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Effectiveness and safety of glycopyrrolate for hyperhidrosis

Ana Isabel Gago Sánchez, DPharm; Roi Arias Rico, DPharm; Virginia Torres Degayon, DPharm; Raul Albornoz López, DPharm

Abstract
Objective: To review the efficacy and incidence of adverse effects of glycopyrrolate (glycopyrronium bromide) solutions for treatment of primary focal hyperhidrosis in patients who were refractory to other treatments.
Methods: This was a prospective observational study in patients with an essential hyperhidrosis. Study participants were recruited from a dermatology unit in a third-level hospital in Spain from July 2007 to January 2008. The pharmacy department prepared glycopyrrolate aqueous solutions of different strengths (0.5%, 1% and 2%) according to prescribed dosing. The solution of glycopyrrolate was applied topically once or twice daily to the affected areas. Pharmacists prospectively recorded the patient's data on a structured data collection sheet. The effectiveness of the solutions was evaluated following proposed improvement criteria: very bad (grade 0), bad (grade 1), medium (grade 2), good (grade 3) and very good (grade 4).
Results: Twenty-five subjects (aged 39 ± 10 years) were treated with topical glycopyrrolate. Three patients were excluded because the solutions were only applied for three weeks or less, and one patient because of communication difficulty. Thus a total of 21 patients were analysed. After applying topical glycopyrrolate, the subjective effects were: very good in three patients (14.28%), good in 12 patients (57.14%), medium in four patients (19.05%), bad in one patient (4.76%) and very bad in one patient (4.76%).
Conclusion: Topical glycopyrrolate is a safe and effective treatment for focal hyperhidrosis without major adverse effects in patients who were refractory to other treatments, e.g. botulinum toxin type A, aluminium chloride and sympathectomy.

Keywords
Effectiveness, glycopyrrolate, hyperhidrosis, safety

Introduction
The socially embarrassing disorder of excessive sweating, or hyperhidrosis, and its treatment options are gaining widespread attention. Hyperhidrosis remains a relatively unknown disorder to the general public and healthcare professionals. The condition results in occupational, psychological and physical impairment, and potential social stigmatisation. Excessive sweating can be a substantial burden afflicting individuals, interfering with daily activities and causing social embarrassment. Besides affecting quality of life, hyperhidrosis predisposes its victims to a host of dermatological disorders [1].

The condition that results when the pseudomotor system (which controls sweat output) functions excessively in isolation with no apparent cause is termed primary or essential hyperhidrosis. Primary hyperhidrosis is classified as focal or generalised on the basis of the stimulus and site of neuromodulation.

Treatment options lie on a continuum based on the severity of hyperhidrosis and the risks and benefits of therapy. In general, treatments for hyperhidrosis can be divided into those which affect the sweat gland directly and those which modify its innervation. Topical agents, including aluminium chloride, formaldehyde, glutaraldehyde and potassium permanganate, produce only a short-term effect. Oral anticholinergics have been tried but adverse effects such as urinary retention limit their efficacy. Endoscopic thoracic sympathectomy may be used for severe cases of palmar-plantar and palmar-axillary hyperhidrosis. However, this can result in significant adverse effects such as compensatory hyperhidrosis and cardiac sympathetic denervation. Iontophoresis is available for palmar-plantar and axillary hyperhidrosis. Botulinum toxin type A is effective for isolated hyperhidrosis not responsive to topical application of aluminium chloride but this requires subcutaneous injections and the high cost of treatment is a limiting factor. No sole therapy of choice has emerged for craniofacial sweating [2].

Contact for correspondence:
Ana Isabel Gago Sánchez, DPharm
Pharmacy Department
Reina Sofía University Hospital
Menendez Pidal Avenue s/n
ES-14004 Córdoba, Spain
Tel: +34 957 010107
anagasa91@hotmail.com

Several studies have shown that the topical anticholinergic, glycopyrrolate, is most effective in the management of gustatory hyperhidrosis [3, 4].

Glycopyrrolate is a quaternary amine that acts as an antimuscarinic agent. On a molar basis, glycopyrrolate is about five to six times as potent as atropine [5]. It does not cross the blood-brain barrier and it penetrates biological membranes slowly, and therefore leads to very few side effects when given topically [6].

The aim of the study was to review the efficacy and incidence of adverse effects of glycopyrrolate solutions for treatment of primary focal hyperhidrosis in patients who were refractory to other treatments.

Methods

Patients

Study participants were patients recruited from a dermatology unit in a third-level hospital in Spain from July 2007 to January 2008.

