

Traditional Treatment of Hyperhidrosis

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Topical Pharmacological Treatment

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The topical pharmacological treatment of hyperhidrosis is synonymous with the application of antiperspirants to circumscribed areas of excessive eccrine sweating. In most cases, antiperspirants are used to curb cosmetically disturbing underarm wetness. Rarely they are applied to the palms or soles or are used to treat other types of localized hyperhidrosis like those of Ross syndrome or auriculo-temporal sweating (Frey syndrome).

Antiperspirants have been known for many years and their use is very common, especially in industrialized countries. They comprise a huge market [7, 9]. Nevertheless, proprietary products may be useful for the average consumer, but in most cases of moderate or severe hyperhidrosis their treatment efficacy is unsatisfying. For heavily sweating patients, medical products and special prescriptions have to be used. They possess, however, the potential of higher irritancy or contact sensitization as possible side-effects.

For the treatment of local hyperhidrosis, different classes of chemicals are used; these include astringent agents, local anaesthetics, acids and aldehydes, metal salt solutions and anticholinergics. All antiperspirants act selectively on the eccrine sweat glands and do not affect the apocrine glands. The deodorant effect of commercial antiperspirants is mainly based on their antimicrobial activity. Astringent agents, acids and aldehydes as well as metal salt solutions directly diminish the resident microflora flourishing in the humid and warm micro-environment of the axillae and prevent the formation of odoriferous substances generated from apocrine sweat by the action of skin surface bacteria [24, 25, 36, 40]. All antihidrotic measures dry the skin surface, thus interfere indirectly with the growth conditions of bacteria and exert an additional deodorizing effect.

In the following, the various aspects of topical antihidrotic agents are discussed with emphasis on the use of metal salt solutions, especially preparations containing aluminium chloride hexahydrate.

Acids and Aldehydes

The astringent agents formaldehyde, glutaraldehyde, tannic acid and trichloroacetic acid denature proteins and, upon topical application to the skin, can generate a superficial closure of the sweat pore by denaturing the keratin of the uppermost layers of corneocytes [6, 22, 32]. Since only the very superficial cell layers are affected, this closure will be repaired by desquamation of the stratum corneum within few days. Treatment would be necessary almost on a daily basis.

A serious adverse effect of formaldehyde is its high potential of inducing contact sensitivity leading to allergic contact dermatitis. About 15–20% of treated patients have been shown to become sensitized. Hexamethylene tetramine, from which formaldehyde is released by the acid eccrine sweat, is thought to possess a weak sensitizing potential and is used in some preparations. Glutaraldehyde is less effective in the axillae and, when applied in higher concentration, leads to disturbing yellow discolouration of the horny layer. Tannic acid, sometimes derived from chestnut or oak extracts, exerts little antiperspirant activity.

In the treatment of hyperhidrosis, astringent agents are mostly obsolete. In some proprietary products, astringents, acids or aldehydes may be found in low concentrations.

Local Anaesthetics

Theoretically blockade of peripheral nerves by local anaesthetics also affects the sympathetic nerve fibres supplying the eccrine sweat glands, thus leading to anhidrosis. In an experimental approach, a mixture of 5% lidocaine and 5% prilocaine was tested for its antihidrotic efficacy [23]. There was sufficient penetration through the stratum corneum and also a measurable suppression of secretory activity. In practice, however, these preparations turned out to be insufficient to control hyperhidrosis. In addition, local anaesthetics have at least a moderate potential to induce contact hypersensitivity. For that reason, the topical application of anaesthetics to control hyperhidrosis is of no practical value.

Anticholinergics

Since the eccrine sweat gland is innervated by postganglionic cholinergic sympathetic fibres, anticholinergics can effectively block the secretory activity of the eccrine sweat glands [35]. Anticholinergic agents would therefore be the ideal antiperspirant, if they sufficiently penetrated the horny layer and acted only locally. There are, however, at least two main problems: (1) the percutaneous

absorption of anticholinergics is not always sufficient to achieve a long-lasting anhidrosis and (2) if larger amounts of anticholinergics are absorbed through the skin, systemic adverse effects will occur. A further drawback is the potential of anticholinergics to induce contact hypersensitivity [1, 27]. In experimental settings, scopolamine hydrochloride and its esters [26], poldine methosulphate [10], propantheline bromide and hexapyrroneum bromide have been used. In some proprietary products, propantheline bromide is used in combination with aluminium hydrochloride [2, 28, 44].

