

Pathophysiology of Clozapine Induced Sialorrhea and Current Treatment Choices

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ÖZET

Klozapine bağlı siyalorenin patofizyolojisi ve güncel tedavi seçenekleri

Klozapin yaklaşık 40 yıldır şizofreni tedavisinde kullanılmaktadır ve kayda değer yan etkileri bulunmasına rağmen, tedaviye dirençli şizofrenide halen altın standarttır. Klozapin tedavisi sırasında sık karşılaşılan ve hastaların yaşam kalitesini önemli düzeyde etkileyebilen bir yan etki de siyaloredir. Klozapinin belirgin antikolinergik yan etkilerine karşın, halen hangi mekanizmayla siyaloreye neden olduğu net biçimde bilinmemektedir. Sık karşılaşılmamasına ve yaşam kalitesini belirgin biçimde etkileyebilmesine rağmen, siyalorenin tedavisinde halen mevcut seçeneklerin başarı oranı kısıtlıdır. Bu yazıda, klozapine bağlı gelişen siyalorenin patofizyolojisi ve tedavi seçenekleri güncel bilgiler ışığında gözden geçirilmiştir.

Anahtar kelimeler: Klozapin, siyalore, patofizyoloji, tedavi seçenekleri

ABSTRACT

Pathophysiology of clozapine induced sialorrhea and current treatment choices

Clozapine has been used for approximately 40 years and it is still the gold standard for treatment resistant schizophrenia even though it may cause considerable side effects. One of the common side effects during the treatment with clozapine is sialorrhea. Although clozapine has anticholinergic side effects, pathogenesis of sialorrhea is still unclear. Despite sialorrhea is quite common and might influence quality of life, treatment choices and their efficacy for this side effect is limited. Thus, in this article, pathophysiology and treatment of clozapine induced sialorrhea is reviewed.

Key words: Clozapine, sialorrhea, pathophysiology, treatment choices

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INTRODUCTION

Although clozapine was discovered in 1959 as an antipsychotic, its widespread use started about 20 years later. It has already been known that clozapine is superior to other antipsychotics in treatment-resistant schizophrenia (1). It has widely been used in suicidal patients, affective disorders, controlling aggression and in some neurological disorders and was shown to be superior to classical antipsychotics (2,3). However, potentially fatal agranulocytosis and other relatively milder side effects such as epileptic seizure, orthostatic hypotension, sedation, weight gain and sialorrhea limit its wider use. Although there are papers which report sialorrhea rate due to clozapine as 30% (4,5), more extensive literature search shows a wider range of 10-80% (6). This rate is about 100 times higher than agranulocytosis prevalence. There are several therapeutic options to treat sialorrhea but due to limited efficacy and higher prevalence of adverse effects it has not been treated adequately till now. (7). Studies on this issue are

limited to case reports or studies with small sample sizes (8).

Clinical Features of Sialorrhea and Its Possible Complications

Sialorrhea is a very disturbing adverse effect which develops in the early period of clozapine treatment. Excess saliva causes pooling in oral cavity and this leads to overflow of saliva from mouth. It may continue throughout the day and more frequently during sleep (9). Patients generally complain of waking up with a wet pillow. Sometimes they may suddenly wake up with a feeling of drowning. Aspiration may occur in some cases (10) and it was reported that risk of aspiration pneumonia has increased (11). While pooling of saliva proximal to vocal cords change vocal quality and cause hoarseness and dysphonia, pooling distal to vocal cords may cause chronic cough (12). Sialorrhea due to clozapine is generally dose-related and with increasing dose sialorrhea increases and with

decreasing dose sialorrhea decreases (13-15). Tolerance generally does not develop to this adverse effect (16) and may continue for several years (17).

Clozapine induced sialorrhea has medical and psychosocial consequences. Continuous sialorrhea irritates and sensitizes jaws and perioral region of the patients. Sialorrhea accompanied by sedation causes aspiration due to reduced peristalsis of pharynx and esophagus and may lead to cough and life-threatening conditions such as drowning (11). Nocturnal saliva collection may cause chronic sleep disorders. Patients need to wake up regularly at night to clean their throats and this may cause fatigue and dizziness during day. Complications are generally more severe in the elderly or very young and in severely disabled patients. A certain amount of air is swollen with saliva every time so due to symptomatic aerophagia, bloating and gastrointestinal distress may occur (12). Vasile and Steingard (17) reported temporary salivary gland swelling regressed in a few days in four patients taking clozapine treatment. This condition is not related to sialorrhea but it is thought to have a similar pathophysiology. According to hypothesis for explaining the pathophysiology, stone formation causes ductal obstruction and swelling and regresses upon drop. Painful swelling of parotid and other salivary glands may also develop following clozapine treatment (18).

