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Oxybutynin 3% gel for the treatment of primary focal hyperhidrosis in adolescents and young adults

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Abstract

Background/Objectives—There are no reliably effective and well-tolerated topical agents for the treatment of hyperhidrosis. We sought to evaluate the efficacy and tolerability of oxybutynin 3% gel in adolescents and young adults with primary focal hyperhidrosis.

Methods—Patients with severe axillary hyperhidrosis were treated with topical oxybutynin 3% gel for 4 weeks. Response to treatment was assessed by calculating change in hyperhidrosis disease severity score (HDSS) from baseline to week 1 and week 4. Change in health-related quality of life was assessed with the Children's Dermatology Life Quality Index (CDLQI) or the Dermatology Life Quality Index (DLQI). Adverse effects were evaluated with patient diaries, investigator global review, and physical examination.

Results—Ten patients, aged 13–24 years, enrolled in the study. Seven patients completed the study. Among patients who completed the study, 4/7 (57.1%) reported reduction in axillary HDSS at week 1 and 7/7 (100%) at week 4. Six patients (6/7, 85.7%) reported reduction in CDLQI/DLQI scores. Anticholinergic adverse effects were infrequent. The majority of treatment-related adverse events were mild to moderate in severity. One patient experienced a severe adverse event.

Conclusion—Oxybutynin 3% gel reduced hyperhidrosis severity and improved health-related quality of life in this small pilot study. Safety and efficacy should be further evaluated in a large, prospective, placebo-controlled study.

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Nicholas Nguyen, Anna Bruckner, Jane Gralla and James Abbott give consent for publication.

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Keywords

hyperhidrosis; oxybutynin; therapy-topical; quality of life; pharmacology

Introduction

Existing topical therapies for hyperhidrosis are limited. Response to topical aluminum chloride is often unsatisfactory. Furthermore, local skin tolerance to aluminum salts in the axillary region is poor¹ and skin irritation often leads to decreased compliance. Oral anticholinergics are an effective treatment for primary focal hyperhidrosis in children and adults.^{2,3} Unfortunately, oral administration is often accompanied by anticholinergic side effects such as xerostomia and constipation. Topical administration of these agents may have the benefit of clinical efficacy with a lower total drug burden and a more favorable side effect profile.⁴

Oxybutynin is well suited for use as a transdermal agent. It is a small (393.95 kDa) tertiary amine molecule, and the unionized free base form of the drug predominates at physiologic pH.⁵ Additionally, the compound has a serum half-life of 62–84 hours when applied topically,⁶ suggesting the treatment may demonstrate a longer duration of action than existing topical therapies such as aluminum chloride. Topical oxybutynin 3% gel is approved for the treatment of overactive bladder in adults. A pharmacologic effect of topical oxybutynin 3% gel on the bladder suggests that the compound may also have an effect at distant, untreated sites such as the hands and feet when applied to the axilla.

Additional studies are warranted to identify an effective and well-tolerated topical agent, which would obviate the need for oral therapy or invasive procedures. To our knowledge, no studies have evaluated topical oxybutynin gel as a treatment of hyperhidrosis. Thus, our primary objective was to determine if daily application of topical oxybutynin 3% gel reduces the symptoms of primary axillary hyperhidrosis in adolescents and young adults. We also evaluated the effect of daily topical oxybutynin 3% gel at distant, untreated sites; assessed the impact of daily topical oxybutynin 3% gel on health-related quality of life (HRQOL); and evaluated the local and systemic tolerability of topical oxybutynin 3% gel over 4 weeks of treatment.

Materials and Methods

This study was approved by the Colorado Multiple Institutional Review Board. Patients were 12–25 years old with moderate to severe axillary hyperhidrosis correlating to a score of 3 (sweating is barely tolerable and frequently interferes with daily activities) or 4 (sweating is intolerable and always interferes with daily activities) on the hyperhidrosis disease severity scale (HDSS).⁷ Hyperhidrosis affected the bilateral axilla in all patients; however, patients with concurrent focal hyperhidrosis affecting the hands and feet were not excluded. Patients were excluded if they had received botulinum toxin injections at any site in the preceding 12 weeks or treatment with other modalities (oral anticholinergics, topical aluminum chloride, iontophoresis, etc.) within 4 weeks of enrollment.

We collected clinical and demographic information including age, gender, age of hyperhidrosis onset, duration of disease, family history of hyperhidrosis, medical history, location of hyperhidrosis, and prior treatments. Before initiating therapy, severity of hyperhidrosis at each site was evaluated with the HDSS. Baseline HRQOL was evaluated with the Children's Dermatology Life Quality Index (CDLQI) in patients 12–17 years old and the Dermatology Life Quality Index (DLQI) in patients 18–25 years old.^{8,9} Scores range from 0–30 where a score of 0–1 = no effect on patient's life and a score of 21–30 = extremely large effect on a patient's life.

