Treatment of uncommon sites of focal primary hyperhidrosis: experience with pharmacological therapy using oxybutynin

Marcelo Passos Teivelis,[I] Nelson Wolosker,[I] Mariana Krutman,[I] Paulo Kauffman,[I] José Ribas Milanez de Campos,[II] Pedro Puech-Leão[III]

[I] Hospital Israelita Albert Einstein, Vascular Surgery, São Paulo/SP, Brazil. [II] Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC/FMUSP), Thoracic Surgery Division, São Paulo/SP, Brazil. [III] Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC/FMUSP), Vascular and Endovascular Surgery Division, Department of Surgery, São Paulo/SP, Brazil.

OBJECTIVES: Primary hyperhidrosis usually affects the hands, armpits, feet and cranio-facial region. Sweating in other areas is common in secondary hyperhidrosis (after surgery or in specific clinical conditions). Oxybutynin has provided good results and is an alternative for treating hyperhidrosis at common sites. Our aim was to evaluate the efficacy of oxybutynin as a treatment for primary sweating at uncommon sites (e.g., the back and groin).

METHODS: This retrospective study analyzed 20 patients (10 females) who received oxybutynin for primary focal hyperhidrosis at uncommon sites. The subjects were evaluated to determine quality of life before beginning oxybutynin and six weeks afterward and they were assigned grades (on a scale from 0 to 10) to measure their improvement at each site of excessive sweating after six weeks and at the last consult.

RESULTS: The median follow-up time with oxybutynin was 385 days (133-1526 days). The most common sites were the back (n = 7) and groin (n = 5). After six weeks, the quality of life improved in 85% of the subjects. Dry mouth was very common and was reported by 16 patients, 12 of whom reported moderate/severe dry mouth. Five patients stopped treatment (two: unbearable dry mouth, two: excessive somnolence and one: palpitations). At the last visit, 80% of patients presented with moderate/great improvement at the main sites of sweating.

CONCLUSION: After six weeks, more than 80% of the patients presented with improvements in their overall quality of life and at the most important site of sweating. Side effects were common (80% reported at least one side effect) and caused 25% of the patients to discontinue treatment. Oxybutynin is effective for treating bothersome hyperhidrosis, even at atypical locations and most patients cope well with the side effects.

KEYWORDS: Hyperhidrosis; Cholinergic Antagonists; Pharmacology.

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E-mail: dr.marcelo@consultoriovasculares.med.br

Tel.: 55 11 2151-5423

INTRODUCTION

Primary hyperhidrosis is a common disease with an incidence of up to 2.8% in the United States (1). Excessive sudoresis negatively impacts quality of life (QOL) (2), and its resolution is linked to QOL improvement (3,4).

The most common sites of primary hyperhidrosis are the axillae, palms of the hands, soles of the feet and cranio-facial region; the vast majority of scientific papers describing primary hyperhidrosis have focused on these regions.

Excessive focal sweating elsewhere (e.g., the thorax, abdomen, back or groin) usually occurs after surgical sympathectomy (as compensatory hyperhidrosis); this condition may be reduced with the use of certain techniques (5), but it is still one of the most common causes of sweating in these areas.

A fraction of patients have a primary complaint of hyperhidrosis at less common sites (e.g., the back and groin), but they do not fulfill the criteria for compensatory hyperhidrosis (as they have never undergone an operation), secondary hyperhidrosis (as no clinical/pharmacological condition has been diagnosed) or generalized hyperhidrosis (as they do not sweat on the majority of their body surface). We studied patients in the former category (primary hyperhidrosis at less common sites).

No potential conflict of interest was reported.

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Oxybutynin is an anti-muscarinic drug that was first associated with the resolution of hyperhidrosis in 1988 (6). Recently, specific therapy was reported (7,8) to be a good initial alternative for treating primary hyperhidrosis; such therapy has been used in plantar (9), axillary (10), palmar (11,12) and facial hyperhidrosis (13) and has been evaluated in a randomized, placebo-controlled trial (14). This therapy is an alternative for patients who are not good surgical candidates (either because of clinical limitations, such as age or co-morbidities, or because of the applicability/efficacy of sympathectomy in certain areas of the body).

