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RESEARCH PAPER

Iontophoresis with glycopyrrolate for the treatment of palmoplantar hyperhidrosis

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SUMMARY

To determine the comparative efficacy of tap water iontophoresis to iontophoresis with the anticholinergic glycopyrrolate, we undertook a single-blinded right-left comparison study in 20 patients with palmoplantar hyperhidrosis. Most patients had their palms treated and one patient had the soles treated. We compared the duration of symptom relief following iontophoresis with glycopyrrolate unilaterally to iontophoresis with glycopyrrolate bilaterally. Patients filled in daily efficacy assessment cards. Each palm was rated as 'dry', 'slightly wet', 'moderately wet' or 'very wet'. Following treatment with unilateral tap water iontophoresis, unilateral glycopyrrolate and bilateral glycopyrrolate, patients reported hand dryness for a median of 3, 5 and 11 days, respectively. As the data was paired, treatment differences were analysed using a sign-rank test. Bilateral glycopyrrolate was superior to both unilateral glycopyrrolate and tap water in most patients. Unilateral glycopyrrolate was superior to tap water in most patients. All differences between groups were found to be statistically significant. We postulate that the increased efficacy of bilateral glycopyrrolate when compared with unilateral glycopyrrolate relates to its systemic absorption. We conclude that glycopyrrolate iontophoresis is more effective than tap water iontophoresis in the treatment of palmoplantar hyperhidrosis and that glycopyrrolate iontophoresis has both local and systemic effects on perspiration.

Key words: idiopathic, primary, sweating, tap water.

INTRODUCTION

Iontophoresis is a safe, reliable and effective treatment for palmoplantar hyperhidrosis.[1–4] A benefit of iontophoresis over other treatments has been shown[5] and a trial of iontophoresis should be considered prior to embarking on sympathectomy. Iontophoresis can be carried out with tap water or an anticholinergic drug such as glycopyrrolate.[6–12] Iontophoresis with tap water is a safe and effective treatment for mild to moderate hyperhidrosis, with a number of units available for home use.[8–12] Iontophoresis with the anticholinergic agent glycopyrrolate is available in specialist centres for the treatment of moderate to severe hyperhidrosis. Systemic side-effects from glycopyrrolate are generally mild.[2] Iontophoresis with glycopyrrolate is said to be more effective than iontophoresis with tap water[1–4,13] and iontophoresis with glycopyrrolate has been used in our clinic for more than 20 years. However, the relative efficacy of these two forms of iontophoresis is not known. We report on 20 patients in our clinic who were treated with both options.

METHODS

Patient selection

Patients attending the iontophoresis clinic at The Alfred Hospital, Melbourne, Australia, were referred for the treatment of palmoplantar hyperhidrosis by their general practitioner, dermatologist or other specialist. Patients who regularly attended this clinic for glycopyrrolate iontophoresis were invited to take part in this study. The experience of 20 patients was compared. Patients were aged between 12 and 50 years, and the group comprised six male and 14 female patients. Nineteen attended for treatment of their palms and soles, with the active treatment, when used, in the palm tray. One patient attended for treatment to the soles only.

Iontophoresis protocol

A detailed treatment protocol is presented in Table 1. Locally manufactured iontophoretic equipment was used in the clinic (Austin and Repatriation Medical Centre, Engineering Department). This consisted of two plastic trays or baths,

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which contained an electrode in the base of each. The electrodes were covered by a plastic mesh and were connected to a battery-operated device that emitted a current. Patients placed their ipsilateral palm and sole in the trays containing fluid for treatment.

For the purpose of this report patients were blinded as to which tray contained glycopyrrolate. Patients placed one hand in glycopyrrolate 0.05% solution, the ipsilateral foot was placed in a tap water bath and the current was turned on for 10 min. The other side was then treated in a similar way, but with tap water in the tray and again the current turned on for 10 min. The current used was varied according to patient tolerance with a maximum of 20 mAmps. Patients controlled the current emitted by the iontophoretic device by adjusting a dial on the unit. The aim was to reach the maximum comfortable current. As the current increased, patients developed dysaesthesia in the hand. The dysaesthesia often dissipated over several minutes and patients gradually adjusted the current upwards during treatment.

In the case of the patient who presented for treatment of the soles only, one foot was placed in the tray containing glycopyrrolate 0.05% solution while the other was placed in a tray containing tap water. In the second part of the treatment, tap water was placed in both trays.

