Hypersalivation – what are the treatment alternatives to glycopyrronium and hyoscine?

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Background

There are three separate Q&A documents to accompany this one which are all concerned with non drug-induced hypersalivation (or sialorrhoea/drooling). They are as follows:

Hypersalivation – what drug treatment options are available?

Hypersalivation – can glycopyrronium be used to treat it?

Hypersalivation – can hyoscine hydrobromide be used to treat it?

This Q&A document outlines possible alternatives to hyoscine hydrobromide and glycopyrronium, which are two of the more commonly used pharmacological treatments, for non drug-induced hypersalivation.

Answer

There are no well-designed, large randomised studies that compare the different therapeutic options available for the management of sialorrhoea (1). 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 (2). 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.

The treatment option with the largest evidence base is botulinum toxin, with a number of studies investigating its use in hypersalivation or sialorrhoea due to various causes reported in the medical literature.

The choice of drug should be based on its pharmacological and adverse effect profile as well as the limited results of the available published studies (1). Selection of a particular compound should be based on individual response and side effects (3). Larger randomised controlled trials are required before the place of any drug in the management of hypersalivation can be established.

None of the following drugs are licensed specifically for the treatment of hypersalivation or sialorrhoea, although trihexyphenidyl hydrochloride (tablets) are licensed for the treatment of excessive salivation, along with other symptoms, associated with Parkinson's disease (4).

Botulinum Toxins

Botulinum toxin A is the most common neurotoxin used in the treatment of hypersalivation or drooling. However, some researchers have also used botulinum toxin B (5-7). It is delivered by injection into the salivary glands where it inhibits the release of acetylcholine, reducing the volume of saliva produced by the glands.

None of the botulinum toxin brands available in the UK are presently licensed for treatment of hypersalivation (8). However, one brand of botulinum toxin A (Xeomin) is in clinical development, awaiting Phase 3 trial results, for sialorrhoea associated with adult Parkinson's disease, and

paediatric cerebral palsy. In these trials Xeomin is to be administered at a dose of 75 or 100 units (or 2 units/kg body weight up to a maximum 75 units in paediatric patients) per treatment cycle, as four injections into the parotid and submandibular glands, bilaterally.

The NICE full Clinical Guideline on the management of Parkinson's disease, suggests (off licence) injection of salivary glands with botulinum toxin A as one option for the treatment of hypersalivation (9).Numerous small studies of botulinum toxins, in particular type A, have been published in the medical literature, using a variety of formulations, dosages, and routes of administration (direct or transductal approach) with varying outcome measures (10,11). A small randomised trial (n=39) compared botulinum toxin A with transdermal hyoscine hydrobromide, and found similar effectiveness for treatment of drooling in children with cerebral palsy, for up to 16 weeks (10,12). With increasing evidence and experience, botulinum toxin has become a well-established therapeutic option for the management of sialorrhoea from various causes, demonstrating efficacy and safety, with limited evidence also available from retrospective reviews indicating long-term safety (13,14).
Systematic reviews and meta-analyses of botulinum toxin in the management of hypersalivation have also been published (15-17). A Cochrane review of interventions for drooling in children with cerebral palsy included 6 studies, and 4 of these were trials using botulinum toxin A (6). The reviewers were unable to reach any conclusionson the effectiveness and safety of this treatment. Another Cochrane review investigated evidence on treatment for sialorrhoea in people with motor neuron disease or Amyotrophic Lateral Sclerosis (ALS) (18). Only one well designed randomised trial was identified and this was a study of 20 patients, in which significantly more patients reported improvement following treatment with Botulinum toxin B versus placebo ($p<0.005$) at 2 and 4 weeks, although the difference did not remain statistically significant at 8 and 12 weeks.
An international consensus statement defining the assessment, intervention and aftercare of patients with drooling treated with botulinum toxin A is available (19).

Since the administration of botulinum toxin is invasive and requires specialist expertise to perform the intervention, patient access to treatment may be variable (20,21). A UK survey of neurologists reported botulinum toxin use for sialorrhoea in patients with motor neuron disease in 14 of 21 centres (21). Respondents indicated that it was not used as a first-line treatment, but was a popular second-line treatment, and respondents felt it had one of the best side effect profiles.

The effect of repeated injections of botulinum toxin over time, or the risk of developing antibodies, are not known (22). A safe maximum dosage and ideal method of administration have not been established (6,7). Dosage also differs among the different products, e.g. one unit of Botox is approximately equivalent to three to four units of Dysport (6). There are concerns that dysphagia may occur due to swelling of the salivary glands, which has been reported to result in the need for gastrostomy (7,21). However this side effect would appear to be rare (21). Generally the treatment appears to be well-tolerated, although its effects may not last long and require repeated administration (7,8).

