Oxybutynin for the Treatment of Primary Hyperhidrosis: Current State of the Art

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Key Words

Botulinum toxin · Children · Hyperhidrosis · Sweat glands · Xerostomia

Abstract

Oxybutynin is an anticholinergic drug with an emerging role in the treatment of hyperhidrosis. Several recent studies have documented that it is effective both in focal and generalized hyperhidrosis and shows universally good response among different groups of patients regardless of age, gender, and weight. The most common adverse event is dry mouth reported by almost all patients treated. The way this might affect long-term compliance and tolerability should be better investigated in the future.

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Introduction

Primary Hyperhidrosis

Hyperhidrosis is a well-known clinical condition characterized by excessive sweating beyond the physiological needs of the patient's body [1]. The burden of the disease is strictly related to its impact on quality of life (QOL) [2].

Excessive sweating may be primary (idiopathic) or secondary to medication or disease. Secondary causes include endocrine diseases such as diabetes mellitus, hyperthyroidism, and hyperpituitarism, or neurological diseases including peripheral nerve injury, Parkinson's disease, reflex sympathetic dystrophy, spinal injury, and Arnold-Chiari malformation. Additional causes to consider are pheochromocytoma, respiratory diseases, and psychiatric diseases.

Primary hyperhidrosis usually develops during childhood and tends to persist throughout adult life. The main areas affected are the axilla, the palms of the hands, the soles of the feet, and the face [3].

Several recent epidemiologic studies have demonstrated a greater prevalence among young, working-age individuals, who are most commonly affected and often seek healthcare professionals [4–6].

The diagnosis of primary hyperhidrosis is essentially clinical and based on the following criteria, according to the Canadian Hyperhidrosis Advisory Committee: excessive sweating of 6 months or more in duration, with 4 or more of the following: primarily involving eccrine-dense sites (axillae/palms/soles/craniofacial sites); bilateral and

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symmetric; absent nocturnally; episodes at least weekly; onset at the age of 25 years or younger; a positive family history, and impairment of daily activities [7].

Treatments for Primary Hyperhidrosis

Increased knowledge about primary hyperhidrosis associated with emerging therapies has contributed to increase patients' demand for effective treatments. Noninvasive treatments include antiperspirant agents, astringent agents, and anticholinergics.

Aluminium salt solutions are the most common antiperspirants in use today [8]. Particularly, aluminium chloride hexahydrate is the most effective antiperspirant currently available [8]. Several studies have shown that aluminium salts are able to induce the obstruction of the distal sweat gland duct: the metal ions precipitate with mucopolysaccharides, damaging epithelial cells along the lumen of the duct and forming a plug that blocks sweat output [8]. Sweat is not really abolished by the treatment, with sweat building up behind the obstruction created by the metallic salt [9]. The effect is transient, since normal sweat production returns with epidermal renewal; thus, patients necessitate retreatment once or twice a week [8].

Several tanning agents have astringent properties and have been used to control hyperhidrosis [8, 10]. These agents act primarily on the stratum corneum layer by inducing a denaturation of the keratin which leads to a superficial closure of the pore that lasts several days, until a desquamation of the cell layer occurs [8]. These astringent agents (formaldehyde, glutaraldehyde, tannic acid, and trichloroacetic acid) previously used to treat hyperhidrosis are now essentially considered obsolete [8], although low concentrations of astringents may be found in some commercial preparations [8].

The use of anticholinergic drugs as topical glycopyrrolate in 0.5% cream was evaluated to treat gustatory hyperhidrosis in a series of patients with diabetes [11]. Compared to placebo, glycopyrrolate cream significantly reduced forehead hyperhidrosis during gustatory challenge by 82% [11]. Another anticholinergic agent, diphephanil methylsulfate, was successfully administered via the oral route in 15 patients with Frey's syndrome.

Botulinum toxin A injection therapy has been used successfully to reduce excessive sweating in all of the body areas affected in primary hyperhidrosis: axillary, palmo-plantar, and facial/gustatory sites. Characterized as a 'minimally invasive treatment option' compared to local surgery and endoscopic thoracic sympathectomy, the use of botulinum toxin A has become an important second-line treatment option for patients not responding to more

conservative therapies, although the price is the major drawback of this type of treatment [12].

Video-assisted thoracoscopic sympathectomy may be considered the third line of treatment for hyperhidrosis; however, surgical risks and the risk of compensatory hyperhidrosis are the main limiting factors [13].

