REVIEW

Intranasal Mometasone Furoate for Treatment of Allergic Rhinitis

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Abstract: Allergic rhinitis (AR) is a chronic nasal disease that affects the upper respiratory tract. This disorder is characterized by inflammation of the mucous membranes and it manifests with several nasal symptoms accompanied sometimes by non-nasal symptoms. Best therapy aims to prevent and improve the AR-clinical picture. Steroids have an important role in the treatment of AR. The development of steroids administrated directly on nasal mucosa has much reduced the systemic adverse affects associated with oral steroids therapy. Mometasone furoate aqueous nasal spray is a synthetic steroid assessed for intranasal use in the therapy of adults and children affected by AR. Such topical nasal steroid is an effective molecule improving clinical picture of AR and it is also approved as prophylactic therapy. In this article, apart from a careful description of its successful clinical use the authors review pharmacokinetic/pharmacodynamic profile, mechanism of action, safety, and efficacy of such steroid molecule.

Keywords: allergic rhinitis, steroids, intranasal steroids, mometasone, steroid therapy
Introduction

Allergic rhinitis (AR) is a common chronic nasal inflammatory disorder characterized by nasal obstruction, aqueous rhinorrhea, sneezing, nasal itching, and postnasal drip.\(^1\) Ocular signs and symptoms including itching, burning, tearing, and redness of the sclera and ocular mucosa and, moreover, itching of the ear, palate, and pharynx may be present.\(^2\) The symptomatology begins after exposure and continues until the allergen is no longer present.\(^3\)

It has been observed that the prevalence of AR is increasing.\(^4,5\) In adults, it ranges from 5% to 40% and is related to age and geographical site, whereas in children it is about 45%.\(^6,7\) The increasing prevalence is possibly due to higher levels of air pollution, increased numbers of dust mites in houses with central heating and reduced ventilation, and changes in the pattern of childhood infection.\(^5,8\) Asthma, otitis, rhinosinusitis, conjunctivitis, and nasal polyposis are also associated with AR.\(^4,9–11\)

While AR is not a life-threatening disease, it nonetheless has a significant impact on the quality of life. Chronic AR may cause negative effects, such as sleeplessness, fatigue, irritability, and poor concentration, as well as decreased performance and productivity, with negative effects on psychological and social wellness and high costs for society.\(^5,11–14\)

AR has been traditionally classified into seasonal AR (SAR) and perennial AR (PAR) in relation to the time of exposure.\(^3\) SAR is caused usually by allergies found outdoors, such as pollen and molds, whereas PAR is most commonly due to allergens found indoors, such as house dust mites, molds, animal dander, and cockroaches. In 2001, the AR and its Impact on Asthma (ARIA) group together with the WHO introduced a new classification system.\(^3\) In Europe, about 50% of the patients have PAR according to traditional SAR/PAR classifications, while approximately one-third have persistent allergic rhinitis in relation to ARIA classification.\(^15\)

The first treatment for AR is allergen avoidance. If this is inadequate, several pharmacological agents are available [ie, decongestants, sedating and non-sedating anti-histamines, mast cell stabilizers (chromones), leukotriene receptor antagonists, intranasal or systemic corticosteroids] that may be administered alone or in various combinations. Immunotherapy is another therapeutic option.

Anti-histamines and intranasal corticosteroids are the cornerstones of therapy and effectively treat the symptoms of AR. Several meta-analysis and reviews have shown that intranasal corticosteroids are superior to anti-histamines for relief of clinical symptoms of AR, such as nasal congestion, which is considered the most important AR-related symptom.\(^14\) Various studies have shown that intranasal corticosteroids begin to control symptoms within the first day of therapy.\(^16–18\) At present, topical nasal corticosteroids represent the recommended first-line therapy for moderate to severe cases of AR.\(^14,19,20\) Intranasal corticosteroids act on nasal mucosa, where the drug is needed, minimizing systemic and adverse effects.\(^21\) To date, six intranasal corticosteroids are available in the USA for treatment of AR: beclomethasone dipropionate (BDP), budesonide (BUD), flunisolide, fluticasone propionate (FP), mometasone furoate (MF), and triamcinolone acetonide (TAA).\(^14\) All these agents are safe and well tolerated. Except for beclomethasone dipropionate, all intranasal corticosteroids are metabolized quickly to less effective metabolites, have minimal systemic absorption, and minimal systemic effects.\(^14\) The goals of treatment with intranasal corticosteroids are to maximize effectiveness and minimize potential systemic adverse effects, while favoring good patient compliance.

