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Case Study

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A CASE REPORT ON CLOZAPINE INDUCED SIALORRHEA

Raveena Rajesh[1]*, Jayalakshmi J.[1] and Roshiny Thankam James[2]

[1]6th year PharmD Students, Nazareth College of Pharmacy, Othera, Thiruvalla.
[2]Assistant Professor, Department of Pharmacy Practice, Nazareth College of Pharmacy, Othera Thiruvalla.

***Corresponding Author: Raveena Rajesh**

6th year PharmD Students, Nazareth College of Pharmacy, Othera, Thiruvalla.

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ABSTRACT

Hypersalivation, or ptyalism also known as sialorrhea or hypersialosis is the excessive production of saliva. It has also been defined as increased amount of saliva in the mouth, which may also be caused by decreased clearance of saliva. Hypersalivation can contribute to drooling if there is an inability to keep the mouth closed or difficulty in swallowing (dysphagia) the excess saliva, which can lead to excessive spitting. Hypersalivation also often precedes emesis (vomiting), where it accompanies nausea (a feeling of needing to vomit). Clozapine is an antipsychotic medicine. It works by changing the actions of chemicals in the brain. Clozapine is also used to reduce the risk of suicidal behavior in people with schizophrenia or similar disorders. Common adverse effects include drowsiness, constipation, hypersalivation (increased saliva production), tachycardia, low blood pressure, blurred vision, weight gain, and dizziness.

KEYWORDS: Clozapine, Drooling, Hypersalivation, Antipsychotics, Sialorrhea.

INTRODUCTION

Clozapine is a psychiatric medication and is the first atypical antipsychotic (also called second- generation antipsychotic). It is primarily used to treat people with schizophrenia and schizoaffective disorders who have had an inadequate response to other antipsychotics or who have been unable to tolerate other drugs due to extrapyramidal side effects. It is also used for the treatment of psychosis in Parkinson's disease. Clozapine is regarded as the gold-standard treatment when other medication has been insufficiently effective and its use is recommended by multiple international treatment guidelines, after resistance to earlier neuroleptic treatment is established. Common adverse effects include drowsiness, constipation, hypersalivation (increased saliva production), tachycardia, low blood pressure, blurred vision, weight gain, and dizziness. Sialorrhea, also known as drooling or ptyalism, is a debilitating symptom which occurs when there is excess saliva in the mouth beyond the lip margin. Pathologic sialorrhea can be an isolated phenomenon due to hypersalivation or occur in conjunction with several neurologic disorders such as amyotrophic lateral sclerosis (ALS), cerebral palsy (CP), Parkinson's disease (PD), or as a side effect of medications. Sialorrhea can be either due to increased production of saliva (idiopathic or drug-induced) or related to failure of mechanisms that clear and remove saliva from the oral cavity. Sialorrhea occurring with neurologic illnesses is usually due to impaired swallowing as a result of impaired neuromuscular function. Neuromuscular activity of swallowing involves efficient coordination of several structures including the oral cavity, pharynx, larynx, and esophagus. These structures coordinate to form three phases; an oral phase which is under voluntary control, followed by the pharyngeal and esophageal phases which are under involuntary control. Spontaneous swallowing is necessary for drool control.

CASE REPORT

A 19 year old female patient was came to the emergency department with complaints of restlessness and agitation occasionally and also had a history of neck stiffness, generalized bodyache, frowning of lips and irritable mood along with difficulty in climbing stairs. She is having bronchial asthma an on inhaler occasionally. During the time of admission all the vitals are found to be as pulse rate -110 bpm, Bp-120/80 mmHg, Respiratory rate -18 /min, her mood was depressed and agitated, memory found as intact. She was diagnosed as depressive disorder with psychotic features. The patient was already on olanzapine 10 mg BD, Haloperidol 2.5mg BD, lorazepam 2 mg ½-½-½ given from outside hospital. During her hospital stay continued her own medications and along with that also given clonidine 100 mcg ½-½-1, sertraline 50 mg OD, Clozapine 50mg-0-75mg. Due to the agitated behavior instead of oral haloperidol and lorazepam, intravenous formulations were given whenever necessary. Hypersalivation found in the patient after administering the medications, clozapine was the offending agent which leads to sialorrhea and which were come in to notice and slowly

tapered the dose of clozapine. After tapered the dose rate of hypersalivation reduced. During the time of discharge the patient was found to be normal.

