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Use of Systemic Therapies to Manage Focal Hyperhidrosis

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Oral therapies can play an important role in treating hyperhidrosis of all types. Although monotherapy is sometimes useful, combining systemic treatments with more focally-based therapy may provide superior results.

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Abstract

Primary hyperhidrosis (excessive sweating) commonly affects the axillae, palms, soles, scalp, face, and the groin. Patients may have multiple areas involved making localized therapy challenging. Systemic therapy may be necessary and can be used as monotherapy or combined with other hyperhidrosis treatments for optimal outcomes. Systemic therapy can also be used to treat secondary hyperhidrosis and compensatory hyperhidrosis. Patient selection and counseling are key, and monitoring for side effects is required throughout therapy.

Introduction

Hyperhidrosis (HH) is a common disorder, affecting approximately 3% of the US population. It is a disabling condition that significantly impacts quality of life (QOL) and can cause considerable emotional stress. Primary HH presents with focal areas of excess sweating such as the axillae, palms, soles, scalp, face and groin. Although some patients have only one focal area of excessive sweating, it is common for patients to have more than one body site producing excessive amounts of sweat.[1] In addition, patients may present with more generalized forms of HH which are usually secondary in nature. In these cases, treatment or removal of the offending cause can be very beneficial, but may not always be feasible. Compensatory hyperhidrosis following sympathectomy occurs in 50-80% of patients and can affect very large areas such as the chest, abdomen and back.[2] Systemic therapy can be beneficial in all of these patients.

There are no oral agents that have an FDA-approved indication to treat HH and there is a paucity of studies on the use of systemic medications for treating HH.

Treatment Indications

In general, treatment for primary HH should be as specific and focal or localized as possible to insure good response and minimize side effects and interactions with other medications. Topical therapies such as aluminum chloride are usually first line treatment but can be ineffective and produce skin irritation. More focally targeted therapies such as botulinum toxin injections, iontophoresis, or microwave thermolysis are focal treatments that should be considered. However, when these treatments are ineffective, intolerable, or not feasible, systemic therapies may be warranted. In addition, oral medications can be added to the above treatments to enhance therapeutic outcomes. This is especially beneficial when patients have multiple areas of HH. In such

individuals, a multi-pronged approach might be needed with the use of botulinum toxin A injections for the axilla, iontophoresis for the hands and feet, and an oral agent to help manage other areas such as the groin, face, or submammary sweating.

Generalized sweating presents a challenge. If a specific etiology is identified, that agent or cause should be removed. However, it is common that an offending agent can't be removed. Patients with psychiatric disease frequently can't lower or change the medications that are controlling their mental illness. In these instances, other options such as oral medications to treat the HH have to be considered.[3] Some patients will have multiple co-founding factors that can induce or worsen HH, and oral therapy may be very helpful.

There are groups of patients that should be considered very carefully before initiating therapy with oral medications, especially anticholinergics which decrease sweating from the entire body. Athletes and individuals who work or play a lot outdoors may become overheated if they are unable to cool their bodies without sweat evaporation, and may have an increased risk of hyperthermia. Small children or individuals who have difficulty self monitoring their body temperature, mentation, and urine output may not be good candidates for oral anticholinergic agents. Allergies, other medications, or health issues need to be reviewed to avoid interactions or worsening of other diseases or health concerns. As an example, beta blockers are generally not given to patients with psoriasis.

It is important to counsel patients on what therapy is being used, how it works, and what to monitor. It is also critical that patients are counseled on realistic expectations. Most patients can expect an improvement but not complete resolution of their HH symptoms. Patients should be warned that they will most likely still have episodes of excessive sweating, and they may be the first to sweat and even sweat more than their counterparts during activity. Setting a step-wise plan for the patient can be very helpful so they don't discontinue therapy. Improvement in symptoms is usually possible to achieve, but anhidrosis is not, nor is it desirable.

