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Clozapine-induced Sialorrhea

INTRODUCTION

Next to sedation, hypersalivation is the most common side effect associated with clozapine therapy¹. It affects approximately 31-54% of patients, usually developing early in the course of treatment, and is more prominent at night². Although generally a benign side effect, hypersalivation can be distressing to the patient. Intense sialorrhea may disturb sleep; some patients may describe a choking sensation and may even aspirate excess saliva at night³. Cases of aspiration pneumonia possibly linked to clozapine-induced hypersalivation⁴ and salivary gland swelling have been reported in literature. In addition, sialorrhea is a socially stigmatizing condition that may lead to non-compliance among patients who are often refractory to other neuroleptics.

Pathophysiology

The underlying etiology of sialorrhea is not well understood. Salivary glands respond to both sympathetic and parasympathetic stimulation. Sympathetic impulses result in the secretion of small amounts of viscous saliva, whereas parasympathetic stimulation causes the secretion of large volumes of watery saliva. Clozapine has a complex receptor affinity. It has antagonistic activity at D₁, D₂, D₃, and D₄ dopamine receptors, α_1 and α_2 adrenergic, 5-HT₂ serotonin, H₁ histamine and M₁, M₂, M₃ and M₅ receptors, with agonist activity at the M₄ muscarinic receptor. Sialorrhea is paradoxical since clozapine has marked anticholinergic properties. It has been suggested that stimulation of both M₃ and M₄ muscarinic receptors present in salivary glands lead to saliva production. The balance of clozapine's opposing effects on M₃ and M₄

receptors may mediate hypersalivation². Clozapine is known to exert a full-agonist effect at M₄ receptors; whereas, its affinity for M₃ receptors is lower. Therefore, it is possible that the effects of M₄ receptor stimulation would exceed those of M₃ receptor blockade, resulting in hypersalivation².

Clozapine-induced sialorrhea may also be explained through its blocking actions at α_2 receptors².

Clonidine, an α_2 -agonist, has been used successfully to treat hypersalivation associated with clozapine; whereas, mianserin, an antidepressant with strong α_2 -antagonist properties, fails to induce hypersalivation. Remoxipride, a discontinued antipsychotic agent without significant α_2 -blocking properties, causes hypersalivation. These findings challenge the proposed adrenergic mechanism for hypersalivation⁵.

Other investigators argue that clozapine does not increase salivation but interferes with the swallowing reflex leading to pooling of saliva in the mouth and subjective sensation of hypersalivation. In fact, two placebo controlled studies failed to show any significant difference in saliva flow rate and composition between patients treated with clozapine and healthy controls^{6,7}. The authors suggested that clozapine interferes with normal deglutition by blocking target receptors located in the pharynx or by disrupting vagal control of esophageal peristalsis. This observation is further supported by reports of clozapine-induced esophageal dysfunction^{8,9}. However, it is important to note that both studies measured salivary flow rate during the day and not at night when it is most troublesome. Clozapine possibly interferes with the normal circadian pattern of salivary flow, which is usually high during the day and low at night.

The exact etiology of clozapine-induced hypersalivation remains unknown. It is most likely to be multi-factorial, due to a combination of hypersalivation and a disturbance in swallowing reflex.

Treatment Options

Managing clozapine-induced hypersalivation effectively can be challenging. At present, there is no single effective treatment option. However, a number of pharmacological agents have been tried with variable success.

Nonpharmacological approaches may be used alone or, more effectively, in conjunction with pharmacological treatments¹⁰. Symptoms may be alleviated by placing a towel on the pillow to absorb excess saliva at night or by encouraging patients to chew sugarless gum to increase frequency of swallowing during the day³.

Pharmacological treatment options are based on the proposed pathophysiology and include antimuscarinic agents, α_2 -adrenoceptor agonists and α_1 -adrenoceptor antagonists.

Antimuscarinic agents

Pirenzepine

Pirenzepine is a selective M_4 muscarinic antagonist used mainly in the treatment of gastric ulcers¹¹. It does not cross the blood-brain barrier; it has a low propensity to cause anticholinergic side effects. Theoretically, pirenzepine should counteract hypersalivation by antagonizing M_4 receptors, which is stimulated by clozapine. Fritze and Ellinger reported the successful treatment of 120 patients experiencing clozapine-induced sialorrhea with 25-100 mg pirenzepine daily¹². These results were not duplicated in a randomized, controlled trial¹¹. In this trial, twenty patients who exhibited clozapine-induced nocturnal hypersalivation were given 25 mg pirenzepine daily for 8 weeks. Response was assessed objectively by measuring the diameter of the wetted surface of a tissue placed

over the patient's pillow. Pirenzepine was found to be no more effective than placebo. Using a fixed dosage and having an exclusively Asian population are limitations of this study. In Canada, pirenzepine is only available through the special access program.

Atropine

Atropine is a non-selective, competitive antimuscarinic agent. Antonello et al. reported treating three patients with severe clozapine-induced sialorrhea using atropine drops¹³. Each patient received one drop of 1% atropine sublingually at bedtime. Patients reported immediate relief of sialorrhea which lasted throughout the night. Only one patient required a further atropine drop as a top-up dose.

