Palmar and plantar hyperhidrosis: a practical management algorithm

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Treatment modalities for palmar and plantar hyperhidrosis include aluminum chloride hexahydrate formulations, either in ethanol or in a salicylic acid gel, iontophoresis, oral anticholinergics, botulinum toxin type A injections and surgical procedures. Failure to respond to these conservative measures is often an indication to use surgical interventions such as thoracic or lumbar sympathectomy, which can be complicated by compensatory hyperhidrosis. Extemporaneous formulations containing appropriate concentrations of aluminum chloride hexahydrate, tailored to the patient's need, prepared by knowledgeable pharmacists, may avert the need for surgery. This report will focus on strategies for optimizing treatment outcomes in palmar and plantar hyperhidrosis used in our hyperhidrosis clinic in Canada over the last 28 years.

Hyperhidrosis (HH) may be defined as excessive sweating beyond the volume needed for thermoregulation. It affects 2.8% of the population, a much larger proportion than previously thought. HH can be focal or generalized. Focal HH is almost always idiopathic and affects armpits (40%), hands and feet (40%) and, less frequently, other regions such as the head and groin [1]. It may have a serious impact on an individual's quality of life (QoL), resulting in psychosocial and professional impairments [2].

Palmar HH seems to be by far the most disabling affliction, since shaking a hand during a job interview or a social encounter becomes problematic [3]. Many HH sufferers end up choosing a different career than the one they originally planned for.

Review of the literature

The historical background of antiperspirants has been reviewed by Laden [4]. Aluminum chloride hexahydrate (ACH) in aqueous solution was introduced in 1916 by Stillians [5]. Many still consider it to be the most effective antiperspirant. Among the aluminium-free formulations prescribed by dermatologists are:

- Formaldehyde, prescribed as 10% formalin [6];
- Glutaraldehyde, prescribed as 10% aqueous solution [7];
- Methenamine, prescribed as 8% in a cream vehicle [8,9].

The problem with these formulations is the potential for developing an allergy in the long term.

The anticholinergic glycopyrollate, prescribed as 0.5% topical aqueous solution, is well tolerated but may cause systemic side effects when absorbed [10].

Tap water iontophoresis is a well tolerated and effective method for controlling palmar and plantar HH; however, the devices may be expensive and the procedure is time consuming [11].

Botulinum toxin type A (Botox®) has recently emerged as a new effective treatment for recalcitrant focal HH, particularly axillary HH [12]. While Botox injections are easily performed under the arms with little or no analgesia, these injections must be preceded by some form of anesthesia on the hands and feet because of the densely innervated skin of the palms and soles. Nerve block is the most common method used, but is not without hazards [13]. Lately, needle-free anesthesia prior to Botox injections has emerged as a new technique obviating the need for a nerve block. Long-term cost–effectiveness and immunoresistance from repeated injections of Botox are examples of the concerns that should be taken into account before opting for this treatment modality.

Surgical procedures, such as sympathectomy, should be sought as a last resort because of compensatory HH and excessive dry hands [14], and the inherent risks of surgery.

Mechanism of action of aluminum salts

Aluminum salts reduce sweat by causing mechanical obstruction to the eccrine sweat duct at the acrosyringium level [15]. Hölzle and

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Kligman suggested that metal ions form precipitating complexes with mucopolysaccharides and cause damage to luminal epithelial cells. The result is an obstructive conglomerate that completely plugs the acrosyringium. The secretory portion of the eccrine gland is not affected by the metallic salts, but long-term blockage of the acrosyringium by aluminum salts may lead to functional and structural degeneration of the eccrine glands with loss of secretory function [16].

Commercially available ACH preparations

ACH in absolute ethanol is the most widely used antiperspirant to control axillary HH. Irritation of the skin and damage to clothing remain its major disadvantages. It is commercially available in a concentration of 6.5% in 95% ethanol vehicle as Drysol Mild® (Person & Covey, CA, USA) and in a concentration of 20% in 95% ethanol as Drysol®. Treatment of palmar and plantar HH is more challenging than axillary HH because of the thick stratum corneum present on the palms and soles that greatly hinders the penetration of ACH. That explains why topical ACH, although very effective for axillary HH, is less useful for palmar and plantar HH, even under occlusion with cellophane paper.

Table 1. Management algorithm for palmar and plantar hyperhidrosis.

