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Clinical studies of sweat rate reduction by an over-the-counter soft-solid antiperspirant and comparison with a prescription antiperspirant product in male panelists

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Summary

Background Individuals with axillary hyperhidrosis have much higher than average sweat rates and are often prescribed anhydrous aluminum chloride ($AlCl_3$) solutions. Topical application of these solutions can be irritating to the skin, resulting in poor compliance and lower than desired efficacy.
Objective Demonstrate the efficacy of an over the counter ''clinical strength'' soft-solid antiperspirant using a night time application regimen and compare to a prescription aluminum chloride (6.5%) antiperspirant using male panelists.
Methods Gravimetric hot room efficacy testing (100 F and 35% Humidity) was performed comparing an over the counter soft-solid antiperspirant to placebo in a single test. Two separate gravimetric tests were placed comparing a prescription aluminum chloride (6.5%) antiperspirant to the same soft solid product using an intent to treat model. Skin irritation was assessed daily by a trained grader.
Results Placebo testing resulted in 85% of panelists having a reduction in sweating rate greater than 50%. Comparison testing showed the over the counter soft solid reduced sweat rate by an average of 34% better than the prescription product while resulting significantly less skin irritation.
Conclusions Over the counter ''clinical strength'' soft-solid antiperspirants can be considered as an alternative treatment to aluminum chloride antiperspirants for the treatment of heavy sweating.

Axillary sweating can have a significant negative impact on quality of life by creating visual sweat stains or a noticeable wet skin feel that reduce an individual's self confidence and social acceptance. This impact can be exacerbated by the production of odour (or anxiety over potential odour) resulting from bacterial growth on the skin and hair of the moist axillae. Many individuals use antiperspirant/deodorant products to control axillary sweating and odour. In fact, more than 90% of individuals use these types of products in some regions of the globe (Procter & Gamble, unpubl data). While the widespread usage of these products is indicative of their efficacy in the general population, most products are not designed to provide relief for individuals with higher than average sweat rate.

Individuals with higher than average sweat rates are more susceptible to the negative quality of life impact of axillary sweating than others. Several studies have documented a wide variety of compensating behaviours to reduce social stigma. These include wearing pads in the axillae or changing shirts several times each day.[1] Many of these individuals are diagnosed with axillary hyperhidrosis and are treated by health professionals using techniques such as anhydrous aluminium chloride ($AlCl_3$) solutions, iontophoresis, botulinum toxin type A injections and, in extreme cases, surgery. Axillary hyperhidrosis is defined as having an excess of eccrine sweat in the axillae beyond that needed for cooling the body.

The Hyperhidrosis Society has identified resting axillary sweat rates of 20 mg min^{-1} for men and 10 mg min^{-1} for women as being indicative of the disease.[2] Often individuals with high sweat rates but not necessarily above those required for a hyperhidrosis diagnosis are treated with solutions of anhydrous $AlCl_3$ in ethanol. Topical application of these solutions can be quite irritating to the skin, even if the product is only applied several times per week rather than daily. This irritation, which reduces product usage compliance, is due to the low pH, high chloride content and ethanol solvent of these solutions. Over the past several years, a class of 'clinical strength' over-the-counter (OTC) antiperspirants has been introduced for both male and female consumers. These products are advertised to provide wetness protection similar to $AlCl_3$ without the high level of skin irritation.

The following provides a background on the mechanism of action for antiperspirant products, considerations in design for men and data from three clinical trials showing the benefit in male panelists, and comparison with an $AlCl_3$ antiperspirant.

