Topical Methenamine Therapy for Hyperhidrosis

Stanley I. Cullen, MD

Methenamine, in a gel stick formulation, effectively decreased palmar and plantar sweating in 24 of 26 individuals studied. All patients had essential hyperhidrosis and were evaluated in a double-blind, placebo-controlled study. Even though methenamine is believed to act by the slow release of formaldehyde, one patient, who had a formaldehyde sensitivity that was proved by a patch test, was able to use the methenamine gel stick without difficulty. Approximately one third of the patients experienced some continuing relief for one to three weeks after discontinuing the trial medication. I conclude that methenamine is a safe, effective addition to the available types of topical therapy for essential hyperhidrosis.

Essential hyperhidrosis is socially embarrassing, damaging to clothing, and makes working with the hands difficult or dangerous. In some patients, the hyperhidrosis and resultant maceration is followed by growth of fungi or bacteria, promoting infection. Symptomatic treatment, when systemic causes are absent, is the most practical approach to the therapy of mild to moderately severe essential hyperhidrosis.

Eccrine sweating is initiated through sympathetic nervous system stimulation by the liberation of acetylcholine at nerve endings. The sympathetic system may trigger eccrine sweating in reaction to either mental, thermal, or gustatory mechanisms. Increased sweat production in response to either exogenous (increased ambient temperature) or endogenous (fever) temperature elevation serves as a protective heat loss mechanism to the body. Thermal sweating occurs primarily on the trunk and face. Mentally stimulated hyperhidrosis represents the individual's psychologic response to stress, and is generally most severe on the palms and soles, in the axillae, and on the forehead. This type of excess sweat production does not occur during sleep or when the patient is under general anesthesia. Gustatory sweating occurs on the lips, forehead, and nose following the ingestion of certain foods or as a manifestation of parotid gland injury, either as the result of surgery or from parotiditis. I present a clinical evaluation of the use of methenamine in a gel stick formulation in the topical therapy of essential or mentally induced hyperhidrosis.

PATIENTS AND METHODS

The test subjects were patients with moderate or severe essential hyperhidrosis. Informed consent was obtained after the nature of the therapy and alternative forms of therapy had been fully explained to all patients. No restriction was made as to age or sex, but I excluded patients with dermatologic disorders of the hands and feet that were not directly attributable to the hyperhidrosis. Therapy with any product that might influence the hyperhidrotic state, such as sedatives or tranquilizers, was not permitted. Thirty-one patients had bilaterally symmetric involvement of the palms and soles, or both, and were studied in a double-blind, placebo-controlled fashion. Twenty-six patients completed the study. Each patient applied the methenamine stick to one hand or one foot, and the placebo control medication to the other hand or foot twice daily for three weeks. Appearance of the active medication and the placebo were identical in all respects.

Methenamine stick is 5% methenamine in a solid gel base composed of SDA-4-ethanol, glycerin, stearate sodium, FDC Blue Dye No. 1 and perfume. Clinical evaluations were made at weekly intervals for the three-week test period, as well as for the three-week post-trial period, in order to determine the duration of effect. The degree of sweat production was assessed on a grade 1 to 4 scale, comparing the side that was treated with placebo control medication with the side that was treated with the methenamine stick. The amount of sweat produced was measured semiquantitatively using the starch-iodine reaction. In performing the starch-iodine sweat tests, the palms or soles were dried with facial tissue and painted with an iodine solution (3% iodine and 3% potassium iodide in 95% ethanol). Immediately after the skin was fanned dry, the patient placed the hand or foot on a sheet of bond paper with a starch-surface sizing for one minute. Iodine, carried onto the paper dissolved in sweat, produces the deep-blue starch-iodine reaction. Because the starch-iodine color fades, copies were made of all prints to preserve them.

RESULTS

My evaluations and those made by the patients corresponded quite

Fig 1.—Palmar sweat ... applied methenamine ... g

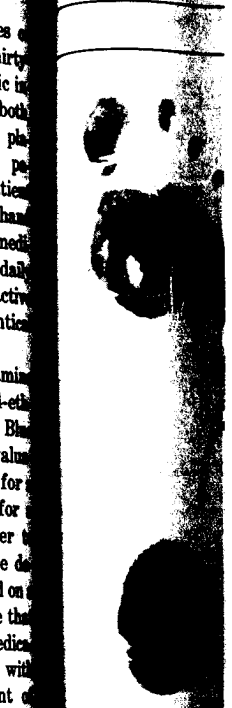

Fig 2.—Plantar ... applied methena...

