Pathophysiology and Management of Risperidone-Induced Sialorrhea

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Background

Sialorrhea is a known potential adverse reaction of antipsychotic medications; however, its incidence varies among antipsychotics, and its pathophysiology is not unanimous.

Salivary flow is predominantly under parasympathetic (cholinergic) control, but the sympathetic (adrenergic) system also modulates saliva production [1].

Among antipsychotics, sialorrhea is most associated with clozapine, and when it occurs, it is uncomfortable, socially stigmatizing, and can contribute to medication nonadherence [2]. Clozapine (including metabolites) has a generally high muscarinic activity compared to the other antipsychotics, which significantly contributes to sialorrhea when it occurs.

In contrast, risperidone has a generally negligible muscarinic activity, and yet, multiple reports of severe sialorrhea associated with risperidone have been reported [3].

Case Presentation

A 46-year-old Caucasian male with a medical history of hypertension was admitted to an inpatient psychiatric hospital for an episode of psychosis associated with schizoaffective disorder.

Clonidine was started for the treatment of hypertension, while risperidone was started for the treatment of psychosis. Mild sialorrhea was observed but worsened as the risperidone dose increased. Clonidine was switched to lisinopril and there was a sudden and drastic worsening of sialorrhea.

The sialorrhea did not respond to treatment with anticholinergic medications but did resolve quickly with discontinuation of risperidone. The patient tolerated quetiapine for the remainder of hospitalization without adverse reaction.

Case Analysis and Scientific Implications

This case report describes risperidone-induced sialorrhea unintentionally masked by simultaneous clonidine administration intended to treat hypertension. There was no relief of sialorrhea with benztropine and minimal relief with atropine.

Clonidine, an α_2-adrenergic receptor agonist, did alleviate sialorrhea and suggests that risperidone's α_2-adrenergic receptor antagonism is a key mechanism in risperidone-induced sialorrhea.

We hypothesize that risperidone-induced sialorrhea has higher protein content (higher viscosity) compared to clozapine-induced sialorrhea due to risperidone's adrenergic stimulation mechanism. Although salivary composition analysis was not obtained in this patient, the physical examination did reveal congruent thick mucinous saliva.

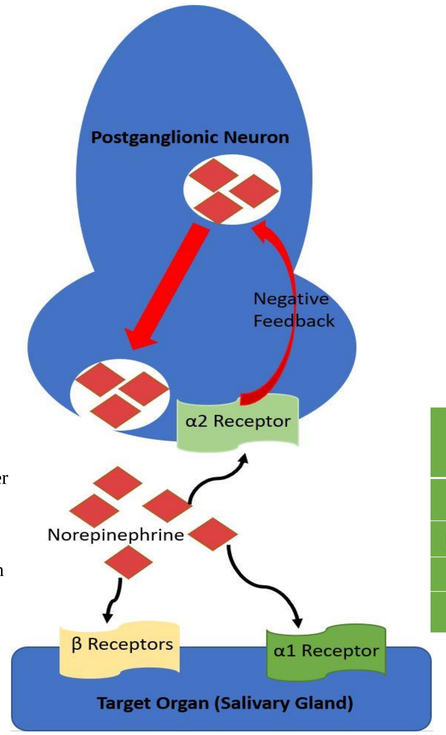

Table 1. Summary of salivary flow by the agonism or antagonism associated with common antipsychotic mechanisms of action. Viscoelasticity describes protein concentration in saliva. [1,2,4,5]

	Saliva Flow Modulation by Receptors of Interest			
Receptor	M1-Muscarinic Receptor	M_3-Muscarinic Receptor	M_4-Muscarinic Receptor	α_2-Adrenergic Receptor
Agonism	Increased Flow	Increased Flow	Increased Flow	Decreased Flow
Antagonism	Decreased Flow	Decreased Flow	Decreased Flow	Increased Flow (Increased viscoelasticity)

Pathophysiology of Risperidone-Induced Sialorrhea

We hypothesize that risperidone-induced sialorrhea is likely a result of potent α_2-adrenergic antagonism. This is in contrast to clozapine-induced sialorrhea, which is predominately a result of muscarinic modulation.

Risperidone-induced sialorrhea may have some pathophysiological contributions from its antimuscarinic activity; however, these neuroreceptor affinities are far less potent than its α_2-adrenergic antagonism (table 2).

Table 2. Antipsychotic receptor binding affinities. Data is represented by the equilibrium constant (Ki), the nanomolar amount required to block 50% of the specified receptor. Pharmacokinetically, the lower an equilibrium constant (Ki), the stronger a receptor is bound (2, 6, 7).

	M_1-Muscarinic Receptor	M_3-Muscarinic Receptor	M_4-Muscarinic Receptor	α_2-Adrenergic Receptor	Dopamine D_2 Receptor	Serotonin 5-HT_{2A} Receptor
Risperidone	>10,000	>10,000	>10,000	8	3.8	0.15
Paliperidone	>10,000	>10,000	>10,000	80	2.8	1.2
Clozapine	1.4	109	27	158	210	2.59
Quetiapine	120	1320	660	80	770	31

Management of Risperidone-Induced Sialorrhea

Sialorrhea is uncomfortable for the individual experiencing it and it has significant psychosocial implications, including the potential to self-discontinue antipsychotic treatment.

Risperidone-induced sialorrhea is most likely to respond to antipsychotic dose reduction, treatment with α2-adrenergic receptor agonists or β-adrenergic receptor antagonists and less likely to respond to anticholinergic (antimuscarinic) medications.

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