Ipratropium bromide

Ipratropium Bromide is a non-selective, long acting anticholinergic agent mainly used as a bronchodilator. It is a synthetic quaternary ammonium compound with minimal systemic side effects. The evidence for its efficacy in the treatment of clozapine-induced sialorrhea originates from a case report and a prospective, open-label, non-comparative study. Tessier *et al.* reported the successful switching of 10 patients who had responded to treatment with atropine drops (but were either experiencing rebound hypersalivation in the early morning or had difficulty manipulating the atropine dropper) to ipratropium nasal spray administered sublingually. Reduction or resolution of hypersalivation was achieved in all cases¹⁴. Another open-label study used intranasal ipratropium in 10 patients who had failed to respond to benzotropine or clonidine⁵. Using a five-point subjective hypersalivation rating scale, the authors found that eight patients responded initially. However, only 6 patients reported sustained improvement by six months.

Trihexyphenidyl

Trihexyphenidyl, a broad antimuscarinic blocker of M_1 , M_2 and M_3 receptors, has good CNS penetration. In an open label, non-comparative trial,

Spivak *et al.* treated 14 patients with up to 15 mg of trihexyphenidyl administered at bedtime for 15 days. Response was measured using a subjective rating scale and a 44% improvement was found¹⁵.

Benztropine

Benztropine, a non-selective, competitive antimuscarinic agent, is mainly used in the treatment of movement disorders associated with Parkinson's Diseases and neuroleptic use.

The evidence for its efficacy in treatment of clozapine-induced sialorrhea also comes from a single study in which 66% of patients (N=15) receiving benztropine 2 mg daily were symptom-free (subjective reporting) at 12 weeks compared to 33% of patients receiving no treatment¹⁶.

Hyoscine hyrobromide

Hyoscine, a competitive acetylcholine antagonist at postganglionic parasympathetic nerve endings, is mainly used in the treatment of motion sickness. Compared to atropine, it has more potent effects on salivary glands. McKane *et al.* reported on use of hyoscine transdermal patches (500-800 µg/day) in four patients experiencing severe clozapine-induced hypersalivation unresponsive to oral anticholinergics¹⁷. They observed a dramatic improvement in each case even in patients not responding to oral hyoscine.

Amitriptyline

Amitriptyline, a tricyclic antidepressant with central and peripheral antimuscarinic actions, has also been used in the treatment of clozapine-induced sialorrhea. Copp *et al.* reported successful treatment of four patients with severe, persistent drooling with amitriptyline given 75-100 mg daily¹⁸. Of note, all patients were concurrently receiving anticholinergic agents for the treatment of EPS as well. The additive or synergistic effect of excessive anticholinergic side effects was not addressed.

Adrenoceptor agonists

Clonidine

Clonidine is a partial agonist at α -adrenoceptors both within the CNS and the periphery. It is more selective for α_2 receptors and is mainly used as a centrally acting hypotensive agent. The evidence for clonidine's efficacy in the treatment of sialorrhea is conflicting and limited. Grabowski reported treatment of four patients with clonidine 0.1 to 0.2 mg transdermal patches once weekly¹⁹. Two patients responded with marked sustained reduction in sialorrhea; however, the third patient only improved transiently and the fourth did not respond at all. Clonidine transdermal patches are not available in Canada.

Lofexidine

Lofexidine is an α_2 -receptor antagonist used for the short-term treatment of opiate withdrawal symptoms. Long term use is associated with depression and exacerbation of psychosis. Corrigan and McDonald reported the use of lofexidine in a patient experiencing severe hypersalivation while receiving clozapine²⁰. Lofexidine 0.2 mg given twice daily significantly improved sialorrhea; however, it had to be withdrawn due to potential for adverse drug reactions. Clozapine was subsequently discontinued as well. Lofexidine is only available in UK.

Adrenoceptor antagonists

Terazosin

Terazosin, an α_1 receptor agonist, is mainly used in the treatment of essential hypertension. An open trial compared terazosin alone, benztropine alone or both combined. Fifteen patients each received either benztropine 2 mg daily, terazosin 4 mg daily or both. 93% of patients receiving terazosin were symptom-free at 12 week compared to 66% in benztropine and 100% in the group receiving both agents⁵.

Conclusion

Sialorrhea is a common side effect of clozapine and can lead to discontinuation of therapy. Recommended pharmacological treatment options are all empirically based, with no comparative efficacy data to support the choice of one agent over another. In clinical practice, this choice is made by side effects and potential drug interactions. For example, antimuscarinic agents, although reportedly effective, have the added disadvantage of compounding the already significant anticholinergic effect of clozapine. Similarly, adrenoceptor agonists and antagonists can potentiate orthostasis and postural hypotension associated with clozapine.

Sialorrhea appears to occur at the site of the salivary glands. Therefore, agents that do not penetrate the blood-brain barrier would be more desirable. Quaternary amines such as glycopyrrolate, an antimuscarinic agent used during operative procedures to reduce excess secretions and propantheline, do not exert central anticholinergic effects associated with amitriptyline, trihexyphenidyl and benztropine²¹. Usefulness of such agents needs to be further explored. Finally, treatment options for clozapine-induced sialorrhea must be investigated in a controlled manner to define an effective treatment for this troublesome adverse drug reaction.

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