Hypersalivation – can glycopyrronium be used to treat it?

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Background

A general description of the pharmacological approach to the management of non drug-induced hypersalivation is contained in a separate UKMi Q&A document: Hypersalivation – what drug treatment options are available?

The evidence for any drug treatment for this indication is limited and there are several weaknesses in published studies (see 'Limitations' section below).

In the UK, licensed formulations of glycopyrronium bromide (glycopyrrolate) available are tablets, oral solution, injection, powder for solution for iontophoresis and capsules containing powder for inhalation (1,2). However most of these products are not licensed to treat hypersalivation. Glycopyrronium injections are licensed for pre-operative use to dry secretions, including saliva (1,3). 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" (2).

Glycopyrronium is a synthetic antimuscarinic compound, which is structurally related to atropine (4-6). Its peripheral effects include decreased production of secretions, such as saliva (2,3). As an antisecretory agent, by injection, it is 2 to 5 times more potent than hyoscine hydrobromide (6). Therefore it may be considered when hyoscine has failed, although efficacy would appear to be similar in clinical practice.

It is long acting and has a limited ability to cross the blood-brain barrier (2-5). Central side effects are therefore greatly reduced, which is an advantage over other antimuscarinics which are also used to treat hypersalivation, including hyoscine hydrobromide (4). Glycopyrronium has an extremely variable and incomplete gastrointestinal absorption followed by a late clinical response, but there is some evidence that even low plasma concentrations cause a significant reduction in saliva flow (7,8). Glycopyrronium is slower in onset and produces less tachycardia than atropine or hyoscine (8).

Some of the published research conducted on glycopyrronium for hypersalivation is summarised below.

Answer

Oral Route

Dosage

Oral doses of glycopyrronium recommended for hypersalivation vary. As with other antimuscarinics, gradual adjustment of the dose, up or down, according to the patient's clinical response and adverse effects is recommended (2,9). Tolerance to treatment may develop, necessitating an increase in dosage (9,10).

Detailed dosing recommendations for Sialanar are provided in the Summary of Product Characteristics (2). The licensed dose is based on the child's body weight, starting at approximately 12.8 micrograms/kg three times per day and increasing every 7 days to a maximum individual dose of 64 micrograms/kg or 6 ml (1.9 mg) three times a day, whichever is less.

All other doses for oral glycopyrronium for hypersalivation are unlicensed.
The BNF for Children suggests a dose of 40 - 100 micrograms/kg (maximum 2mg) three to four times daily adjusted according to response for children aged 1 to 18 years (10).

Doses up to 3mg three times daily have been described in some studies of oral glycopyrronium for drooling in children with various neurological disorders (11-13).

For adults, to treat drooling in palliative care settings, a starting dose of 200 micrograms every 8 hours, increased progressively every 2 to 3 days if necessary to 1mg (2mg maximum) every 8 hours, has been suggested (6).

Use of glycopyrronium oral solution **sublingually** has also been described for 'death rattle' in palliative care patients, to avoid the need for injections, at a dose of 100 micrograms every 6 hours when required (6). There do not appear to be any published studies documenting use of glycopyrronium by this route.

A review of drugs used for treating sialorrhoea in Amyotrophic Lateral Sclerosis (ALS) recommends oral glycopyrronium at a dose of 1 – 2mg three times a day (14).

Efficacy/Safety

Randomised controlled trials (RCTs)

One small double-blind placebo-controlled crossover trial with oral glycopyrronium has been conducted in 23 adults with Parkinson's disease suffering from marked to severe drooling (15). Following a baseline week, patients were randomised to receive glycopyrronium 200 microgram/ml mixture at a dose of 1mg (5ml) three times daily or placebo, with a one week washout period before crossover. Nine patients (39.1%) experienced an improvement in mean drooling symptom scores of 30% or more with glycopyrronium, compared to one patient (4.3%) on placebo (p=0.021). No significant adverse effects were reported.

A prospective double-blind, placebo-controlled, crossover, randomised dose-ranging study of oral glycopyrronium in 39 children (age range 4-19 years) with neurodevelopmental conditions and excessive drooling has been carried out (11). After a 1-week baseline medication-free observation period, patients received either drug or placebo treatment for 8 weeks followed by a 2 week washout and observation period before crossover. Two dosage regimens were used according to the weight category of the child. Those weighing less than 30kg were started at 600 micrograms three times a day and this was increased at weekly intervals to 1.2mg, then 1.8mg, then 2.4mg three times a day. For children over 30kg, the initial dose was 1.2mg three times a day and this was increased at weekly intervals to 1.8mg, then 2.4mg, then 3mg three times a day. Medication was given three times a day, although 4 children received twice daily doses at parental request. The dose of glycopyrronium was increased weekly for 4 weeks to a maximum dose, which was then continued for an additional 4 weeks, unless adverse effects occurred or desired dryness was achieved. 27 (69%) children completed the study and they all demonstrated improvement in drooling. The mean highest tolerated dose was 2.5mg (range 1.2mg – 3mg) which was given three times daily to most participants. Of 36 patients taking glycopyrronium, 25 (69%) experienced side effects. Of the 12 children who did not complete the study, 8 withdrew because of adverse effects, 1 of these while receiving placebo. The authors suggest that individual doses of glycopyrronium should be increased stepwise at intervals no more frequently than once a week.