Antimuscarinic Drugs

1. Amitriptyline. There are few, if any, published reports of the use of amitriptyline in the management of hypersalivation. It has been used anecdotally, but its sedative properties may limit its use to patients experiencing hypersalivation at night. A NICE Clinical Knowledge Summary suggests amitriptyline may be an option, under specialist advice, for excessive salivation in palliative care patients (23). A review of drugs used for treating sialorrhoea in Amyotrophic Lateral Sclerosis (ALS) offers amitriptyline as a treatment option (11). A survey of neurologists in the UK involved in the treatment of patients with motor neuron disease (MND), identified amitriptyline as a popular choice of treatment, first or second-line, for patients experiencing sialorrhoea, with clinicians indicating they felt it was easy to use, and cost effective (21).

2. Atropine. In the NICE full Clinical Guideline on the management of Parkinson's disease, sublingual 1% atropine ophthalmic solution twice daily is one option suggested for the treatment of hypersalivation (9). Surveys of clinicians in the UK and France report atropine as a popular choice of treatment for patients with sialorrhoea due to neurological disorders, although other treatments (e.g. hyoscine hydrobromide) were more popular (12,21). The Palliative Care Formulary also suggests use of atropine 1% ophthalmic solution as a treatment option for sialorrhoea, at a dose of 4 drops on or under the tongue every 4 hours when required (24). The exact dose of sublingual atropine has not

been established, and it should be noted that drop size varies with applicator and technique, producing a variable dose (200 to 500 micrograms) per drop (19,24,25). Some patients may have difficulty manipulating the dropper to ensure proper dosing and there is the potential for accidental overdose with drops. Patients may need to titrate the dose upwards until an adequate effect is achieved. Atropine crosses the blood-brain barrier, and central side effects may therefore be a problem, as well as cardiac effects such as tachycardia (26). It should not be used in patients with cognitive impairment, dementia and hallucinations (20). However, results of a survey of neurologists in the UK indicated they felt it was one of the best treatment options with regard to side effect profile (21). Other advantages cited for atropine include its availability, low cost, fast onset, and reversibility (20,21). Some of the published evidence for atropine are summarised below, but further studies are required to determine if, and under what circumstances, sublingual atropine is effective for the management of hypersalivation (25).

A small randomised double-blind, cross-over placebo-controlled trial evaluated the effectiveness of sublingual atropine sulfate drops (two drops (500 micrograms) every 6 hours for 48 hours) for the management of hypersalivation in 22 patients with advanced tumours of the upper digestive tract (12), This study failed to demonstrate any significant benefits of atropine over placebo but had several limitations including a small sample size, its short duration, reliance on subjective outcome measures, and a high placebo effect.

One small non-comparative study investigated the use of sublingual atropine for the treatment of hypersalivation in 7 patients with Parkinsonism (27). Each patient received one drop (500 micrograms) of atropine 1% eye drop solution sublingually twice a day, and objective and subjective measurements were made at baseline, following the first dose of atropine and after one week. One patient withdrew because of delirium (concurrent with a urinary infection) and two patients experienced worsening of hallucinations (pre-existing active hallucinosis was concealed by both patients). No other side effects were reported. Participants demonstrated statistically significant reductions in saliva production both subjectively and objectively.

A case report describes use of sublingual atropine for the treatment of hypersalivation in a 14-year old boy with metachromatic leukodystrophy (MLD) (25). Ophthalmic atropine 0.5% was given as one drop (250 micrograms) sublingually every six hours as needed. A significant improvement in symptoms was observed within 24 hours, with a perceived onset of action of 15 to 30 minutes, and duration of action of approximately 4 hours. No obvious adverse effects were observed.

3. Benzatropine (benztropine). There are a selection of reports of successful use of this drug in the treatment of patients with drooling, particularly in children with cerebral palsy, but the evidence is limited, with studies having a number of weaknesses, and a Cochrane review was unable to draw any conclusions regarding its efficacy and safety (6,10).

Benzatropine tablets are no longer licensed in the UK.

4. Trihexyphenidyl Hydrochloride (Benzhexol Hydrochloride). The Summary of Product Characteristics states that trihexyphenidyl is effective in reducing excessive salivation associated with Parkinsonism, although no details of supporting evidence from clinical studies are provided (4). The usual dose for symptoms associated with Parkinsonism is 6 – 10mg daily in three or four divided doses. However the optimal dosage should be determined empirically, starting with a low dose and increasing gradually, and doses ranging between 1mg daily and 15mg daily are described.

Evidence from the medical literature is scant. A study of 20 children (aged 3-12 years) with cerebral palsy revealed that trihexyphenidyl, at a dose of 1mg twice daily, increasing to 2mg three times daily, improved drooling in 17 recipients (28). Patients were treated for a minimum of 3 months and adverse effects were reported infrequently despite some patients continuing treatment for up to 2 years.