Patients were treated with 1 gram of oxybutynin 3% gel to each axilla every morning and prospectively followed over 4 weeks. Follow-up visits were conducted at week 1 and week 4, at which time HDSS and CDLQI/DLQI assessments were repeated. Physician assessment of systemic and local skin tolerance was conducted at week 1 and week 4. Physicians graded the degree of cutaneous irritation on a scale of 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = severe), where mild = scattered erythematous papules; moderate = confluent erythema; and severe = bullae, erosion, or ulceration. A global review of adverse events was also conducted at this time. Patient assessment of systemic and local tissue tolerance was performed daily. Patients also graded degree of cutaneous irritation on a scale of 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = severe). A post-treatment phone call was made at week 6 to assess for resolution of local and systemic adverse effects.

Response to treatment was assessed by calculating change in axillary HDSS from baseline to week 1 and week 4. At each of these time periods, we also assessed change in CDLQI/DLQI; change in HDSS at distant, untreated sites (hands and feet); incidence of treatment-emergent systemic adverse effects as measured by daily patient diaries and investigator global review; and incidence and severity of application site skin irritation as measured by daily patient assessments and physician assessment.

Based on a prospective power analysis and sample size determination, we initially planned to enroll 20 patients in this study. The primary outcome measure was change in hyperhidrosis severity from baseline to week 1 and week 4 as measured by the HDSS. We initially defined a treatment responder as any patient whose HDSS score improved from a baseline score of 3 or 4 to a score of 1 or 2 at week 1 or week 4. We had planned to assess the primary outcome measure using a one-sample binomial test. Unfortunately, the drug was discontinued by the manufacturer during the enrollment period and we were unable to achieve our goal enrollment. Due to a small sample size, we elected to present the data descriptively.

Results

Baseline data and non-completers

Patients' baseline characteristics and treatment course are presented in Table I. Ten patients were treated with oxybutynin 3% gel, 1 male and 9 female. Patient ages at treatment initiation ranged from 13–24 years (mean 18.5, SD 4.3 years). Four patients had isolated axillary hyperhidrosis (40%) and 6 (60%) had involvement of axilla, hands and feet. Nine patients (90%) had failed at least one other treatment modality. Prior treatments included

aluminum chloride 20% solution only (5), onabotulinumtoxinA injections only (1), aluminum chloride 20% and onabotulinumtoxinA (2), aluminum chloride 20% and oral glycopyrrolate (1). Seven patients completed the study. Two patients were lost to follow-up (1 patient prior to the week 1 follow-up visit and 1 patient following the week 1 follow-up visit). One patient was removed from the study at day 6 after experiencing a severe adverse event (SAE).

HDSS response

Among patients who completed the study, 4/7 (57.1%) reported reduction in axillary HDSS at week 1 and 7/7 (100%) at week 4 (Figure 1a). Four patients (57.1%) achieved the predetermined primary efficacy measure by week 4 (2 point reduction in HDSS score from baseline). Among all 7 patients who completed the study, the mean axillary HDSS improved from baseline (3.9) to week 1 (2.9) and week 4 (2.4). Among patients with concurrent palmar hyperhidrosis, 4/5 (80%) reported reduction in palmar HDSS at week 1 and week 4. One patient (20%) reported no change (Figure 1b). Among patients with concurrent plantar hyperhidrosis, 2/5 (40%) reported reduction in plantar HDSS at week 1 and week 4. Two patients (40%) reported no change. One patient (20%) reported no change at week 1 followed by increased plantar HDSS at week 4 (Figure 1c).

CDLQI/DLQI

Six patients (6/7, 85.7%) reported reduction in CDLQI/DLQI score at week 1 and week 4. One patient (14.3%) reported an increased score at week 1 and week 4 (Figure 1d). Among all 7 patients who completed the study, mean CDLQI and DLQI scores improved from baseline (14) to week 1 (8.6) and week 4 (7.1).

Adverse events

Adverse effect data was available for 9 patients in total (7 patients who completed the study, 1 patient who was lost to follow-up after the week 1 visit, and 1 patient who was removed from the study at day 6 after experiencing a SAE. Three patients (3/9, 33.3%) experienced a mild systemic adverse event. Two patients (22.2%) reported xerostomia during the first week of treatment. One patient reported constipation and blurry vision (11.1%). One patient (11.1%) experienced a SAE, pyelonephritis on day 6 of treatment resulting in hospital admission. Three patients (33.3%) reported mild (1) or moderate (2) application site skin irritation. Irritation resolved by the end of the study. Physician assessment of local tissue tolerance at week 1 and week 4 revealed no visible skin changes in any patient. All local and systemic adverse events had resolved at the 6 week follow-up phone call.