Antiperspirant mechanism of action and 'clinical strength' antiperspirants

Antiperspirant products reduce eccrine sweat rate by delivering partially neutralized salts of aluminium and zirconium to the opening of an eccrine sweat gland. Once there, the salt is dissolved by sweat and diffuses into the duct. During diffusion the salt reacts with basic components of the eccrine gland discharge that include hydroxide ions, lactic acid salts or proteins to form insoluble aluminium hydroxide species that block sweat from reaching the surface of the skin. The high hydroxide formation constants of aluminium and zirconium allow this reaction to complete at neutral and in even slightly acidic conditions. The distance of diffusion into the duct prior to complete neutralization is generally dependent on the degree of neutralization of the active agent. $AlCl_3$, the most commonly used prescription topical antiperspirant active agent, is typically applied with no neutralization and produces a very resilient plug within the eccrine gland. However, the plug formation process creates a significant amount of hydrochloric acid (HCl), often resulting in skin irritation (stinging, burning and erythema) and low treatment compliance even if application is limited to every second or third day. Commercial OTC antiperspirants are based on partially neutralized salts such as aluminium zirconium trichlorohydrate gly. These materials reduce the amount of HCl produced by as much as 80% and create a more superficial blockage than $AlCl_3$ but allow daily or twice daily application without significant skin irritation. While these blockages are more superficial, there are several literature reports of blockage lifetime lasting more than 7 days, so it is possible to achieve high sweat reduction values provided the active agent is effectively delivered to the opening of the eccrine gland daily.

Effective delivery of commercial antiperspirant active agents is dependent on two major factors: uniform delivery of the active agent across the axillae, and time of application. As antiperspirant products treat each eccrine gland individually via the formation of a physical blockage, there is a need to place active agent near the opening of every duct. This requires the user to coat the entire axillae with product and assure that active agent is delivered through hair to the skin surface. Products with narrow applicators such as roll-ons or dab-ons can leave significant areas without treatment and reduce the overall efficacy. This is particularly important for men, as they typically have a larger axilla than females (135 vs. 65 cm^2) and more axillary hair, making it more difficult to achieve complete coverage with a narrow applicator.[3] Moreover, products that deliver a dissolved active agent can often leave active agent on hair in the axillae, resulting in either untreated areas or a general reduction in dose of the active agent to the skin. This again increases difficulty for men as they have a lower incidence of axillary shaving than females globally.

The most common time to apply antiperspirant products is in the morning as part of a daily grooming regimen but several studies have shown that this is not the most effective application time.[4] Eccrine sweat rates follow a circadian cycle, resulting in an increasing sweat rate during the day and decreasing rates at night. Therefore morning application places the product on skin during a period of increasing sweat rate that make diffusion into the duct less efficient. Conversely, application at night allows diffusion to occur during a period of falling or low sweat rates, thereby improving conditions for the active agent to enter the duct. One published study has shown night-time application to improve efficacy of a commercial soft-solid product from 56% to 73% sweat reduction.[4] As a result of this behaviour, most 'clinical strength' products are designed for and have usage instructions recommending night-time application.

Efficacy testing of a 'clinical strength' product on male panelists

A single study was performed to quantify the antiperspirant performance of a commercial (Gillette) 'clinical strength' soft-solid antiperspirant test product (based on aluminium zirconium trichlorohydrate gly) relative to a placebo. The study enrolled 20 healthy male panelists. The study lasted 32 days and was divided into two parts. The first 21 days were used as a pretreatment conditioning period. During this time panelists were provided a deodorant product (without antiperspirant active agent) to use *ad libitum* in the axilla or they could choose to use nothing in the underarms during this period. The remaining 10 days constituted the treatment period. Within a subject, the two treatments were evaluated (one on each underarm) in a randomized complete block (paired comparison) design.

Sweat collections were obtained four times during the study including a baseline on day 1, as a prerequisite for entrance into the treatment period. Sweating was induced by having subjects enter a hot room (38 ± 1 °C and 30–40% relative humidity) for a total of 100 min. After a 40-min acclimation period, two 20-min sweat collections were performed with a 10-min break between collections. Subjects were eligible for participation in the study based on the inclusion/exclusion criterion of average sweat collection amounts between 150 and 1200 mg during the baseline sweat collections. Moreover, the subjects also had to have a right/left axillary sweat ratio in the range of 0·5–2·0. Treatment assignments were randomized and balanced so that each treatment appeared on each axillary treatment site an approximately equal number of times. Subjects who were accepted into the panel received their first product application by study site technicians directly following the baseline sweat collection and after washing their axillae with a 2% soap solution.

