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Utility of Sublingual Atropine in Clozapine-Induced Sialorrhea: A Case Series

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Abstract

Clozapine-induced sialorrhea (CIS) is a common, treatment-limiting, and stigmatizing side effect. All systemic agents that are used for CIS may increase clozapine side effects such as blood pressure changes, constipation, or arrhythmias or may have a negative impact on cognition. Sublingual application of Atropine might be a low side effect option for treatment of CIS. Our aim is to propose an off-label treatment option of atropine 1% ophthalmic solution given orally via sublingual route for CIS and stimulate further examination. As presented in the three cases below Atropine 1% (1 mg/ml) ophthalmic solution was applied orally via sublingual route 2-3 drops before going to bed initially and then thrice a day. Subjective improvement along with improvement were seen by measuring wet area over the pillow, The Drooling Severity and Frequency Scale (DSFS), Drooling Impact Scale (DIS), Nocturnal Hyper salivation Rating Scale(NHRS), Constipation Assessment Scale(CAS) at baseline visit and at one-week intervals. No side effects were observed. The promising effect should be examined by randomized controlled trials to translate this into clinical practice.

Keywords: CIS; Blood Pressure; CAS; DIS

Abbreviations: CIS: Clozapine-Induced Sialorrhea; DSFS: Drooling Severity and Frequency Scale; DIS: Drooling Impact Scale; NHRS: Nocturnal Hyper Salivation Rating Scale; CAS: Constipation Assessment Scale; CIH: Clozapine-Induced Hyper Salivation; CID: Clozapine-Induced Drooling; VIP: Vasoactive Intestinal Peptide; PANSS: Positive and Negative Symptoms Scale.

Introduction

Clozapine- is the gold standard in treatment-resistant schizophrenia [1-3] but is also associated with a number of serious adverse effects including myocarditis, agranulocytosis, sedation, or seizures. Although the overall mortality in treatment with clozapine is lower than with

other antipsychotic drugs, yet there is an exaggerated fear among many psychiatrists when initiating clozapine [4,5]. Hypersalivation is defined as the excessive production of saliva and is reported in 80% of clozapine-treated patients [6] while the Stedman's Medical Dictionary [7] defines sialorrhea as the excessive flow of saliva without specifying the place of the flow describes the clozapine effect on saliva secretion is reported in 33 to 48% of clozapine-treated patients [8,9].

Drooling saliva can lead to maceration and irritation at the level of the chin and perioral skin, as well as cheilitis. Combined with the sedative effect of clozapine, it can lead to aspiration of the oropharyngeal contents, aspiration pneumonia, and even lead to suffocation in patients. Clozapine-induced parotitis has also been reported in the past [10]. Apart from these, hyper salivation, speech difficulties as well as wet clothing with associated malodor have psycho-social impacts on one's living. These include stigmatizing effect, leading to reduced self- esteem, social isolation, and ultimately to a poor quality of life [11]. The exact mechanism of clozapine-induced hyper salivation (CIH) or clozapine-induced drooling (CID) is unknown. In terms of the clozapine's effect on the various receptors, clozapine is a full or partial agonist at muscarinic M4 and an antagonist at M3 receptors with norclozapine (NMDC) acting as a partial agonist at M1 receptors. Additionally, NMDC's effect on alpha-1 adrenergic receptors may be involved, and positive modulation by vasoactive intestinal peptide (VIP) may act synergistically with clozapine [12,13]. Another possible mechanism is the increase in the sensitivity to cholinergic stimulation due to a receptor upregulation as a result of the strong antimuscarinic effect of clozapine [14,15]. Also reduced laryngeal peristalsis could contribute to the phenomenon [13]. There are no generally accepted guidelines, and none of the treatments is FDA-approved for CIS. Various pharmacological treatment options with possible side effects given in table 1 [16].

