Review Article

Topical and systemic anticholinergic for treating hyperhidrosis

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Abstract: Topical and systemic anticholinergic drugs continue to be useful medications in the management of Hyperhidrosis and accordingly to the International Hyperhidrosis Society (IHHS) algorithm for treatment, they are the initial therapeutic option for all primary forms of excessive sweating. In this article, several topical and systemic agents will be reviewed and information about efficacy, safety and side effects will be discussed.

Keywords: Topical anticholinergic drugs; systemic anticholinergic drugs; hyperhidrosis

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Topical agents

Aluminium salts

The most common active ingredient found in antiperspirants, being used for more than 80 years (most clinical trials were performed more than 20 years ago), they are inexpensive, easily available and safe. Usually the first line therapy for axillary hyperhidrosis, this group includes *aluminium chloride hexahydrate*, very effective and most common agent used in prescribed antiperspirants, *aluminium* chloride, a partially neutralized form used in cosmetic preparations, and *aluminum zirconium tetrachlorohydrex*, found in newer products that claim improvement in sweat reduction with less skin irritation (1,2).

When applied to the skin, perspiration dissolves the aluminium salts that precipitates with mucopolyssacarides, forming superficial plugs, that cause mechanical obstruction to the distal eccrine sweat gland duct, blocking the sweat release (3). Plugs usually remains in place for around 24 hours and are washed away over time, when the sweat output returns (1,3) Therefore, reapplication is required for maintenance of the antiperspirant effect. Long-term blockage may lead to functional and structural degeneration of the eccrine secretory cells. This may be an explanation for long term hyperhidrosis severity reduction over time (4).

Most Clinical strength preparations contain Aluminium Chloride hexahydrate that are effective for mild to moderate excessive sweat cases. They are available in roll on, gels, wipes or soft solid preparations, and should be applied to dry skin at nighttime (1,3). Aerosol formulations are particularly useful for hands and feet. Damage to fabrics can occur resulting in stain in clothes that should be warned to patients.

Effectiveness of 10% preparations is inferior to 15–20% formulations which demonstrated similar results in clinical trials (2,5,6). They are frequently used for axillary hyperhidrosis, where the most efficacy is perceived but may also be indicated for other areas of excessive sweat like palms, soles, submammary, groins, back and craniofacial regions (7).

The most common side effect is mild and transient skin irritation, found in about one third of patients after starting use (2). Skin irritation is a cause of discontinuation of therapy and should be reduced or prevented by guidance of no application in moist skin (it is advisable to dry the area before use), waiting 24 to 48 hours after shaving, lowering

concentration, prolonging intervals, or prescribing topical mild corticosteroids, like hydrocortisone (1,3-7).

Some concerns had been raised regarding the relationship between long term application of aluminium salts and possible risk of breast cancer or Alzheimer disease, especially on the internet (1,2). A recent systematic review concluded that "there is no clear evidence to show use of Al-containing underarm antiperspirants or cosmetics increases the risk of Alzheimer Disease or breast cancer. Metallic Al, its oxides, and common Al salts have not been shown to be either genotoxic or carcinogenic" (8).

Glycopyrronium tosylate

Glycopyrronium tosylate (Qbrexza™, Dermira, Inc.) is a topical anticholinergic that was approved by FDA (US Food and Drug Administration) in June 2018 for primary axillary hyperhidrosis patients (3,9).

A Phase III randomized, double-blind, controlled pilot study showed that this substance has a clinically significant benefit in considerably reducing sweating severity at four weeks of use, as well as reducing the impact of axillary hyperhidrosis on patients' daily lives (10).

The 2.4% glycopyrronium tosylate formulation should be applied, once a day, on clean and dry axillary area using pre-moistened wipes, and the area must not be washed for up to 4 hours from application. This mode of application has been usually well tolerated, with most of the side effects being mild to moderate and transient, rarely leading to discontinuation. Its topical use aims to minimize rather than eliminate the systemic anticholinergic effects, as patients may absorb the drug and show events such as dry mouth and urinary hesitation. In addition, patients not washing their hands following the application might inadvertently transfer the drug to other body areas, such as eyes, and cause unilateral ophthalmological events such as mydriasis and blurred vision (11). The side effects mainly occurred on the first week of treatment and decreased subsequently (12).

Pediatric patients also showed good responses to this treatment, with improved quality of life and a favorable safety profile, similar to those found in the older population. With regard to side effects, the mydriasis found in the pediatric subgroup was bilateral, unlike the over-9-year-old subgroup, where it is usually unilateral. Although difficult to determine, due to the small number of events, this can be attributed to the fact that pediatric patients are more prone to touch their eyes following application (13).