...ely. The st... ...d the produ... ...ctive than d... ...ns. The vali... ...e tests was ... ...rly one thi... ...nts were o... ...icult to de... ...ducts desig... ...crease in ... ...views availa... ...tion of an... ...ses the di...

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From the Department of Medicine, University of Florida School of Medicine, Gainesville, Fla.

Reprint requests to 6628 NW Ninth Blvd, Gainesville, FL 32605 (Dr. Cullen).

Fig 1.—Palmar sweat print before (left) and after (right) three weeks of using topically applied methenamine gel.

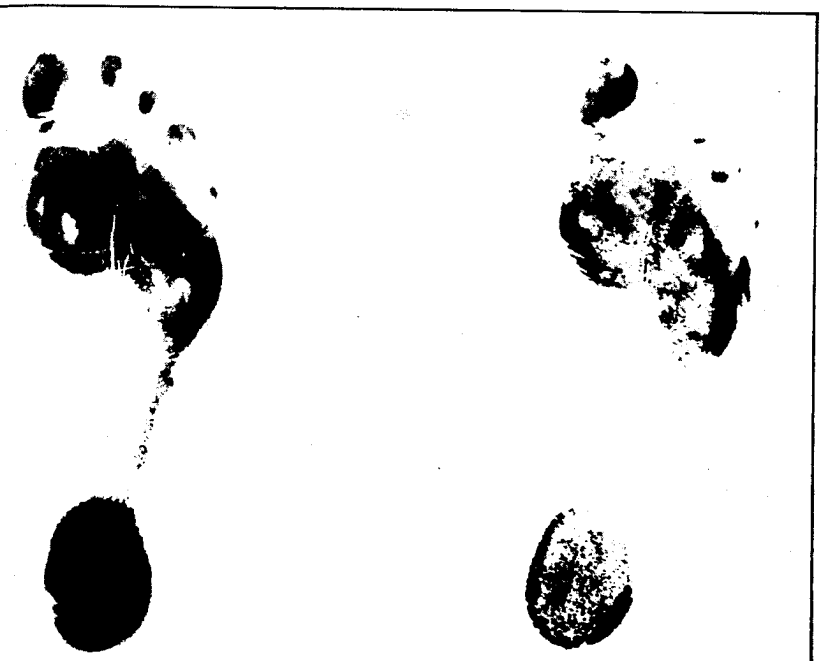

Fig 2.—Plantar sweat print before (left) and after (right) three weeks of using topically applied methenamine gel.

closely. The starch-iodine test indicated the product to be somewhat less effective than did the direct observations. The validity of the starch-iodine tests was difficult to assess since nearly one third of the copies of the prints were only fair in quality. It is difficult to determine the effects of products designed to cause a relative decrease in sweating. Bakiewicz reviews available methods for evaluation of antiperspirants and discusses the difficulties in the interpretation of results obtained.[1]

All patients but one initially had what was termed grade 4 hyperhidrosis. Ten days' to three weeks' application of methenamine stick reduced the severity to grade 2 (nearly normal) in 14 of the 26 patients, and to grade 3 in ten. There was no substantial change in two patients. The left side of Fig 1 shows an example of a patient with grade 4 palmar sweating before treatment, and the right side of Fig 1 shows a hand print of the same patient after three weeks of treatment with the methenamine stick. Fig 2 shows before and after sweat prints of the sole, with equally good results. Reduction to grade 2 was considered to be an excellent result and reduction to grade 3 was a partial or moderately good improvement. The two patients with poor or no improvement remained at grade 4. Statistical analysis of the clinical evaluation supported the hypothesis that the methenamine stick produced an improvement in the disorder by a factor of at least one measurable unit, with a probability coefficient of 0.97. The contrary hypothesis, that the medication does not affect the disorder, can be rejected with a probability of 0.05%. The summary of data in the statistical analysis is as follows: $\Delta 2$(test before-test after) (control before-control after) = 30; Number in sample, 26; average, $1.154 \pm$ SD 0.925.

The number of patients whose feet were treated was not sufficient to permit any final statistical conclusions. Clinically, the medication appeared to be more effective on the soles than on the palms. Five of the patients whose feet were treated had excellent results, and two had good results. In none of the patients did the medication fail to produce some improvement. Eight, or nearly one third of the patients, experienced some continuing relief one to three weeks after the trial. This residual benefit after the medication had been stopped suggests the absence of a placebo effect in influencing the results, and supports the evidence that the medication does produce an effective blockage of the eccrine sweat pores.