In cases with a slight or moderate degree of hyperhidrosis, the topical use of preparations containing anticholinergic agents may be helpful.

Metal Salt Solutions

The most widely used ingredients for topical antiperspirants are metallic salts. Aluminium chloride hexahydrate has already been introduced by Stillians [41] in 1916 and remains, until today, one of the most effective metallic antiperspirants [6, 8, 13, 34, 38]. In cosmetic products, the partially neutralized form is used as aluminium hydrochloride, since this compound is less toxic. Therefore, it causes less skin irritation and less corrosion of fabrics, but it is also somewhat less effective as an antiperspirant in comparison with aluminium chloride hexahydrate. Formerly, preparations containing zirconium salts, which are also highly effective as antiperspirants, were used. In some cases as a rare adverse effect, skin granulomas were observed, probably caused by a delayed-type allergic reaction [39, 43]. For that reason, their use as antiperspirant ingredients has been abandoned.

Mechanism of Antiperspirant Action of Metallic Salt Solutions

All antiperspirants of the metallic salt type have the same mechanism of action by causing an obstruction of the distal sweat ducts within the acrosyringium. This was very convincingly shown by two independent laboratories [16, 31].

If the appropriate metal salt solution of a sufficient concentration is applied to the skin surface, the metal ions diffuse into the distal part of the sweat ducts, which spirals through the acrosyringium, reaching the surface of the stratum corneum. The ions do not penetrate the stratum corneum or the very distal portion of the keratinized part of the acrosyringium, since the keratinized epithelium is a highly sufficient barrier to polar agents. It is only in the lower part of the acrosyringium, where the ductal wall is formed by a non-keratinized epithelium, that metallic ions can form a precipitate with mucopolysaccharides. These



Fig. 1. The acrosyringium 1 week after a 24-hour application of 20% aluminium chloride hexahydrate solution. The acrosyringium is obstructed by an eosinophilic (PAS-positive) plug. HE. $\times 200$.

mucopolysaccharides are likely to be derived from the cuticular lining of the sweat ducts. At the same time, probably due to membrane damage, the luminal cells of the acrosyringium become necrotic, as shown by eosinophilic cytoplasm and pycnotic nuclei in histopathological sections (fig. 1). These damaged cells slough off and form a firm plug together with the metal-mucopolysaccharide precipitate firmly occluding the sweat duct [16, 20, 29]. Repair of the acrosyringium due to renewal of the epidermis in the course of epidermopoiesis restores the normal function of sweat glands. For that reason aluminium chloride solutions have to be applied on a regular basis, mostly once or twice weekly. Long-term

blockage of the sweat duct for many months or several years results in functional and structural degeneration of the eccrine acini with complete resolution of hyperhidrosis [14].

The acrosyringium below the keratinized part of the distal sweat duct represents a site of low resistance against the toxic effect of metal salt solution and other irritants in aqueous solutions [17]. It is at that level that reactions between metal ions and living tissue occur. The closure of the sweat duct is a slowly progressive process and requires several hours. The formation of complexes between mucopolysaccharides of the sweat duct cuticle and the metal ions creates an obstruction against secreted sweat on one side and prevents further penetration of the metal ions on the other. For that reason, penetration through the skin and systemic effects of metal ions from antiperspirant solutions are impossible. All metallic salt solutions acting as antiperspirants exert their effect basically by the same mechanism as described above. It is only the relationship between complex formation and toxic damage to the cells lining the duct that varies. For example, cupric chloride acts in a very damaging way to sweat ducts; however, aluminium chlorohydrate easily forms a precipitate while it is only slightly toxic [17]. Therefore, the latter agent is the most widely metal salt used in proprietary antiperspirants.