DISCUSSION

Clozapine is an FDA-approved atypical antipsychotic medication for treatment-resistant schizophrenia. Clozapine is not the first-line drug of choice due to its range of adverse effects, making compliance an issue for many patients. However, it also has some advantages, including lowering the risk of suicide and tardive dyskinesia and fewer relapses. Common adverse effects include drowsiness, constipation, hypersalivation (increased saliva production), tachycardia, low blood pressure, blurred vision, weight gain, and dizziness. Clozapine is not normally associated with tardive dyskinesia (TD) and is recommended as the drug of choice when this is present, although some case reports describe clozapine-induced TD. Other serious risks include seizures, inflammation of the heart, high blood sugar levels, constipation. Clozapine is an antagonist at the 5-HT2A subunit of the serotonin receptor, putatively improving depression, anxiety, and the negative cognitive symptoms associated with schizophrenia. A direct interaction of clozapine with the $GABA_B$ receptor has also been shown. $GABA_B$ receptor-deficient mice exhibit increased extracellular dopamine levels and altered locomotor behavior equivalent to that in schizophrenia animal models. $GABA_B$ receptor agonists and positive allosteric modulators reduce the locomotor changes in these models. Clozapine induces the release of glutamate and D-serine, an agonist at the glycine site of the NMDA receptor, from astrocytes, and reduces the expression of astrocytic glutamate transporters. These are direct effects that are also present in astrocyte cell cultures not containing neurons. Clozapine prevents impaired NMDA receptor expression caused by NMDA receptor antagonists.

Adverse effects

- **Agranulocytosis**

The risk of developing agranulocytosis is around 1% in patients who take clozapine, whichmay be independent of dosing. Most cases occur early in the treatment, within six weeks to six months, and require extensive monitoring of blood absolute neutrophil counts. Risk factors include old age, female, genetics, and concurrent treatment with other drugs knownto cause

- **Myocarditis**

Clozapine-induced myocarditis is a rare complication, affecting less than 3% of patients. This lethal dose-independent side effect appears more frequently during the first four weeks of treatment. In these patients, signs and symptoms of myocarditis may vary from having a flu-like illness to respiratory and cardiovascular symptoms.

- **Metabolic syndrome**

Clozapine is associated with significant weight gain, diabetes type 2, diabetic ketoacidosis, and increased lipid levels-all due to increased insulin resistance. Both clozapine and olanzapine have higher metabolic side effects than the other atypical and typical antipsychotics due to their high affinity for serotonin 5-HT2C receptors. It is important to note that other factors, including poor diet and a sedentary lifestyle, may contribute to the development of metabolic syndrome.

- **Seizures**

Clozapine may lower the seizure threshold in both patients with epilepsy and normal patients. The risk is usually dose-dependent, around 1% to 6%, especially with rapid titration, and might be more prevalent in younger patients.

- **Excessive salivation**

Sialorrhea is a dose-dependent and benign condition that may be bothersome to some patients. One risk of excessive salivation is aspiration pneumonia.

- **Pulmonary embolism**

A recent study comparing clozapine to several other antipsychotics showed it to be the only drug to increase platelet adhesion and aggregation. The risk seems to be higher in elderly patients and pregnant women taking high doses.

- **Constipation**

Cholinergic and serotonergic properties of clozapine may affect the gastrointestinal system and lead to constipation or even ileus. Constipation affects anywhere from 15% to 60% of all patients taking clozapine and is dose-dependent, making it one of the most common side effects. In severecases, constipation can progress to ileus, leading to bowel obstruction and bowel ischemia Contraindications.

FDA states the following Black Box warnings:

- Neutropenia (Due to the risk of agranulocytosis)
- Orthostatic hypotension
- Seizures
- Myocarditis
- Dementia (Risk of a cardiovascular event)

Monitoring

Serious adverse effects that require monitoring include but are not limited to:

- **Agranulocytosis**

Weekly complete blood count (CBC) to measure ANC levels. ANC levels less than 1500/mm indicate neutropenia. Levels less than 500/mm indicate agranulocytosis. A complete blood count should be taken weekly for the first six months, then every other week for the next six months

- **Metabolic syndrome**

Diet and exercise, blood glucose levels.

