Personalized Medicine in Psychiatry 13–14 (2019) 22–24

Contents lists available at ScienceDirect

Personalized Medicine in Psychiatry

journal homepage: www.elsevier.com/locate/pmip

# Perphenazine-induced sialorrhea successfully treated with sublingual atropine: A case report

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ARTICLE INFO

*Keywords:*
Perphenazine
Sialorrhea
Antipsychotics
Adverse effects
Atropine

ABSTRACT

Although the theoretical risk of sialorrhea exists for all antipsychotics, few cases have been reported with antipsychotics other than clozapine. In this case report, we describe a patient who developed sialorrhea with the use of perphenazine. The patient is a 75-year-old female with a long history of schizophrenia, and had been on perphenazine for about five years. Sialorrhea developed after increasing the dose of perphenazine to 8 mg by mouth twice daily. Administration of sublingual atropine drops alleviated both nocturnal and daytime excessive salivation.

## 1. Introduction

Perphenazine is a medium potency first-generation antipsychotic used in the treatment of schizophrenia. It is often chosen for being inexpensive, having a relatively low risk of development of extrapyramidal symptoms, sedation [1,2], and having comparable cost-effectiveness to second-generation antipsychotics [3]. Some of the side effects of perphenazine include – at an unclear frequency – weight gain, constipation, tremor, salivation and anticholinergic symptoms such as dry mouth, blurred vision, and dizziness [1].

Most antipsychotics, particularly the low-potency first-generation antipsychotics, exhibit strong anticholinergic side effects including dry mouth [4]. Interestingly; clozapine, a second-generation (atypical) antipsychotic, is known to have a high risk of hypersalivation occurring in 30–80% of patients [5], and reportedly as high as 92% in some studies [6]. With clozapine, sialorrhea is dose-dependent, develops early in treatment, and is generally worse at night [7]. Although the mechanism remains poorly understood, researchers have proposed adrenergic alpha-2 antagonism, muscarinic M4 receptor agonism, and decreased laryngeal peristalsis as possible mechanisms of the development of sialorrhea with clozapine [5].

In this case report, we present a case of sialorrhea in a patient taking an increased dose of perphenazine. Although the theoretical risk of sialorrhea exists as a side effect of all antipsychotics, few cases have been reported with antipsychotics other than clozapine. In addition, we discuss potential mechanisms and possible treatment options.

## 2. Case

The patient is a 75-year-old African American female with a history of schizophrenia diagnosed more than 25 years ago. In the past, she has been treated with risperidone (doses up to 8 mg by mouth daily that was stopped due to poor response leading to unresolved distressing auditory hallucinations), quetiapine extended release (doses up to 200 mg by mouth at bedtime) in combination with fluphenazine (doses up to 15 mg by mouth daily that was stopped due to poor response), and aripiprazole (doses up to 5 mg by mouth daily that was stopped in the first month due to dizziness), haloperidol (doses up to 20 mg by mouth daily that was discontinued at patient's request) and historically olanzapine (dose of 20 mg by mouth at bedtime that was discontinued due to an allergic reaction of tongue swelling). Due to intolerable side effects and limited clinical response, the patient has been treated with perphenazine for about four and a half years, over which time the dose has been gradually titrated up for continued paranoid delusions. Her psychotic symptoms have been well controlled on 16 mg by mouth twice daily. Her current psychiatric medication regimen includes perphenazine 16 mg by mouth twice daily, mirtazapine 30 mg by mouth at bedtime, and clonazepam 0.5 mg by mouth at bedtime.

Additionally, the patient has multiple medical comorbidities including hypertension, hyperlipidemia (Cholesterol 178 mg/dL [Ref. Range 150–200 mg/dL], HDL 64 mg/dL [Ref. Range 40–60 mg/dL], Calculated LDL 96 mg/dL [Ref. Range 65–160 mg/dL], Triglyceride 91 mg/dL [Ref. Range 35–135 mg/dL]), Non-insulin dependent diabetes mellitus (HbA1c 7.0% (Ref. range < 6.0%]) with peripheral neuropathy and chronic kidney disease (eGFR African American 41 mL/

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https://doi.org/10.1016/j.pmip.2018.11.001

Available online 23 December 2018
2468-1717/ Published by Elsevier Inc.

min/1.73 $m^2$), atrial fibrillation, and non-ischemic cardiomyopathy with reduced left ventricular ejection fraction (30–35%). As such, her medication regimen is complicated and includes Amlodipine 10 mg by mouth daily, Isosorbide Dinitrate 10 mg by mouth three times daily, Carvedilol 12.5 mg by mouth twice daily, Aspirin 81 mg by mouth EC daily, Hydralazine 50 mg by mouth three times daily, Metformin 85 mg by mouth three times daily, Furosemide 40 mg by mouth twice daily, Valsartan 320 mg by mouth daily, Digoxin 0.125 mg by mouth daily, Rivaroxaban 15 mg by mouth in the evening, Rosuvastatin 20 mg by mouth at bedtime, Glipizide 5 mg by mouth daily, Gabapentin 100 mg by mouth twice daily.