Patients were asked to record their response to the treatment by rating each palm (or sole) each day following treatment as 'dry', 'slightly wet', 'moderately wet' or 'very wet'.

At their next visit, both hands or feet were treated with glycopyrrolate 0.05% solution, as was the usual practice at the clinic. Patients were again asked to rate the response to treatment each day and to compare this with treatment of only one hand or foot with glycopyrrolate and the other with water.

A statistician at the Alfred Hospital carried out the statistical analysis. Treatment differences were analysed using a sign-rank test as the data was paired

RESULTS

Patients were able to rate the severity of their hyperhidrosis prior to any treatment as mild, moderate or severe. Of the 20 patients, 18 suffered from severe and two from moderate hyperhidrosis. Patient demographics are presented in Table 2. The current used for patients varied from 3 to 20 mAmps with a median of 10 mAmps.

The primary determinant of the interval between treatments with iontophoresis was the duration of decreased sweating following each treatment. The average duration of symptom relief following treatment, as assessed by the patients over many treatments, and the average interval between treatments are shown in Table 3.

Table 4 shows the duration of 'dry' hands after treatment. The number of totally dry days was used for statistical analysis, as some patients returned for treatment as soon as their hands became slightly wet, thus only allowing the

Table 1 Iontophoresis treatment protocol

Palmar hyperhidrosis
Treat palm on one side and ipsilateral foot
Begin with glycopyrrolate 0.05% in hand tray
Tap water in foot tray
Remove rings and watch
Cover abrasions with white soft paraffin
With palm and sole immersed in trays, turn current on slowly
Turn current to level of pins-and-needles sensation (not pain)
Treatment time 10 min
Repeat on contralateral limbs
Plantar hyperhidrosis
Glycopyrrolate in foot tray
Tap water in hand tray
Otherwise as above
OR
Glycopyrrolate in foot tray
Tap water in contralateral foot tray
Otherwise as above
Aim to increase current at each visit to a maximum of 20 mAmps
Glycopyrrolate solution can be diluted with tap water if side-effects, e.g. dry throat, are excessive
Glycopyrrolate solution is reused up to three times
Interval between treatments initially 1 week, then increase depending on response
Contraindications to glycopyrrolate iontophoresis
Pregnancy
Past history of cardiac arrhythmia
Cardiac pacemaker
Narrow angle glaucoma
Metallic implants such as intrauterine contraceptive devices and orthopaedic prostheses
The treatment also needs to be used with caution in children, with lower maximum current and adjustment of the concentration and volume of glycopyrrolate solution used (use child's weight as a guide to proportionally decrease volume and decrease concentration). Youngest patient treated at this centre was aged 12 years

duration of dry hands to be compared between patients. The median number of dry days after treatment with tap water, unilateral glycopyrrolate and bilateral glycopyrrolate was 3, 5, and 11 days, respectively (Table 5).

Table 2 Patient demographics and symptom severity

	Male	Female
No.	6	14
Age range (years)	12–50	16–45
Site treated		
Palms	5	14
Soles	1	0
Severity of symptoms prior to any treatment†		
Mild	0	0
Moderate	1	1
Severe	5	13

†Mild was defined as a nuisance; symptoms present but not affecting any life activities. Moderate was defined as interfering with certain activities only, such as sports or social interactions. Severe was defined as interfering with most activities on most days, sweat dripping onto the floor, conscious of the problem most of the time.

Unilateral tap water iontophoresis

Following unilateral treatment with tap water, patients experienced hand dryness for a period of 0–15 days. The median number of dry days following treatment was 3, with a mean of 4.8 days. All patients experienced benefit with tap water iontophoresis. Patients 2, 5 and 20, however, failed to achieve total dryness of the hand following tap water iontophoresis, but did have some symptom relief.

Unilateral glycopyrrolate iontophoresis

The duration of hand dryness varied from 0 to 17 days following treatment with unilateral glycopyrrolate iontophoresis. The median number of dry days was 5, with a mean of 7.4 days. All patients reported some symptom relief, but patients 2, 5 and 20 did not achieve total dryness.

Bilateral glycopyrrolate iontophoresis

Patients were treated with glycopyrrolate to both sides and reported the same duration of symptom relief on each side. The number of dry days following treatment varied from 0 to 31 days, with a median of 11 days and a mean of 11.35 days.

