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A review of the treatment options for clozapine-induced hypersalivation

AIMS AND METHOD

To develop and introduce an evidence-based drug treatment protocol for clozapine-induced hypersalivation, a review of published literature relating to clozapine-induced hypersalivation and its treatment was undertaken in March 2000. The databases searched were Medline, EMBASE and PsychLit, from 1966 to the present.

RESULTS

This paper reviews the evidence of the benefit of using antimuscarinic

agents, adrenergic antagonists and adrenergic agonists. There is a lack of good-quality controlled-trials, with most papers reporting a series of uncontrolled cases dependent on subjective measures of improvement reported by the patients. However, the published literature suggests a benefit for all of the drug categories reviewed. The most effective treatment may be a combination of terazosin and benzhexol.

CLINICAL IMPLICATIONS

Clozapine-induced hypersalivation is not only an embarrassing problem, but can be difficult to treat. An evidence-based prescribing protocol will encourage the use of those drugs found to be the most effective in treating this problem. It will also offer alternatives if a certain treatment is ineffective or intolerable.

Hypersalivation is a common side-effect experienced early in clozapine treatment. It is a socially stigmatising condition that may cause poor compliance among those with schizophrenia who are unresponsive to other neuroleptic medications. However, clinical evidence evaluating the various proposed treatment strategies is sparse, with an absence of any randomised controlled trials. Prescribing guidelines for treatment of this troublesome side-effect are suggested.

Clozapine is an atypical antipsychotic with superior clinical efficacy and minimal motor adverse affects. The primary indication for clozapine is in the treatment of schizophrenia in those patients who are unresponsive to other neuroleptics. Hypersalivation is a common and distressing side-effect of clozapine treatment. It affects approximately 31% of patients, usually developing early in the course of treatment, and is more prominent at night (Safferman et al, 1991). Clozapine-induced hypersalivation can be most troublesome during sleep and may be voluminous, causing disturbed sleep and respiratory problems secondary to aspiration of saliva. Clozapine-induced hypersalivation can also cause painful swelling of the salivary glands and is socially stigmatising. It may therefore lead to poor compliance early on in treatment, despite dramatic improvement in patients' psychiatric condition.

Proposed mechanisms of action of clozapine-induced hypersalivation

Clozapine has a complex pharmacology. It has antagonistic activity at the 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 (Zorn et al, 1994). Hypersalivation is a paradoxical side-effect because clozapine has marked anticholinergic properties. Parasympathetic stimulation causes high salivary flow rates and sympathetic stimulation leads to high protein levels (Baum, 1993). The agonist effect of clozapine on the muscarinic M₄ receptor has been put forward to explain in part the paradoxical hypersalivation. Another proposed mechanism is clozapine's antagonist activity at the α_2 adrenoceptor. While muscarinic blockade leads to diminished salivary secretion, α_2 antagonists can increase salivation (Berlan et al, 1992).

Attempts have been made to measure the flow of saliva in patients with clozapine induced hypersalivation and compare it to the rate in a set of controls (Ben-Aryeh et al, 1996; Rabinowitz et al, 1996). These studies found no significant difference in either the composition of saliva or saliva flow rate between both groups. Possible explanations for the subjective reporting of hypersalivation by patients may lie with either interference with



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normal deglutition through oesophageal dysfunction (McCarthy & Terkelsen, 1994), or a disturbance in the normal circadian pattern of salivary flow, which is usually high during the day and low at night. However, there is a methodological weakness to both these studies because they measured salivary flow during the day and not when it is most problematical, that is, at night.

It is likely that the true explanation for hypersalivation lies in a combination of the above mechanisms. This is supported by the limited clinical and experimental evidence available on pharmacological treatment strategies for clozapine-induced hypersalivation.

Therapeutic options for the alleviation of clozapine-induced hypersalivation

The main targets for pharmacological intervention of clozapine-induced hypersalivation are the muscarinic and adrenergic receptors. Several studies suggest that different receptors located on the salivary glands themselves, including α and β adrenergic and muscarinic receptors can alter salivary flow (Mandel et al, 1975; Ukai et al, 1989). A potential site of action for therapeutic intervention may be alteration in peripheral adrenergic tone to override the central muscarinic effects of clozapine.

Antimuscarinic agents

Amitriptyline

Amitriptyline is a tricyclic antidepressant that, among other actions, is an antagonist of muscarinic receptors both centrally and peripherally. The evidence for its efficacy in treating clozapine-induced hypersalivation comes from a letter in the *British Journal of Psychiatry* (Copp et al, 1991). Four patients with clozapine-induced hypersalivation were given 87–100 mg amitriptyline for an unspecified length of time and this resulted in either an improvement in the hypersalivation or a complete cessation.

Pirenzepine

Pirenzepine is a muscarinic receptor antagonist that shows its highest binding affinity for M_1 receptors and its main application is for the treatment of benign gastric ulcers. It shows little or no affinity for α receptors, and has poor central nervous system (CNS) penetration. More common side-effects include dry mouth and blurred vision. Evidence for its clinical efficacy comes from a letter in *Lancet* (Fritz & Tilmann, 1995), reporting 120 patients who had their clozapine induced hypersalivation treated with daily doses of 25–100 mg of pirenzepine. They report that pirenzepine was successful in the treatment of the hypersalivation but did not use objective measures of salivation. The only reported side-effect was mild diarrhoea.

