# Hyperhidrosis: A Management Dilemma

Capt Eron G. Manusov, MC, USAF, and Maj Mark T. Nadeau, MC, USAF
*Tachikawa, Prefecture, Japan*

*Hyperhidrosis is excessive sweating in response to psychological stress and emotional stimuli. The sweat is usually limited to the palms, soles, and axillae, and is greatly accentuated by mental stimuli rather than temperature and exercise. The severity is such that for many, sweating has become socially and emotionally devastating and may predispose to other cutaneous diseases. More than 60 research papers on eccrine glands and sweating have been published since 1978. Little progress, however, has been made on the control of hyperhidrosis, and the process remains a treatment dilemma among both family physicians and dermatologists. The many treatment modalities documented in the literature have been for the most part unsuccessful or unacceptable.*

*This report describes the use of phenoxybenzamine, an α-adrenergic antagonist, for control of excessive sweating in two patients. After a trial of topical medication, phenoxybenzamine is useful for the reduction of sweating to an acceptable level.*

Sweating is a normal physiologic response to stimuli, which most Americans consider to be only of cosmetic consequence. Americans, however, spend in excess of $500 million annually on sweat-reducing products. For some, sweating is so severe that it becomes disabling, often leading to social isolation, low self-esteem, and even medical illness. Primary hyperhidrosis is a disorder of sweating characterized by an exaggeration of the normal response of both eccrine and apocrine sweat glands to mental stimuli.[1] Hyperhidrosis usually involves the palms, soles, and axillae. Patients find the symptoms embarrassing and may complain that the anticipation of sweating has resulted in repeatedly avoiding certain activities. Axillary hyperhidrosis is particularly socially embarrassing. As much as 26 mL/h of sweat from each armpit may be delivered and this causes wetness, staining, and rotting of clothes.[2] Palmar hyperhidrosis may range from annoying damp hands to such an excessive sweat production that it becomes hazardous. Plantar hyperhidrosis leads to infection, bromohidrosis, and blisters.

For both patient and physician, hyperhidrosis can be frustrating. Many treatment methods have been offered, often with limited success. Treatment is aimed at the mechanism of sweat production, which is under both local and neuronal control. For this reason, it is important to be aware of the pathophysiology and neuroanatomy of sweat production so as to direct the management.

Two cases of the use of phenoxybenzamine, an α-adrenergic antagonist, for control of excessive sweating are presented with emphasis on the pathophysiology of sweat production and neuropharmacology of phenoxybenzamine. After a trial of topical antiperspirant, a trial of phenoxybenzamine may reduce excessive sweating to an acceptable level.

## ILLUSTRATIVE CASES

### Case 1

A 57-year-old woman, followed in the Department of Family Practice for mild hypertension, hypothyroidism, and depression, complained of severe, incapacitating sweating. She described multiple clothes changes each day and would soak her clothes a half hour after a shower. Her sweating seemed to worsen when she became anxious. She had tried, without success, multiple antiperspirants and body powders.

Results of an outpatient laboratory evaluation showed her to have normal values on blood chemistry determination and thyroid function tests. Since a possible side effect of antidepressants is hidrosis, her antidepressants

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*From the 475th Medical Group, Yokota Air Base, Japan. The opinions expressed herein are those of the authors and do not reflect the opinions of the US Air Force or the Department of Defense. Requests for reprints should be addressed to Capt Eron Manusov, PSC Box 4487, APO San Francisco, 96270.*

were changed and finally discontinued, but she still complained of hyperhidrosis. Finally, she was begun on 10 mg of phenoxybenzamine by mouth twice a day. On the third day she described a remarkable decrease in her sweating. Improvement was such that her family remarked on the improvement, and she described only infrequent clothes changes. She continued to sweat under strenous activity, but her sweating was limited to an acceptable level. Her antidepressants were reinstated, and she continued to remain dry. She was maintained on 10 mg of phenoxybenzamine twice a day without any side effects.