Table 3 Frequency of treatment and average duration of symptom relief following usual treatment with bilateral glycopyrrolate, as rated by patients

Time (weeks)	Time interval between treatments (no. of patients)	Duration of symptom relief following bilateral glycopyrrolate (no. of patients)
<1	1	3
1–2	2	4
2	6	5
2–3	4	3
3	1	1
>3	3	4
Total	20	20

Table 4 Patient results: duration of symptom relief following treatment

Patient no.	Duration of relief of symptoms (no. dry days following treatment) Tap water	UG	BG†	Patient comparison of BG with UG and tap water
1‡	15	15	15	No difference
2	0	0	1	Improved
3	15	15	11	Worse
4	1	1	3	Improved
5	0	0	0	Worse
6	2	2	10	improved
7	7	7	11	Improved
8	2	3	6	Improved
9	11	15	15	Improved
10	1	3	13	Improved
11	3	5	11	Improved
12	1	5	9	Improved
13	9	14	15	Improved
14	2	3	7	Improved
15	5	17	19	Improved
16	4	15	31	Improved
17	3	5	19	Improved
18	12	12	16	Improved
19	3	11	15	Improved
20	0	0	0	Improved

†Left side = right side. ‡Both feet treated. BG, bilateral glycopyrrolate; UG, unilateral glycopyrrolate.

All patients noted benefit with bilateral glycopyrrolate iontophoresis; however, patients 5 and 20 did not achieve total dryness. Patient 5 showed better results with unilateral tap water iontophoresis. Patient 20 improved from 8 days 'moderately wet' with tap water and unilateral glycopyrrolate to 6 days 'slightly wet' and 2 days 'moderately wet' with bilateral glycopyrrolate iontophoresis. Patient 2, who had not previously been dry, improved to 1 day of dryness with bilateral glycopyrrolate.

Bilateral glycopyrrolate versus unilateral tap water iontophoresis

Of the 20 patients, 17 noticed an increase in the number of dry days, one noted an equal number of dry days and two showed a decrease in the number of dry days when comparing bilateral glycopyrrolate with tap water iontophoresis. A statistically significant difference was found between the duration of dryness following bilateral glycopyrrolate (median 11 days) when compared with tap water iontophoresis (median 3 days), with a *P*-value of 0.0001.

Bilateral glycopyrrolate versus unilateral glycopyrrolate

When treatment with unilateral glycopyrrolate was compared with bilateral glycopyrrolate, 17 of 20 patients noted an increase in symptom relief with the bilateral glycopyrrolate treatment. Many patients noted an improvement both in the degree of dryness achieved, for example, improving from 'slightly wet' to 'dry' and in the number of days of symptom relief in each category. Two of the 20 patients showed no improvement from unilateral glycopyrrolate to bilateral glycopyrrolate and one patient showed deterioration in symptoms. A statistically significant difference in the duration of dry days was found following treatment with bilateral glycopyrrolate (median 11 days) when compared with unilateral glycopyrrolate (median 5 days), with a *P*-value of 0.001.

Unilateral glycopyrrolate versus unilateral tap water iontophoresis

Of the 20 patients, 12 noted a significant difference between the two sides when only one hand (or sole) was treated with glycopyrrolate solution (Table 4), with the glycopyrrolate side showing a better response. Another three patients showed initial dryness for the same number of days, but the hand treated with tap water deteriorated more quickly than the glycopyrrolate-treated side. An example of this situation was with patient 6, who reported both hands to be 'dry' for 2 days, but the tap water-treated hand then became 'moderately wet', whereas the glycopyrrolate-treated hand became only 'slightly wet'. The addition of these three patients to the other 12 who noted a more obvious difference between the two sides brings the total number of patients who noted a difference between the glycopyrrolate-treated side and the side treated with tap water to 15 of 20. Of the patients who did not notice a difference between the two sides, four rated their response to treatment on both sides as 'dry' for an equal number of days and one patient 'moderately wet' both sides for an equal number of days. Unilateral glycopyrrolate (median 5 days) showed a statistically significant difference in the duration of dryness when compared with treatment with unilateral tap water iontophoresis (median 3 days), with a *P*-value of 0.001.

Many patients did not report side-effects. When present, they consisted only of dry/sore mouth or throat. No other side-effects were reported. A total of eight patients reported dry/sore throat: six patients noted an increase in side-effects when treated with glycopyrrolate bilaterally compared with unilateral glycopyrrolate, one patient noted a decrease in dry/sore throat when treated with bilateral glycopyrrolate iontophoresis and one patient experienced the same degree of sore/dry throat with bilateral glycopyrrolate and unilateral glycopyrrolate.