Oxybutynin

Oxybutynin is a small tertiary amine molecule (393.95 kDa), with a half-life of 62–84 hours when applied topically, suggesting that the treatment may have a longer duration of action than the existing topical therapies, such as aluminum chloride. The 3% oxybutynin topical gel applied on the axillary region is already being used for the treatment of overactive bladder, suggesting that it has a remote effect on untreated sites (14).

A pilot clinical trial showed that the daily application of 3% oxybutynin gel on the axillary region for 4 weeks reduced axillary and primary palmoplantar hyperhidrosis symptoms, with significant reduction of HDSS (Hyperhidrosis Disease Severity scale) scores and improvement of DLQI (Dermatology Life Quality Index) scores in all patients completing the study. The onset of treatment effect was evidenced at week 1, and this response was maintained at week 4 in all patients and at all sites. Local side effects, such as irritation, were reported; however, they did not affect compliance with the treatment protocol and showed spontaneous resolution (14).

Systemic side effects were rarely observed. This is because the transdermal application avoids the hepatic and gastrointestinal first-pass metabolism and reduces the formation of N-desethyloxybutynin (N-DEO), a pharmacologically active metabolite that results in a higher incidence of anticholinergic side effects, such as xerostomia. However, there may be some passive diffusion of the gel through the stratum corneum and a small systemic absorption, resulting in mild, limited conditions of dry mouth, blurred vision, constipation, difficulty in urination, and cognitive and memory deficiencies (14).

In the pilot study, a single patient experienced a severe adverse effect (pyelonephritis) and was withdrawn. Thus, this drug should be used with caution in patients with a history of urinary retention or recurrent urinary tract infections, once oxybutynin may cause or exacerbate urinary retention (14).

Discontinuation of the 3% oxybutynin gel by the manufacturer encouraged the conduction of a new study with the 10% formulation of the medication (Gelnique®, Actavis Co. Ontario, Canada), which is still available in the market. In this second study, the gel was applied either on the right or left axilla, palms, and soles twice a day and showed a significant reduction in the HDSS and DLQI scores as well (15). Despite the drug having been applied in only one area, the control regions also showed

improvement. The authors attributed this finding to the passive diffusion of the gel across the stratum corneum and its systemic absorption, and concluded that topical oxybutynin is effective and safe but suggest new studies to measure the extent of drug absorption and to optimize dosage (15).

Systemic agents

Oral anticholinergic agents have been used in hyperhidrosis therapy, especially when large or multiple areas are affected (16). They can be used concomitantly with other topical therapies, such as iontophoresis and botulinum toxin, but they have to be considered with caution in athletes or outdoor workers who may become overheated or with risk of hyperthermia, when unable to cool their bodies through sweat evaporation (16).

They act as competitive inhibitors of acetylcholine at the muscarinic receptors present all over the central and autonomic nervous systems (2,16). However, besides its effects on the eccrine glands, they also act at nicotinic and muscarinic receptors of other organs like urinary bladder, eyes, gut, heart and salivary glands, leading to the unwanted but expected systemic side effects, like eye and dry mouth, urinary retention, palpitation and obstipation (17).

Oral anticholinergic drugs used to treat excessive sweating are from two main groups: non charged tertiary amines like bornaprine and oxybutynin that crossing the blood-brain barrier may induce additional central nervous system effects like blurred vision (secondary to transient loss of accommodation), confusion, dizziness, somnolence and sedation. For the other hand, the other group of anticholinergic medications, with quaternary ammonium compound like metanteline, propantheline or glycopyrronium bromides, cannot pass the blood-brain barrier because of their polarity and lacks other central nervous systems effects (2).

Oxybutynin

Oxybutynin (Oxytrol®, Ditropan XL®, Retemic®) acts by lessening the stimulation of eccrine sweating glands, once primary hyperhidrosis patients have higher expression of acetylcholine receptors and alpha-7 nicotinic receptors at sympathetic ganglia (18,19). This drug was first associated with the treatment of hyperhidrosis in 1988 (20,21). Since then, numerous studies (including clinical trials) supported its efficacy and safety in the treatment of hyperhidrosis, in multiple anatomic areas both in children and adults (22,23).

A 2016 systematic review on oral cholinergic medications for primary hyperhidrosis identified 16 studies with oxybutynin out of 23 (22). Oxybutynin therapy improved symptoms in an average of 76.2% (range, 60–97%) patients and improved QOL in 75.6% (range, 57.6–100%) of subjects.

