Research

Introduction

The mouth contains nearly 600-1000 salivary glands, with three pairs being clinically important, namely parotid, submandibular, and sublingual [1]. Salivary secretion is mainly controlled by the parasympathetic nervous system [2]. Sialorrhea, or hypersalivation, is associated with neurological disorders, oral cavity abnormalities, or drug effects [3-5]. Disorders in any phase can lead to hypersalivation or sialorrhea. Neurological diseases, such as cerebral palsy, Parkinson disease, and amyotrophic lateral sclerosis can cause impaired swallowing and sialorrhea [6, 7]. Other causes include oral inflammation, tooth decay, infections, and exposure to toxins. Meanwhile, causes of sialorrhea can include the side effects of medications (e.g. antipsychotics, tranquilizers, anticonvulsants, cholinergic agonists, and lithium) [2, 8, 9].

Schizophrenia is a complex mental disorder characterized by hallucinations, delusion, and disorganized speech [10, 11]. Antipsychotic drugs, such as clozapine are used to treat schizophrenia, and studies indicate that approximately 30% of schizophrenia patients may have treatment-resistant forms of the disorder, making clozapine an essential option for a substantial subset of the population [12]; however, they can cause serious side effects like weight gain, sialorrhea, and seizures [13, 14]. Clozapine-induced sialorrhea is a common side effect in 30% to 80% of schizophrenic patients and is dose-dependent and can worsen over time [15, 16] and typically exacerbated during sleep [17].

There are different proposed mechanisms for clozapine-induced sialorrhea. Clozapine has an agonistic effect on the M4 muscarinic receptors and an antagonistic effect on α-adrenergic receptors. Moreover, it reduces the gastrointestinal tract movement, including the esophagus. As a result, it leads to increased sialorrhea by reducing swallowing [18]. Despite different treatment methods, sialorrhea treatment is still challenging. It is affected by various factors, including mental and cognitive abilities, healthy swallowing ability, lack of oral and dental problems, as well as the ability to keep the head upright [4].

Treating clozapine-induced sialorrhea poses several challenges, including the need to balance the medication's efficacy for treatment-resistant schizophrenia with the management of side effects. Reducing clozapine dosage to alleviate sialorrhea may compromise its effectiveness while adding anticholinergic agents could lead to drug interactions and complicate treatment. Patient compliance can be affected by frustration over side effects, and those with comorbid conditions may face limitations in available treatments [16, 18-20]. In this case report, we reported a schizophrenic patient whose clozapine-induced sialorrhea was reduced after a change in the residence and summering in a mountainous climate area without taking atropine. This report helps physicians notice the probable changes in the drug effects on patients with a change in the residence due to changes in the local climate.

Case Presentation

The case was a 39-year-old woman living in the coastal area of the Caspian Sea who had suffered from schizophrenia in the last 15 years. Her condition was associated with hallucinations, delusions, and aggressive behavior. She was under pharmacological treatment with typical and atypical antipsychotics; however, clozapine was prescribed for her due to her lack of response to any other drugs. Then, the symptoms of the disease were controlled by a gradual increase in the dosage to 200 mg/day. Due to improvement in the symptoms, the dosage was reduced to 125 mg/day, but the psychotic symptoms and irritability of the patient worsened. Hence, the dosage was increased, and the symptoms were controlled by taking 150 mg of clozapine per day and she did not receive any other treatment. Since the beginning of the treatment with clozapine, the patient had a normal complete blood count, electrolyte panel, thyroid function tests, liver function tests, kidney function tests, urinalysis, and imaging studies and has not been affected by any blood complications.

As she complained about sialorrhea, an atropine drop was prescribed. Based on the Greenberg visual scale, she had grade III (severe/fulsome) sialorrhea. During three years of the treatment, she had at least 5 visits to the clinic. In regular visits to the psychiatric clinic of the hospital, she talked about the occasional improvement of sialorrhea when traveling to mountainous areas (less humid places). She said that sialorrhea diminished in mountainous areas, and she did not need to take an atropine drop. Meanwhile, based on the Greenberg visual scale, she had grade I (dry) sialorrhea. Also, she did not receive any medical drugs that might have anticholinergic properties while living in the mountain. With the arrival of warmer seasons and the increase in the humidity, some people living near the sea summer in the neighboring mountainous areas where the climate is better. This condition was inspected for 5 episodes when the patient went there. Given that there may have been a change in the patient's diet due to specific vegetation in

the mountainous area, her diet was carefully examined. In all cases, her diet was similar to the one in her original residence. Clozapine-induced sialorrhea of the patients is not normally related to the humidity.