A randomised placebo-controlled trial investigated the efficacy of glycopyrronium oral solution (1mg/5ml) in 36 patients aged 3-16 with cerebral palsy, mental retardation, or another neurologic condition associated with problem drooling (12). Data from this trial were used to demonstrate efficacy for Sialanar (2). Patients were randomised to receive matching placebo or glycopyrronium 20 microgram/kg three times a day titrated over 4 weeks to a maximum dose of 100 microgram/kg or 1.5 - 3mg per dose (based on weight) three times a day, whichever was less, and remained on that dose for a further 4 weeks. Doses were administered at least one hour before or two hours after meals. The mean daily dose of glycopyrronium was 150 microgram/kg. At week 8, 14 of 19 patients (73.7%) in the glycopyrronium group and 3 of 17 (17.6%) in the placebo group showed at least a 3-point improvement in the modified Teacher's Drooling Scale (mTDS) score (p=0.0011). The most common adverse reactions were dry mouth, vomiting, nasal congestion and constipation. One patient in each treatment group withdrew from the study due to adverse effects.

The National Institute for Health and Care Excellence (NICE) have considered the evidence from the above trials in a review of oral glycopyrronium in the treatment of hypersalivation, and more recently in a review of Sialanar oral solution (16,17). These reviews draw attention to the limited clinical trial evidence, particularly in adults, and the lack of long-term efficacy and safety data, and suggest that further, large RCTs are required. In the review of Sialanar, the reviewers highlight that, as all trials are versus placebo, it is not possible to compare the effectiveness of glycopyrronium with other treatments for severe

sialorrhoea, and recommend the effectiveness should be balanced against the adverse effects associated with treatment (17).

Non-comparative studies

In a non-comparative study of no fixed duration, 40 patients (age range 4-27 years) with cerebral palsy and related neuro-developmental disabilities with severe or profuse drooling were prescribed oral glycopyrronium, starting at a dose of 500 micrograms once or twice daily (5). Patient responses and side effects were initially monitored subjectively by telephone every 5 to 10 days to establish the effective dose and to monitor benefits and side effects. 36 patients (90%) had reduced drooling in response to treatment. Overall, 12 (30%) of the 40 patients discontinued treatment: 9 because of unacceptable side effects (including 2 with allergic reactions), 2 because of lack of benefit and 1 because of personal preference. 70% of the patients have continued to receive long-term treatment, with follow-up ranging from 8 months to 4 years. The final effective medication doses ranged from 10 – 820 microgram/kg/day (median was 90 microgram/kg/day) with dosing schedules ranging from 1 to 5 times each day (twice daily was most common).

In another non-comparative study, 24 children and young adults (age range 3-23 years) with disabilities and moderate to profuse drooling were treated with oral glycopyrronium (13). The dose of glycopyrronium was 40-100 microgram/kg/day with a maximum of 175 microgram/kg/day, starting with the lower dose and increasing it until a significant decrease in, or cessation of, drooling occurred. The dose was given as a single daily dose in the morning. Duration of therapy lasted between 5 weeks and 28 months and after the trial parents were asked to complete a questionnaire to assess the effect of the glycopyrronium. 22 questionnaires were returned and the majority of patients showed improvements in both the severity and frequency of drooling while taking glycopyrronium. There were 8 reports of known antimuscarinic-type adverse effects, which did not lead to discontinuation of therapy.

A subsequent 24-week open-label study investigated the safety and efficacy of glycopyrronium 1mg/5ml oral solution in 137 patients aged 3-18 years with cerebral palsy, mental retardation, or any other neurologic impairment or condition with chronic drooling (18). After a washout, screening period and 2-day baseline period, patients received 20 microgram/kg glycopyrronium three times daily, titrated by 20 microgram/kg every 5-7 days for 4 weeks to an optimal dose or a maximum dose of 100 microgram/kg (maximum dose 3mg three times a day). The mean daily glycopyrronium dose was 150 microgram/kg. The most commonly reported adverse effects included constipation, vomiting, diarrhoea and pyrexia and four serious treatment-related adverse events were observed (nystagmus, oesophageal candidiasis, dehydration and gastrointestinal motility disorder). Of the 34 patients who did not complete the study, 14 withdrew due to adverse effects. At 24 weeks, 52.3% (95% confidence interval 43.7 to 60.9) of patients had an at least three-point decrease in mTDS from baseline and were classified as responders. 15% of patients no longer drooled.