Here, we report a case series of 20 patients with primary focal hyperhidrosis whose main complaint was associated with the less frequent sites of hyperhidrosis (e.g., the back or groin) and who have been treated with the anticholinergic oxybutynin for a median follow-up period of 385 days (range: 133 – 1526 days).

PATIENTS AND METHODS

This investigation was a non-randomized, uncontrolled study; the data were retrospectively retrieved from our dedicated and prospective institutional protocol, which is standardized and has been in use at our facilities since 2001 for all patients with primary or compensatory hyperhidrosis.

From September 2007 to September 2013, 20 patients with a primary complaint of focal hyperhidrosis at the dorsum (n = 7), groin (n = 5), anterior thorax (n = 5), genitals (n = 1), thighs (n = 1), and abdomen (n = 1) were included in our pharmacological protocol using oxybutynin.

The inclusion criteria were as follows: patients with at least two follow-up visits, patients who underwent an extensive clinical investigation to exclude causes of secondary hyperhidrosis and patients with a detailed history of previous drug use. The exclusion criteria were as follows: contra indication to oxybutynin treatment (e.g., closed-angle glaucoma or intestinal obstruction), report of night sweats or climacterium and previous surgery involving the sympathetic system (including oncologic or other procedures in operative fields that could inadvertently include the sympathetic ganglia, such as open aortic surgery).

The patient demographics are summarized in Table 1 and a detailed description is provided in Table 2.

All subjects were treated following the same protocol. During the first week, they received 2.5 mg of oxybutynin once per day at bedtime. From days 8 to 21, they received 2.5 mg twice per day and from day 22 onward, they received 5 mg twice per day. If necessary, the total dose was increased up to 20 mg/day to balance the therapeutic and side effects. Oxybutynin was provided by the hospital pharmacy.

Three evaluations were performed for the purpose of this study. The first occurred before medication was given, the second occurred after six weeks of treatment and the final evaluation occurred at least 24 weeks following the initiation of the protocol (except for the patients who stopped treatment earlier because of side effects). The following information was evaluated: **1st)** the patient's QOL was evaluated using a validated (and previously employed (15)) questionnaire for patients with hyperhidrosis (3) before pharmacological treatment (Appendix 1); **2nd)** the patient's clinical improvement at the main site of hyperhidrosis was evaluated after six weeks; **3rd)** the patient's QOL was evaluated after six weeks of oxybutynin treatment (Appendix 1); **4th)** the patients' clinical improvement at the main and other sites of hyperhidrosis was evaluated at the final visit; and **5th)** the patient's complaints of pharmacological side effects were evaluated after six weeks and at the final visit.

Table 1 - Patient demographics.

		%
Male	**n = 10**	**50**
Female	**n = 10**	**50**
Age at initiation of the protocol	**17-72**	
Pre-pharmacological treatment quality of life (QOL)		
Very poor	N = 6	30
Poor	n = 9	45
Good	n = 5	25
Very good	n = 0	0
Excellent	n = 0	0
Total	n = 20	100.0
QOL after six weeks of pharmacological treatment		
Much worse	0	0
Worse	n = 0	0
The same	n = 3	15
Slightly better	n = 4	20
Much better	n = 13	65
Total	n = 20	100.0

Patients completed the clinical improvement questionnaire according to their subjective perception of the improvement in sudoresis. They evaluated this improvement using a scale ranging from 0 to 10, in which 0 represented no improvement and 10 represented the absence of hyperhidrosis based on their own estimate. The improvement was recorded as null when the score was 0, slight when it was 1 to 4, moderate when it was 5 to 7 and great when it was 8 to 10.

