I don't want to Apply Minoxidil: Hairsplitting this Common Complaint

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Abstract

Minoxidil (MNX), the first drug approved for androgenetic alopecia (AGA) in both genders by the US-FDA is most commonly prescribed as 2% or 5% minoxidil topical solution (MTS) for local scalp application. However, the cosmetic unacceptability and other local adverse effects including allergic contact dermatitis associated with the conventional alcoholic MTS often results in markedly reduced patient compliance. Although a patch test is essential to differentiate between allergic reaction to the solvents, namely ethanol and/or propylene glycol (PG) versus MNX molecule, the most common source of the allergic reactions and flaking of scalp with MTS is the alcoholic solvent vehicle. Alcohol-free MTS formulations have been launched but brands with tall claims need to be scrutinized before prescription. Shifting to the aerosolized foam preparation is one viable option, albeit a little costlier. Low dose oral MNX may be tried in patients recalcitrant to topical MNX or developing intolerable local adverse effects. Nanoxidil 5%, the new congener with a lower molecular weight and expectedly better penetration and tolerance may offer a leap over MNX but needs to be validated in large randomized controlled trials.

Keywords: Minoxidil topical solution; Androgenetic alopecia; Female pattern hair loss; Male pattern hair loss; Hair loss; Allergic contact dermatitis; Alcoholic solution; Propylene glycol; Patch Test; Minoxidil foam; Oral minoxidil; Nanoxidil

Introduction

Topical minoxidil (MNX) was the first drug to receive US-FDA approval for treatment of androgenetic alopecia (AGA) both in men and women [1]. The 2% and 5% topical formulations of the product were first marketed in the United States for hair regrowth in men with AGA in 1986, and 1993 respectively [2]. But it was not until August 1988 and November 1997, that the topical 2% and 5% solution of MNX received FDA-approval for treatment of AGA in men [3,4]. While the 5% 'extra strength for men' solution got approved in November 1997, approval of the same strength solution for women was given in 2006. In the latter year, the foam (aerosol) preparation of 5% MNX also got FDA-approval for men with

the benefit of being less irritating than the solution due to lack of propylene glycol [5]. The 5% foam got FDA-approved for once-a-day use for AGA in women much later in 2014 [6]. Topical MNX has also been in use for diverse off-label indications in trichology including (AA), telogen effluvium (TE), chemotherapy-induced alopecia (CIA), post hair transplant, monilethrix, hereditary alopecia/ hypotrichosis, and even scarring alopecias [7].

The exact mechanism of action of MNX remains to be confirmed, but it has been postulated that its hair growth stimulation effect results from opening ATP-sensitive potassium channels and promoting synthesis of VEGF in dermal papilla cells [8].

Problems with the conventional minoxidil topical solution

Despite the satisfactory results of minoxidil topical solution (MTS) in AGA, the occurrence of scalp irritation, flakiness, worsening of seborrheic dermatitis, and scalp allergic contact dermatitis (ACD) in a substantial number of patients constitutes a huge problem. The cosmetic unacceptability of MTS stemming from the aforementioned local adverse effects often leads to patient non-compliance.

The role of ethanol and propylene glycol in MTS

Conventional MTS consists of propylene glycol (PG)–water–ethanol solution [9]. The rationale of having an ethanol-based solution was that ethanol would reinforce the thermodynamic activity of MNX onto the stratum corneum *in situ* after the solvent evaporates, and also enhance the diffusion of the drug through the layers of the skin to the deepest levels possible [10]. Allergic reactions to topical MNX solution such as scalp dryness, irritation, burning, redness, and ACD may arise from either the vehicle (ethanol, PG) or the molecule, i.e. MNX itself the latter being less common [11].

Differentiating between ACD to solvent vehicle VS minoxidil

Patch test has been used to distinguish between the two [12]. It is important to understand that true ACD to MNX molecule ultimately depends on the cutaneous delivery of the allergen. Thus, the ideal patch testing should include the 'as it is' proprietary minoxidil preparation, minoxidil in propylene glycol, minoxidil 5% in ethanol, PG, and ethanol. In patients with allergy to the solvent (ethanol and/ or PG), many therapeutic approaches may be tried and have been propounded.