Anticholinergic Agents

Since the sweat glands are innervated by the sympathetic postganglionic nerves and have acetylcholine as the primary neurotransmitter, the use of anticholinergic agents is a logical choice to treat hyperhidrosis.[4] Anticholinergic agents work by competitive inhibition of acetylcholine at the muscarinic receptor. Muscarinic receptors are present throughout the central and autonomic nervous system, accounting for the widespread and varied side effects that can develop.

There are several anticholinergic agents available; however there are differences in the side effect profile. Glycopyrrolate as a quaternary amine, has limited passage across lipid membranes such as the blood-brain barrier. This is in contrast to agents such as atropine or scopolamine, which are tertiary amines and can easily penetrate lipid barriers. This is probably the reason why glycopyrrolate has fewer central nervous system side effects and may have less effect on the heart rate at lower doses.[5] The most common side effect is dry mouth due to inhibition of salivary glands. There are many potential side effects (See Table 1), and concurrent use with other medications with anticholinergic activity such as phenothiazines,

Table 1
Anticholinergic Therapy Side Effects

Gastrointestinal
- Dry Mouth
- Constipation
- Nausea
- Vomiting
- Bloated Feeling
- Loss of Taste

Ocular
- Mydriasis
- Cycloplegia
- Dry or Gritty Eyes
- Blurred Vision
- Photophobia

Respiratory
- Bronchodilation
- Reduced Secretions

Genitourinary
- Urinary Retention
- Slow Voiding
- Urinary hesitancy
- Erectile Dysfunction
- Loss of Libido

Cardiac
- Bradycardia (lower doses)
- Tachycardia (higher doses)
- Arrhythmias
- Palpitations

Central Nervous System
- Headache
- Dizziness
- Insomnia
- Drowsiness
- Mental confusion and/or excitement (usually in elderly)
- Seizures

Skin
- Decreased sweating
- Urticaria
- Pruritus

antiparkinson drugs or tricyclic antidepressants, intensify the antimuscarinic effects and increase side effects. Anticholinergic therapy may be contraindicated in patients with glaucoma, obstructive uropathy, obstructive diseases of the GI tract, paralytic ileus, severe ulcerative colitis, and myasthenia gravis.

Glycopyrrolate

Glycopyrrolate is the authors' most commonly used anticholinergic drug to treat HH. Dosing is variable and is usually started at a dose of 1 mg twice daily. The patient is asked to increase the dose by 1 mg per day at two-week intervals based on the therapeutic response and side effects. Dry mouth is the most common side effect and usually the limiting factor in dosing. If side effects are minimal, management can allow patients to continue their medication. Managing dry mouth could include use of artificial saliva preparations, increasing water intake, keeping candy or mints available, etc., and increased fiber consumption and light exercise can help to improve mild constipation. Over the counter eye drops can improve dry eye symptoms, but many patients will have to discontinue therapy due to intolerable side effects. The side effects of therapy are generally dose-dependent.

Walling published a retrospective review of 45 patients who used glycopyrrolate to treat HH of various body sites. Overall 67% were responders and 33% failed treatment.[6] Of the treatment failures, 40% were nonresponders and the rest had adverse effects requiring medication cessation (xerostomia, GI disturbance, headache, rash, and mental status change). Only one-fourth of these patients used it as monotherapy, while the majority of patients combined therapy with topical aluminum chloride, botulinum toxin, and iontophoresis. These patients most commonly took 1 mg daily and the highest dose that was used was 3 mg BID. Bajaj and Langtry reported on 19 patients treated with glycopyrrolate and found that 80% responded to therapy.[5] The most common dose was 2 mg twice daily or three times daily but one patient took 4 mg BID. Side effects were reported in 80% of the patients and about one-third of their patients had to stop the glycopyrrolate due to side effects. Typically my patients will require daily maintenance, but a few will take on a "as-needed basis." Doses range from 1 mg BID to 8 mg BID and does not seem to correlate significantly with age, gender or body mass.