COMMENT

A wide variety of substances have antiperspirant effects when applied topically. Aluminum salts and other astringents are the most popular. They work by precipitating protein with resultant blockage of the eccrine sweat duct near the skin surface. Dusting of the feet or axillae with corn starch, talcum, or similar powders is helpful in absorbing the accumulated sweat. This also adds a

degree of comfort and reduces the likelihood of secondary dermatologic problems. Formaldehyde and related compounds can be effective topically applied antiperspirants, but their potential for allergic sensitization discourages chronic use. A 10% solution of glutaraldehyde has been reported to decrease plantar sweating.[2] My clinical experience has shown that concentrations of glutaraldehyde as low as 5% may also reduce palmar and plantar sweating. The annoying, but not serious, yellow-brown staining of the stratum corneum by this compound precludes its regular use on the palms or in the axillae. Anticholinergic substances have been reported to have local action when applied topically, but apparently not to a degree that would encourage widespread use.[3-5] Recently, glycopyrrolate has been reported as an effective antiperspirant in essential hyperhidrosis of the palms and soles, when introduced into the skin by direct current iontophoresis.[6]

Methenamine is a condensation product of formaldehyde and ammonia, and has been used as a urinary tract antiseptic for many years. Methenamine has been recommended at concentrations of 3% or higher as a preservative in ointments, and is an ingredient in contraceptive gels. When used in the past as an accelerator in the vulcanization of rubber, methenamine was found to cause an extensive, pruritic, erythematous, vesicular eruption on the exposed skin of many factory workers.[7] The eruption could be controlled by washing with a sodium bicarbonate solution.[8] It was suggested that the alkaline sodium bicarbonate solution inhibits both the breakdown of methenamine to formaldehyde and its subsequent oxidation to the irritating formic acid.

Review of the literature revealed only two references to the topical use of methenamine. Davis studied the effectiveness of a methenamine conjugate, methenamine undecylenate, as a topical agent for hyperhidrosis and bromidrosis.[9] The other is a reference made by Davis to a paper that was read before the Clinical Conference for the Practitioner, University of Cincinnati, 1959. The majority of the patients in the study by Davis had dermatologic problems either related to or unrelated to their hyperhidrosis. Many patients were reported as having a vesicular disorder, although the report did not indicate whether the disorder was dyshidrosis, vesicular tinea pedis, or allergic contact dermatitis. Methenamine (Antihydral) has been marketed in Germany and Austria for topical use in hyperhidrosis. This product contains 13% methenamine in a fat-free, drying ointment base and it is suggested for use in cases of acute perspiration of the foot, hand, and axillae. Antihydral has been available as an over-the-counter product for about ten years, but no data are available concerning adverse effects, except the warning that "should the skin become dry and brittle during treatment, a fatty ointment is recommended." The recommended oral dosage of methenamine for urinary tract infections is 1 to 2 gm/day, 10 to 20 times more than the dosage recommended for hyperhidrotic conditions.

Methenamine in solution releases formaldehyde at a rate depending on the acidity of the medium. As the pH of the sweat varies from 4.2 to 5.6, depending primarily on the rate of sweat production, it can be assumed that methenamine releases free formaldehyde and that the resultant anhidrosis is essentially the result of precipitated protein plugging of the sweat duct. Experiments by Papa revealed that transparent tape-stripping of the stratum corneum does not restore normal sweating to aluminum chloride-induced anhidrotic skin.[10] Anhidrosis obtained by formaldehyde application could be reversed by the stripping technique. Anhidrosis was brought on by the occlusive application of either a 20% aluminum chloride solution, or a 3.7% formaldehyde solution. Sweat production and delivery to the skin surface was assessed by direct observation of sweat droplets on the skin surface, or on a layer of topically applied starch-castor oil mixture. Methylene blue iontophoresis confirmed the stripping experiments, suggesting that formaldehyde anhidrosis results from the formation of a keratin plug in the distal sweat duct, and that aluminum salts act by a mechanism other than poral occlusion. Clinical experience indicated that topical methenamine was considerably less irritating than formaldehyde.

I suggest that the release of formaldehyde from the nearly neutral solution of methenamine in eccrine sweat is so gradual, that primary irritation is avoided. It is interesting to note that one of the patients who had a proven sensitivity to formaldehyde was able to use methenamine without difficulty. Perhaps the slow release of formaldehyde from the methenamine was able to keep its concentration below that critical level necessary to develop an allergic contact dermatitis. The possibility of developing an allergic contact dermatitis in formaldehyde-sensitive individuals is real and should be recognized.

The methenamine stick was supplied by Westwood Pharmaceuticals Inc., Buffalo, NY.

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