Factors Influencing Antiperspirant Efficacy

Effect of Concentration

Higher concentrations enhance the antiperspirant effect of metal salt solutions as is shown in figure 2 for aluminium chloride and aluminium chlorohydrate. At higher concentrations there seems to occur a saturation effect. As expected, aluminium chloride was more effective at all concentrations [19].

pH Value

When different aluminium salt solutions are compared at equal molar concentrations in relation to the content of aluminium (0.83 M equals a 20% solution of aluminium chloride hexahydrate), a strong and significant correlation was established (fig. 3). It is to be noted that aluminium hydrochloride represents an exception [19]. Probably it already represents a partially complexed large molecule and precipitates very easily despite its rather high pH value of 3.9 at that molar concentration. Because of its ease in forming complexes, aluminium chlorohydrate diffuses only in the very distal portion of the acrosyringium and creates a superficial obstruction. The duration of its antiperspirant activity is, therefore, short. Experimental observations and histopathological findings confirm this notion [17].

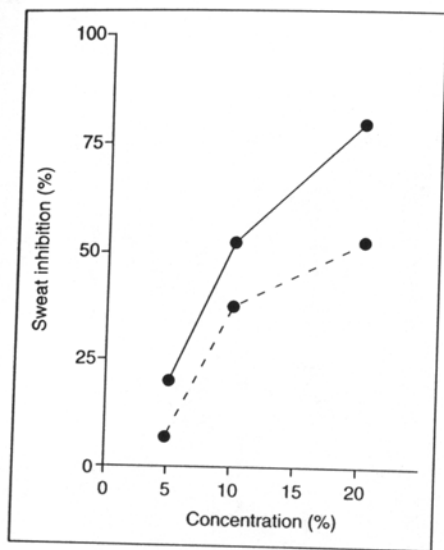


Fig. 2. Relationship between concentration of the solution and antiperspirant efficacy. Aqueous solutions of AlCl₃ (—) and Al₂(OH)₅Cl (- - -) are compared. n = 5.

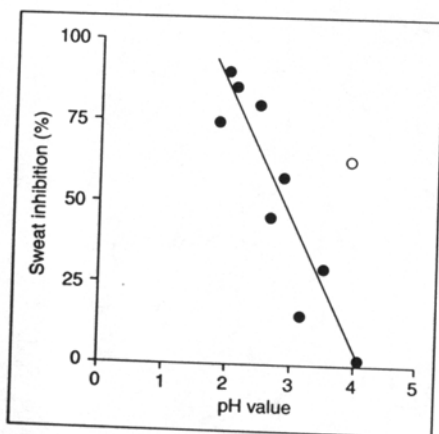


Fig. 3. Direct correlation between antiperspirant efficacy and pH value of 0.83 M aqueous solution of different aluminium salts. Al₂(OH)₅Cl represents an exception (○). Further information is given in the text. n = 5.

Different Metallic Salt Solutions

In addition to aluminium and zirconium salts, a wide variety of metallic salt solutions interfere with the distal sweat duct and induce at least partial anhidrosis [19]. Screening different salts revealed vanadium compounds to be even more effective than aluminium chloride solutions (table 1). Indium chloride proved to be equal to aluminium chloride. Others, including salts of hafnium, gallium, zinc, zirconium, tin, neodymium, erbium, gadolinium and lanthanum, are less

Table 1. Sweat inhibition in relation to pH value of 0.83 M solutions with respect to aluminium as evaluated in the forearm test [19]

Substance	Sweat inhibition, %	pH value
Al nitrate	90.0	2.0
Al chloride	87.5	2.1
Al bromide	80.0	2.5
Al perchlorate	75.0	1.9
Al chlorohydrate	67.5	3.9
Al phenolsulphonate	57.5	2.1
Al sulphate	45.0	2.7
Al lactate	30.0	3.5
Al oxalate	15.0	4.1
Al acetate	0	4.1

effective. Since aluminium salts have been in use for more than eight decades, are inexpensive, non-toxic and non-allergic, they still comprise the chief components of proprietary antiperspirant formulations and medical prescriptions.

