TOPICAL SUPPRESSION OF ECCRINE SWEAT DELIVERY WITH A NEW ANTICHOLINERGIC AGENT*

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An anticholinergic agent (AHR–483)[1] has been investigated for its property of suppressing or totally inhibiting eccrine sweat gland function when applied topically—over large areas of the body—without inducing other significant local or systemic side effects.

Studies of effectiveness and toxicity have been carried out in human volunteers. *In vitro* penetration studies of C^{14} labelled material have also been done.

This agent (AHR–483) (See Fig. 1) is closely related to glycopyrrolate which has been used extensively for control of peptic ulcer and has been studied extensively in animals and man (1–6).

METHODS

A. AHR-483 was prepared for topical use by dissolving in distilled water to make solutions from 0.05 to 0.5%. Concentrations of 0.05, 0.1 and 0.5% were applied to the forearms of 30 young adult volunteers. 0.1 cc of the solutions were applied from a pipette and allowed to dry on the forearm. After a period of 90–120 minutes the subjects washed the area with tap water. The starch-iodine method for detecting sweating was used. The subjects were put into a thermal chamber in which the temperature was kept at 88–94° F and the humidity at 70–80%. The degree of sweating was determined visually after 20–30 minutes in the thermal chamber.

B. Solutions for topical application to axillae were prepared by dissolving 0.5% AHR-483 in 0.4% carboxymethylcellulose in distilled water. This was dispensed in a commercial roll-on type bottle. The subjects applied this material to the right axillary vault b.i.d. The left axillary vault had no medication of any kind applied during the test period.

Delivery of fluid to the axillary vault was measured by a gravimetric technic. This involved the placement of absorbent cotton in both axillary vaults and measuring the weight of the cotton (in petri dishes) before and immediately after exposure of the subject for 30 minutes in the thermal chamber. Gravimetric tests of both axillae were done twice on most subjects before the test material was applied. The subjects stopped all axillary medication two weeks before entering the study.

C. AHR-483 was prepared for intradermal injection in the forearms of young adults by dissolving AHR-483 in normal saline under sterile conditions to make solutions varying in concentration from 10^{-5} to 10^{-10}. These concentrations were injected (0.1 cc) intradermally into the forearms of 10 subjects. The areas were tested for sweating responses by using the starch-iodine visual method while the subjects were subjected to the thermal chamber under the conditions described above.

D. *In vitro* percutaneous absorption was measured in human skin (leg or breast) removed at surgery. The skin was placed in a modified skin penetration chamber. C^{14} labeled AHR-483 was placed on the epidermal surface and the fluid bathing the corium was sampled for radioactivity at given intervals. This technic has been used in our laboratory previously and is described in detail elsewhere (7, 8).

E. Toxicity studies were carried out with aqueous and alcoholic solutions of AHR-483. Ten (10) cc of 0.5% aqueous solution were applied with a pipette over the arms, trunk and legs of 20 normal adult subjects. The material was spread over areas which covered the entire arms, legs and trunk. The material was allowed to dry. The subjects were watched closely for any local or systemic signs of toxicity (cutaneous reactions, pupillary changes, dry mouth, urinary difficulties, gastro-intestinal reactions, dizziness, or any subjective complaints) for 7–10 days.

Another 15 subjects were tested with 70% alcoholic solutions (0.5% AHR-483) by topical application in the same way as outlined above. The subjects were observed in the same way.

Ten additional subjects were treated with 15 cc of 0.5% AHR-483 in aqueous solutions as above.

Another group of 15 subjects was treated with topical application of 8 cc of 0.5% AHR-483, aqueous solution, to arms and legs. The arms and legs were then encased in Saran Wrap for 14–16 hours. These subjects were watched closely for any local or systemic reactions.