Oxybutynin

Oxybutynin is another common anticholinergic drug that can be used to treat hyperhidrosis. It is classified as a tertiary amine. It comes in several different preparations including a tablet, slow-release tablet, topical gel, and a transdermal patch. For oral administration, 5-10 mg daily is usually required for relief of HH, but doses up to 15 or 20 mg daily may be required.[7, 8] Wolosker did a randomized placebo-controlled trial using oxybutynin for palmar and axillary HH. Fifty patients were enrolled, and the drug was initiated at 2.5 mg daily, increased to 2.5 mg BID during weeks two and three, and then treated with 5 mg BID. Approximately 70% of the patients reported improvement in their axillary and palmar HH, while 90% of patients with plantar involvement reported improvement in their plantar sweating. The majority of treated-patients reported improvement in their QOL, while one fourth had no change in their QOL. Side effects were limited to dry mouth that was rated as moderate to severe by 30% of the subjects during the first three weeks (lower dose) and reached 35% by six weeks with the higher dose of oxybutynin.[9] Tupker reported 13 patients with generalized HH and one with paroxetine-induced HH that were treated with oxybutynin (2.5 mg TID, and 5 mg TID), with all of the generalized HH patients responding (the drug-induced HH patient did not respond). Therapy was well tolerated with the most common side effects being dry mouth, urinary difficulty, GI complaints, headache, and lassitude; although 30% had to discontinue therapy due to side effects. Therapy seems to work well in both men and women, as well as overweight and obese individuals.[10, 11]

There are no guidelines to use when choosing which anticholinergic drug to use for hyperhidrosis. Because of the more limited penetration into the CNS, glycopyrrolate is a good option. Patients may respond to one anticholinergic drug better than another, or may experience fewer or different side effects with one drug compared to other anticholinergics.[6] Additionally, there may be better compliance with the once-daily slow release oxybutynin. It is reasonable to switch anticholinergic drugs when faced with nonresponse. Another option is to try a topical formulation.

Other Anticholinergic Agents

Different options are available in various parts of the world. One of the best studied is methantheline bromide, which is a quarternary amine available in Germany. A multicenter placebo-controlled randomized study of 339 patients with axillary or palmar-axillary HH was performed.[12] Methantheline 50 mg or placebo was used TID: gravimetric measurements of sweat, Hyperhidrosis Disease Severity Scale (HDSS) and QOL was measured. At day 28, there was a reduction of sweat production of

40% compared to the placebo-treated group who had a 19% reduction in sweat production. The measured reduction in sweat was greater in the axilla compared to the palms. The researchers hypothesized that the decreased efficacy in the palmar sweating may be due to the fact that a significant proportion of methantheline is excreted through the sebaceous glands and these are lacking in the palms. Tolerability was good, with dry mouth, impaired accommodation, and dry eyes reported. There was a statistically significant decrease in the HDSS and an improvement in QOL in the methantheline-treated subjects compared to placebo-treated subjects.

Anticholinergic Use in Pediatric Patients

In general, I avoid the use of systemic anticholinergic therapy for my young patients with HH since they have less control of their environment at school, may be exposed to heat stresses during playtime, and may not be able to monitor themselves for signs or symptoms of hyperthermia. However, Amy Paller, MD, reported on 31 pediatric patients that were treated with glycopyrrolate and found that 90% had improvement while 10% had no improvement in their hyperhidrosis. Most of her patients were teens with the average age at the time that the glycopyrrolate was prescribed being 14.8 years ± 2.9. The mean dose for these teens was 2 mg daily but ranged from 1-6 mg daily. Approximately 30% had side effects including dry mouth, dry eyes, and blurred vision. One patient had to stop therapy due to palpitations.[13] Oxybutynin has been studied extensively in children for urologic problems with a good safety profile, although there is a higher number of CNS adverse event cases reported in pediatric patients as compared with adult patients.[14, 15] Glycopyrrolate is FDA-approved to treat children with sialorrhea and in this population side effects are dose-dependent and include behavioral changes, constipation, excessively dry mouth, urinary retention, facial flushing, nasal congestion, vomiting, and diarrhea.[16]