Subjects returned to the test facility for product application by study technicians once daily for the next nine consecutive

evenings after washing their axillae with a 2% soap solution. Treatment was performed with 0·6 g of product per axilla. Post-treatment sweat collections were performed, using the same methods and conditions as at baseline, approximately 12 and 24 h after the fourth product treatment and 12 h after the tenth treatment.

At 12 and 24 h post-treatment 4, antiperspirant effectiveness was evaluated by determining shifts in ratios of the sweat output of the treated axilla to the control axilla adjusted for the ratio of right-to-left axillary sweating rate for each panelist. The Wilcoxon signed rank test was applied to compare the adjusted ratio to 0·80, the value which corresponded to a 20% reduction in moisture due to treatment, that is recommended in the guideline for Effectiveness Testing of OTC Antiperspirant Drug Products, June 2003.

Two additional separate studies were performed to quantify the antiperspirant performance and irritation potential of the same commercial (Gillette) 'clinical strength' soft-solid antiperspirant test product relative to a marketed prescription antiperspirant product containing 6·5% $AlCl_3$ using an intent-to-treat (ITT) design. Each study enrolled 35 healthy male panelists. These studies lasted 27 days and were divided into two parts. The first 17 days were used as a pretreatment conditioning period. During this time panelists were provided with a deodorant product (without antiperspirant active agent) to use *ad libitum* in the axilla or they could choose to use nothing in the underarms during this period. The remaining 10 days constituted the treatment period. Within a subject, the two treatments were evaluated (one on each underarm) in a randomized complete block (paired comparison) design. Treatment assignments were randomized and balanced so that each treatment appeared on each axillary treatment site an approximately equal number of times.

Sweat collections were obtained three times during the study including a baseline on day 1, as a prerequisite for entrance into the treatment period. Sweating induction and sweat collections were performed as described before.

After the baseline sweat collection and initial product application, subjects returned to the test facility for product application once daily in the evening for nine consecutive days. Study site technicians applied the product after subjects washed both axillae with a 2% soap solution. Product treatment was performed as per the usage instructions for each product. Skin irritation was graded post-treatment using a range of 0–3 for none to strong irritation. Sweat collections were performed, using the same methods and conditions as at baseline, approximately 24 h after the sixth and ninth product treatments on days 7 and 10, respectively.

Analyses were conducted on the 'full analysis set' which is as close as possible to the ITT ideal of including all randomized subjects.[5] Measurements taken at the time of discontinuation for subjects who did not complete the study were included in the primary analysis. This analysis method provided a conservative strategy and estimate of treatment effects that are more likely to mirror those observed in actual practice.

Average sweat level was log transformed and analysed using a mixed model with terms for treatment, side, log transformed baseline sweat amount and a random subject effect. If the lower limit of the 95% one-sided confidence interval was less than or equal to a percentage difference of 20%, it was concluded that the antiperspirant prototype was not inferior to the prescription product based on historical consumer data.

A total irritation score was calculated for each subject's axillary side as a sum of the expert graded irritation scores over the study period. In the case of subject discontinuation, the last irritation score was carried forward in the calculation of the total irritation score reflecting irritation while on treatment. A mixed model was used for analysis.