The patient presented with sialorrhea after increasing the dose of perphenazine to 8 mg by mouth in the morning and 16 mg by mouth at bedtime (for a total daily dose of 24 mg). After that time, it was also noted that excessive salivation worsened while increasing the dose of perphenazine to 16 mg by mouth twice daily (for a total daily dose of 32 mg). She endorsed significant impact on her quality of life, including difficulty with sleeping and speech. Initially, non-pharmacologic measures were attempted for one month without clinical improvement, including swallowing training, sleeping habits, and increasing water intake.

The patient was trialed on benztropine for prophylaxis of extrapyramidal symptoms at 0.5 mg by mouth twice daily, and increased to 1 mg by mouth twice daily, with poor response after 2 years. We subsequently initiated sublingual 1% atropine 2 drops every 6–8 h. The patient noted significant clinical improvement and her excessive salivation symptoms subsided after about 1–2 weeks of daily treatment with atropine sublingual drops, with satisfactory resolution of both nocturnal and daytime hypersalivation.

## 3. Discussion

This case contributes to the literature in regards to the occurrence of sialorrhea with perphenazine use. The incidence of this adverse effect has not been quantified and the mechanism remains not well understood. The details of this patient's case present several interesting points regarding possible mechanism of action. For outpatient management of schizophrenia, perphenazine is generally dosed 4–8 mg three times daily. Thus, our patient has been managed on a relatively high dose at 16 mg twice daily. Given that clozapine-induced sialorrhea is dose-dependent and that our patient's sialorrhea worsened following treatment with this high dose [4], it is possible that perphenazine-induced sialorrhea may also be dose-dependent. With regards to potentially implicated receptors, perphenazine may have similar alpha-2 receptor binding properties as clozapine; however, its M4-receptor activity has not been characterized [4]. The improvement of our patient's sialorrhea with atropine drops suggests a mechanism with possible muscarinic receptor involvement. Atropine, as detailed below, is a nonselective muscarinic antagonist. It is thus possible that the action on M4 muscarinic receptors in the salivary glands may be responsible for the improvement in sialorrhea.

In clozapine-induced sialorrhea, nonpharmacologic management options are generally the initial approach and include sleeping on one's side to prevent aspiration, using a towel over the pillow and shirt, patient education on techniques to increase swallowing, lowering the clozapine dose, and preventing rapid titration [8]. One common pharmacologic treatment is antimuscarinics such as benztropine, trihexyphenidyl, glycopyrrolate, and atropine. Atropine sublingual drops, which have long been used for drooling in disorders such as cerebral palsy [9], have demonstrated efficacy in clozapine-induced sialorrhea [7,8,10]. Another approach is the use of a centrally-acting alpha-2 adrenergic agonist, most often clonidine, usually used as a patch to prevent rapid fluctuations in blood pressure [7,8,11]. Other treatments that have been trialed include agents that act on multiple receptors such as amitriptyline [8], botulinum toxin injection into the parotid glands [12], and oxybutynin [13] (Table 1). In addition, aripiprazole has been shown to reduce sialorrhea in multi-medication antipsychotic therapy [4].

For our patient with perphenazine-induced sialorrhea, nonpharmacologic management was attempted with no success. In addition, switching or decreasing the dose of the perphenazine we deemed not an option given extensive history of failure on multiple other antipsychotics and prior exacerbation of psychosis with decreasing the dosage. As such, we chose medical management for the sialorrhea. Clonidine, a centrally-acting alpha-2 adrenergic agonist, is often a first choice in the treatment of clozapine-induced sialorrhea [14]. However, due to her significant history of cardiac pathology and extensive antihypertensive treatment, we determined clonidine should not be first line treatment for management of the sialorrhea.

Atropine is a nonselective antimuscarinic which we chose for the benefit of sublingual administration minimizing systemic effects [10]. In using ophthalmic atropine off-label as sublingual drops, we – as providers – must ensure that the patient is properly educated on correct usage, and that appropriate doses are used so as to prevent systemic effects. In addition, the possibility of rebound sialorrhea, given the short half-life of atropine, is a significant consideration [15].