A retrospective chart review for 101 children (aged 1-18 years) with cerebral palsy, who received trihexyphenidyl for dystonia, sialorrhoea or both, reported that sialorrhoea was reduced in 60.4% of patients (29). The mean initial dose was 95 microgram/kg/day (given twice daily), and the mean maximum dose was 550 microgram/kg/day (given two or three times a day). Side effects were reported in 69.3% of patients including constipation, decreased urinary frequency, behavioural changes and excessive dry mouth, and 36 patients (35.6%) discontinued treatment including 8% due

to intolerable side effects. The authors suggest that trihexyphenidyl should be started at a low dose with a gradual stepwise increase over several weeks to promote tolerability and to account for a potentially delayed response to treatment.

5. Ipratropium Bromide One randomised, double-blind, placebo-controlled, crossover study investigated the safety, tolerability and efficacy of ipratropium bromide spray in the management of Parkinson's disease related hypersalivation (30). In the study 17 patients were recruited and 15 completed the trial. Patients used one or two metered doses (sprays) of ipratropium bromide (21 microgram/metered dose) or placebo sublingually up to four times per day for 2 weeks, with a one week washout before crossover. Ipratropium bromide had no significant effect on the amount of saliva produced, but was well tolerated.

Others

Modafinil In two children (aged 13 and 6 years) with spastic cerebral palsy, treatment with modafinil for spasticity resulted in a dramatic improvement in drooling (31). In the first case, the modafinil was gradually increased from 50mg daily to 200mg daily over several months, and drooling stopped, although irritability developed at this dose. This resolved on discontinuation of treatment and modafinil was then restarted at 100mg every other day with a view to increasing the dose stepwise back to 150mg in the morning. In the second case, modafinil was started at 25mg in the morning and was gradually increased to 100mg in the morning over a few months. No side effects are mentioned and it is reported that the patient stopped drooling.

Ranitidine plus cisapride A combination of ranitidine and cisapride proved ineffective in reducing drooling in 9 children with cerebral palsy and gastro-oesophageal reflux (32). Cisapride is no longer marketed in the UK.

Piracetam In two children (aged 4 and 5 years), piracetam initiated for low cognitive ability at 200mg daily and increased to 200mg twice daily, was reported to resolve sialorrhoea within 2 to 3 weeks, with no recurrence after 6 months of treatment (33). The author hypothesised that this may be due to the effects of piracetam on the central nervous system indirectly impacting salivation, but that further studies would be needed.

Rotigotine A small, open label pilot study of 7 patients observed that transdermal rotigotine up to 4mg/24hours significantly improved drooling of Parkinson's disease, measured using three different clinical scores before and after 4 weeks of therapy (34).

Summary

- This Q&A presents possible alternatives to hyoscine hydrobromide and glycopyrronium in the treatment of non drug-induced hypersalivation.
- There are no well-designed, large randomised studies that compare the different therapeutic options, so drug choice should be based on the pharmacological and adverse effect profile as well as the limited results of the available published studies.
- Probably the best-studied treatment is botulinum toxin, particularly type A, delivered by injection into salivary glands. With increasing evidence of efficacy and safety from numerous small studies, along with systematic reviews and meta-analyses, and increasing experience of use among specialists, botulinum toxin has become a well-established therapeutic option for the management of sialorrhoea from various causes. Results from large randomised controlled trials are lacking, but one brand of botulinum toxin A (Xeomin) is in clinical development, with Phase 3 trials in progress, for treatment of sialorrhoea associated with Parkinson's disease and cerebral palsy. Since administration of botulinum toxin is invasive and requires specialist expertise, patient access to treatment may be variable, and it is usually considered as a second-line option. A safe maximum dosage and ideal method of administration of botulinum toxin have not been established. Dosage differs among the different products. Generally the treatment appears to be well-tolerated, although there are concerns about a risk of dysphagia. Its effects may not last long and require repeated administration. Evidence for long-term safety is limited.
- Other alternatives with limited evidence of efficacy include various antimuscarinic drugs, such as amitriptyline, atropine (eye drops administered sublingually), benzatropine (not available in the UK), trihexyphenidyl/benzhexol, and ipratropium bromide (nasal spray administered sublingually).

- Case reports of modafinil and piracetam, prescribed for alternative indications, describe resolution of sialorrhoea in children. A combination of ranitidine plus cisapride (latter not available in the UK) was found to be ineffective. A small study reported significant improvement in drooling in 7 patients with Parkinson's disease with transdermal rotigotine.

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.
- Treatments intended to 'thin' secretions (e.g. mucolytics) have not been considered in this Q&A.
- This Q&A has not addressed the management of drug-induced hypersalivation.

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Search strategy:

Medline (via Ovid Online): exp *SIALORRHEA/dt
Embase (via Ovid Online): exp HYPERSALIVATION/dm, dt
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