Mode of Application

In search of measures to enhance antiperspirant activity, a broad variety of factors have been investigated. These include different modes of application, the addition of surfactants to the antiperspirant solution [5, 33], pretreatments of the skin surface prior to application of the antiperspirant, the effect of massaging the skin during application and the influence of sweat gland activity during application. It was found that one single occlusive application to the axillary cavity for 24 h was more effective than repeated short-term occlusive exposures for 15 min twice daily for 3 days [15, 42]. By massaging the skin during repeated open applications, efficacy could be enhanced. Treatment of the skin with lipid solvents had no effect. Addition of surfactants to the antiperspirant solutions, again, did not enhance their antiperspirant effect [5, 12, 21]. As expected, the sweat gland activity during application time had a strong influence on the efficacy. When sweating was induced during the repeated short application of antiperspirants, the antiperspirant effect was completely abolished. Presweating before application enhances the effect. In view of the mechanism of action, these findings are explicable and expected [15]. Filling the sweat ducts provides a continuous medium for the diffusion of metal salts into the eccrine ducts. Antiperspirant activity increases provided that the glands remain inactive during and after

Table 2. Algorithm for topical treatment of hyperhidrosis

Type of hyperhidrosis	Type of treatment
Axillary hyperhidrosis	(1) Aluminium chloride (2) Botulinum toxin (3) Iontophoresis
Palmoplantar hyperhidrosis	(1) Iontophoresis (2) Botulinum toxin (mainly on the palms)
<u>Frey syndrome</u>	<u>(1) Aluminium chloride</u> <u>(2) Botulinum toxin</u>
Ross syndrome	(1) Aluminium chloride (2) Botulinum toxin (3) Iontophoresis (experimental)

the aluminium exposure. Is the solution applied during sweating, diffusion of aluminium ions into the acrosyringium is impossible.

Clinical Use of Aluminium Chloride Hexahydrate

Indications

These are disorders with local hyperhidrosis. They include idiopathic hyperhidrosis of the axillae, palms and soles as well as Frey syndrome and selected cases of Ross syndrome. It could also be tried in naevus sudoriferus, which probably comprises a functional naevus with hyperactivity of eccrine sweat glands in a circumscribed anatomical region mainly on the forearms.

Aluminium chloride hexahydrate solutions are mostly effective in the treatment of axillary hyperhidrosis and have been very useful in the treatment of Frey syndrome. Guidelines for the treatment of local hyperhidrosis with different measures are given in table 2.

The first-line treatment of axillary hyperhidrosis would be aluminium chloride hexahydrate followed by botulinum toxin and the use of tap water iontophoresis. In palmoplantar sweating, the treatment of choice would be tap water iontophoresis followed by the injection of botulinum toxin, which is well tolerated on the palms but very difficult on the soles.

Frey syndrome may be treated with aluminium chloride solutions or botulinum toxin injections. In Ross syndrome, aluminium chloride solutions may be tried. If only small areas are to be treated, botulinum toxin may be the choice to be favoured [11]. In some patients, experimental application of tap water iontophoresis has been shown to be useful [30].

Mode of Application

Taking into account the mechanism of action and the factors influencing the efficacy of aluminium chloride solutions, the following procedure was found to be optimal. Patients should be advised to apply the antiperspirant solution overnight, when the eccrine sweat glands are inactive. Occlusion in the axillary cavity has been proposed [3, 34] but is unnecessary, since this intertriginous area is semi-occluded for anatomical reasons. Gentle rubbing and massaging of the product into the distal portion of the sweat ducts enhance efficacy [15]. This might be easily accomplished by the use of roll-on bottles. The patients also should be advised that higher concentrations of aluminium chloride are corrosive to fabrics and may destroy nightclothes.

Prescription

For axillary hyperhidrosis, the optimal concentration was found to be 15% [13]. The solution should be thickened by the addition of methylcellulose at concentrations of 1 or 2% to form a viscous gel, which allows the solution to stick onto the skin and prevents it from running off.