Adverse effects were frequent, although mild and tolerable, during treatment and were dose-related (the higher the dose, the higher the incidence) (22). To minimize them, some authors propose to increase doses progressively, up to no more than 7.5–10 mg daily doses. The initial dose suggested for adults and children weighing 40 kg or heavier is 2.5 mg at bedtime. After one week, it may be increased to 2.5 mg twice a day, and after 3–5 weeks, to 5 mg twice a day. Higher doses than 15 mg a day show an increased risk of xerostomia (the most commonly seen side effect), constipation, and urinary retention; therefore, this should be avoided. Other less common effects include visual disturbances, nausea, constipation, gastro-esophageal reflux, headache, weakness, asthenia, flush, and difficulty in urination. Oral oxybutynin shows best results for plantar hyperhidrosis, followed by palmar and axillary hyperhidrosis (2).

In order to combat side effects, like dry mouth, a new fixed-dose medication (THVD-102), has been developed combining oxybutynin, a muscarinic antagonist, and pilocarpine, a muscarinic agonist. The pilocarpine dose level and release profile were optimized to correct salivary flow impaired by oxybutynin but not interfering in its muscarinic antagonist effect upon the sweat glands (24). A recent trial, with 19 subjects, found no statistically significant differences between THVD-102 and oxybutynin in Primary Focal Hyperihidrosis treatment efficacy, but THVD-102 was associated with significantly reduced dry mouth compared to oxybutynin and the medication may be an option for future use (24).

Glycopyrrolate

A recent systemic review, found 52 articles for glycopyrrolate and hyperhidrosis, but a lack of randomized controlled trials (22). Glycopyrrolate (Robinul® Casper Pharma LLC, New Jersey, USA; and Cuvposa®, Pediapharm Inc. Quebec, Canada) is the most commonly used oral anticholinergic drug to treat hyperhidrosis. Its dosage is variable, usually initiating with 2 mg twice a day with progressive increments of 1 mg a day at 2-week intervals, and it should not exceed 10 mg divided into two doses. Its efficacy and side effects

are generally dose-dependent (16).

The most commonly seen side effect is xerostomia, predominantly of mild intensity or tolerable. Other less commonly adverse effects include gastrointestinal disorders, headache, rash, mental state shifts, anxiety, tachycardia, increased urinary frequency, ocular and nasal dryness (2).

Methantheline bromide

Two randomized controlled trials were performed with this drug in Germany, including 307 patients, showing good evidence of efficacy and safety (25,26).

Methantheline bromide (Vagatin®, Riemser Pharma GmbH, Hannover, Germany) is a quaternary ammonium, used at doses of up to 150 mg/day, with anticholinergic effects and higher efficacy on axillary than palmar sweating. It shows good tolerability with occasional dry mouth and eyes and impaired visual accommodation (16). Side effects seems to be related to dose: lower incidence of xerostomia were observed with dose reduction (2).

Propantheline bromide

Propantheline bromide (Pro-Banthine®, Haupt Pharma Wulfing GmbH, Gronau, Germany) is an agent structurally similar to methantheline, and it shows potential efficacy in the treatment of profuse sweating associated with spinal cord injuries. It acts by competitively inhibiting the post-ganglionic action of acetylcholine, but it does not cross the blood-brain barrier, and therefore, its adverse effects on central nervous system must be minimal at the usual clinical dosages (27).

There are no recent experimental or observational studies evaluating the efficacy and safety of oral propantheline bromide in primary hyperhidrosis, only few case reports. The initial dose for the treatment of hyperhidrosis cited in the literature is 15 mg/day, with escalations up to 15 mg three times a day being possible (2).

Bornaprine

Bornaprine (Sormodren®, Mylan Healthcare GmbH, Hannover, Germany) is a synthetic anticholinergic drug that antagonizes the M1 e M2 muscarinic receptors of acetylcholine, in a non-selective manner. It is often used in the treatment of Parkinson's disease. However, in the literature, its use for the treatment of hyperhidrosis is limited. The initial dose is suggested to be 2 mg a day with dose increments up to 8 mg twice a day, with no side effects being mentioned (28,29).

A 2008 study demonstrated that bornaprine treatment for 4 months was effective and safe for hyperhidrosis secondary to traumatic spinal cord injury. The beneficial effects were maintained one month after therapy discontinuation (28).

Others

Anecdotal reports have been found with several drugs, like beta blockers, alfa adrenergic agonists and benzodiazepines indicated to hyperhidrosis related to anxiety and social phobia. They may be options in selected cases when other therapies had no success.

Conclusions

Topical and oral anticholinergic agents are usually the first line therapeutic option for patients suffering from excessive sweating. They play a beneficial role, improving quality of life of affected subjects, and they are safer and less expensive than interventional therapies. For the other hand, they have limited efficacy and duration, requiring maintenance treatment and side effects that maybe tolerable or not. Development of new drugs, combining medications to minimize side effects may be a hope for the near future.

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