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Pharmacology and Treatment

The treatment of idiopathic hyperhidrosis by glycopyrronium bromide and tap water iontophoresis

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SUMMARY

A method of treating idiopathic hyperhidrosis using direct current iontophoresis is described. Employing a solution of glycopyrronium bromide, such treatment produces prolonged periods of suppression of palmar and plantar hyperhidrosis but only occasionally do useful periods of dryness result from treatment of axillary hyperhidrosis.

Tap water iontophoresis can also be used to produce sweat suppression but its effects are generally less satisfactory.

The medical treatment of hyperhidrosis is usually ineffective in all but the mildest cases. Many topical agents have been used, including aluminium chloride (Shelley, 1954), potassium permanganate, formaldehyde (Shelley, Laskas & Satonove, 1954; Papa, 1966), glutaraldehyde (Juhlin & Hansson, 1968), in addition to a large number of anticholinergic compounds (Shelley & Horvath, 1951; MacMillan, Reller & Sunder, 1964; Grice & Bettley, 1966). All have shortcomings in practice. The anticholinergic compounds, particularly, have little effect when used directly on palms and soles and when taken orally, the severity of the intestinal and ocular side effects limits their usefulness.

The surgical approach to palmar and plantar hyperhidrosis by sympathectomy is an effective procedure but has occasional complications, including Horner's syndrome and damage both to pleura and phrenic nerves (Cloward, 1969; Greenhalgh, Rosengarten & Martin, 1971). The few long term studies available suggest that the anhidrosis is usually permanent (Greenhalgh *et al.*, 1971; Ellis & Naunton Morgan, 1971). Axillary hyperhidrosis may now be effectively treated by local axillary resection (Hurley & Shelley, 1966; Gillespie & Kane, 1970; Davis, 1971).

In 1968, Levit described the use of iontophoresis of tap water for palmar and plantar hyperhidrosis. Grice, Sattar & Baker (1972) have recently published results of iontophoresis of tap water and of poldine methosulphate (Nacton).

Glyco- and hexopyrronium bromide are closely related quaternary ammonium compounds showing marked anticholinergic properties (Sun, 1962), and glycopyrronium bromide (Robinul) has been extensively used for the treatment of peptic ulceration (Feder, Hadidi & Kahn, 1963; Lampier, Soegell & Goldberg, 1962; Amure, 1965; Barman & Larson, 1963). Hexopyrronium bromide was found by Stoughton *et al.* (1964) to produce satisfactory sweat suppression when used topically and was without local or systemic side effects.

It failed, however, to show measurable suppression of palmar sweat. Shelley & Horvath (1951) also found this when using scopolamine hydrobromide which they attributed to failure of penetration. After introducing scopolamine by iontophoresis they were able to show an effect lasting 10 days. Iontophoresis of hexa- and glycopyrronium bromide was therefore undertaken in patients with moderate or severe idiopathic hyperhidrosis and the results compared with those previously obtained using tap water.

MATERIALS AND METHODS

Ionization was undertaken using a direct current apparatus similar to that described in detail by Levit (1968) and widely available in physiotherapy departments. Malleable electrodes (tin) of a size comparable to the treated part were uniformly separated from the skin surface by several layers of lint. A shallow plastic tray containing the electrode allowed the addition of tap water or of an 0·1% solution of the anticholinergic drug in distilled water to a sufficient depth to cover the palmar or plantar skin. This electrically formed the anode. For axillary treatment the lint was soaked in the solution and the electrode held in place by bandaging. The cathode, a similar electrode system, using tap water in all cases, was attached to an untreated limb. Gradually increasing current was administered to skin tolerance (15–20 mA adults, 7–12 mA children) and maintained at each site for 15 min.

Twenty-six cases (sixteen female, ten male) of average age 25 years were treated with tap water twice weekly and subsequently weekly where possible. Seven received treatment to both hands and feet concurrently. Glyco- or hexopyrronium bromide was used on twenty-seven patients (fifteen female, twelve male) of average age 25 years at intervals determined by the duration of freedom from excessive sweating.

RESULTS

Table 1 briefly indicates the results of tap water iontophoresis. After a variable number of treatments

TABLE 1. Tap water iontophoresis

	No. of cases	Treatment interval	Mean no. of treatments before continuous suppression of hyperhidrosis	Case no.	Comment
Palms	21	Twice-weekly (17)	7	4	Continuous suppression of sweating not achieved
		Weekly (4)		5	Improved for up to 8 weeks on stopping treatments
Soles	9	Twice-weekly (7) Weekly (2)	9	3	Improved for up to 8 weeks on stopping treatments
Axillae	3	Twice-weekly (3)	12	1	Continuous suppression of sweating not achieved

to hands the hypohidrotic effect was usually sufficient to suppress symptoms between the twice-weekly visits. Four remained dry between weekly attendance. Treatments were not continued for more than 6 months, and the length of treatment did not influence the final result. Five patients did however continue to remain symptom free for between 4 and 8 weeks before relapsing, after receiving five to