Benzhexol (trihexyphenidyl)

Benzhexol is a competitive antagonist of acetylcholine at muscarinic receptors and has good penetration of the CNS. It is most commonly used in the adjunctive therapy of Parkinson's disease. Common side-effects include dry mouth, blurred vision and occasionally confusion. The evidence for its efficacy as a treatment for clozapine-induced hypersalivation comes from one study (Spivak et al, 1997). Fourteen patients with chronic schizophrenia, who exhibited nocturnal hypersalivation during clozapine treatment, were administered 5–15 mg benzhexol at night for 15 days. Response was measured using a subjective rating scale and a 44% improvement was found.

Benzatropine

Benzatropine is a non-selective competitive antagonist of acetylcholine at muscarinic receptors; like benzhexol, its main application is as an adjunct in the treatment of Parkinson's disease. It is well-tolerated, although the usual anticholinergic side-effects of blurred vision, dry mouth and confusion may occur. The evidence for its efficacy in the treatment of clozapine-induced hypersalivation is also from a single study (Reinstein et al, 1999). Fifteen patients with chronic schizophrenia, and clozapine-induced hypersalivation, were treated with benzatropine 1 mg twice daily for 12 weeks and using subjective reporting found a satisfactory decrease in their hypersalivation had occurred in 66% of patients. The main criticism of both this and the benzhexol study is that they were not randomised control trials and treated only a small number of subjects.

Atropine

Atropine is a non-selective competitive antagonist of acetylcholine at muscarinic receptors. Common side-effects are dry mouth and blurred vision. Antonello (1999) described three patients who were treated with atropine for clozapine-induced hypersalivation. The patients were given one drop of 1% atropine solution sublingually at bedtime and, if required, could have a further drop in a bedside glass of water to use as a 'top up'. They reported immediate relief from the hypersalivation, which was both instantaneous and lasted throughout the night.

Hyoscine hydrobromide

Hyoscine is a competitive antagonist of acetylcholine at postganglionic parasympathetic nerve endings. Its main use is in the treatment of motion sickness and as a premedication. There are no publications supporting its efficacy in the treatment of clozapine-induced hypersalivation.

Ipratropium bromide

This is a non-selective muscarinic antagonist, most commonly used as a bronchodilator in the treatment of



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asthma and chronic obstructive airways disease. A single study used intranasal ipratropium bromide on 10 patients with clozapine-induced hypersalivation who had failed to respond to benztropine or clonidine (Calderon *et al*, 2000). By using an intranasal route they hoped to minimise anticholinergic systemic absorption and therefore, side-effects. This was a non-comparative trial with no control group. Using a five-point subjective hypersalivation rating scale they found initially that eight patients reported an initial improvement with minimal side-effects. However, after 6 months two patients dropped out of the study and two reported no sustained improvement. The other six patients reported a statistically significant improvement had been maintained.

Adrenoceptor agonists

Clonidine

Clonidine is a partial agonist at α adrenoceptors both within the CNS and the periphery. It is more specific for α_2 receptors than α_1 . Its main use is as a centrally acting hypotensive agent. Though uncommon with doses less than 1 mg a day, there is a withdrawal syndrome associated with cessation of clonidine treatment with a rapid rebound hypertension. More common side-effects are sedation, dry mouth, bradycardia and contact dermatitis. A 0.1 mg once-a-week clonidine patch was administered to four patients with clozapine induced hypersalivation (Grabowski, 1992). The author reports a sustained improvement in two patients, a limited and short-lived improvement in another and no improvement in the fourth. Clonidine patches are not available in the UK.

Lofexidine

Lofexidine is an α_2 agonist that is only licensed in the UK for the short-term treatment of opiate withdrawal symptoms. A single case was reported where a patient with clozapine-induced hypersalivation was given 0.2 mg twice daily lofexidine over an unspecified time period. The patient showed significant improvement in his hypersalivation (Corrigan & MacDonald, 1995). However, lofexidine could not be used long-term without running the risk of depression or exacerbation of psychosis.

Adrenoceptor antagonists

Terazosin

Terazosin is an α_1 receptor antagonist. Its main application is in the treatment of mild to moderate essential hypertension. The main side-effect associated with terazosin is first dose hypotension. There is one study measuring the efficacy of terazosin (Reinstein *et al*, 1999). This was a non-randomised trial comparing terazosin and benztropine and both combined. There were 15 patients in each of the groups. The terazosin only group received 2 mg at night for 12 weeks. It was found that at 12 weeks 93% of patients reported

discontinuation of their hypersalivation. In contrast, the benztropine group reported only a 66% discontinuation. In the combined group where subjects received 2 mg terazosin and 1 mg twice daily benztropine, there was a 100% discontinuation of hypersalivation.

Other strategies

The lowering of the clozapine dose and the use of sugarless candy or gum to increase swallowing has also been employed 'in practice' to help alleviate hypersalivation. The avoidance of rapid titration when starting clozapine may reduce the chances of experiencing hypersalivation. Although these strategies may be useful adjuncts to the above pharmacological interventions, they are unlikely to prove sufficient on their own.

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