All the above-mentioned therapeutic approaches show a specific safety and effective profile to control primary hyperhidrosis localized at the axilla, the palms of the hands, the soles of the feet, and the face, and some of them have also demonstrated efficacy in segmental compensatory hyperhidrosis. However, none of them were able to exert a control of symptoms in the case of primary extensive hyperhidrosis. In the second half of the last decade, specific treatment with oxybutynin began to be reported [14, 15], since an overexpression of acetylcholine and α_7 -nicotinic receptors in sympathetic ganglia [15] has recently been demonstrated in hyperhidrotic patients.

Oxybutynin Pharmacology

Mechanism of Action

Oxybutynin is an anticholinergic medication able to antagonize the M1, M2, and M3 subtypes of the muscarinic acetylcholine receptor. It is generally used to relieve urinary and bladder difficulties, including frequent urination and the inability to control urination (urge incontinence), by decreasing muscle spasms of the bladder [16]. It also has direct spasmolytic effects on bladder smooth muscle as a calcium antagonist and local anesthetic, but at concentrations far above those used clinically [16].

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. It exhibits one fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle but 4–10 times the antispasmodic activity [16]. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Absorption

Following the oral administration of oxybutynin chloride tablets, oxybutynin is rapidly absorbed achieving the maximum concentration within an hour, after which plasma concentration decreases with an effective half-life of approximately 2–3 h. The absolute bioavailability of oxybutynin is reported to be about 6% (range 1.6–10.9)

for the tablets. Wide interindividual variation in pharmacokinetic parameters is evident following the oral administration of oxybutynin [16–18].

Data in the literature suggest that oxybutynin solution coadministered with food resulted in a slight delay in absorption and an increase in its bioavailability by 25% (n = 18) [19].

Distribution

Oxybutynin is widely distributed in body tissues following systemic absorption. The volume of distribution is 193 liters after intravenous administration of 5 mg oxybutynin chloride [16–18]. The major binding protein is α_1 acid glycoprotein [16–18].

Metabolism

Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4, found mostly in the liver and gut wall. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyl oxybutynin, which is pharmacologically active [16–18].

Excretion

Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desethyl oxybutynin [16–18].

Indications for Oxybutynin Use

Actually, oxybutynin chloride is indicated for the relief of symptoms of bladder instability associated with voiding in patients with an uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, and dysuria) [16–18].

Contraindications

Oxybutynin chloride is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma, and in patients who are at risk of these conditions [16–18].

Carcinogenesis, Mutagenesis, and Impairment of Fertility

A 24-month-study in rats receiving oxybutynin chloride doses of 20, 80, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25, and 50 times those of the maximum human expo-

sure, based on the surface area [16–18]. Oxybutynin chloride showed no increase in mutagenic activity when tested in *Schizosaccharomyces pompholiciformis*, *Saccharomyces cerevisiae*, and *Salmonella typhimurium* test systems. Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility [16–18].

Pregnancy

According to its teratogenic effects, oxybutynin is ascribed to category B. Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility or harm to the animal fetus. The safety of oxybutynin chloride administered to women who are or who may become pregnant has not been established. Therefore, oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards [16–18].

Drug Interactions

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects [16–18].

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index. Mean oxybutynin chloride plasma concentrations were approximately 3- to 4-fold higher when oxybutynin chloride was administered with ketoconazole, a potent CYP3A4 inhibitor.

Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter the oxybutynin mean pharmacokinetic parameters (i.e., maximum concentration and area under the curve). The clinical relevance of such potential interactions is not known [16–18].

Oxybutynin in Hyperhidrosis: Mechanism of Action and Efficacy

Oxybutynin is an antimuscarinic drug whose effect was first associated with hyperhidrosis in 1988 [20]. This medication has been increasingly used as an initial or alternative therapy, especially in older patients who are not

candidates for surgery, or in patients suffering from primary extensive hyperhidrosis.

Over the years, several studies designed for specific focal hyperhidrosis – axillary [21], facial [22], palmar [23], and plantar [24] – demonstrated a good safety profile of the molecule. The first randomized, single-blinded, placebo-controlled trial was conducted in 2012 [25] on a group of 50 patients affected by palmar and axillary hyperhidrosis and demonstrated an improvement in symptoms in over 70% of patients when compared to placebo. Patients received 2.5 mg daily for the first week, then 2.5 mg twice daily from day 8 to day 21, and 5 mg twice daily starting at day 22. A significantly greater improvement was observed in the oxybutynin group compared with the placebo group for palmar, axillary, and plantar hyperhidrosis. More than 70% of patients in the oxybutynin group treated for palmar or axillary hyperhidrosis noted significant improvement, whereas only 27.3% of the corresponding placebo group experienced moderate improvement [25]. More than 90% of the oxybutynin-treated plantar hyperhidrotic patients achieved moderate or great improvement, versus 13.4% of the placebo-treated group.