### Case 2

A 31-year-old healthy man described heavy perspiration, especially axillary and facial. The condition was exacerbated by situations that created anxiety, such as unexpected or misunderstood events or conversations. A pretreatment questionnaire revealed hidrosis as a signal of anxiety. The patient would be noticeably wet at routine physician appointments. He had tried multiple local measures without success. Friends and family remarked on the degree of hidrosis, which he ascribed to a "genetic disorder," as his father also suffered from hyperhidrosis. He was begun on 10 mg of phenoxybenzamine twice a day, and a tolerable level of sweating was attained with 40 mg by mouth twice a day. Subsequent patient visits revealed a dry patient who described a remarkable decrease in hidrosis to a personally acceptable level. Weekly blood pressure readings remained unchanged, and he reported no side effects of the medication. It was noticable in the office when the patient had not taken the medication, and several trials at discontinuation of the phenoxybenzamine resulted in hyperhidrosis, which resolved with the reinstatement of phenoxybenzamine.

## PATHOPHYSIOLOGY

There are 3 to 4 million sweat glands distributed over the body surface.[3] Sweating is under the control of both circulating catecholamines and sympathetic innervation. Although the neurotransmitter for these fibers is acetylcholine, the activity at these nerve endings is dependent upon a complex arrangement of excitatory and inhibitory input.[4] Reports vary, and both eccrine and apocrine glands have been shown to be stimulated by cholinergic, as well as $\alpha$- and $\beta$-adrenergic, agonists. Studies on a cellular level have shown cyclic adenosine/ monophosphate (cAMP) to play a significant role in the sweating process.

The hypothalamus is responsible for integration of information for chemoregulatory control. Afferent impulses from sensors for skin and core temperature are received in the hypothalamus, and efferent impulses, originating in the preoptic area of the anterior hypothalamus, are carried by sympathetic fibers to the periphery. The head and neck are supplied by spinal cord segment T2 through T4, the upper limbs are supplied by T2 through T8, T6 through T10 supply the trunk, and T11 and L2 supply the lower extremities.

Sweating rate is also modulated by local physical variables. Local skin temperature, wetness, and blood flow all decrease sweat activity. Sweat rate is highly variable among individuals and seems to be a function of acclimatization, sex, age, and possibly diet.[4]

## TREATMENT

Previous attempts at treatment of hyperhidrosis have been disappointing, and range from topical application to surgical sympathectomy and axillary dissection (Table 1). Treatment is aimed at the reduction of sweat to an acceptable level.

Topical medications should be attempted before other methods of intervention are considered. Aluminum chloride is the preferred agent, is successful for many, and is, in general, well tolerated.[1] A proposed mechanism of action for sweat reduction is an actual mechanical obstruction of the eccrine sweat gland. There is some evidence, however, that atrophy of the secretory cells may be responsible for the decreased sweating.[1]

Aluminum chloride should be applied at night to take advantage of the relative decreased sweating, since contact with water results in hydrochloric acid formation. Approximately 50 percent of patients will experience skin irritation, which often becomes the limiting factor to its use. A once-a-day application of 1 percent hydrocortisone often decreases the irritation and improves compliance.

Glutaraldehyde and tannic acid (strong tea) have been used for plantar and palmar hyperhidrosis and are both effective. Undesirable side effects such as brown staining of the skin, however, often preclude their use. Gluteraldehyde concentrations range from 2 to 10 percent, and applications up to four times a week are often necessary to maintain control.

Iontophoresis is fairly effective for plantar and palmar hidrosis. The procedure is well tolerated and should be repeated five to six times a week until the desirable results are obtained, and then as needed. The mechanism of action is believed to be blockage of the gland at the level of the stratum corneum, although there are no structural changes on histologic examination.[1]

Systemic and topical anticholinergics have been used with transient effect in most patients with hyperhidrosis. The unpleasant anticholinergic side effects are not well

**TABLE 1. TREATMENT OF HYPERHIDROSIS**

- Topical medication
  - Aluminum chloride
  - Gluteraldehyde
  - Tannic acid
- Iontophoresis
- Anticholinergics
- Surgical
  - Axillary excision
  - Sympathectomy

tolerated, and long-term success is variable. Anticholinergics, such as glycopyrronium bromide (glycopyrrolate), may be most useful as an adjunct to other therapy. Glycopyrrolate may be used topically or systemically, and it may also be used as an adjunct with iontophoresis.

Surgical management is rarely indicated because of the adverse sequelae and expense. The area corresponding to the hairy region of the axilla is excised. The excision must extend down through the fat with the normal skin creases. Although there are many modifications of the technique, it is common for sweating to resume and contractures to result.