Sialorrhea causing continuous wetness and bad smell causes social withdrawal and reduced self-esteem due to embarrassment in interpersonal relations and social stigmatization. Electronic devices in the environment may get wet and broken (19). In severe sialorrhea patients carry napkins (12). This situation causes severe social withdrawal and sometimes stopping the treatment (20).

Pathophysiology

There is not a single mechanism explaining its pathophysiology. However, it is known that saliva flow is basically under parasympathetic (cholinergic) control (21) and sympathetic (adrenergic) system has a smaller role in controlling saliva production. Hypersalivation is

a paradoxical side effect of clozapine because clozapine has strong alpha-2 antagonistic (22) and M4-muscarinic (M1, M2, M3 ve M5) activities (23).

Adrenergic alpha-2 antagonism: Yohimbine, which is an alpha-2 adrenergic antagonist increases saliva amount in humans (24). Clozapine has antagonistic effect on both alpha-1 and alpha-2 adrenergic receptors. Salivary glands have both these receptors and their blockage increases blood flow to salivary glands and consequently increases saliva as well (25). According to Rogers and Shramko (4) alpha-adrenoreceptor blockage of clozapine partially releases the repression of beta-adrenoreceptors in salivary glands and further stimulation of beta-adrenoreceptors causes imbalance and hypersalivation. The hypothesis that states alpha-2 adrenoreceptor antagonism causes clozapine-induced sialorrhea is countered by the absence of hypersalivation by mianserine which has a higher affinity to alpha-2 adrenoreceptors and causes hyposalivation (26-28). Furthermore, remoxipride which is an atypical antipsychotic has an extraordinarily low affinity to alpha-2 adrenoreceptors but causes hypersalivation (28).

Muscarinic M4 agonism: Clozapine has antagonistic effect on M3 and M5 muscarinic receptor sub-types; in vitro, it is fully agonistic to M4 muscarinic receptors (23,29) or partially agonistic (30). It is not clear whether it is antagonistic or partially agonistic to M1 and M2 muscarinic receptors yet (29). Selective stimulation of M4 muscarinic receptors in salivary glands increases secretion (23). Sanchez and Lembol reported that muscarinic stimulation is mainly regulated by M3 receptors in salivary glands, these receptor sub-types dominate salivary glands and their activity is diminished by pyrenzepine (31). M4 muscarinic receptor stimulation in patients using clozapine may increase M3 receptor blockade and cause sialorrhea. Role of muscarinic receptors in clozapine induced sialorrhea is rather complicated.

Reduction of laryngeal peristalsis and abolition of swallowing reflex: Approximately 3,5 liters of saliva is produced by the human body daily (32). When there is no problem in the swallowing mechanism, this high amount of liquid passes to

the gastrointestinal system continuously and being absorbed (12). Terry et al. (33) could not find any difference of saliva flow in clozapine users and reported that clozapine shows its effect in target cells at pharynx and in muscles responsible from gag reflex. In a patient with hypersalivation due to clozapine use, reduction in laryngeal peristalsis was found after barium swallowing test (34). Baldessarini et al. reported that all target cells of acetylcholine, norepinephrine, dopamine and serotonin which are neurotransmitters responsible for the swallowing centre of nervous system (35) can be blocked by clozapine. In this context, clozapine can both affect the normal impulses from oral cavity to the brain and affect cranial nerves responsible from typical swallowing reflex. Although it could not be shown that clozapine reduces the amount of saliva, patients complain from excessive saliva which causes drowning sensation especially at nights (6,26). Anti-muscarinic effects of clozapine on M2 and M3 receptors (23) alters smooth muscle peristalsis of pharynx and esophagus and reduces elimination of saliva from oral cavity. Sialorrhea generally occurs at night and there are reports which propose a relationship between nighttime sialorrhea and circadian rhythm (6).

Therapeutic Options

Non-pharmacological strategies: By using these methods in milder cases, training patients and preventing possible embarrassment and anxiety in adolescents and young adults become possible. Chewing non-sugar containing gums may help some patients. Bourgeois et al. (31) reported 60% decrease in patients chewing sugar-free gums. Using multiple pillows can be recommended to patients waking up with a feeling of drowning at night. Patients with severe sialorrhea can be recommended to lie down in lateral decubitus position and aspiration can be prevented (11). Covering the pillow with a towel may help to prevent wetness (3). A special small cup located around jaws may help child, elderly and chronic patients whom self-care has already been diminished.

Pharmacological strategies: In the treatment of clozapine induced sialorrhea, abovementioned

precautions should be taken before the onset of medication. Preventing rapid titration when starting clozapine treatment reduces the risk of sialorrhea and orthostatic hypotension (5). Although it is not that effective, the dose of clozapine may be reduced if clinically possible (36).