Discussion

To the best of the authors' knowledge and according to the searches they did in the databases, no study has investigated the effect of climate on reducing clozapine-induced sialorrhea. Sialorrhea associated with several neurological disorders or is a side effect of drugs is excessive saliva secretion [7]. One of the most efficient antipsychotic drugs is clozapine, particularly prescribed for chronic schizophrenic patients, although it has some adverse effects such as sialorrhea [16]. Sialorrhea brings about some physical and psychosocial complications. Physical complications include perioral skin irritation with secondary infection, bad odor, speech disorder, and an eating disorder. Those with drooling are at risk of the aspiration of saliva, food, or fluid into their lungs. On the other hand, psychosocial complications embrace isolation, greater dependency on care, damage to electronic devices, low self-esteem, difficult social interaction due to messy faces, dirty clothing, and bad odor [2]. A schizophrenic patient who suffers from severe cognitive problems has excessive drooling and should change her/his dress several times a day. Sialorrhea can have considerable negative effects on the patient's and the caregiver's quality of life [4]. It can make the patient hesitate to continue the treatment with clozapine [20]; on the other hand, stopping taking clozapine puts the patient at risk of recurrence and exacerbation of the symptoms.

Change in the residence, which results in a new climate, has considerable effects on human health and drugs. The effect of climate on human health is the result of the interaction between the climate and drugs. This interaction can be the effect of climate on drug storage conditions, heat intolerance due to medication-induced heat, climate and pharmacokinetics, and sensitivity to light due to medication [21].

In hot and humid regions like the area near the sea, the north of Iran, people most often travel to the neighboring mountainous areas during the hot seasons. These areas have different types of vegetation, and people use these plants in their diet. Some plants have anticholinergic manifestations and can act as atropine, such as *Datura stramonium*, *Atropa belladonna* [22], and *Hyoscyamus niger* [23]. However, the patient, reported in this case study, did not take any of these herbs and her diet was quite similar to her normal diet in her original residence (near the sea). Therefore, we can propose that climate areas with higher humidity and milder temperatures may help improve sialorrhea symptoms for some individuals. In such environments, the moisture in the air can assist in managing excessive salivation by preventing the mouth from feeling dry, which can sometimes exacerbate the perception of sialorrhea. Additionally, a more temperate climate can reduce overall stress and discomfort, potentially lessening anxiety-related salivation. For patients, living in or temporarily relocating to a more favorable climate might provide symptomatic relief and improve their quality of life while they navigate treatment options for managing sialorrhea.

Conclusion

Physicians should monitor the side effects of the drugs in patients because of environmental factors. Since a change in the residence brings about the experience of a new climate, the diet of the patient is likely to improve or exacerbate the side effects of the drugs. Evaluating more similar patients may contribute to some relationship between sialorrhea and a change in the climate.

Ethical Considerations

Compliance with ethical guidelines

Written informed consent was obtained from the patient for the case report. The present study was conducted in compliance with the Declaration of Helsinki.

Funding

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors equally contribute to preparing all parts of the research.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors would like to thank the patient for agreeing to describe the case.

References

[1] Brazen B, Dyer J. Histology, salivary glands. Treasure Island: StatPearls; 2023. [Link]

[2] Hockstein NG, Samadi DS, Gendron K, Handler SD. Sialorrhea: A management challenge. Am Fam Physician. 2004; 69(11):2628-34. [PMID]

[3] Güvenç IA. Sialorrhea: A guide to etiology, assessment, and management. In: Güvenç IA, editor. Salivary glands-new approaches in diagnostics and treatment. London: IntechOpen; 2018. [Link]

[4] Vashishta R, Nguyen SA, White DR, Gillespie MB. Botulinum toxin for the treatment of sialorrhea: A meta-analysis. Otolaryngol Head Neck Surg. 2013; 148(2):191-6. [DOI:10.1177/0194599812465059] [PMID]

[5] Taş SA, Çankaya T. An investigation of the relationship of drooling with nutrition and head control in individuals with quadriparetic cerebral palsy. J Phys Ther Sci. 2015; 27(11):3487-92. [DOI:10.1589/jpts.27.3487] [PMID] [PMCID]