F. Fifty (50) subjects were used for repeat insult patch tests. 0.1 cc of 0.5% aqueous solution AHR-483 was applied to a piece of soft linen. The linen patch was applied to the upper arm

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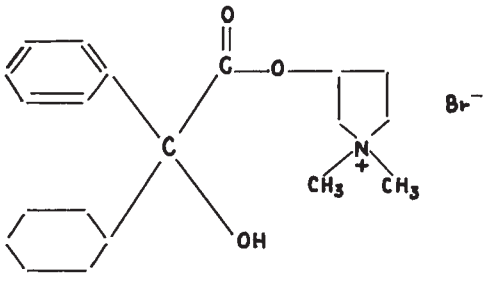

FIG. 1. AHR-483 (1-methyl-3-pyrrolidyl α-phenylcyclohexaneglycolate methobromide).

and covered with an elastoplast[2] bandage for 48 hours. This test was repeated in 7 days and again in 21 days. The areas were inspected at the time of removal of the patch and at 48 and 96 hour intervals following removal of the patch.

G. In 7 adult subjects with severe atopic dermatitis (erythema, erosions, scaling, lichenification and, in 2 subjects, oozing and crusting) 8 cc of aqueous solution of 0.5% AHR-483 was applied to arms and legs and covered with Saran Wrap for 14–16 hours. These subjects were watched closely for any local or systemic signs of toxicity. They were observed for 10–20 days following the application.

RESULTS

A. AHR-483 in 0.5% concentrations consistently inhibited sweating of the forearm. The inhibition was more marked after 3–4 daily single applications than after one single application. Figure 2 shows the inhibition of sweating of the treated forearm after 3 days of daily, single applications of 0.5% AHR-483 to the entire forearm. The untreated forearm shows normal sweating. Concentrations below 0.5% (0.1% and 0.05%) are capable of inhibiting sweating but are not as consistently reliable as the 0.5% concentration. With 0.1 cc of 0.5% aqueous solution, 16 of 30 subjects showed inhibition after single application. With 0.1 cc of 0.5% aqueous solution applied to the forearm (about 3 sq cm) once daily for 3 days, 20 of 20 subjects showed complete inhibition of sweating in the area of application.

B. Inhibition of axillary sweating can be accomplished by repeated daily applications of 0.5% AHR-483. The inhibition is consistent and quite dramatic. Table I gives the quantitative data in regard to base line measurements of axillary delivery as well as measurements taken after one to seven weeks of twice daily applications. It is evident that most subjects respond with marked inhibition of sweating. The variation of effect among subjects remains unexplained. A few of these subjects have been tested after 3 months of continuous use and the inhibition remains to the same degree. The average subject used 15 cc of 0.5% AHR-483 per week. There was no evidence of local or systemic reaction of any kind in any of these subjects.

In most subjects the right axilla delivered more fluid than the left axilla in the base line measurements. The AHR-483 was applied to the right axilla in all of the eighteen subjects. All of the subjects were young adults. Ten were males and eight were females.

It is of interest to note that of the 43 observations only one (Subject No. 8; week 1; −3.3%) indicates an increase in sweating in the right axilla.

The average per cent inhibition of sweating in the treated axilla for the weekly estimations varies from 40.75% to 68.77%.

None of these subjects complained of any irritation or discomfort of any kind.

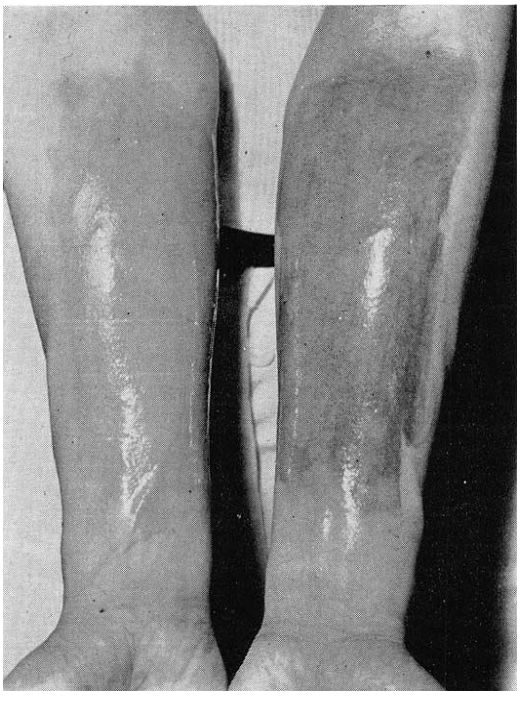

FIG. 2. Right forearm treated with AHR-483 (viewer's left) shows inhibition of sweating as indicated by lack of black discoloration (starch-iodine-castor oil technic) after exposure in thermal chamber.