Agents used for the treatment of sialorrhea due to clozapine are alpha-2 adrenergic receptor agonists, antimuscarinic agents and other agents.

Centrally acting alpha-2 adrenergic receptor agonists

This classification consists of clonidine, lofexidine, guanfacine, guanabenz, alpha-methyl dopa and moxonidine. Anti-hypertensive clonidine and other "clonidine-like" medications are centrally-acting alpha-2 adrenergic receptor agonists. Although antihypertensive effect is regulated via imidazoline I1 receptors as well as alpha-2 adrenergic receptors, saliva production is inhibited by the stimulation of alpha-2 adrenergic receptors.

Clonidine: Using clonidine in clozapine induced sialorrhea was first reported by Grabowski (20). By administration of 0.1-0.2 mg/day sustained-release clozapine sialorrhea significantly relieved in two patients but no change was observed in the remaining four patients. When the drug is administered as transdermal patch, it takes approximately 3-4 days for the drug to reach steady state. After the patch, steady drug concentration continues for 8 hours and diminished in several days (37). If clonidine patches can not be purchased, 50-100 mcg/day oral clonidine can also be used (before going to sleep) (38). Concomitant administration of both methods reduce blood pressure substantially and may cause falls due to orthostatic hypotension. Thus, close monitoring of blood pressure is important. Clonidine may stimulate norepinephrine secretion and worsening of depression and psychosis (4). Tolerance to the medication may hinder the long-term use of the drug (20).

Lofexidine: This agent is an alpha-2 adrenergic receptor agonist used for opioid withdrawal treatment in some countries. In a case report, 0.2 mg b.i.d. improved clozapine induced sialorrhea (22).

Guanfacine: When compared to guanfacine, clonidine does not cause sedation due to its relative selectivity to alpha-2 receptor sub-group (37). Webber et al. (39) treated a patient with clozapine induced sialorrhea by using 1 mg guanfacine and reported efficacy in 4 days.

Anticholinergic (antimuscarinic) medications

There are selective (e.g., pirenzepine) and non-selective (atropine, trihexiphenidyl, benztropine, procyclidine) muscarinic receptor agonists in this classification. All these medications may increase anticholinergic side effects (e.g., constipation, urinary retention, blurred vision) of clozapine and should be used with caution in narrow-angle glaucoma and prostate hyperplasia.

Pirenzepine: Pirenzepine is a selective M1 and M4 muscarinic receptor antagonist which cannot pass blood-brain barrier so having lower anti-cholinergic side effects. It is used 25-50 mg OD or tid in the treatment of peptic ulcer. Its efficacy in clozapine induced sialorrhea is controversial. Fritze and Elliger (40) reported reduction in sialorrhea by 25-100 mg/day pirenzepine in 120 patients. On the other hand, Bai et al. (41) found no efficacy in their 8-week, double-blind and placebo controlled study of 20 patients. Similar results were found in the study of Schneider et al. (42) in 29 patients.

Benztropine mesylate: This agent is a non-selective, competitive muscarinic receptor antagonist being used in the treatment of Parkinson's disease. Bourgeois et al. (31) reported efficacy in a single case whom they used 1-2 mg/day benztropine.

Trihexyphenidyl (Benzhexole): This agent is a centrally-acting M1 antagonist and being used in the treatment of Parkinsonism. Spivak et al. (43) treated 14 patients with chronic schizophrenia whom have clozapine induced sialorrhea by trihexyphenidyl 5-15 mg/day and reported 44% improvement in the hypersalivation scale.

Biperidene: This agent has a centrally-acting antimuscarinic activity and being used in the treatment of Parkinsonism. Richardson et al. (44) reported

reduction in sialorrhea in a single case by biperidene 6 mg/day.

Propantheline: It has few central anticholinergic side effects. Rogers and Schramko (4) reported reduction in clozapine induced sialorrhea by 7.5 mg propantheline taken nighttime. In two studies which propantheline was compared to astemizole and placebo, there was no significant difference in hypersalivation (45). When propantheline (30-120 mg/day) was compared to diphenhydramine (50-200 mg/day) or doxepine (25 mg/day) no significant difference was reported in hypersalivation (46).

Hyoscine (Scopolamine): This agent is anticholinergic and may cause cognitive impairment. Hyoscine hydrobromide tablets 300 mcg (up to 900 mcg) taken at night is a first line treatment in treatment of clozapine induced sialorrhea in Maudsley Prescribing Manual (15). McKane et al. (47) used retroauricular hyoscine patches in 4 cases of severe and disabling clozapine induced sialorrhea and obtained positive results. It was reported that patch form was more convenient from side effects point of view.