A subsequent study conducted over a period of 6 years by Wolosker et al. [26] sought to evaluate the long-term effects of oxybutynin in 431 patients with axillary hyperhidrosis. A similar dosing schedule was employed. Ultimately, of the original 431 patients, only 181 were evaluated for more than 6 months, with 34 patients lost to follow-up on the first visit and others failing to improve with oxybutynin after 6 weeks [26].

Among the 181 patients (129 females and 52 males) treated for at least 6 months with oxybutynin, 93.4% reported an improvement at 6 weeks, while 82.9% of the patients maintained substantial improvement after 24 weeks [26]. Twenty-six patients demonstrated good results with oxybutynin treatment after 6 weeks, even if they were referred for video-assisted thoracoscopic sympathectomy due to their unwillingness to remain on long-term medication. Six patients stopped treatment due to side effects. When the investigators compared the level of improvement at 6 weeks and at final evaluation (median of 17 months), 57.4% of patients maintained the original level of improvement, while 23.3% further improved, and 19.4% reported degradation of symptom resolution ($p = 0.001$) [26].

Although a number of studies have demonstrated short- and long-term efficacy of oxybutynin in the treatment of primary hyperhidrosis, anticholinergic side effects and the requirement for chronic pharmacologic

therapy limit the use of this medication for some patients. Dry mouth, headache, constipation, and urinary retention are relatively minor side effects seen with oxybutynin, particularly when the daily dose exceeds 15 mg [26]. Wolosker et al. [26] also suggest that for those patients for whom side effects are intolerable or who fail to improve over 6 weeks (considered oxybutynin failure), sympathectomy or other treatment may be considered.

In 2014, Costa Ada et al. [27] conducted a prospective, randomized study to compare the effects of oxybutynin 10 mg daily and placebo in 32 women with persistent plantar hyperhidrosis. The assessment was performed using a QOL questionnaire for hyperhidrosis and sweating measurement with a device for quantifying transepidermal water loss. This ‘vapometer’ (Defin[®], Finland) was a battery-operated portable device with a humidity sensor in a closed chamber able to measure the evaporation on a 1-cm-diameter patch of skin.

The authors found that there were no significant differences between the groups prior to treatment. After oxybutynin treatment, there was a decrease in symptoms and clinical improvement based on the QOL questionnaire. The placebo group showed only modest and no significant improvement. The outcomes of the transepidermal water loss measurements in the placebo group showed no differences, whereas the oxybutynin group revealed a significant decrease. The most common side effect was dry mouth (100% in the oxybutynin group vs. 43.8% in the placebo group; $p = 0.001$). The authors conclude that oxybutynin is effective in the treatment of persistent plantar hyperhidrosis, resulting in a better QOL in women who had undergone thoracoscopic sympathectomy.

In 2014, Teivelis et al. [28] evaluated the efficacy of oxybutynin as a treatment for primary sweating at uncommon sites (e.g., the back and groin), conducting a retrospective study on 20 patients (10 females) who received oxybutynin for primary focal hyperhidrosis at uncommon sites. The subjects were asked to evaluate their QOL before beginning oxybutynin therapy and 6 weeks afterwards, and they were assigned grades to measure their improvement at each site of excessive sweating after 6 weeks and at the last consultation.

The median follow-up time with oxybutynin therapy was 385 days (range 133–1,526). The most common involved sites were the back ($n = 7$) and groin ($n = 5$). After 6 weeks, the QOL had 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 because of the side effects (2 for unbearable dry mouth, 2 for excessive somnolence,

and 1 for palpitations). At the last visit, 80% of patients presented with moderate/great improvement at the main sites of sweating.

After 6 weeks, more than 80% of the patients presented with improvements in their overall QOL 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. The authors concluded that oxybutynin is effective for the treatment of hyperhidrosis, even when it involves uncommon body sites, and most of the patients tolerate side effects well.

Efficacy in Special Population Groups

Primary hyperhidrosis is mainly considered an adult burden; however, 1.6% of adolescents and 0.6% of prepubertal children are affected. The efficacy of oxybutynin in children with palmar hyperhidrosis has recently been investigated in a study published by Wolosker et al. [29]. The 45 children between 7 and 14 years of age included in the analysis were given 6 weeks of treatment with oxybutynin. Treatment improved hyperhidrosis in 85% of the children. More than half experienced adverse effects (most commonly, dry mouth), although treatment discontinuation was not necessary.