All muscarinic receptor subtypes are antagonised by atropine, including M1 and M3, which play a major role in salivary secretion. In rats, the administration of atropine abolishes the effect of clozapine-induced saliva secretion in submandibular glands [11]. Orally administered atropine appears safe and well tolerated up to doses of 0.03mg/ kg. The duration of sublingual atropine is probably close to orally and intramuscularly administered atropine: up to 4 hours [17-19]. NHRS is a validated single-item 5-point self-report scale for measuring the degree of nocturnal salivation which a respondent experiences. It consists of the five points: 0, absent; 1, minimal (signs of saliva on the pillow in the morning); 2, mild (hypersalivation wakes the patient once during the night); 3, moderate (hypersalivation wakes the patient twice during the night); and 4, severe (hypersalivation wakes the patient at least thrice during the night). Similarly, other tools like- Drooling Severity and Frequency Scale (DSF) [10], Drooling Impact Scale (DIS), Objective methods such as the measurement of the diameter of the saliva on a patch on the pillow can also be used to quantify the severity of CIS.

Case Presentation 1

A 38-year-old female inpatient who had a psychotic disorder for a duration of 14 years had a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). She had been on tab. Clozapine 300 mg, tab. Glycopyrrolate 2 mg, syrup lactulose 3 tsp per day and per rectal enema twice weekly. Her clozapine could not be hiked due to severe constipation and hypersalivation. Her drooling was continuous and severe as drool dripped off her chin during the day and at night leading to midnight awakening. Informed consent was obtained from the patient's relative for off-label use of atropine. Atropine 1% (1 mg/ml) ophthalmic solution was initiated as 2 drops (total dose 0.1 ml) orally before going to bed as monotherapy for CIS. The administration was 2 drops below the tongue followed by rinsing to cover the whole buccal mucosa initially and then the dose was increased to 2 drops thrice a day after two days to achieve a total dose of 0.3 ml per day and then further increased to 3 drops thrice a day after 3 days to achieve a total dose of 0.45ml per day. The wet area over the pillow, Nocturnal Hypersalivation Rating Scale (NHRS), Positive and negative symptoms scale (PANSS), The Drooling Severity and Frequency Scale (DSFS), Drooling Impact Scale (DIS), Constipation Assessment Scale (CAS) were administered at baseline visit and at one-week intervals.

During the follow-up of 12 weeks, no side effects were observed associated with atropine. Assessment of sialorrhea at night according to NHRS yielded a score 5 (extreme) before atropine was initiated. After 2 drops of tropicamide (total dose 0.1 ml per day), the score was 4 (severe) and after 2 drops thrice a day (total dose of 0.3 ml per day), it was 2 (mild) and after 3 drops thrice a day (total dose of 0.45 ml per day), it was 1 (minimal). After two months of follow-up, Tab. Glycopyrrolate and syrup lactulose had been slowly tapered down and stopped and Bisacodyl 20mg was added. The PANSS score decreased from 36 to 25 after increasing clozapine to 600mg and maintenance MECT. The wet area over the pillow was also measured during each rating and it was reduced to just spotting near the mouth with no awakening in night, and no drooling during the day.

Case Presentation 2

A 42-year-old male, diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (duration of illness-15

years), was admitted to the psychiatric inpatient in view of exacerbation of symptoms was on Tab Clozapine 400mg, Tab Trihexyphenidyl 2 mg, Tab Lorazepam 2mg and Tab Glycopyrrolate 2 mg since 14 years and had complains of hypersalivation since 8 years which was causing slurring of speech, midnight wakening due to drooling over most areas of the pillow and diminishing his confidence to interact with others, thereby causing distress. For monitoring the response, Nocturnal Hypersalivation Rating Scale (NHRS) and The Drooling Severity and Frequency Scale (DSFS) were applied at baseline and every third day. At baseline, NHRS and DSFS ratings were severe (frequent soaking of pillow and clothes) and severe with frequent drooling, respectively. Informed consent was taken from the caregivers for off-label use of atropine. Atropine 1% (1 mg/ml) ophthalmic solution was given as 2 drops (total dose 0.1 ml) sublingually at night for managing CIS after taking consent from the patient. Sublingual application was followed by spreading the drug to cover whole buccal mucosa evenly. By day 6, significant improvement was seen in hypersalivation as the patient reported having an uninterrupted, comfortable sleep after a long period of time. By day 8 of admission, an overwhelming response was seen as evidenced by the NHRS score being zero (no hypersalivation) and DSFS suggestive of nil severity score and occasional frequency. While the patient was admitted inpatient for another two weeks, he continued to use atropine sublingually with maintained response which was later advised on followup too.