They were initially considered as suitable participants if they met the following inclusion criteria:

1. Diagnosis of essential hyperhidrosis confirmed by the dermatology unit.
2. Hyperhidrosis was refractory to other treatments.
3. Glycopyrrolate solutions were prescribed.

Patients were excluded from the study if their treatment with glycopyrrolate solutions was disrupted or if they were having other treatments in combination with glycopyrrolate.

Procedure

This was a prospective observational study. Patients were invited to receive treatment with aqueous solutions of glycopyrrolate if they had a clear history of hyperhidrosis. All subjects were given a full explanation on how to apply the topical glycopyrrolate and the possible complications of treatment. Solutions of glycopyrrolate of different strengths were applied topically once or twice daily to the affected areas, avoiding contact with the eyes, nose and mouth; the solutions could not be applied to the scalp; and the areas could not be washed for two hours after each application. Signed written informed consent was obtained from all subjects.

Glycopyrrolate was made up into an aqueous solution. Formulations of different strengths (0.5%, 1% and 2%) were prepared by the pharmacy department according to the doctor's prescription. As part of the study, pharmacists prospectively recorded the patient's data on a structured data collection sheet (see Figure 1) every month as part of routine clinical practice. Within one month after the first application, adverse effects and subjective evaluation of efficacy were recorded. Those who chose to participate responded via telephone directly to the study investigators about the effectiveness of treatment and any side effects they noticed.

Figure 1: Glycopyrrolate data collecting sheet

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QUESTIONNAIRE TREATMENT WITH GLYCOPYRROLATE

Questionnaire n$_o$ ☐ Interviewer code ☐ Date ☐

Patient data :

Surname ☐ Name ☐

Age ☐ Sex : ☐ Male or ☐ Female

Telephone number ☐

Medical History :

-
-
-

Areas mainly affected by Hiperhidrosis :

-
-

Previous Treatment with Botulinum Toxin type A : YES ☐ NO ☐

Previous Thoracic Sympathectomy YES ☐ NO ☐

Treatment with GLYCOPYRROLATE :

- Strengths : ☐ 0,5 % ☐ 1 % ☐ 2 %
- Application :
- Starting : ☐ Months
- Quantify Effectiveness : 1 2 3 4 5

  (1 = Very Bad ; 2 = Bad ; 3 = Medium ; 4 = Good ; 5 = Very Good)
- Adverse Drug Events:

Measurements

A sweat challenge was performed at baseline and at the end of each treatment period. There are no well-established simple methods to quantify effectiveness and so it was evaluated according to the proposed improvement criteria: very bad (grade 0), bad (grade 1), medium (grade 2), good (grade 3) and very good (grade 4). In addition, the pharmacists carrying out the study recorded the frequency and existence of noticeable adverse effects, such as headache,

drowsiness, dizziness, confusion, blurred vision, rapid heartbeat, dry mouth, nausea, vomiting, rash, difficult urination, difficulty in focusing the eyes, and severe diarrhoea.

Results

Twenty-five subjects (n = 25, aged 39 ± 10 years) were treated with topical glycopyrrolate. Three patients were excluded because the glycopyrrolate treatment lasted three weeks or less and one patient because of communication difficulty. No patient was excluded because of disrupted or concomitant treatment. Thus a total of 21 patients were analysed.

The background clinical data are shown in Table 1, and demonstrate that the areas mainly affected by hyperhidrosis were palmar-plantar and axillary.

The recruited patients had not responded to other therapies, which included antiperspirants, botulinum toxin and sympathetic denervation. Table 2 shows these data. Antiperspirants, most commonly aluminium chloride, had been applied to 12 patients previously. After relapse, botulinum toxin was used in five patients (n = 5) and sympathetic denervation was reserved for more severe cases (n = 4).

Glycopyrrolate solutions of different strengths were used. Specifically, 0.5% solutions were used by seven patients, 1% solutions were used by 11 patients and 2% solutions were used by three patients.

After applying topical glycopyrrolate, the subjective effects were: very good in three patients (14.28%), good in 12 patients (57.14%), medium in four patients (19.05%), bad in one patient (4.76%) and very bad in one patient (4.76%). Figure 2 shows the evaluation of effectiveness of treatment according to patients' opinions.

The drug was well tolerated, and apart from the one patient with a local reaction, no other adverse effects were reported. Nineteen of the 21 patients who completed the trial wished to continue using the topical drug. The other three subjects did not feel the treatment was effective.

