Hypersalivation – what drug treatment options are available?

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Date prepared: 3rd April 2017

Background

This is the first of a series of five Q&A documents to address the drug treatment of hypersalivation. Links to the others are included in the ‘Answer’ section below.

Hypersalivation is the excessive production of saliva and may result in involuntary loss of saliva from the mouth, i.e. drooling or sialorrhoea (1,2). The pathophysiology of sialorrhoea is often not clear and in some cases, particularly neurological disorders such as cerebral palsy or Parkinson’s disease, it is thought to be due to a poor swallowing mechanism and an inadequate rate of swallowing rather than increased saliva production (2-5).

First-line management of drooling should be directed at the cause, which may be multifactorial and patient-specific. Often this will require a multidisciplinary team approach, using a combination of treatments (2,3,6). Several options are available, including practical aids, speech therapy, behaviour therapy, physiotherapy, radiotherapy, surgery and medication (2-5). Each option has varying degrees of acceptability and success (7).

Drug therapy is aimed at decreasing the volume of saliva without addressing impaired swallowing (8). Salivation is primarily mediated by parasympathetic innervation of the salivary glands and historically, a range of drugs with antimuscarinic actions has been used in an attempt to control hypersalivation (2-4). Blockade of cholinergic muscarinic receptors reduces salivary volume, but a lack of selectivity may result in widespread and undesirable central and peripheral effects, including drowsiness, restlessness, irritability, urinary retention, constipation, and flushing (3,8).

Hypersalivation may occur as an adverse effect of drug treatment, e.g. clozapine. A specific UKMi Q&A document addresses the subject of drug-induced hypersalivation: Drug-induced hypersalivation – what treatment options are available?

Answer

There are various drug treatments (see below), which have been used in the management of hypersalivation, and some are discussed in more detail in additional UKMi Q&A documents. The majority are not licensed in the UK for this indication. However, one brand of glycopyrronium oral solution (Sialanar®) is licensed for “the treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders” (9). Procyclidine (injection, tablets and oral solution) and trihexyphenidyl hydrochloride (tablets) are licensed for the treatment of the symptoms of Parkinson’s disease, which include excessive salivation, or sialorrhoea/drooling (10-13).

1. Antimuscarinic Drugs

- Amitriptyline
- Atropine
- Benztropine* (benztropine)
- Glycopyrronium bromide (glycopyrrolate)
- Hyosine (scopolamine) hydrobromide
- Ipratropium bromide
- Procyclidine
- Trihexyphenidyl hydrochloride (benzhexol hydrochloride)
2. Botulinum Toxins

3. Other drugs

Anti-reflux medications (e.g. ranitidine and cisapride*)
Modafinil
Piracetam
Rotigotine

* Drugs that are no longer marketed in the UK.

There are few, if any, good quality studies (e.g. randomised controlled trials) to compare the different therapeutic options available for the management of sialorrhoea (4). For further discussion on the weaknesses in evidence refer to the ‘Limitations’ section below.

An in-depth systematic review of the medical literature investigating the efficacy of anticholinergic drugs to treat drooling in children with multiple disabilities found that, because of the methodological drawbacks within the studies and the small number of reports, no general conclusion could be reached and a meta-analysis could not be performed (14). The authors concluded that there was some evidence that at least three anticholinergic drugs (benzatropine, glycopyrronium and trihexyphenidyl hydrochloride) are effective in the treatment of drooling in this patient group. However, it could not be concluded that one anticholinergic drug was preferable to others.

A Cochrane review examining interventions for drooling in children with cerebral palsy identified six trials eligible for inclusion, four using botulinum toxin A, and two using the pharmacological interventions, benzatropine or glycopyrronium (15). However the reviewers were unable to reach a conclusion on the effectiveness or safety of the treatments, and insufficient evidence was found to inform clinical practice for the management of drooling in this patient group.

A more recent review of management of drooling in children concluded that evidence for interventions was limited, but possible drug therapies may include transdermal hyoscine, oral glycopyrronium or salivary gland botulinum toxin injections (3). The review found that evidence of efficacy remains limited to small, short-term studies, despite the long-term nature of treatment, and that treatments were associated with adverse effects, with little data on long-term safety. A recommendation was made to ensure careful discussion of treatment decisions, and follow-up of patients to assess efficacy and adverse effects.