Strategies to maintain patient compliance on minoxidil therapy

Shifting the patient from MTS to the aerosolized foam preparation (which is free of PG) has been trial-proven to reduce the local scalp adverse effects and enhance cosmetic acceptability [13].

Alcohol-free preparations of MTS are being manufactured by replacing ethanol and PG with an alternative solvent vehicle such as polysorbate, or glycerol, or multilamellar liposomes prepared from soy phosphatidylcholine and cholesterol, or niosomes containing mixture of alkylpolyglucoside (APG) surfactants, cholesterol, and dicetylphosphate, or alginate-based hydrogel containing MNX/β-Cyclodextrin Inclusion Complex [14-16].

However, it is important to note that although many pharmaceutical companies are marketing 'alcohol-free' MTS, many of them are only ethanol free and contain PG. Chemically PG is 1,2-propanediol, a synthetic organic alcohol with potent humectant property. And as stated above, an ethanol-free but PG containing solution of MNX is neither truly alcohol-free nor free from the possibility of solvent (i.e. PG) induced ACD. Recently a proprietary alcohol and PG-free brand of MNX 5% solution called ANASURE 5% has been launched in India by Sun Pharmaceuticals in which the vehicle used is Volarest™ F**,** an acrylate-based polymer**.**

Sticking to lower and US-FDA approved concentrations of MTS (not exceeding 5%) is helpful in patients who are otherwise comfortable with the 5% preparation. There is no evidence favoring higher efficacy of 10% or 15% MTS over 5% solution. Infact, a higher concentration of MNX requires more amount of ethanol/PG to dissolve it in solution form. This explains the higher incidence of scalp dryness, flaking, dandruff, and overall cosmetic unacceptability of 10-15% MTS.

Moreover, US-FDA issued a drug alert in 2012 [17] advising strictly against the use of these high concentrations of MTS owing to the risk of systemic absorption leading to low blood pressure, palpitations and associated cardiac symptoms.

Oral minoxidil for hair loss – Dose, Efficacy, Safety, and Evidence

A 'recalled' option worth exploring is oral administration of low dose (0.25-2.5 mg/day) MNX tablets for upto 12 months. Recent studies have shown improvement in patients with CTE, FPHL, as well as other hair loss conditions many of which were refractory to long-term MTS application [18-20]. Except for manageable facial hypertrichosis in few patients, authors did not report any other significant adverse effect. Importantly, oral MNX did not lead to clinically significant lowering of blood pressure or any biochemical abnormality. In the author's personal observation of administering 2.5 mg MNX tab/day to 8 patients (5 males, 3 females) with AGA for upto 12 months, no adverse effects were noted, except for 2 patients complaining of dizziness around half an hour after the tablet. Thus, I recommend the tablet preferably be taken at bedtime.

Nanoxidil 5% - The New Kid on-the-block

Another novel option is the use of nanoxidil 5%, a congener of MNX with lower molecular weight; which may provide better penetration and absorption, although no there is lack of robust evidence to support this assumption [21]. In an open labeled study 49 female patients with trichoscopically proven early FPHL who complained of increased hair shedding were treated with a novel proprietary nanosomal delivery system called Spectral. DNC-N® (DS Laboratories, Inc.) containing combination of 5% nanoxidil with numerous hair growth promoters and anti-inflammatory molecules, including pyrrolidinyl diaminopyrimidine oxide, azelaic acid, lysophosphatidic acid, copper tripeptide-1, myristoyl pentapeptide-17, adenosine, piroctone olamine, retinol, and caffeine [22]. There was a statistically significant decrease in hair shedding and a corresponding increase in hair mass index at 3 months. By the end of 6 months, the hair shedding score was reduced further and the hair mass index was maintained [22]. The treatment was very well tolerated.

Conclusion

In absence of a definitive and consistently efficacious medical option for hair restoration in AGA, the huge experience with the possible adverse effects of MNX – MNX shall continue to remain on the frontiers of trichotherapy. Dermatologists need to assess their patient's requirement, psychology and prefer to give them alcohol-free preparations instead of the convention MTS based protocol. The only problem with the former (aerosolized foam, alcohol-free MTS) is the modestly higher cost of these formulations. Low-dose oral MNX is worth trying, but under utmost care. The new congener nanoxidil 5% may be a true advancement over MNX, but needs validation with many more planned randomized controlled trials with large cohort size.

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