Table 1: Sites affected by hyperhidrosis

Sites	Number of patients (n)
Palmar-plantar	10
Axillary	6
Facial	4
Abdomen	1
Total	**21**

Table 2: Treatments for hyperhidrosis

Treatment	Number of patients (n)
Antiperspirants	12
Botulinum toxin	5
Sympathetic denervation	4
Total	**21**

Discussion

Treatment of primary hyperhidrosis remains challenging. Although it is often embarrassing and troublesome, no simple and acceptable treatment has previously been shown to be effective. The location of the ailment can dictate the treatment attempted.

Topical agents used include aluminium chloride, potassium permanganate, glutaraldehyde and formaldehyde, but their effects are only short term.

The oral anticholinergics propantheline and oxybutynin, as well as the centrally acting alpha-2 blocker, clonidine, have all been reported to be effective [3, 4, 7], but their use can be limited by side effects. Other oral anticholinergic agents have also been used, but these have many undesirable systemic side effects such as blurred vision, tachycardia and urinary retention.

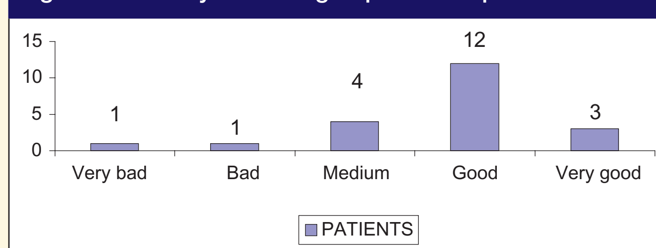
Antiperspirants produce discomfort associated with feeling as if a "film" was covering the face as well as limited duration of action and a total loss of efficacy after washing the face.

Tranquillisers such as diazepam, as well as central-acting alpha-adrenergic agonists such as clonidine, have been used but are limited by their neuro-cardiovascular side effects.

Beta-blockers have been used to treat sweating associated with anxiety; their efficacy in primary hyperhidrosis lacks support from the literature.

Surgical excision of affected areas has been useful in some cases [8], but is generally limited to the axillae.

Figure 2: Efficacy according to patients' opinions



Although endoscopic sympathectomy has a success rate of 92% to 99%, the complications are significant and include permanent Horner's syndrome, compensatory hyperhidrosis, gustatory sweating, haemothorax, intercostal neuralgia and cardiac sympathetic denervation [7].

Iontophoresis has been shown to control palmar and plantar sweating successfully via a mechanism thought to be due to plugging of pores in the skin [9].

Finally, subcutaneous botulinum toxin injections have also been recommended as a desirable treatment option for the palms [3], axillae [4] and forehead [10], but they are expensive; the injection is painful and can result in neurological impairment such as a weakened hand grip or weakness of forehead muscles.

Glycopyrrolate is not manufactured as a cream, but is available as a powder to be made into a solution for its licensed use in hyperhidrosis. Aqueous solutions of different strengths were therefore made locally from the powder.

The first clinical trial, by Hays, of topical glycopyrrolate in patients with Frey's syndrome involved more than 1,000 individual applications with only seven cases of minor side effects [11]. Hays had already described the successful use of topical glycopyrrolate applied to the face for the treatment of Frey's syndrome and had shown that the effect of a single application could last for several days. Two subsequent clinical trials using topical glycopyrrolate [12, 13], showed no side effects associated with its use, with the exception of one patient who had a local eczematous reaction. Shaw et al. demonstrated that topically applied glycopyrrolate is most effective at reducing both the severity and frequency of diabetic gustatory hyperhidrosis [14].

Three individual case reports [15-17], showed that topical glycopyrrolate is well tolerated when used on the face, and there were no reported side effects [8]. Evidence from other studies, such as that of Hurley and Shelley, suggests that by increasing the strength of a solution to 1% or 2%, the response could be safely improved in some subjects [8].

This study shows a few cases reflecting this, and an increased dose improved the condition. There was no simple and reliable method of quantitative measurement of hyperhidrosis improvement, so subjective evaluation of the patients' opinions was used. Patients could have been biased towards filling in only those more serious reactions and could, retrospectively, mistakenly scored minor reactions as absence of sweating. However, in this group of carefully selected and well-motivated patients, we believe that this would have been only a minor effect.

In summary, topical glycopyrrolate is an acceptable, safe and effective treatment for focal hyperhidrosis. It can be used either on a regular basis or, as some patients expressed a preference, before social events. The results from the current study demonstrate major subjective improvement without adverse effects.

Conclusion

Topical glycopyrrolate is a safe and effective treatment for focal hyperhidrosis without major adverse effects in patients who were refractory to other treatments such as botulinum toxin type A, aluminium chloride and sympathectomy.

We consider that for those suffering hyperhidrosis, their lives have been dramatically transformed by the topical use of a glycopyrrolate solution, which is a cheap and effective treatment.

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