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An overview of oxybutynin and its use in primary hyperhidrosis

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Abstract
Primary hyperhidrosis typically starts in childhood and lasts until maturity. The main areas affected are the face, palms of the hands, soles of the feet, and the axilla.
A patient with hyperhidrosis who started taking oxybutynin for urinary urgency is described in a case report from 1988; the patient's episodes of intense sweating stopped after a few hours. Numerous investigations conducted in recent years have confirmed its effectiveness in treating hyperhidrosis.
Since it has recently been established that people with hyperhidrotic conditions have an overabundance of acetylcholine and 7-nicotinic receptors in their sympathetic ganglia, targeted treatment with oxybutynin has started to be reported. In 2003, the FDA approved oxybutynin transdermal administration for the first time in the form of a transdermal patch. The first transdermal delivery system (TDS) for oxybutynin was a patch that could be applied to the buttocks, hips, or abdomen.
The transdermal patch was found to have less negative side effects and to be just as efficient in reducing the symptoms of overactive bladder when compared to oxybutynin taken orally. In the senior population, which is more likely to develop overactive bladder, transdermal distribution may also lessen the amount of pills required, memory loss, and drug-drug interactions, all of which are desired outcomes. Adults with hyperactive bladders may benefit from topically applied oxybutynin gel treatment. Oxybutynin chloride gel has been shown to be effective in treating primary focal hyperhidrosis in studies. Oxybutynin may have a longer half-life than other topical drugs like aluminium chloride, with a serum half-life of 62–84 hours following topical treatment.
Patients' primary focal hyperhidrosis is treated less severely and have better health-related quality of life thanks to oxybutynin 3% gel.

Keywords: Hyperhidrotic conditions, oxybutynin, health-related

Introduction
The M1, M2, and M3 subtypes of the cholinergic receptor, which are commonly present in bladder smooth muscle, are selectively targeted by the synthetic anticholinergic drug oxybutynin. Oxybutynin is used to treat the primary symptoms of urge and frequency incontinence as well as overactive bladder. 1975 saw the legalisation of oxybutynin use in the US, and it is still a common practise today [1].
Primary hyperhidrosis typically starts in childhood and lasts until maturity. The main areas affected are the face, palms of the hands, soles of the feet, and the axilla.
A patient with hyperhidrosis who started taking oxybutynin for urinary urgency is described in a case report from 1988; the patient's episodes of intense sweating stopped after a few hours [2]. Numerous investigations conducted in recent years have confirmed its effectiveness in treating hyperhidrosis [3]. Targeted treatment with oxybutynin has begun to be discussed as it has recently been demonstrated that people with hyperhidrotic illnesses have an excess of acetylcholine and 7-nicotinic receptors in sympathetic ganglia [4, 5].
Recent studies have demonstrated that people of different ages, genders, and weights respond well to it and that it is effective in treating both focal and generalised hyperhidrosis. The majority of people who undergo treatment state that the most frequent side effect is dry mouth. Future studies should concentrate more on the potential implications for long-term compliance and tolerance [6]. This research was done to show how oxybutynin is used to treat hyperhidrosis, as well as how it works, what its pharmacodynamic and pharmacokinetic profiles are, how it interacts with other drugs, and what its negative effects are.

Mechanism of action

The anticholinergic, direct muscle relaxant, and local anaesthetic effects of oxybutynin are among its pharmacological characteristics *in vitro*. Oxybutynin is thought to primarily act as an antimuscarinic drug when administered systemically [7]. The active metabolite of oxybutynin is n-desethyloxybutynin (N-DEO). It blocks acetylcholine's muscarinic effect by competitively inhibiting the postganglionic muscarinic 1, 2, and 3 receptors. As a result, the bladder's smooth muscles relax, enhancing bladder capacity and lowering frequency and urgency of urinating. It has also been shown to delay the initial need to urinate. Similarly, oxybutynin chloride can reduce the impact of acetylcholine on sweat glands and, in contrast to other anticholinergics, has a lower propensity for crossing the blood-brain barrier [1, 8].