Discussion

This study provides prospective pilot data on the use of topical oxybutynin 3% gel for the treatment of axillary hyperhidrosis in adolescents and young adults. Daily application of oxybutynin 3% gel reduced the symptoms of primary axillary hyperhidrosis measured by HDSS in all 7 patients who completed the study. Four of these patients experienced a meaningful reduction in their symptoms (2 point reduction in HDSS score). Among the 5 patients with concurrent palmoplantar hyperhidrosis, all experienced reduction in HDSS in

at least 1 untreated site. The onset of site-specific treatment effect was evident by week 1 at 10/13 (76.9%) sites evaluated, correlating with the time at which the drug reaches steady state. This response was sustained at week 4 in all patients and at all sites. Three patients experienced continued improvement in axillary sweating between the week 1 and week 4 follow-up visits, but it is unclear if continued use beyond the 4 week follow-up visit would have yielded additional clinical benefit. We also observed an improvement in HRQOL, as measured by CDLQI/DLQI, in all but one patient who completed the study.

Although we observed a modest number of patients with application site irritation (3/9 patients), patient-reported irritation was mild to moderate in severity, did not impact adherence to treatment protocol, and resolved spontaneously during treatment without intervention. Additionally, physician assessment of application site did not reveal physical evidence of application site reaction in any patient, including those who reported subjective irritation. When used for overactive bladder, oxybutynin gel is applied to the abdomen or proximal extremities. Drug application to a non-occlusive site may mitigate application site irritation.

Compared to the oral formulation, topical oxybutynin gel has a favorable pharmacokinetic profile. When taken orally, oxybutynin is subject to hepatic and gastrointestinal first pass metabolism.⁶ Its primary metabolite, N-desethyloxybutynin (N-DEO), is pharmacologically active but has a higher side effect-to-efficacy ratio than the parent compound, oxybutynin.^{4,6} Transdermal application mitigates first-pass metabolism and reduces both formation of N-DEO and the incidence of associated anti-cholinergic side effects such as xerostomia. In this study, 2 patients reported xerostomia; however, their symptoms resolved spontaneously after 1 day during the first week of treatment with continued use of the drug. One patient experienced constipation and blurry vision, which was temporally associated with opioid use following an elective surgery and unlikely related to the study drug. Oxybutynin does cross the blood-brain barrier, however, anticholinergic central nervous system effects were not reported. The effect of long-term topical administration on neurocognitive function is unknown.

Oxybutynin may cause or exacerbate urinary retention. Patients in our study did not report change in urinary habits, however, one patient developed pyelonephritis during the study, possibly related to the study drug. This patient had a history of kidney transplant, immunosuppression, and recurrent urinary tract infections. For these reasons, the drug should be used with caution in patients with history of urinary retention and/or recurrent urinary tract infections.

This study provides limited prospective data supporting the use of topical oxybutynin 3% gel for the treatment of axillary hyperhidrosis. Unfortunately, the study drug was discontinued by the manufacturer during the enrollment period and we were unable to achieve our goal enrollment. The decision to discontinue the product was 'business-related' and not due to product safety or efficacy. Oxybutynin 10% gel is also approved for the treatment of overactive bladder and remains commercially available. This study did not evaluate the drug's duration of action, an area of potential future research given the drug's long serum half-life and the short duration of action of existing topical therapy with aluminum salts. All

patients in this study applied the drug to axillary skin. The effect of drug application to other sites should be evaluated in a larger study. A large, randomized, double-blinded, placebo-controlled trial which addresses these limitations is warranted.

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Table I

Baseline Characteristics and Treatment Course

Patient no./Sex	Age (y) at starting oxybutynin	Duration of disease (y)	Family history of hyperhidrosis	Prior treatment	Location	Baseline Axillary HDSS	Axillary HDSS Wk4	Baseline CDLQI/DLQI	CDLQI/DLQI Wk4
1/f	13	3	N	None	A	4	2	16	2
2/f	21	7	Y	OnabotulinumtoxinA	A	4	DNC	7	DNC
3/f	21	9	N	Aluminum chloride 20%	AHF	4	2	21	7
4/f	24	7	Y	Aluminum chloride 20%, onabotulinumtoxinA	A	3	DNC	5	DNC
5/f	21	8	N	Aluminum chloride 20%, oral glycopyrrolate	AHF	3.5	1.5	16	4
6/m	21	7	N	Aluminum chloride 20%, onabotulinumtoxinA	A	4	3	10	7
7/f	22	10	N	Aluminum chloride 20%	AHF	4	3	12	9
8/f	16	13	N	Aluminum chloride 20%	AHF	3	DNC	18	DNC
9/f	13	2	N	Aluminum chloride 20%	AHF	4	3	17	18
10/f	13	4	Y	Aluminum chloride 20%	AHF	4	2	6	3

A, axilla; AHF, axilla, hands, feet; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; DNC, did not complete study; HDSS, Hyperhidrosis Disease Severity Score