Case Presentation 3

A 21 year old male diagnosed with intellectual disability and Psychosis NOS taking tab. Clozapine 150mg , tab. Divaloprex 1500mg/day , tab. Trihexyphenidyl 2mg, tab. Chlorpromazine 300mg/day with improvement in behavioural symptoms but currently reporting complaint of hypersalivation and constipation in patient. Patient was started on tab. Glycopyrrolate 2mg with no significant improvement in hypersalivation but it led to further worsening of constipation. Atropine 1% (1 mg/ml) ophthalmic solution was given as 2 drops (total dose 0.1 ml) sublingually at night for managing CIS after taking consent from the patient. Sublingual application was followed by spreading the drug to cover whole buccal mucosa evenly. At baseline, NHRS and DSFS ratings were applied which came to be severe (frequent soaking of pillow and clothes) and severe with frequent drooling, respectively. By day 2 patient family members starting reported decrease wetting of pillow than earlier. Gradually the patient dose was increased 2 drops of Atropine 1% thrice a day to get the effect throughout the day. A significant response was seen as evidenced by NHRS score being zero (no hypersalivation) and DSFS suggestive of nil severity score and occasional frequency and also significant improvement reported by patient.

Discussion

Clozapine Induced Sialorrhea is a frequent and bothersome adverse effect of clozapine [6]. As presented in the three cases above, CIS can occur at different clozapine doses; during various stages of treatment; and is an important reason for treatment discontinuation. Oral anticholinergic medications have been used to treat CIS with variable efficacy in the above cases, but caused various systemic anticholinergic side effects, especially constipation. Constipation is an enormous problem in patients with clozapine; one does not wish to add to this anticholinergic burden through the unnecessary use of systemic anticholinergics unless it is absolutely necessary.

Drug	Dosage	Comments
Tablet Hyoscine bromide	300-900ug/day Divided doses can be used for daytime hypersalivation	Tablet can be sucked or chewed for optimal effect Half-life – 4 hours Worsens the anticholinergic adverse effects of clozapine
Hyoscine patches	1.5mg/72h	Easier to use than the tablet form
Ipratropium bromide nasal spray 0.03%	2 puffs sublingually at night or twice daily	Easier to use than sublingual atropine drops
Glycopyrrolate	2-4mg at night Divided doses can be used for daytime hypersalivation	Has no central anticholinergic effects but can increase peripheral anticholinergic effects Expensive
Pirenzepine	25-100 mg at night or divided dose	Mild diarrhoea; less likely to cause central anticholinergic side effects
Propantheline	30-120 mg at night or divided dose	Constipation, drowsiness and dry mouth
Diphenhydramine	100-200mg at night	Sedation and dry mouth
Amisulpride	Up to 400mg/day	May improve psychotic symptoms, likely to cause hyperprolactinemia

Atropine eye drops 1%(sublingually)	1-2 drops sublingually, initially at bedtime, and if needed upto three times a day Recommended that patient swish and spit to spread the medication around the mucosa	Less likely to cause systemic anticholinergic effects Short half-life and risk of rebound hypersalivation The bitter taste can be a limiting factor
Trihexyphenidyl	5-15mg day	Worsening of anticholinergic adverse effects
Amitriptyline	10-100mg at night	additive anticholinergic adverse effects postural hypotension and seizures
Alpha-2 agonist, e.g clonidine	Clonidine 100-500ug/day	Sedation, dry mouth, depression and hypotension

Table 1: Various drugs to treat CIS.

Our case series shows that sublingual 1% atropine can be a rapid and effective treatment for CIS that is both safe and practical. There are no generally accepted guidelines, and none of the treatments is FDA-approved for CIS. Therefore, trying safe and tolerable off-label interventions may be reasonable. Besides systemic agents, Atropine when given orally via sublingual route may be a low side effect options for treating CIS. Improvement on atropine drops allowed us to stop systemic agents like Glycopyrrolate and optimise the dose of Clozapine helping us achieve better clinical outcomes with less systemic anticholinergic side effects. From our study finding can infer that dose range of 0.1-0.30 ml sublingual atropine was found optimal to treat CIS.

NHRS Score	Case 1	Case 2	Case 3
Before initiation	5	4	5
0.1 ml	4	0	3
0.3 ml	2		0
0.45 ml	1		

Table 2: Dose of topical Atropine and scores in NHRS.