Overweight and obese patients have greater difficulty in maintaining normal body temperature levels and, therefore, produce excessive perspiration as a compensatory mechanism [30]. A retrospective analysis of 121 overweight and 27 obese patients with primary hyperhidrosis treated with oxybutynin compared the efficacy of treatment with that of 411 normal-weight hyperhidrosis patients treated with oxybutynin [31]. The oxybutynin dose protocol was the same regardless of body weight, with 2.5 mg of oxybutynin administered once a day for the first week, 2.5 mg twice a day for the next 5 weeks, and 5 mg twice a day to the end of the 12th week. Improvements in hyperhidrosis after treatment were similar in all three groups, with 34.3% of the normal weight, 28.9% of the overweight, and 29.6% of the obese patients showing partial improvement and 37.7, 38.9, and 33.4% reporting great improvement, respectively, suggesting that overweight and obese patients benefit similarly to normal-weight patients.

Clinical practice suggests that young people more often seek treatment for primary hyperhidrosis, a fact attributed by many authors to the greater impact of hyperhidrosis in the working environment and social activities. Elderly people are more often concerned with complica-

tions and more prone to decline invasive treatment of focal hyperhidrosis. Since oxybutynin is an agent that can be prescribed regardless of age, treatment efficacy in different age groups is an important issue to be investigated. A recent study compared the efficacy of oxybutynin treatment of primary hyperhidrosis in 87 patients who were divided into two age groups: one including patients aged 40–49 years and one including patients ≥ 50 years old [32]. Both groups demonstrated excellent response when treated with 2.5 mg/day oxybutynin during the first week, 2.5 mg twice a day for the next 2 weeks, and 5 mg twice daily to the end of the 6th week. No, partial, and great improvement was seen in 12, 23, and 52% of patients in the 40- to 49-year age group and in 13, 31, and 56% of patients in the ≥ 50 -year age group, respectively.

The difference in the efficacy of oxybutynin has been reported to be statistically nonsignificant when comparing gender [33]. A retrospective analysis reported that 67% of men and 70% of women with primary focal hyperhidrosis who were treated with oxybutynin reported partial or greater improvement.

Oxybutynin has also been successfully administered in postmenopausal women reporting associated secondary generalized hyperhidrosis. Most of the 21 women enrolled in a recent study were treated with 5 mg of oxybutynin per day for 3 months. All women reported at least a 1.0-point improvement on the 4-point Hyperhidrosis Disease Severity Scale, with a statistically significant improvement reported to be 1.9 ± 0.4 [34].

Improvement in QOL

Treatment with oxybutynin has been reported to improve the QOL of patients with primary and secondary hyperhidrosis. However, QOL has been evaluated through the dermatology life quality index (DLQI) questionnaire in a limited number of studies.

In the study reporting the outcome of oxybutynin treatment of secondary generalized hyperhidrosis in postmenopausal women, the mean DLQI score was decreased from 8.4 ± 1.0 before treatment to 4.4 ± 0.9 after treatment [34]. Another study reported even greater improvement in patients with primary hyperhidrosis with a reduction in the DLQI score from 17.0 ± 5.1 before treatment to 4.6 ± 4.4 after 4 weeks of 7.5 mg oxybutynin daily [35]. The main drawback in using the DLQI is that the index cannot account for noncutaneous adverse events such as dry mouth that may lower the impact of sweat reduction in the daily routine of patients.

Wolosker and colleagues used a validated questionnaire developed by Amir et al. [36] to assess the QOL on a 20- to 100-point scale in all of their studies. Most of the patients (65%) reported an improvement in their QOL after treatment, with a maximum dose of 10 mg of oxybutynin daily for 6 weeks [21]. Patients with a very poor QOL before the treatment presented greater satisfaction levels after treatment. Subsequent studies confirmed these results. The QOL before and after treatment was evaluated in 50 patients with axillary, palmar, and plantar hyperhidrosis treated with oxybutynin. All patients reported poor to very poor QOL before treatment. After treatment, oxybutynin resulted in significantly improved QOL (73.8%) compared with placebo (13.6%) across the three anatomical hyperhidrosis groups [25]. Treatment of a pediatric population showed that almost 80% of the children who initially reported poor or very poor QOL were slightly or much better after the treatment [29]. The study assessing the efficacy of oxybutynin in normal-weight, overweight, and obese patients with hyperhidrosis showed that approximately 69% of the normal BMI group classified their QOL before treatment as 'very poor', whereas over 80% of obese individuals ranked their QOL as simply 'poor'. The questionnaire was reapplied after the proposed period of treatment; over 65% of patients demonstrated improvement in QOL for all three groups, with no statistical difference between them [31]. More than 77% of patients aged over 40 years demonstrated improvement in their QOL after treatment with oxybutynin. Especially good outcomes were observed in patients over 50 years old, of whom 87.1% presented 'slight' (41.0%) or 'much better' (46.1%) improvement [32].