Beta Adrenergic Blockers

The use of beta blockers to treat patients with HH stem from their use to improve symptoms of social phobias and performance anxiety.[17] Performance anxiety can affect anyone in a multitude of situations but studies are often aimed at those who are frequently in the "spotlight" such as actors, musicians, or surgeons.[18] Sweating may develop throughout the day, but many HH patients complain that severe episodes develops at times of performance-related stress or when just a perception that sweating may interfere with performance, such as meetings, public speaking, school performance. In these instances the use of a beta blocker such as propranolol can be helpful. Propranolol is a highly lipophilic drug that binds to both β1 and β2 receptors with equal affinity. Peak concentration is 1 to 1.5 hours post ingestion, although food may delay peak concentration.[19] Contraindications to therapy are numerous (See Table 2), and a thorough history needs to be obtained, but low doses are generally used infrequently, making this therapy well tolerated. A resting blood pressure and heart rate should be taken in the office prior to prescribing the drug.

Table 2

Contraindications for Propanolol Therapy

- Bradycardia*
- AV block*
- Asthma
- COPD
- Depression
- Diabetes Mellitus
- Heart Failure
- Hepatic Disease
- Hypotension
- Hypoglycemia
- Cerebrovascular Disease
- Myasthenia Gravis
- Psoriasis
- Renal Disease
- Thyroid Disease

** Absolute Contraindication*

Small doses such as 10 mg of propranolol taken approximately one hour prior to the planned performance may be very helpful. For patients with low resting blood pressure, slow baseline heart rates or very small body mass index, 5 mg may be used initially. Patients should take a "test run" at home to monitor for hypotension, orthostatic hypotension, depressed cognition, or poor performance in general before using in a "real" performance situation.

Alpha Adrenergic Agonist

Clonidine is a sympatholytic medication used to treat hypertension as well as some anxiety/panic disorders. It is classified as a centrally acting α2 adrenergic agonist and has been successfully used to treat some patients with HH, and with flushing and sweating associated with menopause.[6, 20, 21,22] Doses used to treat menopausal hot flashes are low, ranging from 0.025 mg to 0.1 mg BID. Walling reported on 13 patients with HH that were treated with Clonidine with an average dose being used 0.1 mg BID. Overall there was a 46% response rate and the

majority of his patients used Clonidine as monotherapy. Interestingly, the patients with craniofacial HH comprised most of his responders. Of the seven patients who failed treatment, 3 were non-responders and four had to discontinue due to side effects, all were related to decreased blood pressure.[6] Other side effects seen with the use of clonidine are dry mouth, dizziness, constipation, and sedation.

As with propranolol, a thorough history and exam including blood pressure, should be performed prior to initiating therapy. Doses of 0.1 mg BID are most commonly used and the drug can be combined with other therapies to treat HH. [6, 22] Anecdotally, I have found it most useful in my middle-aged patients with craniofacial HH and sweating associated with flushing. I have prescribed it for generalized HH especially when there are several factors contributing to the overall sweating and to those patients with anxiety disorders requiring anti-anxiety medications.

Benzodiazepines

Benzodiazepines are sometimes listed as a treatment for HH, social anxiety disorders, and performance anxiety.[17, 23] Diazepam 5-20 mg/day is recommended, but there is no real primary literature supporting the efficacy in patients with HH. Since HH is a chronic disease, one has to carefully weigh the risks of addiction or dependence. Propanolol would be the authors' first choice to treat performance-based sweating. If anxiety appears to be the over-riding problem, referral to psychiatry for cognitive therapy or other drug management is prudent.

Conclusions

Oral therapies can play an important role in treating HH of all types. Although monotherapy is sometimes useful, combining systemic treatments with more focally-based therapy may provide superior results. Due to side effects and drug interactions, a thorough assessment should be performed prior to initiating systemic therapy, and working with other health care team members can be valuable to monitor for and reduce the risks of systemic therapies.

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