The negative impact of hyperhidrosis on the patient's QOL before oxybutynin was classified into five different categories, calculated as the summed total score from the protocol. When the total scores were >83, 68-83, 52-67, 36-51 and 20-35, the QOL was considered very poor, poor, good, very good and excellent, respectively.

The QOL improvement after treatment was also classified into five different categories. When the totals were greater than 83, 68-83, 52-67, 36-51 and 20-35, the QOL was considered much worse, slightly worse, the same, slightly better and much better, respectively.

Statistical analysis

Means and standard deviations (SDs) were used in the descriptive analysis of parametrically distributed continuous variables, whereas frequencies were used for categorical variables. McNemar's test was used to compare self-reported improvements in hyperhidrosis and dry mouth over time at the two consecutive analysis time points.

The significance level for all tests was $p = 0.05$.

Ethics

This study was approved by the ethics committees of our institutions, with the following protocol numbers: 374.680/2013 at the Israelita Albert Einstein Hospital and 399.867/

Table 2 - Detailed information about the 20 patients.

Patient number	Gender	Age at start of protocol	Body Mass Index at start of protocol	Primary hyperhidrosis complaint	Second site of hyperhidrosis complaint	Third site of hyperhidrosis complaint	Pre-treatment QOL	Improvement in main site of hyperhidrosis after six weeks	QOL after six weeks of treatment	Days of follow-up	Improvement in main site of hyperhidrosis at last consult	Improvement in second most disturbing site of hyperhidrosis at last consult	Dry mouth severity at last consult	Ceased medication?	Observations
1	Male	69	33.7	Abdomen	Palm of hands	Cranio-facial	Poor	Moderate improvement	Much better	1,526	Great improvement	Great improvement	Absent	No	
2	Male	21	22.9	Thighs	Palm of hands	Sole of the feet	Very poor	Slight improvement	Much better	616	Slight improvement	Moderate improvement	Intense	No	
3	Female	45	31.2	Genitalia	Sole of the feet	Palm of hands	Poor	Slight improvement	Much better	357	Great improvement	Great improvement	Intense	No	
4	Male	31	26.8	Groin	Back	Armpit	Good	Slight improvement	The same	595	Great improvement	Great improvement	Moderate	No	
5	Female	47	27.3	Groin	Inframammary	Abdomen	Very poor	Null improvement	The same	329	Great improvement	Great improvement	Light	No	
6	Female	68	27.3	Chest			Poor	Slight improvement	The same	231	Moderate improvement	Did not have second site of hyperhidrosis	Intense	No	
7	Male	17	19.6	Back	Palm of hands	Armpit	Poor	Great improvement	Much better	212	Great improvement	Great improvement	Absent	No	
8	Male	21	21.6	Chest	Armpit	Palm of hands	Very poor	Great improvement	Much better	209	Great improvement	Great improvement	Intense	Yes	Severe dry mouth lead to discontinuation of the drug
9	Male	31	21.5	Chest	Back	Armpit	Poor	Moderate improvement	Slightly better	707	Moderate improvement	Moderate improvement	Absent	No	
10	Female	30	27.7	Back	Legs		Good	Moderate improvement	Much better	133	Moderate improvement	Great improvement	Intense	Yes	Patient presented complaint of tachycardia, which she atributed to medication use and decided to cease medication
11	Female	72	19.1	Back	Chest	Legs	Very poor	Great improvement	Much better	464	Great improvement	Great improvement	Light	No	
12	Female	39	28.9	Back	Armpit		Good	Moderate improvement	Much better	184	Null improvement	Null improvement	Moderate	Yes	Severe somnolence lead to discontinuation of the drug
13	Male	28	26.0	Back	Armpit	Chest	Very poor	Great improvement	Slightly better	974	Great improvement	Great improvement	Light	No	

Table 2 - Continued.