There has been much debate about the vehicle to be used. Some authors felt that solutions in absolute ethanol would be superior with respect to skin tolerance and antiperspirant efficacy [3, 34]. Other experimenters, however, have shown that aqueous solutions are even more effective than preparations based on alcohol [4]. With respect to tolerance, absolute ethanol seems to be slightly less irritating than aqueous solutions, as revealed by itching and visible dermatitis. In our own study [13], 691 patients were monitored for up to one decade. It was found that 15% aluminium chloride hexahydrate in aqueous solution thickened by 2% methylcellulose in order to form a gel represented the optimal formulation. Lower concentrations are less effective and an increase in the concentration did not appreciably enhance efficacy, although it did reduce skin tolerance. If aluminium solutions are to be used on the palms or soles, the concentrations must be higher and raised up to 30%.

Efficacy and Side-Effects

Efficacy

In a study of our own [13] between 1978 and 1988, 691 patients with idiopathic localized hyperhidrosis were treated with aluminium chloride solutions. 163 patients were examined after the initial treatment course of 4 weeks, 336 patients were followed up for an average of 5 months [13]. After the initial

treatment, 82% of patients achieved satisfying results with either complete dryness of the axillae or at least reduction to a level of sweating which was perceived as normal and well tolerable by the patients. During maintenance treatments this effect could even be enhanced; 87% of the patients were completely satisfied with the treatment.

On an average, patients achieved the initial therapeutic effect after 4 consecutive applications on every second day. During maintenance treatment, intervals varied from 7 to 12 days. This depended on the severity of hyperhidrosis. More severely affected patients required shorter treatment intervals.

In this study different concentrations of the aluminium chloride solutions were compared, too. 10% solutions were unsatisfying and were found only suitable to treat bromhidrosis or low-grade hyperhidrosis. Between 15 and 20% virtually no difference was seen in efficacy. 15% solutions, however, were much better tolerated. For that reason, as a standard concentration, 15% aluminium chloride solution was used.

Acute Side-Effects

As side-effects, only itching or stinging immediately following the topical applications or some degree of skin irritation in the axilla were found [13]. In 70% of the patients, pruritus was only slight and short-lived; in 21% it was found moderate and in 9% it was severe. Similarly skin irritation occurred in 50% to a modest degree, was found moderate in 36% and severe in 14%. In the course of maintenance treatment, side-effects were found reduced. 52% of patients reported itching and 17% skin irritation. In more than 80% of the patients, the pruritus was only transient, immediately following the application of aluminium chloride solutions.

A regular concomitant of sweat duct obstruction at the level of the acrosyngium is miliaria. This can indeed be seen, when aluminium chloride solutions are applied to forearm or back skin [16]. In the axilla, with its soft dermal texture, eruptions of miliaria are never observed. Some patients, however, experience slight itching, when sweating is induced during anhidrosis after the use of aluminium chloride solutions. This reaction may be considered as subclinical miliaria. None of the patients ever discontinued the treatment due to this transient mild reaction.

In general, treatment with 15% aluminium chloride solutions overnight is a highly effective and well-tolerated regimen in about 80% of the patients with hyperhidrosis of the axillae. It is, therefore, considered the treatment of choice. Only, if it is ineffective or associated with intolerable side-effects or is unfeasible for other reasons, further treatment options should be considered. These are injections of botulinum toxin or surgical methods.

Antimicrobial Effect

The generation of axillary body odour requires breakdown of apocrine secretion by skin surface bacteria. Apocrine sweat by itself is odourless [36]. Notably aerobic diphtheroid bacteria generate the typical apocrine odour [25]. Thus, keeping the microbial flora in check prevents the formation of odoriferous volatile substances. The antimicrobial activity of aluminium salts has been known for a long time. In the last century, Burow's solution, a mixture containing mainly aluminium acetate, was used particularly for its antibacterial action. The use of aluminium chloride solution was also recommended in the treatment of symptomatic athlete's foot [24] and chronic folliculitis [37]. In an experimental study [18], inhibition of microbial growth lasted more than 3 days after a single topical application of 15% aluminium chloride solution to the axilla.