Results and discussion

Results of the clinical trial of the commercial 'clinical strength' product vs. placebo are shown in Table 1. Each sweat collection showed a significant benefit for the treatment leg vs. placebo. Mean reductions were substantially higher than required for product labelling in most countries. Typically antiperspirants are required to have more than 20% sweat reduction in 50% of panelists. In this trial, average sweat reductions were two to three times higher than that defined as minimum. In fact, a majority of panelists demonstrated a benefit of more than 50% sweat reduction after four applications, whether the benefit was measured 12 or 24 h after the last application. The similarity of sweat reduction after four and 10 applications indicates a fairly rapid response to this product as compared with previous literature reports that between 7 and 10 days were required to reach maximum efficacy in antiperspirant products.[6] There were no adverse effects seen in this study and 19 of the 20 enrolled panelists completed all sweat collections.

Table 1 Comparison with placebo

Evaluation	Treated/placebo, mean (mg)	Mean % reduction ± 95% CI	Significance level vs. placebo	% panelists with > 50% sweat reduction
Baseline	573/547			
12 h after application 4	216/612	64·47 ± 10·59	< 0·0001	85
24 h after application 4	249/523	48·52 ± 16·03	< 0·0001	68
12 h after application 10	188/494	65·12 ± 9·02	< 0·0001	84

CI, confidence interval.

Table 2 Average sweat collections for each time point in the two comparison clinical studies, and statistics

Treatment	Adjusted mean sweat collected (log mg)	Adjusted mean sweat collected (mg)	Difference log(PP) − log(CS) [95% one-sided CI]	PP/CS [95% one-sided CI]	% difference [(CS − PP)/CS] × 100% [95% one-sided CI]	One-sided P-value
Study 1, post-treatment 6						
CS	2·0735	118	0·2066 [0·1415, –]	1·609 [1·385, –]	−60·9 [−38·5, –]	< 0·0001
PP	2·2801	191				
Study 1, post-treatment 9						
CS	2·0456	111	0·1587 [0·0871, –]	1·441 [1·222, –]	−44·1 [−22·2, –]	0·0004
PP	2·2044	160				
Study 2, post-treatment 6						
CS	2·313	205·7	0·054 [−0·001, –]	1·132 [0·998, –]	−13·2 [–, 0·2]	0·0530
PP	2·367	232·8				
Study 2, post-treatment 9						
CS	2·261	182·4	0·085 [0·034, –]	1·216 [1·081, –]	−21·6 [–, −8·1]	0·0045
PP	2·346	221·8				

CI, confidence interval; CS, clinical strength soft-solid; PP, prescription product.

Table 3 Sweat collection results based on meta-analysis of both comparison clinical studies

	Sweat collected (mg)	Difference (mg)	% difference	One-sided P-value
Post-treatment 6				
CS	155	54	−35·5	< 0·0001
PP	209			
Post-treatment 9				
CS	141	47	−33·0	< 0·0001
PP	188			
Overall				
CS	148	50	−34·0	< 0·0001
PP	198			

CS, clinical strength soft-solid; PP, prescription product.

The two ITT comparisons between the commercial 'clinical strength' product and the prescription product were performed with identical protocols to create a larger base size via meta-analysis without over crowding the hot room during sweat collection. Data from each sweat collection are shown in Table 2. As per the protocol, data at each point were compared against a noninferiority criterion of a < 20% positive difference between the commercial and the prescription product (i.e. the commercial product gave a lower sweat collection than the prescription product). The commercial 'clinical strength' product met that criterion at each time point and significantly outperformed (i.e. gave a lower sweat collection) at both sweat collections in the first clinical trial and after nine treatments in the second clinical trial with more than 95% confidence.