[6] Panara K, Ramezanpour Ahangar E, Padalia D. Physiology, swallowing. Treasure Island: StatPearls; 2023. [Link]

[7] Lakraj AA, Moghimi N, Jabbari B. Sialorrhea: Anatomy, pathophysiology and treatment with emphasis on the role of botulinum toxins. Toxins. 2013; 5(5):1010-31. [DOI:10.3390/toxins5051010] [PMID] [PMCID]

[8] Freudenreich O. Drug-induced sialorrhea. Drugs Toda. 2005; 41(6):411-8. [DOI:10.1358/dot.2005.41.6.893628] [PMID]

[9] Thaxter Nesbeth KA, Samuels LA, Nicholson Daley C, Gossell-Williams M, Nesbeth DA. Ptyalism in pregnancy-A review of epidemiology and practices. Eur J Obstet Gynecol Reprod Biol. 2016; 198:47-49. [DOI:10.1016/j.ejogrb.2015.12.022] [PMID]

[10] Häfner H. From onset and prodromal stage to a life-long course of schizophrenia and its symptom dimensions: How sex, age, and other risk factors influence incidence and course of illness. Psychiatry J. 2019; 2019:9804836. [DOI:10.1155/2019/9804836] [PMID] [PMCID]

[11] McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia-An Overview. JAMA Psychiatry. 2020; 77(2):201-10. [PMID]

[12] Lewis SW, Barnes TR, Davies L, Murray RM, Dunn G, Hayhurst KP, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull. 2006; 32(4):715-23. [DOI:10.1093/schbul/sbj067] [PMID] [PMCID]

[13] Okada M, Fukuyama K, Shiroyama T, Murata M. A working hypothesis regarding identical pathomechanisms between clinical efficacy and adverse reaction of clozapine via the activation of connexin43. Int J Mol Sci. 2020; 21(19):7019. [DOI:10.3390/ijms21197019] [PMID] [PMCID]

[14] De Fazio P, Gaetano R, Caroleo M, Cerminara G, Maida F, Bruno A, et al. Rare and very rare adverse effects of clozapine. Neuropsychiatr Dis Treat. 2015; 11:1995-2003. [DOI:10.2147/NDT.S83989] [PMID] [PMCID]

[15] Taylor D, Paton C, Kerwin R. Prescribing guidelines London:CRC Press; 2007. [DOI:10.1201/b21605]

[16] Syed R, Au K, Cahill C, Duggan L, He Y, Udu V, et al. Pharmacological interventions for clozapine-induced hypersalivation. Cochrane Database Syst Rev. 2008; (3):CD005579. [DOI:10.1002/14651858.CD005579.pub2] [PMID]

[17] Young CR, Bowers MB Jr, Mazure CM. Management of the adverse effects of clozapine. Schizophr Bull. 1998; 24(3):381-90. [DOI:10.1093/oxfordjournals.schbul.a033333] [PMID]

[18] Gupta S, Khastgir U, Croft M, Roshny S. Management of clozapine-induced sialorrhoea. BJPsych Adv. 2020; 26(2):106-8. [DOI:10.1192/bja.2019.58]

[19] Bavikatte G. Management of drooling of saliva. Br J Med Pract. 2012; 5(1):5071. [Link]

[20] Davydov L, Botts SR. Clozapine-induced hypersalivation. Ann Pharmacother. 2000; 34(5):662-5. [DOI:10.1345/aph.19259] [PMID]

[21] Beggs PJ. Impacts of climate and climate change on medications and human health. Aust N Z J Public Health. 2000; 24(6):630-2. [DOI:10.1111/j.1467-842X.2000.tb00531.x] [PMID]

[22] Soulaidopoulos S, Sinakos E, Dimopoulou D, Vettas C, Cholongitas E, Garyfallos A. Anticholinergic syndrome induced by toxic plants. World J Emerg Med. 2017; 8(4):297-301. [DOI:10.5847/wjem.j.1920-8642.2017.04.009] [PMID] [PMCID]

[23] Devaki R, Santhosh Kumar R. Anticholinergic herbs featured in Siddha system of medicine-A review. World J Pharm Res. 2022; 11(5):460-7. [Link]