Administration

Various methods can be used to provide oxybutynin. The most popular form is a tablet, which can be either long-acting or quick release. For both the immediate and long-acting versions, the starting dose is 5 mg. It can also be taken as a syrup with a formulation of 1 mg/ml [1].

To reduce side effects and increase acceptability, oxybutynin has been developed in a number of different formulations. This flexible compound's therapeutic index and tolerance can be enhanced by changing the way it is delivered [9].

Initial research using intravesical and other parenteral delivery techniques showed that it is possible to prevent the high rates of antimuscarinic side effects connected to oxybutynin chloride treatment following fast release while maintaining efficacy [9].

These other forms include transdermal patch, transdermal gel, rectal and vaginal suppositories, vaginal gel and vaginal rings [1, 9]. These formulations, in particular the topical gel and transdermal version, lessen N-DEO synthesis in an effort to lessen systemic side effects, particularly dry mouth [7].

Therapeutic uses

Oxybutynin reduces the unpleasant urge incontinence symptom linked to idiopathic DI and detrusor hyperreflexia and corrects inaccurate objective measures. In noncomparative trials, 55 to 70% of patients who received oxybutynin for up to 2 years reported subjective improvements that were "great or good." Although this trial offers some early signs of efficacy, placebo-controlled studies are necessary to demonstrate a treatment's effectiveness because DI patients have a high rate of placebo response. Oxybutynin increases bladder volume at first desire to void, improves maximum bladder capacity, and lowers maximum detrusor pressure during filling, according to numerous investigations in ambulatory people. Also less frequent, less urgent, and less frequent is urge incontinence [10].

Although reports of potentially harmful increases in residual urine volume associated with its usage have been made, oxybutynin appears to have different degrees of efficacy in curing nocturia. Similar to other medications, a cure is difficult to find. Additionally, despite the low patient numbers, older institutionalised patients typically did not improve after getting oxybutynin medicine, in contrast to unselected groups. Oxybutynin gave older ambulatory patients in one placebo-controlled experiment a small subjective improvement, but both the placebo and oxybutynin equally relieved urge incontinence [10].

Use of oxybutynin in hyperhidrosis

It has been shown that the sympathetic ganglia of people with primary hyperhidrosis contain greater concentrations of acetylcholine and alpha-7 nicotinic receptors. Thus, the ability of oxybutynin to reduce excessive sweating is due to its anticholinergic properties (figure 1) [4].

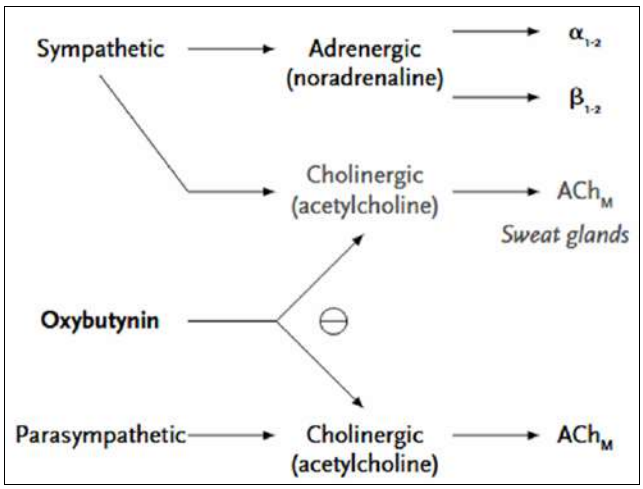

Fig 1: a description of how oxybutynin affects the autonomic nervous system and eccrine sweat glands.

In 1988, oxybutynin was first linked to the treatment of hyperhidrosis. Over the past ten years, reports of particular use of this medication as an effective initial treatment for excessive sweating have increased [11].

There have been unconfirmed accounts of the drug being used on diabetics who perspire while eating [12, 13]. There have been published several series of oxybutynin-treated patients, including those from specific populations such postmenopausal patients [14], children, the elderly, obese patients, and those with certain symptoms like extensive hyperhidrosis or in unusual places like the back or groyne or the plantar, palmar, axillary, or face regions [15].