Women report a heavier impact of hyperhidrosis on QOL. Over 70% of the women in the study comparing the differences of oxybutynin treatment between genders classified their QOL as 'very poor' prior to treatment, which demonstrates that women, in addition to seeking medical assistance more frequently, are also more affected by hyperhidrosis than men. On the other hand, women benefited the most from oxybutynin treatment, presenting a 'great improvement' in the level of hyperhidrosis in over 40% of the cases [33].

Safety and Tolerance

Oxybutynin is an anticholinergic drug that has been widely used for the treatment of an overactive bladder. Consequently, multiple years of experience on safety and

adverse events have been accumulated. The agent has an absolute contraindication – closed angle glaucoma. Contraindications should also include patients with urinary retention, gastric retention, and demonstrated hypersensitivity to the drug substance or other components of the product.

Apart from these concerns, it is a safe agent, albeit with a limited tolerability due to antimuscarinic side effects. These effects are more frequent with doses over 15 mg/day [37]. A maximum dose of 10 mg/day reached through slow and progressive increase in dosage over a period of 3 weeks has been reported to lower the incidence of side effects, maintaining effectiveness and improving compliance to treatment [25]. Schedules of a 1.25-mg initial dose and an increase by 1.25 mg every 4 days up to 7.5 mg/day, or 2.5 mg/day for the first week, 2.5 mg twice a day for the next 2 weeks, and 5 mg twice daily for the rest of the treatment have been successfully employed in the literature [35].

Dry mouth was the only side effect observed in several studies. Dry mouth is experienced by 70–100% of the patients treated with oxybutynin for primary or secondary hyperhidrosis. However, cessation of oxybutynin therapy due to dry mouth in the studies with 6–12 weeks duration of treatment is infrequent (1.56%) [38].

Other adverse events observed include constipation in up to 31% of the patients [27] and drowsiness in up to 18% [27], while a feeling of mild urinary retention, dry eyes, dizziness, diarrhea, mydriasis, and flushing should be considered as rare.

Long-term tolerance and compliance in patients treated with oxybutynin for primary hyperhidrosis leaves a lot to be desired. In the study conducted over a period of 6 years by Wolosker et al. [26], only 181 of the original 431 patients were evaluated for more than 6 months, with 34 patients lost to follow-up on the first visit and others failing to improve with oxybutynin after 6 weeks [26].

Position of Oxybutynin in the Treatment of Hyperhidrosis

According to the Canadian Hyperhidrosis Advisory Committee [7], topical treatment with aluminium chloride is recommended as first-line treatment for focal hyperhidrosis. For axillary hyperhidrosis, botulinum toxin injections are recommended as second-line treatment and oral medications as third-line treatment. For palmar and plantar hyperhidrosis, iontophoresis is considered the second-line therapy; oxybutynin could also be consid-

ered as second-line therapy due to the low cost, convenience, and the emerging literature supporting its reasonable efficacy and safety as well as due to the higher cost of botulinum toxin injections. For craniofacial hyperhidrosis and primary extensive hyperhidrosis, oxybutynin should be considered as first-line therapy [39]. The fact that its use in the treatment of hyperhidrosis is off label and not compensated for by the insurance is offset by the low cost. The lack of data on the prolonged use of oxybutynin is a matter for scepticism; compliance to the treatment could be compromised due to mouth dryness affecting almost all of the patients, which does not tend to become worse over time, but it could reduce the adherence to long-term treatment. Moreover, another concern about the prolonged use of oxybutynin is the risk of tachyphylaxis development.

Conclusions

Oxybutynin is an anticholinergic drug with an emerging role in the treatment of hyperhidrosis. It is effective both in focal and generalized hyperhidrosis and shows good response among different groups of patients regardless of age, gender, and weight; however, in a minority of cases, side effects are severe enough to drive the patients to stop the treatment. What we really should be waiting for in the future is the establishment of an ideal protocol of administration with gradually increasing dosage and data on long-term compliance in order to assess the long-term tolerability of the treatment.

Disclosure Statement

The authors declare no conflicts of interest.

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