Patient number	Gender	Age at start of protocol	Body Mass Index at start of protocol	Primary hyperhidrosis complaint	Second site of hyperhidrosis complaint	Third site of hyperhidrosis complaint	Pre-treatment QOL	Improvement in main site of hyperhidrosis after six weeks	QOL after six weeks of treatment	Days of follow-up	Improvement in main site of hyperhidrosis at last consult	Improvement in second most disturbing site of hyperhidrosis at last consult	Dry mouth severity at last consult	Ceased medication?	Observations
14	Female	67	27.5	Back			Poor	Moderate improvement	Slightly better	213	Null improvement	Did not have second site of hyperhidrosis	Intense	Yes	Severe dry mouth, associated with inefficacy during the summer lead to discontinuation of the drug
15	Female	26	23.9	Groin	Palm of hands	Sole of the feet	Very poor	Great improvement	Much better	190	Great improvement	Great improvement	Moderate	Yes	Severe somnolence lead to discontinuation of the drug
16	Female	53	23.7	Back	Chest		Good	Moderate improvement	Much better	455	Moderate improvement	Moderate improvement	Moderate	No	
17	Male	30	25.8	Chest	Armpit	Cranio-facial	Poor	Great improvement	Much better	413	Slight improvement	Null improvement	Intense	No	
18	Male	32	27.7	Groin	Buttocks		Poor	Slight improvement	Slightly better	492	Moderate improvement	Moderate improvement	Absent	No	
19	Female	24	18.6	Groin	Abdomen		Good	Moderate improvement	Much better	280	Great improvement	Great improvement	Moderate	No	
20	Male	45	31.7	Chest	Cranio-facial	Armpit	Poor	Moderate improvement	Much better	694	Great improvement	Great improvement	Light	No	

Table 3 - Improvement at the main site of hyperhidrosis after six weeks and at the last consult (median: 385 days).

			Improvement at the main site of compensatory hyperhidrosis at the last consult				Total	McNemar's *p*
			Null	Slight improvement	Moderate improvement	Great improvement		
Improvement at the main site of compensatory hyperhidrosis after six weeks	Null	Count	0	0	0	1	1	0.139
		%	0.0%	0.0%	0.0%	100.0%	100.0%	
	Slight improvement	Count	0	1	2	2	5	
		%	0.0%	20.0%	40.0%	40.0%	100.0%	
	Moderate improvement	Count	2	0	3	3	8	
		%	25.0%	0.0%	37.5%	37.5%	100.0%	
	Great improvement	Count	0	1	0	5	6	
		%	0.0%	16.7%	0.0%	83.3%	100.0%	
	Total	Count	2	2	5	11	20	
		%	10.0%	10.0%	25.0%	55.0%	100.0%	

Consistency: 45%; Improvement: 40%; Worsening: 15%.

2013 at Hospital das Clínicas. This study is registered at Plataforma Brazil's site as CAAE 01582112.6.1001.0071.

RESULTS

There were ten males and ten females. All patients were followed for at least four months. The median follow-up period was 385 days (range: 133 – 1526 days).

The most bothersome sites for hyperhidrosis were the back (Seven patients) followed by the groin (n = 5). Five patients reported that they were more uncomfortable with hyperhidrosis on the thorax. The second and third sites of hyperhidrosis for each patient are displayed in Table 2.

QOL data before and six weeks after treatment are presented in Table 1. Fifteen patients (75%) presented with a poor or very poor QOL before pharmacological therapy with oxybutynin. After six weeks, seventeen patients (85%) reported some improvement in QOL.

The improvements in sweating at the main site after six weeks and at the last visit are presented in Table 3. After six weeks, 70% of the patients reported moderate/great improvement in sweating, while 80% (16 out of 20) reported moderate or great improvement in sweating at the last visit. At the second most disturbing site of hyperhidrosis, 88.9% (16 out of 18) of the cases showed moderate or great improvement.

Comparing the improvement at the six-week analysis with the last evaluation (Table 3), 45% of patients remained in the same category of improvement, 15% ''downgraded'' and 40% improved over the course of the study. The change in sub-categories was not statistically significant (McNemar's test: $p = 0.139$).