Other indications of oxybutynin

I. Oxybutynin for hot flashes

Oestrogen withdrawal is considered to cause hot flashes by upsetting the hypothalamus thermoregulatory system. Giving oestrogen to them is normally the course of treatment. HRT should not be used by anyone, not even individuals with breast cancer or a family history of the disease. As a result, scientists continue to study non-hormonal pharmacotherapies for the management of hot flashes. Even though these are just preliminary findings, oxybutynin may be helpful for some individuals who cannot benefit from hormone therapy. However, much more research is needed to determine its clinical utility in the therapy of hot flashes [16, 17].

Obstructive sleep apnea

An atomoxetine and oxybutynin combination may lower the severity of obstructive sleep apnea, according to a new study. Recent studies revealed that muscle compensation was not enhanced by oxybutynin alone, just the collapsibility during spontaneous breathing during sleeping.

Oxybutynin and atomoxetine may work better together to activate the upper airway muscles and reduce the incidence of obstructive sleep apnea [18, 19].

Adverse effects of oxybutynin

Dry mouth, lightheadedness, constipation, sleepiness, and nausea are side effects of quick release oxybutynin. Vision blurring, urine hesitancy, urinary retention, and dyspepsia are less frequent side effects. A noteworthy side effect related to dosage was dry mouth [20, 21].

The only unfavourable effect consistently reported in studies was dry mouth. When taking oxybutynin for primary or secondary hyperhidrosis, 70–100% of patients report feeling it. However, in studies with 6–12 weeks of treatment, stopping oxybutynin medication owing to dry mouth is rare (1.56%) [11].

Additionally, up to 31% of individuals experienced constipation, and up to 18% reported feeling sleepy. Mild urinary retention, dry eyes, dizziness, diarrhoea, mydriasis, and flushing should be thought of as quite uncommon. Aside from these issues, it is a safe agent, however its tolerance is constrained by adverse anti-muscarinic effects [22]. Even though the adverse effects of immediate-release oxybutynin are similar to those of extended-release, they have been seen to happen less frequently [1].

These negative effects happen more frequently at doses higher than 15 mg/day. A maximum dose of 10 mg/day that is gradually increased over the course of three weeks has been found to reduce the occurrence of side effects while maintaining effectiveness and improving treatment compliance [23]. The literature has effectively used regimens that start with a 1.25-mg dose and raise it by 1.25 mg every four days to 7.5 mg/day, or 2.5 mg/day for the first week, 2.5 mg twice a day for the following two weeks, and 5 mg twice daily for the remainder of the treatment [24].

Central nervous system adverse effects of oxybutynin

The blood-brain barrier is known to be crossed by tertiary amines like oxybutynin, which may have negative effects on the central nervous system and impair cognitive performance [9]. It suggests that using oxybutynin raises the risk of dementia, and that other anticholinergic drugs that easily cross the blood-brain barrier may do the same [25].

Oxybutynin has a neutral charge, a low molecular weight, and a high lipophilicity, which allow it to pass through the blood-brain barrier. The effects of various formulations' serum concentrations appear to regulate the behaviour of the substance. Theoretically, this would make the more contemporary transdermal and vaginal oxybutynin formulations safer than the more conventional oral forms, which appear to maintain essentially constant low serum levels [9].

Contraindications

Anyone with a clogged bladder, urinary retention, poorly managed narrow-angle glaucoma, obstructive gastrointestinal problems, or stomach dysmotility shouldn't use oxybutynin. It must also not be administered to anyone who is extremely sensitive to the medication or any of its ingredients. Patients who are elderly, frail, have dementia being treated with cholinesterase inhibitors, have Parkinson's disease, myasthenia gravis, or have renal or hepatic impairments shouldn't take this medication, according to the FDA.

The dose of the extended-release formulation must be decreased or terminated if the patient displays oxybutynin-induced adverse effects on the anticholinergic central nervous system. If you have autonomic neuropathy, use extended-release formulation with caution as it may make your symptoms of impaired stomach movement worse [26].