Data from the combination of these studies via meta-analysis are shown in Table 3. The commercial 'clinical strength' product outperformed the prescription product after six and nine treatments as well when all data points were included in a single analysis (Overall). This result was somewhat unexpected based on previous reports[3] that showed similar efficacy for testing in female panelists. Our hypothesis for this result is

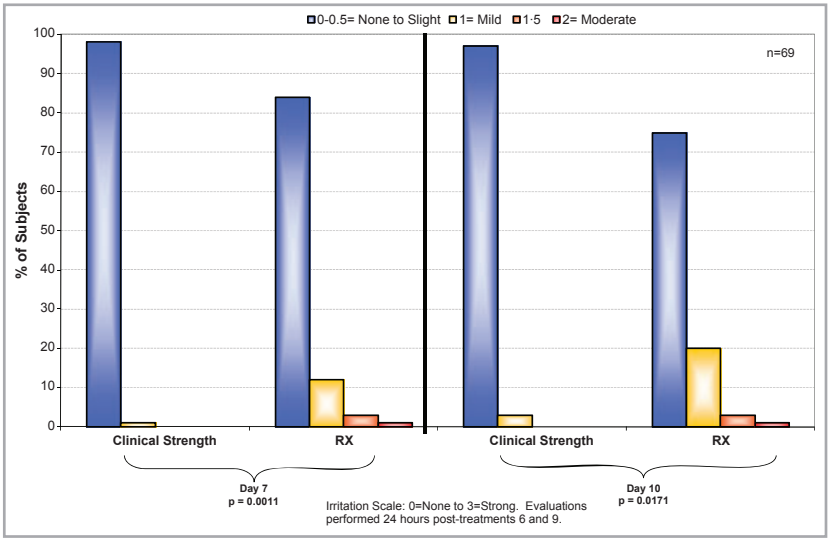

Fig 1. Combined irritation scores from the two comparison clinical studies. RX, prescription product.

that the dose of $AlCl_3$ in the prescription products delivered to the skin surface was reduced by the hair mass in the unshaven axillae of male panelists. The dissolved $AlCl_3$ in the prescription product is highly charged and is capable of strongly binding to any anionic functional group on the hair surface. Any binding would prevent a fraction of the active agent from reaching the duct opening and being capable of forming a plug within the duct. Conversely, the 'clinical strength' product employs a powdered active agent in a highly shear thinning matrix that limits loss of the active agent to the hair surface during product application.

The irritation evaluation for this test is consistent with the performance hypothesis. Combined irritation data from both studies are shown in Figure 1. As expected, the commercial 'clinical strength' formulation had very low skin irritation potential. This results from both the use of an active agent with less potential to produce acid on the skin surface and the use of dimethicone and petrolatum in the product matrix. The prescription product, while more irritating than the 'clinical strength' product, was less irritating than expected based on previous testing in female panelists.[3] The lower than expected irritation is consistent with loss of the potentially irritating $AlCl_3$ to the hair in the unshaven axillae of the male panelists vs. the shaven axillae in previous tests in women. Therefore, we believe that the prescription product would be more irritating had the male panelists in these tests been required to shave.

Conclusions

Based on these results, the reduction of sweat by a commercial 'clinical strength' antiperspirant product can provide comparable if not superior performance to $AlCl_3$ prescription products for men regardless of axilla shaving habits. For men who do not shave their axillae, the commercial 'clinical strength' antiperspirant product is recommended to provide high efficacy via efficient active transport through hair. For men who do shave their axillae, the commercial 'clinical strength' antiperspirant product is recommended to provide high efficacy and low skin irritation.

What's already known about this topic?

- Individuals with axillary hyperhidrosis have higher than average sweat rates.
- Patients with axillary hyperhidrosis are often treated with prescription products containing aluminium chloride ($AlCl_3$) solutions.
- Topical application of anhydrous $AlCl_3$ solutions can cause skin irritation.
- Men have larger axillae and more axillary hair than women.

What does this study add?

- Reduction of sweat by a commercial 'clinical strength' antiperspirant product can provide superior performance to $AlCl_3$ prescription products, with higher antiperspirant efficiency and lower skin irritation.
- Efficiency is driven by product formulation design which limits loss of the active agent to the hair surface during product application.
- Application at night allows diffusion to occur during a period of falling or low sweat rates, thereby improving conditions for the active agent to enter the duct.

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