One limitation of its utilization is the dose-related dry mouth, which can be addressed by lowering the number of drops [20]. The relative efficacy and less side effect burden of sublingual atropine as compared to other agents- it a good treatment option. We propose that sublingual Atropine, be initiated at 3 drops bedtime. It can be further optimized to three drops as needed up to thrice daily to achieve good control of the sialorrhea and an improvement in overall quality of life. Further well-designed research will be able to provide information on the appropriate use, potential risks, and benefits of this off-label agent to provide the best possible care for patients.

Conclusion

Clozapine-induced sialorrhea is a common adverse effect. It is stigmatizing and frequently associated with treatment non-adherence in patients taking clozapine. While, management of CIS with popular anticholinergic agents is helpful yet it adds to the unwanted anticholinergic side effects. Sublingual Atropine is a safer and well-tolerated alternative for the management of CIS.

References

1. Tandon R, Nasrallah HA, Keshavan MS (2010) Just the Facts" 5. Treatment and prevention past, present, and future. Schizophr Res 122(1-3): 1-23.

2. Samara MT, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, et al. (2016) Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: A network meta-analysis. JAMA Psychiatry 73(3): 199-210.

3. Lewis SW, Barnes TRE, Davies L, Murray RM, Dunn G, et al. (2006) Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull 32(4): 715-723.

4. Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Niskanen L, et al. (2009) 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet 374(9690): 620-627.

5. Cohen D (2014) Prescribers fear as a major side-effect of clozapine. Acta Psychiatr Scand 130(2): 154-155.

6. Syed R, Au K, Cahill C, Duggan L, He Y, et al. (2008) Pharmacological interventions for clozapine-induced hypersalivation. Cochrane Database of Syst Rev 3: CD005579.

7. Stedman T (1920) Stedman's medical dictionary. Dalcassian publishing company.

8. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, et al. (2006) Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to

prior atypical antipsychotic treatment. Am J Psychiatry 163(4): 600-610.

9. Liang CS, Ho PS, Shen LJ, Lee WK, Yang FW, et al. (2010) Comparison of the efficacy and impact on cognition of glycopyrrolate and biperiden for clozapine-induced sialorrhea in schizophrenic patients: a randomized, double-blind, crossover study. Schizophr Res 119(1-3): 138-144.

10. Van der Poorten T, De Hert M (2019) The sublingual use of atropine in the treatment of clozapine-induced sialorrhea: A systematic review. Clin Case Rep pp: 2108-2113.

11. Maher S, Cunningham A, O'Callaghan N, Byrne F, Mc Donald C, et al. (2016) Clozapine-induced hypersalivation: an estimate of prevalence, severity and impact on quality of life. Therapeutic Advances in Psychopharmacology 6(3): 178-184.

12. Ekstrom MP, Bornefalk HA, Abernethy AP, Currow DC (2014) Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. BMJ 348: g445.

13. Praharaj SK, Arora M, Gandotra S (2006) Clozapine-induced sialorrhea: pathophysiology and management strategies. Psychopharmacology 185(3): 265-273.

14. Jackson DM, Westlind DA (1994) Dopamine receptors: molecular biology, biochemistry and behavioural aspects. Pharmacol Ther 64(2): 291-370.

15. Levin H, Chengappa KN, Kambhampati RK, Mahdavi N, Ganguli R (1992) Should chronic treatment-refractory akathisia be an indication for the use of clozapine in schizophrenic patients? J Clin Psychiatry 53(7): 248-251.

16. Gupta S, Khastgir U, Croft M, Roshny S (2020) Management of clozapine-induced sialorrhoea. BJPsych Advances. Cammbrige University Press 26(2): 106-108.

17. Saarnivaara L, Kautto UM, Iisalo E, Pihlajamäki K (1985) Comparison of pharmacokinetic and pharmacodynamic parameters following oral or intramuscular atropine in children. Atropine overdose in two small children. Acta Anaesthesiol Scand 29(5): 529-536.

18. Gervais HW, el Gindi M, Radermacher PR, Volz ZC, Palm D, et al. (1997) Plasma concentration following oral and intramuscular atropine in children and their clinical effects. Paediatr Anaesth 7(1): 13-18.

19. Takemoto CK, Hodding JH, Kraus DM (2004) Lexi-Comp's Pediatric Dosage Handbook. Hudson: Lexi-Comp, USA.

20. Darriba HB (2021) The sublingual use of atropine in the treatment of clozapine-induced sialorrhea. Eur Psychiatry 64(1): S779.