Severity	Management
Mild	30–40% ACH in a hydroalcoholic gel containing 4% SA*
Moderate	**(A)** 40–55% ACH in a hydroalcoholic gel containing 4–6% SA
	(B) Iontophoresis (with or without the 40% ACH gel) – Drionic [102] – Fischer [103] – i2m [104]
	(C) Botox® injections 100 units per hand or 150 units per foot‡
	(D) Step C + iontophoresis + 55% ACH in SAG containing 4–6% SA
Severe	**(A)** Botox injections 150 units per hand or 200–250 units per foot
	(B) Step A + iontophoresis + 55% ACH in a SAG containing 4–6% SA
	(C) ETS (for palmar HH) or ELS (for plantar HH)

**Anticholinergics such as glycopyrrolate 1–2 mg three-times daily as needed or oxybutinine 2.5–5 mg three-times daily as needed have been found to be useful as an adjunct to the above-mentioned therapies.*

‡Anesthesia during Botox injections on the hands and feet is achieved through needle-free lidocaine injection with the Med-Jet MBX [26].

ACH: Aluminum chloride hexahydrate; ELS: Endoscopic lumbar sympathectomy; ETS: Endoscopic thoracic sympathectomy; HH: Hyperhidrosis; SA: Salicylic acid; SAG: Salicylic acid gel.

Lowe and colleagues recommend the use of ACH as a first-line therapy in treating focal HH [12,17]. ACH is inexpensive and easily applied on the affected areas.

ACH in a gel vehicle containing salicylic acid

In the early seventies, hydroalcoholic gels such as Saligel® (Stiefel) and Keralyt® containing 5–6% salicylic acid (SA) were available on the market to treat acne or psoriasis. These preparations were also used to concoct extemporaneous formulations containing supersaturated concentrations of ACH to treat palmar and plantar HH. Unfortunately, these products were all discontinued in Canada in the early 1990s owing to a lack of financial profit.

Hydroalcoholic gels containing SA and 15% ACH, such as Hydrosal® Gel, are now back on the market and knowledgeable compounding pharmacists are capable of using this gel, or in-house-formulated gels, to reach higher concentrations of ACH [101]. Adequate experience and know-how will lead to the right composition in an active pharmaceutical ingredient (API) and adequate additional excipients tailored to the patient's need.

Results of specific studies

The advantage of SA gel (SAG) as a vehicle to carry ACH has been previously reported [18]. Cases that failed to respond to 20% ACH in 95% ethanol have responded to the same concentration of ACH in SAG and avoided surgery on the axillae. Cases of palmar and plantar HH, refractory to Drysol, responded favorably to these formulations.

The rationale for using SA is twofold:

- SA is a penetration enhancer and may help ACH to reach the eccrine glands through the thick horny layer present on the palms and soles
- SA has antiperspirant properties of its own [19,20] and could act in synergy with ACH to provide a stronger antiperspirant effect

Alcohol gels are known to cause less irritation than alcohol solutions [21,22]. Besides, alcohol gels allow ACH to reach supersaturated concentrations. While ACH is soluble 1 in 1 in water, it is only soluble 1 in 4 in the ethanol vehicle [23]. In the gel vehicle, ACH is dispersed in the form of microcrystals, reaching supersaturated concentrations of up to 55%. The presence of a cellulose polymer in the gel probably helps to achieve this goal [24]. Alcohol gel formulations may also

diminish or eliminate the drying effect of alcohol and, by maintaining normal skin hydration levels, they may further improve the percutaneous absorption of ACH.

For optimal results, ACH extemporaneous formulations should be tailored to the patient's need, taking into consideration: the severity of HH, its anatomical location, its previous response to treatments and the age of the patient. The formulation should always be applied at bedtime, when the activity of the eccrine glands somewhat diminishes.

In our HH clinic 80% of the patients are satisfied with 40% ACH in a 4% SAG.

The preparation of a 100-g batch of this formulation using Hydrosal Gel involves the following steps:

- Obtain 15% w/w of ACH in a SA gel. An additional quantity of this active ingredient (32.5 g %), finely pulverized, is partially dissolved/dispersed in the heated adequate solvent/co-solvent mixture;
- On the other hand, a gelling/thickening/anticrystallizing/emollient blend is dispersed in a bowl containing 50 g of Hydrosal Gel (7.5 g ACH);
- While agitating, the hot dispersion is added to the preceding mixture and the whole blend is brewed with an electric mixer until cooling. Thus, we obtain a clear, homogeneous and uniform gel, which is kept refrigerated;
- It should be noted that the additives (excipients, APIs) are calculated to obtain final concentrations of ACH (and eventually SA) in the right percentages. As the high API concentrations might cause irritancy, all the additional excipients are carefully chosen in order to minimize this.

Table 1 shows the current management algorithm for palmar and plantar HH.