- **Cardiovascular**

Baseline troponin I or T levels, high sensitivity CRP levels, echocardiography, and BNP levels, as well as vitals and weekly laboratory testing of troponins, CRP, and BNP levels.[3]

- **Seizure**

EEG and clozapine blood levels

Sialorrhea, also known as drooling or ptyalism, is a debilitating symptom which occurs when there is excess saliva in the mouth beyond the lip margin. Pathologic sialorrhea can be an isolated phenomenon due to hypersalivation or occur in conjunction with several neurologic disorders such as amyotrophic lateral sclerosis (ALS), cerebral palsy (CP), Parkinson's disease (PD), or as a side effect of medications. In children, the most common cause of sialorrhea is CP, which persists in 10%–38% of these individuals. In adults, PD is the most common cause with 70%–80% of PD patients demonstrating sialorrhea. In 30%–80% of schizophrenic patients, hypersalivation when taking clozapine is manifested .Sialorrhea can be either due to increased production of saliva (idiopathic or drug-induced) or related to failure of mechanisms that clear and remove saliva from the oral cavity. Disturbance in the coordination of orofacial and palate—lingual musculature is one mechanism that can lead to pooling of saliva in the anterior portion of the mouth. Ultimately, muscle incoordination inhibits the initiation of the swallow reflex, thereby further disrupting the path of saliva. Sialorrhea usually is caused by neuromuscular dysfunction, hypersecretion, sensory dysfunction, or anatomic (motor) dysfunction. The most common cause is neuromuscular dysfunction. In children, mental retardation and cerebral palsy are commonly implicated; in adults, Parkinson's disease is the most common etiology. Pseudobulbar palsy, bulbar palsy, and stroke are less common causes. Hypersecretion commonly is caused by inflammation, such as teething, dental caries, and oral cavity infection. Other causes of hypersecretion include side effects from medications (i.e., tranquilizers, anticonvulsants), gastroesophageal reflux, toxin exposure (i.e., mercury vapor), and rabies.

Assessment of Sialorrhea

System for Assessment of Frequency and Severity of Drooling

Drooling	***Points***
Severity	
Dry (never drools)	1
Mild (wet lips only)	2
Moderate (wet lips and chin)	3
Severe (clothing becomes damp)	4
Profuse (clothing, hands, tray, objects become wet)	5
Frequency	
Never drools	1
Occasionally drools	2
Frequently drools	3
Constantly drools	4

Management

Anticholinergic medications

Agent	***Dosage***	***Side effects***
Glycopyrrolate	Adults: Start at 0.5 mgorally, one to three times daily; titrate to effectiveness and tolerability‡	Constipation, excessive oral dryness, urinary retention, blurredvision, hyperactivity, irritability
Glycopyrrolate	Children: 0.04 mg perkg per dose orally, two to three timesdaily; titrate to effectiveness andtolerability	
Scopolamine (Transderm Scop)	Apply patch every day	Pruritus at patchsite, urinaryretention, irritability, blurredvision, dizziness, glaucoma
Botulinum toxin A	Under ultrasoundguidance, injectionsof 10 to 40 units into each submandibularand parotid gland	Pain at injection site, excessive oral dryness

Botulinum toxin

Intraglandular injection of botulinum toxin type A recently has been reported to improve sialorrhea Under ultrasound guidance, botulinum toxin type A was injected into the bilateral parotid and submandibular glands of 10 adult patients. Nine of the patients improved, and no patient had complications. Treatment response lasted approximately five months, making

repeat treatments necessary for long-term control.

Gastroesophageal reflux control

Many developmentally delayed or neurologically impaired patients who have sialorrhea also have significant gastroesophageal reflux. It has been postulated that controlling reflux will reduce drooling; however, this conjecture has not been confirmed by research, and it is unlikely that control of reflux has any clinically significant effect on sialorrhea

Radiation therapy

Radiation to the salivary glands is a reasonable treatment option in elderly patients who are not candidates for surgery and cannot tolerate medical therapy. Radiation produces xerostomia that may last months to years. The dose may be titrated to reach the desired effect, and treatment can be repeated as necessary. Malignancies induced by radiation therapy typically do not occur until 10 to 15 years after treatment and, therefore, are less of a concern in patients who are elderly anddebilitated.20

Surgical options

Surgical options in the treatment of sialorrhea include surgery on the salivary glands and ducts, and surgery to denervate the glands. Surgery to denervate the salivary glands is performed through the middle ear, where the tympanic plexus and chorda tympani travel before entering the major salivary glands. The procedure is relatively simple and fast, and does not require general anesthesia. This surgery has few side effects, and patients typically do not complain of loss of taste. Unfortunately, salivary function returns within six to 18 months, when nerve fibers regenerate.

CONCLUSION

Sialorrhea is one of the adverse effects caused by clozapine. Hence, physicians should evaluate the patient's condition in order to prevent the progression of the adverse event. Although the patient gets recovered after reducing the dose of offending agent and need follow up whether anyrecurrence.

Conflicts of interest

The authors have obtained the necessary patient consent forms where the patients have given their approval for participation in the investigation, followed by representation in the concerned article. The patients do understand that the authors will ensure that their identities won't be revealed.

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