[2] Duke Laboratories, Norwalk, Conn.

TABLE I

*Axillary sweat delivery and per cent inhibition**

Subject Number	Arm	Pre-Drug Base			Weeks Post-Drug and Per Cent Inhibition											
		1st	2nd	Mean	1		2		3		4		5		7	
		Mgm	*Mgm*	*Mgm*	*Mgm*	%	*Mgm*	%	*Mgm*	%	*Mgm*	%	*Mgm*	%	*Mgm*	%
1	R	240	216	228.0	135	37.5			62	72.1						
	L	205	175	190.0	180				185							
2	R	192	185	188.5	95	51.0			70	67.3						
	L	142	140	141.0	145											
3	R	450	376	413.0	145	56.1			56	89.5						
	L	340	310	325.0	260				420							
4	R	460	485	472.5	210	59.1			84	83.0						
	L	350	368	359.0	390				375							
5	R	210	262	236.0	180	29.6			85	59.9						
	L	250	285	267.5	290				240							
6	R	201	185	193.0	168	8.9			152	21.4						
	L	175	160	167.5	160				168							
7	R	210	225	217.5	127	38.7			42	82.7						
	L	198	197	197.5	188				220							
8	R	223	140	181.5	184	−3.3	202	54.9					112	46.7	108	79.8
	L	274	160	217.0	213		536						251		639	
9	R	137	135	136.0			612	3.5			133	55.1				
	L	74	107	90.5			422				197					
10	R	76	73	74.5	87	36.0	92	19.2			180	48.0			90	60.0
	L	39	63	51.0	93		78				237				154	
11	R	515	235	375.0	62	92.8	149	85.0			796	69.8			315	66.5
	L	390	117	253.5	582		670				1784				635	
12	R	300	109	204.5	24	86.3	51	88.7								
	L	155	80	117.5	100		259									
13	R	269	213	241.0			112	78.1					344	34.8		
	L	202	113	157.5			334						345			
14	R	220		220.0	183	36.0										
	L	184		184.0	239											
15	R	107	263	185.0			92	41.9	140	70.3	91	42.8				
	L	117	246	181.5			155		462		156					
16	R	53	32	42.5			52	54.1	99	27.6						
	L	48	39	43.5			116		140							
17	R	283	124	203.5			492	27.7	1191	28.9	413	51.9				
	L	226	64	145.0			485		1194		612					
18	R	2864	692	1778.0	1335	3.7					372	48.8				
	L	2741	765	1753.0	1368						715					
Number of subjects					13		9		10		6		2		3	
Mean per cent inhibition					40.95		50.33		60.27		52.73		40.75		68.77	
95% upper confidence limit					58.34		73.44		78.05		62.50				93.86	
95% lower confidence limit					23.56		27.22		42.49		42.96				43.68	

* Axillary sweat delivery in grams for right and left arms prior to therapy and at weekly intervals following twice daily applications of 0.5% AHR-483 to the right arm only. The per cent axillary sweat inhibition has been calculated as follows:

$$\text{Per cent inhibition} = 100\% = \frac{\text{Per cent of base for R}}{\text{Per cent of base for L}} \times 100$$

$$\text{Per cent of base for } R_1 = \frac{\text{Mgm sweat after one week of therapy}}{\text{Mgm sweat during base}} \times 100 \text{ (e.g.)}$$

Table I is a summary of all the data for 18 subjects in whom axillary sweating was measured before and after application of AHR-483. Ninety-five per cent (95%) upper and lower confidence limits are expressed for each of the time periods.

C. Table II shows the results of intradermal injection of 0.1 cc of AHR-483 in different concentrations. Most subjects show definite inhibition of sweat delivery in concentrations as low as 10^{-8} although some variation is apparent among the subjects tested.