Atropine: It is a centrally-acting antimuscarinic agent and has long been used to reduce saliva and secretion of respiratory pathways during surgical interventions (48). Atropine solutions administered sublingually at night responded sialorrhea immediately but it should be kept in mind that it might cause early rebound of sialorrhea in the due to its short half-life (49). Hyson et al. (50) used atropine in sialorrhea secondary to Parkinson's disease with success. There are also studies done with belladonna, atropinum hyocyanine and hyoscine (51).

Ipratropium: Ipratropium bromide is an anticholinergic agent which structurally related with atropine, having no central nervous system penetration and poorly absorbed after oral ingestion. It is indicated in allergic rhinitis, rhinorrhea and chronic obstructive pulmonary disease by intranasal administration up to 4 times a day (52). Systemic absorption is under 10% by intranasal administration. Calderon et al. (53) used intranasal ipratropium in 10 sialorrhea cases who were non-responder to benztropine or clonidine and observed mild reduction in sialorrhea in 8 cases.

Patients should be trained for sublingual use because glaucoma attack can be triggered by eye contact.

Amitriptyline: It is a tertiary amine tricyclic antidepressant and blocks norepinephrine and serotonin reuptake and neuronal uptake. It exerts alpha-2 adrenergic receptor antagonism, M4 muscarinic receptor agonism and reduces laryngeal peristalsis. Copp et al. (54) obtained positive results in 4 patients having clozapine induced sialorrhea by 87-100 mg amitriptyline taken at nighttime. Praharaj et al. (55) reported a 35 year old male patient with treatment-resistant paranoid schizophrenia whom nighttime sialorrhea and nocturnal enuresis developed after 400 mg/day clozapine and enuresis completely and sialorrhea partially relieved after 25 mg/day amitriptyline. Amitriptyline can be used in high doses in the treatment of sialorrhea (100 mg/day). Different mechanisms may also be involved for enuresis due to clozapine use and amitriptyline can be used for treatment (55).

Other tricyclic agents (e.g., imipramine) are expected to show similar efficacy theoretically.

Other agents

Beta-adrenoreceptor blockers (e.g., propranolol): Due to alpha-adrenoreceptor blockade of salivary glands by clozapine, beta-adrenoreceptors are disinhibited and may cause hypersalivation (4). These agents reduce the thickness of saliva but do not change its amount significantly (56). Severe hypotension is an issue that should be taken into consideration.

Diphenhydramine: This agent is a centrally-acting H1 histamine receptor antagonist and can be effective for sialorrhea due to clozapine by its antimuscarinic effects (4). In a study which diphenhydramine and placebo was compared, it was reported that hypersalivation is reduced by 50 mg/day diphenhydramine (57, 58).

Botulinum toxin injection: Botulinum toxin injection to parotid glands for treatment of sialorrhea in neurological diseases such as Parkinson's disease, motor neuron disease (59, 60) and cerebral palsy (61) seems to be effective. Kahl et al. (62) reported a very

good response to botulinum-A toxin injection (150 IU to each parotid gland) in a patient with clozapine induced sialorrhea. This effect lasted about 12 weeks.

Sulpiride: There are studies with this antipsychotic drug used in treatment of hypersalivation. Kreinin et al. (8) used mean 150-300 mg/day sulpiride in 18 patients with treatment-resistant schizophrenia and reported reduction in sialorrhea in their follow-up. Sulpiride or amisulpiride are non-anticholinergic and non-adrenolytic agents. Their mechanism of action is thought to function via peripheral nervous system.

In a study which traditional Chinese drug suo quan wan and placebo was compared, suo quan wan was reported to cause less hypersalivation than placebo. In these studies astemizole and propantheline was compared and less side effects were reported (63). However, when two other traditional Chinese drugs were compared to placebo, no significant difference was reported (64, 65). In a study which antimuscarinic oils called orizanole or orizanolum was derived from rice shell was used 30-60 mg/day, positive results were achieved in 92 patients (66,67).

CONCLUSION

Pathophysiology of clozapine induced sialorrhea is multifactorial and varies from patient to patient so treatment is also different in every patient. Most of the studies were limited due to small samples, absence of a control group and short follow-up durations. There is need for further studies. It is already known that agents like amitriptyline, sulpiride/amisulpiride and biperidene which are widely used in clinical practice are often inadequate to control clozapine induced sialorrhea. Though none of the current medications does better than the other, new treatment strategies such as pirenzepine, transdermal hyoscin, intranasal ipratropium and sublingual atropin solution can be safely used concomitantly with clozapine without an additional side effect profile. With the help of molecular and genetic studies, it will be possible to understand the pathophysiology of clozapine induced sialorrhea and discover specific medications.

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