Finally, sympathectomy can be offered to patients with intractable hyperhidrosis. As discussed earlier, the neuroanatomy is well defined, and reports of technique and results are well documented in the literature.[1,5–7] Early complications, such as infection, pneumothorax, and Horner's syndrome, and late complications, such as resumption of sweating and compensatory hyperhidrosis in nondenervated areas, are the main disadvantages associated with sympathectomy.

## NEUROPHARMACOLOGY OF PHENOXYBENZAMINE

Phenoxybenzamine is an $\alpha$-adrenergic blocking agent that has been used in the treatment of causalgia, neurogenic bladders, and sweating in the spinal-cord-injured patient.[2,5] The success seems to be secondary to the sympatholytic activity; in essence, patients receive a medical sympathectomy. An understanding of the pharmacology of phenoxybenzamine is crucial to its use in treatment for the patient complaining of hyperhidrosis.

There are two known mechanisms by which phenoxybenzamine affects the sympathetic influence on sweating. Although cholinergic stimulation is generally felt to have a greater effect, $\alpha$-adrenergic agonists have also been shown to have the potential to stimulate sweating by modifying the summation of inhibitory and excitatory responses at the postganglionic level. Phenoxybenzamine binds to the $\alpha$-adrenergic receptor and has an in vitro half-life of about 24 hours. The success with the two patients reported here is in part due to this $\alpha$-adrenergic blockade; however, phenoxybenzamine can attenuate the effect of sympathetic nerve stimulation by the inhibition of uptake of neurochemical transmitters, such as norepinephrine, at the postsynaptic site. The complex mechanism of action provides an efficient sympatholytic activity with minimal side effects.

Clinical experience has shown that low doses of oral phenoxybenzamine are well tolerated.[2,5] The side effects of the medication are related to $\alpha$-adrenergic blockade and are transient. The most bothersome of the side effects are mild orthostatic hypotension and inhibition of ejaculation. Higher doses and intravenous use have the potential for serious complications, but doses less than 80 mg/d usually go unnoticed by the patients. Resolution of orthostatic hypotension may disappear despite continued blockade but may recur under conditions that promote vasodilation, such as eating a large meal, exercising, or consuming large amounts of alcohol. Chemicals that stimulate both $\alpha$-adrenergic and $\beta$-adrenergic receptors can have an exaggerated $\beta$-adrenergic receptor response because $\beta$-adrenergic receptors are left unopposed.[8]

Effects that may not be related to $\alpha$-adrenergic blockade include a general feeling of lethargy and tissue irritation, which may account for the nausea that is sometimes noted with oral doses. In the two cases reported here and in the cases reported by Shessel et al[2] and Ghostine et al,[5] the patients described only mild orthostatic changes.

To initiate therapy, the patient should document a subjective degree of hidrosis. Potential side effects should then be discussed with the patient, and 10 mg of phenoxybenzamine daily by mouth may be instituted. The dose may be increased until patient satisfaction is obtained, side effects are unable to be tolerated, or a maximum of 80 mg/d is achieved. The signs of hypotension should be emphasized, and weekly blood pressures measurements documented until a level dosage is obtained. The patient can then manipulate the dosage according to lifestyle and situation. As with the second patient, it became obvious when the phenoxybenzamine was discontinued.

## SUMMARY

Little progress has been made in the control of hyperhidrosis, and the process remains a treatment dilemma for both family physicians and dermatologists. For some, hyperhidrosis is so bothersome that they become social recluses, are inhibited in their jobs, and may be predisposed to other cutaneous disease. Topical antiperspirants remain the cornerstone of treatment. Surgical management, however, may be offered for intractable hyperhidrosis.

Although phenoxybenzamine has been used successfully for control of other diseases of the sympathetic nervous system, its use in hyperhidrosis has not been previously suggested. The success with the two cases reported here suggests that phenoxybenzamine may be helpful when topical medication has failed. The side effects are minimal, and the drug is well tolerated. The paucity of literature on the clinical use of phenoxybenzamine makes dose and length of therapy difficult to determine. Experience suggests that success may be achieved with doses as small as 20 mg/d. It must be made clear to the patients that sweating is an adaptive mechanism, that some sweat production is necessary, and that the long-term success of this medication is unknown. For those patients in whom sweating is uncontrolled after a trial of topical antiperspirant, the use of phenoxybenzamine may be effective to decrease sweating to a acceptable level.

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