D. The penetration of C^{14} labelled AHR-483 was measured *in vitro* using excised human breast skin. Seven determinations were made on a single specimen. 0.25 ml of an ethanol solution saturated at room temperature was applied to 3.14 cm^2 of the epidermis and the specimens were incubated for 24 hours at 40° C with a relative humidity of 88%. The average penetration in per cent of applied counts penetrating in 24 hours was 0.02% with a range of 0.002 to 0.035 %.

E. We have not yet seen any local or systemic signs of toxicity from 0.5% AHR-483 using the the amounts and technics described. We have used up to 75 mgm topically over large areas without occlusive wrap, and up to 40 mgm over arms and legs with occlusive wrap. No local or systemic signs of toxicity have been observed.

F. Repeat insult patch tests have not revealed any evidence of sensitization or irritation in 50 subjects.

TABLE II

AHR-483 injected intradermally into forearm (0.1 cc)

Subject	Concentration					
	10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}	10^{-10}
1	+	+	+	+	0	0
2	+	+	+	0	0	0
3	+	+	+	+	0	0
4	+	+	0	0	0	0
5	+	+	+	+	0	0
6	+	+	+	+	0	0
7	+	+	+	+	0	0
8	+	+	+	+	0	0
9	+	+	+	+	0	0
10	+	+	+	+	0	0

+ = Complete inhibition.
0 = No inhibition.

G. One of the 7 adult subjects with severe atopic dermatitis developed a mild dryness of the mouth with occlusive wrapping after topical application of 8 cc of 0.5% AHR-483. This subject had many areas of oozing and excoriations under the occlusive wrap. The other 6 subjects did not develop any signs of systemic effect of the drug.

One might expect such signs as pupillary changes, dryness of mouth, difficulty of urination, drowsiness, etc., due to the drug's anticholinergic activity. However, the fact that only one subject developed the mild symptom of dryness of mouth with such exaggerated conditions of exposure is encouraging in view of possible clinical use of this agent.

DISCUSSION

Shelley and Horvath demonstrated that oral administration of anticholinergic agents is relatively ineffective for control of sweating. They state "anhidrosis is not a therapeutic result of systemically administered anticholinergic drugs. Rather, it is a sign of over-dosage." They also demonstrated that scopolamine hydrobromide, 1% aqueous solution, will inhibit sweating when applied topically. They expressed considerable concern that scopolamine hydrobromide might be hazardous if used over large areas or on skin already involved in an inflammatory process where penetration might be enhanced (9).

The features of AHR-483 which make it an agent of potential use clinically are:

1. It is effective by topical application.

2. There is no evidence in our studies that it induces local or systemic reaction even when applied in amounts up to 75 mgm over large areas. Also, the lack of any systemic effects after 40 mgm were applied to the arms and legs under occlusive wrap is impressive. Previous work has shown that occlusive dressings are capable of enhancing penetration by a factor of 100 fold (10).

3. The almost complete lack of signs of systemic reactions after applications of 40 mgm under occlusive wrap over large areas of skin severely involved in atopic dermatitis.

4. Lack of irritation or sensitization in the studies performed to date.

We were unable to show any inhibition of sweating on the palms with topical application. Shelley and Horvath were unable to show inhibition of sweating of palms or soles with scopolamine hydrobromide (3). This follows the

general observations of poor penetration of palms and soles by any agents tested in the past (11, 12). We have observed good inhibition of sweating on forearms, chest, back, forehead, and axillae. These have been the only areas tested in addition to the palms and soles. As there is definite need for an effective agent for the control of eccrine sweating in man, AHR-483 seems worthy of further study.

SUMMARY

1. A new anticholinergic has been found to be very effective in suppressing eccrine sweat delivery by topical application.

2. This agent is capable of suppressing sweating over large areas without inducing signs of toxicity.

3. Exaggerated exposure to this agent, including occlusive dressings, reveals that systemic signs of toxicity are highly unlikely from topical application of this agent.

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