Supersaturated concentrations of ACH in the treatment of palmar & plantar HH

The advantages of supersaturated concentrations of ACH in the treatment of palmar and plantar HH are as follows:

- As a first-line therapy for palmar and plantar HH;
- As an adjunct treatment with iontophoresis when iontophoresis alone fails to control severe palmar and plantar HH;
- As an adjunct treatment with Botox injections, when these injections fail to control HH;
- Moreover, the supersaturated concentrations of aluminium chloride in a 4–6% SA gel obviate the need for higher doses of Botox and extend the interval between Botox injections. It is well known that high doses of Botox and/or shorter intervals between treatment sessions may generate antibodies to Botulinum toxin, which renders the Botox injections totally ineffective [25].

Clinical experience at our HH clinic during 2006

A total of 549 cases presented at our clinic for focal HH from January 4–December 22 2006. Of these, 250 patients suffered from plantar HH, with 206 suffering from palmar HH. A total of 172 of these had combined palmar and plantar HH. Combined axillary and palmar HH was found in 130 cases and 144 had combined axillary and plantar HH. Finally, 392 cases presented with axillary HH, 60 cases for craniofacial HH and 27 for inguinal HH.

Treatment of palmar and plantar HH was mostly initiated with 40% ACH in a 4% SAG. Patients were seen a month later to adjust the dose, either higher (55% ACH if the response was inadequate) or lower (if the response was adequate but the dryness was excessive).

When 55% ACH in a 6% SAG failed, 100 units of Botox per hand or 150 units per foot were injected. At our clinic, Botox injections alone, at these doses, were successful in 75% of palmar HH and a little less in plantar HH.

When Botox injections fail to show any response, after 3–4 weeks, supersaturated concentrations of ACH (40–55% ACH in SAG) are added with or without iontophoresis as a last attempt to stop HH before resorting to surgery.

Table 2. Supersaturated concentrations of aluminum chloride hexahydrate.

Number	Concentration (%)
Plantar hyperhidrosis (total n = 250)	
78	55
127	40
27	30
18	20
Palmar hyperhidrosis (total n = 206)	
78	55
99	40
19	30
10	20

Table 3. Total dose of Botox injected on both sides.

Number	Units
Plantar hyperhidrosis (total n = 7)	
1	200
5	300
1	400
Palmar hyperhidrosis (total n = 35)	
2	100
26	200
6	300
1	400

Failure to respond to this last measure is a definite indication to refer to surgery. By following this kind of management algorithm, during the year 2006, only one male patient suffering from palmar HH has been referred for endoscopic thoracic sympathectomy and a single female patient suffering from plantar HH referred for endoscopic lumbar sympathectomy.

Table 2 shows the frequency of ACH concentrations prescribed at our clinic to control palmar and plantar HH while Table 3 shows the number of unresponsive cases injected with Botox from our clinic as well as those referred by fellow dermatologists.

Discussion

The optimal therapeutic option at the least possible cost should be sought for each patient. The therapeutic options vary according to the age of the patient, the area involved, the severity of the disease and the patient's own tolerance to previous medications. Extemporaneous formulations, tailored to the patient's need, compounded by knowledgeable pharmacists could make a big difference in the QoL of palmar and plantar HH sufferers.

We tried to present a management algorithm for palmar and plantar HH in order to help dermatologists, plastic surgeons, thoracic surgeons and primary care physicians to treat this condition in an optimal way. The future of ACH in SAG looks promising in the treatment of this embarrassing and sometimes disabling condition, either alone or in combination with other modalities, such as iontophoresis or Botox injections. ACH in SAG may play a major role, not only in avoiding higher doses of Botox to control HH, but also extending the interval between these injections when their effect starts to fade away.

Finally, we wish to invite other investigators to join us to run multicenter prospective studies to corroborate the enhanced antiperspirant effect obtained when aluminum chloride is formulated in a SAG.

Future perspective

In the year 2000, only one or two patients per month consulted a dermatologist for focal HH. Patients feel a great embarrassment to talk about this condition, even to their closest family members and friends. Thanks to the internet, where they are able to express their pain anonymously, the number of patients consulting for focal HH has steadily increased in the last 7 years. Physicians should be ready to face that reality by offering the optimal therapeutic option at the least possible cost.

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Executive summary

- Treatment of palmar and plantar hyperhidrosis (HH) in adults should be started with 40% aluminum chloride hexahydrate (ACH) in salicylic acid gel (SAG).
- If excessive dryness develops, the concentration is lowered to 30% ACH in SAG.
- If ineffective, the concentration should be increased to 55% ACH in SAG.
- If 55% ACH in SAG fails, iontophoresis should be added.
- If both these measures fail, Botox can be injected at 100 units per hand or 150 units per foot.
- If Botox injections fail, add 40–55% ACH in SAG and iontophoresis.
- If all of the above fail, consider referral for sympathectomy.

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