Case reports

One case study assessed the effect of oral glycopyrronium tablets on drooling in a 51-year-old man with cerebral palsy (19). After establishing a 2-week baseline without the administration of tablets, the number of daily 1mg glycopyrronium tablets was increased weekly from one to four tablets (given in divided doses) and then reduced to no tablets over a further 9 weeks. This study found that for this patient glycopyrronium at a dose of 3mg-4mg daily (in divided doses) was helpful in reducing the drooling to an acceptable level as judged by caregivers and unwanted side effects were not experienced. Profuse drooling was experienced on withdrawal of the drug although it is not known whether this was coincidental or caused by the withdrawal of the glycopyrronium. The authors conclude that for this patient and for shorter periods, a controlled dose of glycopyrronium tablets may safely be used after medical assessment.

One case report describes the administration of glycopyrronium oral solution 600 micrograms -1mg three times a day via a percutaneous gastrostomy (PEG) tube for the management of drooling in an 84-year-old woman (7). She had undergone numerous operations for cystic adenocarcinoma of the submandibular salivary gland. She remained on enteral glycopyrronium for 6 months with no apparent ill effects.

Another case report describes a 59-year-old patient with tongue cancer who was successfully treated for drooling with oral glycopyrronium 400 micrograms three times daily (8). After one month she was still experiencing beneficial effects and no side effects from treatment.

Other studies
In one retrospective survey, questionnaires were sent to 54 parents/carers of children with cerebral palsy (9 months to 20 years) for whom medication had been prescribed for the treatment of either excessive drooling or tracheal secretions (76% response rate) (4). Of the 41 patients, 37 had been or were being treated with glycopyrronium and the mean dose was 51 micrograms/kg/dose with a range of 10 to 140 micrograms/kg/dose; this was most commonly given three times a day (route of administration not specified). 46% reported that their children did experience side effects while taking glycopyrronium. 30% (n=11) of the patients had discontinued the medication anywhere from 1 to 20 months after starting treatment, one because of ineffectiveness and ten because of side effects. Of the original 41 respondents, 37 of 39 patients who completed the subjective rating scale section of the questionnaire reported significant improvement in drooling with anticholinergic medication and two reported no change.

No efficacy data comparing the different oral formulations of glycopyrronium have been published (20).

Parenteral route

Dosage
The BNF for Children recommends the following (unlicensed) doses of subcutaneous, intramuscular or intravenous glycopyrronium for the treatment of hypersalivation in children (10):

Child age	SC/IM/IV injection	SC infusion
1 month – 12 years	4 – 10 micrograms/kg (max 200 micrograms) four times/day when required	12 – 40 micrograms/kg/24 hours (max 1.2 mg)
12 years – 18 years	200 micrograms every 4 hours when required	0.6 - 1.2 mg/24 hours

Although hypersalivation is not specifically described, the same dose of parenteral glycopyrronium as for children aged 12 to 18 years (see above) is generally recommended for drying secretions in palliative care settings in adults (1,3,6).

Case reports
A case report describes administration of an overnight subcutaneous infusion of 600 micrograms glycopyrronium over 12 hours via a syringe driver to a 51-year-old woman with bulbar onset amyotrophic lateral sclerosis and treatment resistant hypersalivation (21). This improved her symptoms and facilitated the use of overnight non-invasive ventilation (NIV) for 6-8 hours. Her symptoms subsequently deteriorated but improved with a dose increase to 1000 micrograms (1mg) subcutaneous glycopyrronium over 12 hours enabling her to tolerate 4 to 6 hours of NIV without untoward effects.

One case report describes the administration of the injection solution by **nebuliser** to a 51-year-old woman with motor neurone disease and drooling secondary to dysphagia, at a dose of 400 micrograms twice daily (22). The drug was well tolerated and the patient noticed an improvement in her symptoms within an hour of administration. This was continued for 2 months until she developed a rash around her mouth necessitating discontinuation of treatment. She subsequently received subcutaneous glycopyrronium 100 micrograms in the morning and 200 micrograms at night, which continued to be effective until she died one year later.

Summary

- Glycopyrronium is available in the UK in various formulations, although most are not licensed for the treatment of hypersalivation. One brand of glycopyrronium oral solution (Sialanar) is licensed for the treatment of severe sialorrhoea in children (aged 3 years and over) with chronic neurological disorders.
- Benefits of using glycopyrronium include its long duration of action and it is less likely to cause central or cardiac adverse effects. By injection it is more potent than hyoscine hydrobromide so may be considered when hyoscine has failed.
- Although oral absorption is poor, most of the published evidence of efficacy is for administration by the oral route, particularly in children and young adults with neurodevelopmental disabilities, where it has been used with some success in relatively small studies. Parenteral use, mainly by subcutaneous injections or infusion, has also been described for reducing excessive secretions,

including saliva, in palliative care. A case report also describes nebulised use of glycopyrronium injection solution.

- Recommended doses vary, and should be titrated carefully according to the patient's response and tolerance. As with other antimuscarinics, the side effects may limit chronic use of glycopyrronium.
- No efficacy data exist to compare different formulations of glycopyrronium or to compare its efficacy to other antimuscarinics used for treatment of hypersalivation.
- Data are also lacking for long-term efficacy and safety.

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.

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