Regarding side effects, no patients reported intestinal obstruction, urinary retention, or decreased visual acuity. Dry mouth was the most common complaint, as only four patients (20%) did not report some degree of dry mouth. Twelve subjects rated dry mouth as moderate/severe and two of these subjects stopped treatment because of this complaint. Two patients reported somnolence (which made both of them cease treatment), and one case of alleged heart palpitation/tachycardia was noted (the patient was not thoroughly investigated because she decided to stop the medication and did not want to try it again). In total, five patients ceased taking the medication.

Comparisons of dry mouth complaints after six weeks and at the last visit are shown in Table 4; 85% of the patients remained in the same category (absent/light or moderate/severe) throughout the study period and 15% reported

Table 4 - Comparison of dry mouth complaints after six weeks and at the last consult.

			Dry mouth complaint at the last visit		Total	McNemar's *p*
			Absent/Mild	Moderate/Intense		
Dry mouth complaint after six weeks of treatment	Absent/Mild	Count	5	0	5	0.250
		%	100.0%	0.0%	100.0%	
	Moderate/Intense	Count	3	12	15	
		%	20.0%	80.0%	100.0%	
	Total	Count	8	12	20	
		%	40.0%	60.0%	100.0%	

Consistency: 85%; Improvement: 0%; Worsening: 15%.

worsening of this symptom. The change in the subcategories was not statistically significant (McNemar's test: $p = 0.250$).

DISCUSSION

It is estimated that there are up to 600-700 sweat glands/cm^2 on the palms and soles, 350/cm^2 on the forehead, 64/cm^2 on the back and 60/cm^2 on the thigh (16-18). This estimation correlates with epidemiological findings that palmar and plantar (along with axillary) hyperhidrosis are among the most common presentations (19).

Our service treats primary hyperhidrosis in a large number of patients. When we classify patients by their primary site complaint, we observe the following approximate figures: 500 patients with palmar, 400 with axillary, 100 with cranio-facial and 75 with plantar hyperhidrosis. In our service, we estimate that the incidence of primary sweating at uncommon sites is approximately 1.85%, which might be the reason for underreporting in the literature.

Maillard et al. (20) coined the term ''primary extensive hyperhidrosis'' for patients with at least three sites of excessive sweating, including both ''typical'' (hands and feet) and ''unusual'' sites (trunk and groin); however, the association of the primary complaint with ''unusual'' sites is not critical to their definition.

Focal primary hyperhidrosis at common sites (hands, armpits, feet and face) has been extensively studied, and different methods of treatment have been described (21), including topical therapy (22) (iontophoresis, botulin toxin and aluminum compounds), surgery (either excision of sweat glands in axillary hyperhidrosis (23), thoracic sympathectomy for upper limb/face sweating (24) or lumbar sympathectomy for plantar sudoresis (25)) and pharmacological therapy with anticholinergics, such as oxybutynin (12), glycopyrrolate and clonidine (26).

Widespread sudoresis – also referred to as generalized hyperhidrosis, a condition that has not been precisely defined – is usually considered to be a secondary effect that is associated with drug side effects (or drug withdrawal) or with clinical conditions (e.g., menopause, pheochromocytoma, carcinoid syndrome, thyrotoxicosis, or diabetes mellitus) (18,27).

Primary focal sweating in uncommon sites, on the other hand, does not share the same profile. Local therapies (e.g., iontophoresis or aluminum compounds) do not have great applicability; botulin toxin may harbor a significant risk, as there have been case reports of clinical botulism after treatment for axillary and palmar hyperhidrosis (28). Additionally, the likelihood of contracting botulism is theoretically increased if a larger (e.g., abdominal) area is treated. Removal of sweat glands, which may be done in axillary hyperhidrosis, is not readily achievable at many other sites. Surgical sympathectomy is not considered routine for unusual sites and may aggravate hyperhidrosis in other locations (as observed with compensatory hyperhidrosis).