These antimicrobial properties of aqueous aluminium chloride solutions provide the basis for their deodorant effect. Applications of aluminium chloride solutions as treatment for hyperhidrosis at least twice weekly keep the axilla virtually sterile and, as a consequence, odourless. Only if applications are made in longer intervals, the additional use of a deodorant is recommended to control eventual body odour.

Long-Term Effects

Metallic salt solutions generate an obstructive plug in the acrosyringium. The secretory portion is not primarily affected and remains active as is vividly demonstrated by the eruption of miliaria under heat stress in sites rendered anhidrotic by aluminium chloride solutions [16]. Patency of the epidermal sweat duct is restored by renewal of the acrosyringium due to epidermopoiesis. As a consequence, treatment of hyperhidrosis requires repeated exposures of aluminium chloride for prolonged periods of time.

During long-term treatment, however, the severity of hyperhidrosis seems to decrease as was reflected by a marked reduction in the frequency of treatments required to control hyperhidrosis. This observation suggests that long-term application of aluminium salt solutions may alter the secretory portion of the eccrine glands functionally or structurally. In fact, histological examination revealed conspicuous morphological changes of axillary eccrine glands under long-term treatment conditions (fig. 4). The secretory epithelium exhibited vacuolization and the eccrine accini were widely dilated with atrophy of secretory cells and accumulation of PAS-positive, diastase-resistant material in the dilated accini of the secretory portion [14].

This demonstrates that long-term blockade of the distal acrosyringium leads to functional and structural degeneration of the eccrine acini and, finally, to complete loss of their function. Apocrine glands are not affected. Long-term use of aluminium chloride solutions is probably a permanent treatment of

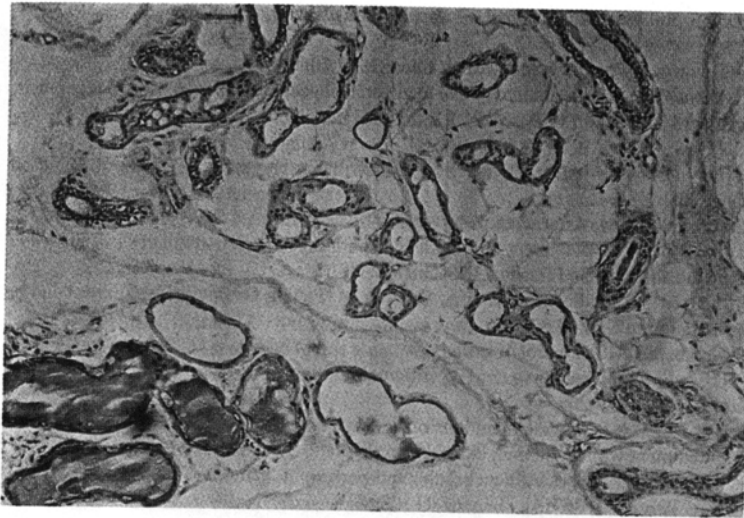


Fig. 4. Eccrine acini under long-term treatment with aluminium chloride hexahydrate solutions. There is dilation of the acini and atrophy of the secretory epithelium. PAS. $\times 80$.

axillary hyperhidrosis. Although hyperhidrotic patients are pleased to find their condition improving during long-term treatment, its consequences are not completely understood. Further studies on the kinetics and reversibility of the observed changes are necessary.

Algorithm for Topical Treatment of Hyperhidrosis

Topical applications are the mainstay of treating focal hyperhidrosis. The use of astringent agents, acids and aldehydes is considered to be obsolete. Practical means for topical treatment are the use of aluminium chloride solutions and injections of botulinum toxin. Also tap water iontophoresis is feasible as a physical localized therapy. Aluminium salt solutions are the first choice for topical treatment in axillary hyperhidrosis and in Frey syndrome. Alternative treatment modalities and further indications are discussed above and are given in table 2.

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