

RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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Clozapine-induced hypersalivation

Clozapine is an atypical antipsychotic indicated for the use in schizophrenia in people unresponsive to, or intolerant of, other antipsychotics. Although effective in treatment-resistant patients, the optimal use of clozapine can be compromised by its potential to cause side effects including neutropenia and agranulocytosis, seizures, cardiomyopathy, myocarditis, orthostatic hypotension, sedation, weight gain and hypersalivation.

Although agranulocytosis is potentially life-threatening, it has a relatively low incidence and other side effects, though less serious, are often the main grounds for non-compliance and increased discontinuation rates in an already at-risk population. Clozapine-induced hypersalivation (also called sialorrhea or ptyalism) is one side effect often assumed to be relatively trivial but which can be very distressing and problematic.

The incidence of clozapine-induced hypersalivation has commonly been cited as 31%, although reported incidence rates have ranged from 30% to 80%. Symptoms are often described as occurring early in treatment and frequently at night. The severity of excess salivation can range from mild to moderate, in some cases wearing off with time, through to being severe and persistent. Persistent hypersalivation can potentially cause disturbance in sleep, social impairment and embarrassment. Chronic hypersalivation can also lead to swelling of the salivary glands, parotitis, skin irritation or infection, and aspiration pneumonia.

Several mechanisms have been proposed for the pathophysiology of clozapine-induced hypersalivation, an effect that appears paradoxical considering clozapine's strong anticholinergic effects. Clozapine is a potent agonist at muscarinic M₄ receptors and it has been postulated that stimulation of these receptors causes an increase in salivation. Alternative hypotheses include alpha₂ adrenoreceptor antagonism causing increased salivation; disruption in the circadian secretion of salivary flow resulting in increased salivation at night; and interference with the normal swallowing process causing pooling of saliva. Evidence against the first two proposed mechanisms has been published with studies of hypersalivation failing to show significant differences in either the composition or flow rate of saliva in those taking clozapine compared with controls.

A range of pharmacological treatments have been suggested to alleviate the problem of clozapine-induced hypersalivation. Unfortunately, evidence for these treatments is largely limited to case reports or open-label studies, and some studies have relied on subjective measures of salivation. Medications trialled include anticholinergic agents, alpha₂ adrenergic agents, antipsychotic agents and botulinum toxin. The majority of the literature focuses on the use of anticholinergic agents, with support mainly for topical agents with less systemic effects, the potential systemic adverse effects appearing to limit any benefits of these drugs.

In order to avoid polypharmacy, other non-drug measures should be trialled before considering medication to treat this troublesome side effect. Suggestions to help manage the problem include placing a towel on a pillow to reduce soaking at night and chewing sugarless gum during the day to facilitate swallowing. Consideration must be made as to whether other factors such as anatomical defects, neuromuscular disorders or other medications could be contributing and possibly addressed. Although the relationship between clozapine dosage and hypersalivation is unclear, dose reduction of clozapine could also be considered providing that psychotic symptoms are able to be controlled.

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FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@rgh.sa.gov.au
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