REFRESHMENT

Management of clozapine-induced sialorrhoea

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SUMMARY

Sialorrhoea (hypersalivation) is a common adverse effect of clozapine. If severe, it can affect patients' quality of life and adherence to the treatment. Clinicians therefore need to proactively manage this effect. At present, no drugs are licensed to manage clozapine-induced sialorrhoea, although there are many off-label treatment options, with variable effectiveness. Anticholinergic medications are commonly prescribed for it, but they have limited effect and can worsen constipation. This article gives a brief overview of other practical and pharmacological management options.

DECLARATION OF INTEREST

None

KEYWORDS

Antipsychotics; clozapine; adverse effects; sialorrhoea.

Clozapine is the most effective antipsychotic drug for treating resistant schizophrenia. It is associated with severe adverse effects, such as agranulocytosis and myocarditis, and a lot of less severe but distressing adverse effects such as sialorrhoea and sedation.

What causes clozapine-induced sialorrhoea?

Sialorrhoea (drooling or excessive salivation) is defined as saliva beyond the margin of the lip. Sialorrhoea can be due to either an increase in the production of saliva or difficulty in swallowing. The pathophysiology of clozapine-induced sialorrhoea (CIS) remains elusive as clozapine is associated with anticholinergic effects. There are many putative etiological theories, with variable supportive evidence. These include agonist effects of clozapine on M_4 muscarinic receptors and antagonist effects on α-adrenergic receptors. As clozapine reduces gastrointestinal motility, including that of the oesophagus, it can also lead to hypersalivation due to reduced swallowing.

Prevalence and consequences

Clozapine-induced sialorrhoea is reported by about 30–80% of patients. Its severity varies from mild nocturnal hypersalivation that causes little problem for the patient to severe daytime drooling associated with significant distress; and in some rare situations, it can lead to serious consequences such as aspiration pneumonia (Citrome 2016). The other consequences of CIS are social embarrassment, reduced self-esteem, sleep problems leading to daytime sleepiness and painful swelling of the salivary glands. In a cross-sectional survey of people on clozapine, 24% of the participants ranked it as one of the three most important adverse effects. Daytime drooling affects the quality of life more than nocturnal hypersalivation (Maher 2016). Hypersalivation has also been reported as one of the reasons for non-adherence to treatment.

Reporting and identification in clinical practice

In clinical practice, patients tend to underreport these adverse effects. Moreover, sometimes clinicians consider them to be inevitable consequences of clozapine and do not always proactively manage them. Unfortunately, even when attempts are made to manage CIS, the available treatment options are not very effective.

CIS usually starts soon after the initiation of clozapine. Most patients develop tolerance to a variable degree with time. So far, there has been limited information to suggest that it is a dose-related effect.

The management of CIS depends on its severity and impact on the patient. Clinicians should routinely inquire about the common adverse effects of clozapine, including CIS. The use of subjective rating scales such as the Nocturnal Hypersalivation Rating Scale and the Drooling Severity and Frequency Scale to measure the severity of hypersalivation, or measuring the diameter of wet pillow in the morning might help in determining the severity of CIS and monitoring responses to interventions.

Practical interventions

Daytime drooling due to CIS is less of a problem because patients can swallow the excessive saliva. If daytime drooling is distressing, chewing sugarless gums might help in reducing the dribbling of saliva since it promotes swallowing. At night, covering

the pillow with a towel, elevating the head and sleeping on the side reduces sleep disruption and the risk of aspiration due to CIS.

Pharmacological management

With regard to pharmacological treatment, the first step should be to review the clozapine dose and reduce it if possible. This might help in reducing sialorrhoea, although there is little evidence to support this approach. The second step is to consider adding another drug to reduce sialorrhoea. Table 1 describes the pharmacological treatment options, which include anticholinergic, antihistaminergic and adrenergic drugs and substitute benzamides such as amisulpride (Bird 2011). None of these drugs has been licensed for CIS. The evidence for these drugs largely comes from short-term case reports, case series and a few randomised controlled trials. Therefore, it has not been possible to assess their comparative effectiveness (Syed 2008).

Oral hyoscine or hyoscine patches are the most commonly prescribed medications for CIS, but so far there is limited research evidence to support their use. The choice of drug should be based on the potential risks and benefits, availability and the acquisition cost. Before adding oral anticholinergic drugs, one should carefully consider additive adverse effects such as worsening of constipation, blurring of vision and cognitive impairment. Constipation is a common adverse effects of clozapine and further worsening it can have serious consequences. Sublingual atropine drops are less likely to have these adverse effects. The effect of anticholinergic drugs lasts only a few hours, and therefore the frequency of administration depends on when CIS is most troublesome to the patient.

The addition of amisulpride is an option for patients who have partially responded to clozapine, and amisulpride has also been found to be an effective drug to treat CIS. Therefore, the addition of sublingual atropine drops (which has fewer systemic anticholinergic effects) and amisulpride (for its effect on the psychotic symptoms) is a potential alternative to systemic anticholinergic and adrenergic drugs.

In people with severe CIS that has not responded to other treatments, injecting botulinum toxin into the salivary glands has been proved to be successful (Yeşilyurt 2010). The effect of a botulinum toxin injection can last up to 12 weeks.

There are no guidelines and research evidence to suggest how long these drugs should be continued. As tolerance develops for CIS, the use of the medication should be regularly reviewed and drug-free periods should be considered to assess the ongoing need for medication.

TABLE 1 **Off-label pharmacological interventions for clozapine-induced sialorrhea**

Drug	Dosage	Comments
Hyoscine hydrobromide oral tablet	300–900 µg/day Divided doses can be used for daytime hypersalivation	The tablet must be sucked or chewed for optimal effect Half-life is around 4 h Worsens anticholinergic adverse effects of clozapine
Hyoscine patches	1.5 mg/72 h	Easier to use than the tablet form
Atropine eye drops (sublingually) 1%	1–2 drops sublingually, initially at bedtime, and if needed up to three times a day Recommend that patients 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	5–15 mg day	Worsening of anticholinergic adverse effects
Amitriptyline	10–100 mg at night	Additive anticholinergic adverse effects, postural hypotension and seizure
Ipratropium bromide nasal spray 0.03%	2 puffs sublingually at night or twice daily	Easier to use than sublingual atropine drops
Glycopyrrolate	2–4 mg at night Divided doses can be used for daytime hypersalivation	Longer-lasting effect than atropine and hyoscine Half-life is around 4 h Has no central anticholinergic effect but can increase peripheral anticholinergic effects Expensive
Pirenzepine	25–100 mg at night or divided dose	Mild diarrhoea; less likely to cause central anticholinergic adverse effects
Propantheline	30–120 mg at night or divided dose	Constipation, drowsiness and dry mouth
Diphenhydramine	100–200 mg at night	Sedation and dry mouth
Alpha-2 agonist, e.g. clonidine	Clonidine 100–500 µg/day	Sedation, dry mouth, depression and hypotension
Amisulpride	Up to 400 mg/day	May improve psychotic symptoms Likely to cause hyperprolactinemia

As clozapine is the best treatment available for resistant schizophrenia, it is essential to ensure early detection and proactive management of its adverse effects for its safe and effective use.

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