Patient had a baseline heart rate of 76–82 BPM (beats per minute) and arterial blood pressure of 136–178/65–82 mmHg prior to initiating sublingual atropine drops. Vital signs remained within a similar range with a heart rate of 67–84 BPM and arterial blood pressure of 125–169/62–83 mmHg. Electrocardiograms (EKG) done for about 7 years prior to initiating sublingual atropine drops showed a normal sinus rhythm, left ventricular hypertrophy with repolarization abnormality, nonspecific ST and T wave abnormality and a QTc duration of 387–424 ms. EKG obtained 2 weeks after initiating sublingual atropine drops showed a normal sinus rhythm with a nonspecific ST and T wave abnormality with a QTc of 412 ms. EKG obtained 2 years later showed a normal sinus rhythm with a QTc of 435 ms.

Patient continued to follow up with her primary care physician and her cardiologist due to her heart condition. Despite no major concerns or clinical changes since initiating sublingual atropine drops, it is important to note the potential cardiovascular anticholinergic dose-related adverse effects with the use of systemic atropine including blood pressure changes as well as heart rate changes. Ophthalmic atropine drops have a bioavailability of 19%–95% and is well absorbed from all dosage forms. Therefore, it is highly advisable to continue to monitor vital signs and EKG changes and follow up with a primary care physician.

Other possible treatment approaches would mirror those essayed in clozapine-induced sialorrhea. In addition to atropine, glycopyrrolate is another antimuscarinic administered sublingually, with higher specificity for the M3–M5 muscarinic receptors. It has shown efficacy in multiple disorders of drooling, and researchers have proposed investigation into its efficacy in clozapine-induced sialorrhea [16]. Further approaches might include systemic antimuscarinics, other alpha-adrenergic medications, and in serious cases, botulinum toxin injection into the salivary glands [7,8]. However, we suggest sublingual atropine, which demonstrated significant improvement in our patient, as an early pharmacological intervention due to its local action with minimal systemic effects.

Sialorrhea is an important symptom to address due to significant impacts on health and quality of life. Patients suffering antipsychotic-induced sialorrhea can have complications such as chronic cough, aspiration and pneumonia risk, difficulty with speech, and a "drowning" sensation [11]. Indeed, our patient endorsed a much improved quality of life following treatment of her hypersalivation. This case therefore serves as an important example that sialorrhea is a possible side effect of perphenazine to monitor for and treat accordingly.

A potential flaw in this case is the patient's polypharmacy; it is possible that another medication or perhaps a drug-drug interaction may have contributed to the sialorrhea. However, the patient's sialorrhea appeared after the increase of dose of Perphenazine and we

**Table 1**
Common management options for antipsychotic-induced sialorrhea.

| Treatment | Mechanism | Considerations |
|---|---|---|
| Nonpharmacologic | Management of symptoms | Limited efficacy |
| Swallowing techniques | Prevention of aspiration | Requires good patient understanding and cooperation |
| Sleeping on side | | |
| Use of towels | | |
| Chewing gum | | |
| Clonidine | Centrally-acting alpha-2 adrenergic agonist | Patch form and PO form available |
| | | Oral form requires monitoring BP for fluctuations and hypotension |
| Atropine sulfate | Antimuscarinic | Sublingual form |
| | Likely acts on M4 receptors in salivary glands | Fewer systemic adverse effects, but still crosses blood-brain barrier |
| | | Short half-life, often requires administration multiple times daily |
| | | May have morning rebound hypersalivation |
| Guanfacine | Centrally-acting alpha-2 adrenergic agonist | Limited evidence in the literature |
| Ipratropium bromide | Antimuscarinic | Sublingual spray |
| | | Similar efficacy and side effect profile to atropine |
| PO Antimuscarinics | Antimuscarinic | Systemic anticholinergic side effects |
| Benztropine | | Biperiden not available in US |
| Trihexphenidyl | | |
| Glycopyrrolate | | |
| Biperiden | | |
| Amytriptyline | TCA with antimuscarinic properties | Watch for anticholinergic effects, increased sedation, hypotension when combined with antipsychotics |
| Botulinum toxin | Inhibition of parotid gland secretion of saliva | Injection in parotid glands |
| | | Requires periodic injections, intervals not well defined |

therefore can fairly presume perphenazine is the likely cause.

## 4. Conclusion

This case contributes to the literature due to the uncommon incidence of sialorrhea in a patient taking perphenazine, which improved with sublingual atropine treatment. Although relatively infrequent with antipsychotics other than clozapine, it is important to consider this adverse effect of perphenazine, as it can have significant impacts on the patient's quality of life. Possible management approaches may mirror those used in clozapine-induced sialorrhea, including non-pharmacologic techniques, antimuscarinics, and alpha-adrenergic agents. We suggest off-label use of sublingual atropine drops for demonstrated efficacy and minimal systemic effects.

## Acknowledgements

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