A UK survey of 23 neurologists with a special interest in motor neuron disease identified the most popular first-line treatments for sialorrhoea in their patients as: hyoscine hydrobromide patches (65% of clinicians), amitriptyline (52%), carbocisteine (30%) and atropine eye drops topically to the tongue (26%) (16). Second-line preferences were: oral glycopyrronium (43%), botulinum toxin (39%), carbocisteine (35%), amitriptyline (30%) and subcutaneous glycopyrronium (26%). The authors noted the variation in treatment strategies, and suggested this reflected the lack of evidence based guidelines.

The National Institute for Health and Care Excellence (NICE) full Clinical Guideline on the management of Parkinson’s disease includes a section on sialorrhoea. Suggested treatment measures include sublingual 1% atropine ophthalmic solution twice daily and injection of salivary glands with botulinum toxin A (17). A NICE Clinical Knowledge Summary also suggests botulinum toxin A, as well as hyoscine hydrobromide patches as specialist treatment options for excessive salivation associated with Parkinson’s disease (18).

A NICE Clinical Knowledge Summary covering the management of oral problems in palliative care includes a section on excessive salivation (19). Specialist advice is recommended, with little data available to guide drug or dosage recommendations. Suggested drug treatments are based on expert opinion, and include hyoscine hydrobromide (oral, sublingual or transdermal) or amitriptyline.

The BNF for Children suggests oral glycopyrronium or oral/transdermal hyoscine hydrombromide as options for hypersalivation in palliative care and in children unable to control posture or with abnormal swallowing reflex (3,20).
Three Q&A documents have been prepared about non drug-induced hypersalivation, which look at the evidence behind various treatment options in more detail. These are:

**Glycopyrronium**: Hypersalivation – can glycopyrronium be used to treat it?

**Hyoscyne Hydrobromide**: Hypersalivation – can hyoscine hydrobromide be used to treat it?

**Other antimuscarinic drugs, Botulinum Toxin and Other Drugs**: Hypersalivation – what are the treatment alternatives to glycopyrronium and hyoscine?

The choice of drug should be based on its pharmacological and adverse effect profile as well as the limited results of available published studies (4). Selection of a particular compound should be based on individual response and side effects (21). Clearly, larger randomised controlled trials are required before the place of each of these drugs in the management of hypersalivation can be established.

**Summary**

- Hypersalivation is the excessive production of saliva and may result in drooling or sialorrhoea.
- Drooling is not always due to hypersalivation, and may be due to poor swallowing mechanism and an inadequate rate of swallowing. Nonetheless, drug therapy for drooling is aimed at reducing the volume of saliva.
- Evidence to support efficacy and safety of drug therapy in hypersalivation is limited. Drugs with antimuscarinic actions, particularly hyoscine hydrobromide and glycopyrronium, are most commonly used. Botulinum toxins are another option, as well as a selection of other drugs.
- Most drugs are unlicensed for this indication in the UK, although glycopyrronium oral solution (Sialanar®) is licensed for the treatment of sialorrhoea in children with neurological disorders, and procyclidine and trihexyphenidyl are licensed for excessive salivation or drooling associated with Parkinson’s disease.
- Good quality comparative studies are lacking, so prescribers should consider evidence for effectiveness, potential side effects and available routes of administration when choosing between treatments. Specialist advice may be required, with little data available to guide drug or dosage recommendations.
- The various treatment options and evidence are discussed in more detail in other UKMi Q&As (links provided in this Q&A), and another Q&A discusses treatments for drug-induced hypersalivation.

**Limitations**

- To date there are no large randomised controlled trials for any drug to treat hypersalivation, so the amount of published evidence is limited. Few comparative studies are available. The evidence for the use of some of these drugs is limited to anecdotal reports only.
- The majority of the studies are short-term so long-term efficacy and safety data are not available.
- Most of the studies included small numbers of patients.
- The majority of the studies rely on subjective outcome measurements since it is difficult to assess saliva production objectively, particularly as there is inter-individual variation in saliva production. No single method of measurement of salivary flow and outcome presentation is available.
- This Q&A has not addressed the management of drug-induced hypersalivation.

**References**


Quality Assurance

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Date Prepared
3rd April 2017

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Date of check
23rd May 2017

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