Pregnancy

Group B includes oxybutynin for expectant mothers. Investigations on animals have not led to definitive proof of harm to the foetus, despite the fact that safety for women who are pregnant or may become pregnant has not been proven. Additionally, there is no evidence that nursing mothers use oxybutynin. Watch for any signs that the mother's milk production may be diminishing when breastfed infants are repeatedly exposed to medications (e.g., in-satiety, poor weight gain) [27].

Drug Interactions

The frequency and/or severity of these side effects may be increased by taking oxybutynin concurrently with other anticholinergic medications or with substances that cause dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects, such as phenothiazine and tricyclic antidepressants [10].

The cytochrome P450 enzyme system also breaks down additional antimuscarinic drugs, most frequently with the aid of the enzymes CYP2D6 and CYP3A4. Any of these therapies carries the risk of drug interactions, which could change the plasma concentration of the antimuscarinic and/or interacting drug (Enzyme induction) in one of two ways (Enzyme inhibition, substrate competition) [28].

When oxybutynin is administered along with a potent CYP3A4 inhibitor, the result is an increase in mean oxybutynin plasma concentrations (antimycotic drugs like itraconazole or macrolide antibiotics like erythromycin). There doesn't seem to be a connection between the administration of oral contraceptives and oxybutynin [28].

Oxybutynin transdermal gel

In 2003, the FDA initially approved the use of oxybutynin transdermally in the form of a transdermal patch [9]. The first transdermal delivery system (TDS) for oxybutynin was a patch that could be applied to the buttocks, hips, or abdomen. It was developed to reduce negative side effects, especially dry mouth, and to enhance the ratio of oxybutynin to the metabolite N-desethyloxybutynin (N-DEO) [29]. Oxybutynin is administered non-orally, which bypasses presystemic, first-pass metabolism and significantly reduces plasma levels of N-DEO. Since skin CYP3A4 levels are just 5% of those in the liver and gut, this is assumed to be the case [9].

The transdermal patch was found to have less side effects and to be as effective at treating the symptoms of overactive bladder when compared to oxybutynin taken orally [9]. The elderly, who are more likely to experience overactive bladder, may require fewer tablets, experience less memory loss, and experience fewer drug-drug interactions thanks to transdermal delivery. These are all desired results [30].

However, an occlusive patch that over time exposes the wearer to penetration enhancers and constantly peels the stratum corneum may irritate the skin [29]. The main motivation behind the hunt for a new oxybutynin transdermal administration method was these negative effects [9]. The newest generation's distribution strategy was

a transdermal gel formulation [31].

Mechanism of transdermal delivery

The epidermis, dermis, and subcutaneous tissue make up the skin. The keratinized, avascular stratum corneum on the skin's surface makes it necessary to use molecules with low molecular weights (i.e. >500 Da) and high lipophilicity for drug penetration [32]. The molecular weight of 393.95 Da and lipophilicity of oxybutynin chloride make it a good candidate for transdermal administration. After being applied as a gel, oxybutynin penetrates the stratum corneum and epidermis before being absorbed into the dermal capillaries [9].

Factors affecting absorption

The skin's natural ability to absorb pharmaceuticals may be affected by radiation, solvents, exfoliating skin disorders, blood flow, and other transdermal medications. The cytochrome P-450 enzymes in the skin, which can metabolise between 10% and 20% of the drug administered, may also have an effect on absorption [30].

Indications

Adults with overactive bladders may be treated with oxybutynin gel applied topically. Studies have demonstrated the efficacy of oxybutynin chloride gel in treating primary focal hyperhidrosis. The fact that oxybutynin has a serum half-life of 62–84 hours when administered topically raises the possibility that the treatment will last longer than currently available topical medications like aluminium chloride [33, 34].

Conclusion

Oxybutynin 3% gel reduces hyperhidrosis severity and improves health-related quality of life in patients with primary focal hyperhidrosis.

Conflict of Interest

Not available

Financial Support

Not available

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