DISCUSSION

The mechanism of action of iontophoresis in the treatment of hyperhidrosis is unknown.[5,14–16] As miliaria rubra is associated with anhidrosis and can be artificially reproduced using cling wrap occlusion of the skin, it has been used as a model for the study of anhidrosis associated with iontophoresis. Based on these experiments, it was initially suggested that iontophoresis produced epidermal damage and that a hyperkeratotic plug obstructed the eccrine orifice. However, this theory is now discounted.[14,17] There are two theories currently offered to explain the mechanism of action of tap water iontophoresis. In the first, iontophoresis is postulated to selectively target areas with high concentrations of electrolytes because of enhanced current flow. In these areas, local electrochemical coagulation of proteins is induced that disrupts eccrine gland function.[18] The second

Table 5 Statistical analysis†

	Duration of relief of symptoms (no. of totally dry days following treatment)			Differences between treatments using sign-rank test		
	Tap water	UG	BG‡	BG versus tap water	BG versus UG	UG versus tap water
Total for 20 patients	96	148	227	131	79	52
Median	3	5	11	4.5	3.5	1
q25-q75	(1,8)	(2.5,14.5)	(6.5,15)	(1.5,10)	(0.5,5)	(0,4)
P-value				0.0001	0.001	0.001

†Only totally dry days included for this analysis. ‡Left side = right side. BG, bilateral glycopyrrolate; UG, unilateral glycopyrrolate.

theory postulates that tap water iontophoresis induces a functional disturbance of the secretal mechanism by interrupting the stimulus–secretion coupling.[15]

Iontophoresis permits the transdermal delivery of drugs that are charged or very large.[19] Iontophoresis can also exert a pharmacological effect on sweat glands by the delivery of anticholinergic drugs. While tap water iontophoresis does induce temporary anhidrosis,[1,2,9–12,20] our results show that the duration of the effect is greater when iontophoresis is used with an anticholinergic agent. While this does expose patients to anticholinergic side-effects for 12–48 hours, they are generally mild and well tolerated.[1,2]

It is important to clarify that each patient in this study was treated with unilateral tap water iontophoresis and unilateral glycopyrrolate iontophoresis at one visit and bilateral glycopyrrolate iontophoresis at another visit. Bilateral tap water was not used. Also, unilateral glycopyrrolate and unilateral tap water were not used in isolation. The hand treated with unilateral tap water is likely to be influenced by the systemic effects of glycopyrrolate. We therefore postulate that bilateral tap water iontophoresis will show a shorter period of 'dryness', as there will not be any systemic effect of glycopyrrolate, as seen in this study. The increase in the duration of dryness following bilateral glycopyrrolate compared with unilateral glycopyrrolate iontophoresis can be explained by the systemic absorption of glycopyrrolate contributing to symptom relief.

Tap water iontophoresis using maximally tolerated current was inferior to glycopyrrolate iontophoresis for most of our patients. Tap water iontophoresis may be a satisfactory treatment for hyperhidrosis for the minority of patients in our study who have no additional benefit from glycopyrrolate iontophoresis. To confirm this benefit, treatment with glycopyrrolate needs to be compared with treatment with tap water bilaterally to eliminate the systemic effect of glycopyrrolate. Tap water iontophoresis offers the advantage of treatment at home with one of the commercially available home units.[9] Of note, the patients in this study represent the severe end of the spectrum of hyperhidrosis. Patients with lesser degrees of sweating may have different degrees of benefit from treatment.

A number of other anticholinergic drugs have been used to treat hyperhidrosis with iontophoresis,[4] of which atropine sulphate is currently the only alternative available in Australia. It is not known whether atropine sulphate has a similar safely profile to glycopyrrolate when delivered by iontophoresis. Cardiac side-effects and, in particular, palpitations, are uncommon with glycopyrrolate. None of the 20 patients in this group noted these symptoms, but all patients had been screened for any cardiac condition prior to commencing treatment. One patient has reported palpitations following treatment in the past and occasional patients report transient blurred vision.

Most of the patients who present for treatment are fit, young adults who have no contraindications to treatment. Iontophoresis with glycopyrrolate is an effective and well-tolerated treatment for palmoplantar hyperhidrosis and is superior to treatment with tap water alone. Patients treated with bilateral glycopyrrolate iontophoresis showed a longer period of dryness than unilateral treatment. This can be explained by glycopyrrolate exerting both a local and systemic effect.

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