TABLE 2. Glycopyrronium bromide iontophoresis

	Case	Sex	Age (years)	Mean duration dry per treatment (days)	No. of treatments	Comment
Palms	1	M	23	49	2	
	2	M	21	38	4	
	3	F	17	31	11	
	4	F	8	18	3	
	5	F	19	35	4	Discontinued as hyperhidrosis did not recur
	6	M	27	35	1	
	7	F	17	24	6	Abdominal discomfort
	8	F	23	28	10	
	9	F	44	35	5	
	10	F	17	28	9	
	11	F	23	42	3	Discontinued as hyperhidrosis did not recur
	12	M	20	35	1	
	13	F	27	28	5	
	14	M	40	28	6	
	15	M	21	56	6	
	16	M	38	28	3	
				Mean 33·7		
Soles	17	M	22	56	5	Discontinued as hyperhidrosis did not recur
	18	M	32	77	3	
	19	F	17	7	4	
	20	M	38	49	1	
				Mean 47·2		
Axillae	21	M	34	3	4	
	22	F	27	5	3	
	23	F	26	1	1	
	24	M	24	1	2	
	25	F	23	6	3	Abdominal discomfort
	26	F	21	14	1	
	27	F	32	21	3	
				Mean 7·3		

eighteen treatments (mean twelve). Plantar and axillary iontophoresis showed similar results but required more treatments before achieving useful dryness. Provided adequate care is taken in positioning the electrodes, no side effects result from this technique.

Table 2 sets out in detail the results of glyco- and hexopyrronium bromide iontophoresis. The two drugs produced exactly similar effects and glycopyrronium is now used exclusively as it is cheaper. It became immediately apparent that a prolonged hypohidrotic effect resulted from iontophoresis of these

drugs into palmar and plantar skin. In only two cases (4 and 19) did this effect last for less than 14 days after the initial treatment, and subsequent treatments generally led to extended periods of absence of visible sweating. Two cases (15 and 18) were eventually controlled by iontophoresis at 3-monthly intervals. Three patients (cases 5, 11 and 17) were discharged free from hyperhidrosis for 3 months and all were still dry after 6 months.

However, disappointingly transient periods of hypohidrosis followed axillary treatment except in one case.

All patients experienced some effects of systemic absorption. Marked dryness of the mouth of 6–24 h duration was a constant feature but was rarely troublesome. Difficulty in visual accommodation was noticed by one patient and in two, treatment was ultimately withdrawn because of mild abdominal discomfort and difficulty in micturition (cases 7 and 25).

Theoretically, ionization as described should not produce bromide uptake (Scott, 1955). Serum bromides were measured on six patients directly after iontophoresis on the fifth and sixth treatment and a maximum level of 10 mg/100 ml found. Irritation and sensitization were not seen.

DISCUSSION

Histological investigation of sweat inhibition 1 week after iontophoresis of saline and other solutions by Shelley *et al.* (1948) revealed keratinous blockage of the upper epidermal part of the sweat duct of similar type to that produced by formaldehyde (Papa, 1966). Gordon & Maibach (1969) demonstrated that the anhidrosis produced by tap water iontophoresis could be reduced by skin stripping and suggested that this partially removed the sweat duct obstruction.

Papa (1966) has also shown that methylene blue is deposited in the sweat duct on iontophoresis, a technique which he used to demonstrate patency of the ducts. It seems probable that the glycopyrrolate is introduced into both epidermis and sweat gland largely by this route, but the reason for its prolonged effect is unclear. That the drug may be held in the epidermis and slowly released is suggested by the increasingly prolonged effect with increasing epidermal thickness of the treated site. A dermal site of binding for such a readily water soluble compound seems less likely, particularly since oral therapy does not have such sustained effects.

Tap water iontophoresis is much less satisfactory, as continuous dryness is only achieved by repeated treatments at short intervals and only occasionally is improvement maintained more than a few days after cessation. Grice *et al.* (1972) found similar results using tap water but poldine was noticeably more effective on palms and soles though it still required twice-weekly iontophoresis. A few patients did achieve benefit lasting up to 3 months after withdrawal. However, axillary hyperhidrosis was not adequately controlled.

The present study, using glycopyrronium bromide for palmar and plantar hyperhidrosis in adults, rarely required treatment more frequently than every 4 and 6 weeks respectively.

Despite the occurrence of mild transient systemic anticholinergic symptoms this technique appears to offer a simple reliable means of therapy. Axillary hyperhidrosis would still appear to be best dealt with by local surgery.

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