Nevertheless, our results indicate that this illness considerably affects QOL (75% presented poor/very poor QOL before treatment). This result is comparable to most studies that have assessed the impact of hyperhidrosis on QOL.

Oral systemic therapy appears to be an ideal solution for complaints that are not amenable to local/surgical therapy. Our group decided to study the effect of oxybutynin in clinical scenarios in which patients presented with a poor QOL due to excessive sweating. Our cohort presented an 85% improvement in QOL (using the Milanez de Campos scale, which has been used by other authors (15) for this purpose); these findings are similar to those achieved with certain treatments at typical sites, after which the QOL is usually greatly enhanced (3,11,29,30).

The QOL significantly improved after six weeks of treatment, which is similar to the improvement observed after the use of oxybutynin for common sites.

To evaluate the improvement in sweating, we relied on patient self-assessment, although objective measures are technically feasible with sudorometers (31) or with the Minor test (i.e., the starch-iodine test, in which a 2% iodine solution is applied to the hyperhidrotic area and allowed to dry; next, starch in powder form is subsequently applied to the area and the transformation from brown to dark purple demonstrates the area of sweating, which can be photographed and compared during follow-up visits). These results are available only at a specific time point instead of throughout the day. Hyperhidrosis is a bothersome – but not lethal – condition and the goal of treatment is the subjective amelioration of symptoms; thus, patient self-reporting is an adequate method for data collection.

When we compare the self-improvement after six weeks with the results of the last visit (Table 3) after a median of 385 days, only 15% of patients ''downgraded'' their evaluation, which means that after one year, most patients tended to maintain a pharmacological response to hyperhidrosis. Gender did not appear to affect the outcomes, as the proportion of good responses did not differ between males and females. This finding is comparable to the outcomes after sympathectomy for palmar hyperhidrosis (32), in which the improvement was unrelated to gender.

Unfortunately, systemic therapy has its drawbacks: dry mouth was the most common side effect (12 patients reported moderate/severe dry mouth at the last visit) and led to two withdrawals from treatment. This dry mouth, although not statistically significant (McNemar's $p = 0.25$), tended to become worse in 15% of patients by the last visit when compared to the six-week follow up visit.

Other significant side effects that led to cessation of treatment were somnolence, which heavily interfered with daily activities in two patients and one complaint of palpitations and tachycardia associated with the medication. Although transient tachycardia has been reported in a case of oxybutynin poisoning at a dose of 100 mg (33), this is not a typical finding; other diagnoses should have been investigated, but the patient decided to stop the medication and never take it again.

Anticholinergics have been successfully used in compensatory hyperhidrosis (15), which has a different pathophysiological mechanism with a clinical presentation that is similar to that observed in our patients with primary hyperhidrosis at uncommon sites. Our study indicates that oxybutynin yields significant improvement in both self-perceived sweating and QOL in these patients, with a reasonably tolerable side effect profile. Additionally, this improvement is maintained over the long term.

Our retrospective analysis indicates that, even for patients who presented with hyperhidrosis at uncommon sites, there was a generally good response to oxybutynin and these results were longstanding. Obviously, such treatment must be performed only after extensive investigation to rule out

secondary hyperhidrosis, which may be less common, but potentially more dangerous (e.g: pheocromocytomas, and B symptons associated with lymphomas).

AUTHOR CONTRIBUTIONS

Teivelis MP, Wolosker N, de Campos JR and Puech-Leão P were responsible for study conception and design as well as supervision. Teivelis MP, Wolosker and Krutman M participated in data acquisition, analysis and interpretation. Wolosker N, Teivelis MP, Krutman M and de Campos JR drafted the manuscript. Teivelis MP, Wolosker N, Krutman M, de Campos JR, Kauffman P and Puech-Leão P critically revised the manuscript for important intellectual content. Teivelis MP, Krutman M, and Kauffman P performed the statistical analysis. De Campos JR, Kauffman P and Puech-Leão P provided administrative, technical or material support. All authors have participated sufficiently in the work and take public responsibility for the appropriate portions of the content.

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