MF is a potent synthetic 17-heterocyclic corticosteroid glucocorticoid, topically active and effective, initially introduced for treatment of dermatological diseases.\(^22\) Subsequently, an aqueous nasal spray form was found to be effective in AR, non-AR, nasal polyposis, adenoid hypertrophy, and uncomplicated rhinosinusitis.\(^22–28\) MF has a high affinity for the glucocorticoid receptor and a highly lipophilic nature. These characteristics contribute to its minimal systemic absorption and prolonged nasal contact time.\(^20\)

Mechanism of Action, Metabolism, and Pharmacokinetic Profile

MF has a chemical structure similar to cortisol. The presence of a double bond in the 1, 2 position on ring A and of an esterified furoate moiety in the 17\(\alpha\) position leads to high glucocorticoid activity and major affinity to the glucocorticoid receptor, respectively. Occupying a lipophilic pocket in the glucocorticoid receptor, the furoate moiety increases receptor binding and activation.\(^20\) The binding between glucocorticoids and
the glucocorticoid receptor produces a complex that enters the cell nucleus and regulates the expression of pro- and anti-inflammatory genes. The binding affinity with synthetic glucocorticoids, which is higher than with endogenous cortisol, correlates with several parameters of pharmacologic activity such as topical anti-inflammatory activity, glucocorticoid-induced dermal blanching activity, inhibition of T-cell cytokine production, inhibition of histamine and vascular cell adhesion molecule-1 levels.

When compared with FP, BUD and TAA, MF has the highest relative receptor affinity (RAA). This important characteristic indicates that a drug with higher affinity will occupy the same number of receptors at a lower drug concentration than a drug with a lower affinity.20

The glucocorticoids act through 2 pathways: 1) transactivation, when the receptor complex binds to glucocorticoid-response elements in the promoter region of glucocorticoid-responsive genes and activates the transcription of anti-inflammatory genes, and 2) transrepression, when the receptor complex represses transcription of pro-inflammatory genes. Differences in the transactivation-action among intranasal corticosteroids have been found in vitro experiments; MF was more potent than FP, TAA and BUD. Transrepression is a complicated process that involves the glucocorticoid receptor complex, inhibitory transcription factors and cofactors, and DNA. MF and FP are effective in inhibiting pro-inflammatory activity.

Intranasal corticosteroid administration allows slow uptake through nasal mucosa with a high time of contact between steroidal molecule and nasal mucosa.30 A prolonged nasal residency time depends on the presence of slowly dissolving drug particles.31 An increase in lipophilicity usually results in drug particles that dissolve more slowly in nasal mucosa, so that the intranasal residency time is longer. Lipophilic suspension-based formulations have a higher nasal residency time than hydrophilic or solution-based formulations.30 Slow-dissolving, lipophilic, suspension-based formulations represent a way to increase the nasal residency time of intranasal corticosteroids. A second mechanism to increase nasal residence time is through the formation of lipophilic esters in target cells. A glucocorticoid molecule with a free C-21-hydroxy group enters the cell where it is transformed into lipophilic esters that are released in the target tissue.20 For MF, suspension-based glucocorticoid formulations are removed from nasal mucosa by the mucociliary transport system to the nasopharynx and are then swallowed. The mucociliary clearance rates vary in different sites of the nose, and so an optimal residency time depends on the anatomic region of drug delivery.

Systemic adverse effects of corticosteroids occur when plasma concentrations exceed normal physiological ranges or modify diurnal hormonal regulation.32 The hypothalamic-pituitary-adrenal axis (HPAA) controls the cortisol level reducing cortisol secretion when additional exogenous steroid is added. Long-term use of systemic corticosteroid therapy may produce adverse effects such as HPAA suppression,33 impairment of linear bone growth,34 and inhibition of growth hormone (GH) release.34 Moreover, glucocorticoids can inhibit osteoblast function, collagen synthesis, chondrocyte mitosis, and decrease absorption and increase excretion of calcium. Some authors have reported a decrease in total bone mass, bone mineral density, serum osteocalcin and alkaline phosphatase in adults, whereas adverse effects on bone metabolism have not been observed in children.20

Systemic activity of intranasal corticosteroids is in relation to systemic bioavailability, plasma protein binding, systemic clearance, and pharmacologic activity.30 The systemic bioavailability of MF is 0.46%, while it ranges from 0.42% to 0.51% for FP; it is 31%, 44%, and 46% for BUD, BDP, and TAA, respectively.20,35

Moreover, systemic bioavailability depends on systemic absorption through the nasal and gastrointestinal tracts.36 Thirty percent of an intranasal corticosteroid dose remains in the nose, whereas 70% is swallowed.37 This latter steroid fraction may be likely absorbed by the gastrointestinal tract. Drugs administrated as a suspension (lipophilic drugs) such as MF dissolve slowly after prolonged contact with nasal mucosa, and mucociliary clearance removes solid drug particles from nasal mucosa. Thus, only a small fraction of the delivered dose enters the nasal tissues and bloodstream. Removal of solid drug particles from the nose by mucociliary clearance leads to a very small amount of systemic spill-over, while the amount of MF remaining in the nasal cavities is sufficient to obtain a therapeutic effect.21
MF is relatively stable in human plasma, with a half-life ranging from 18.4 to 24 hours. Its degradation results in 9, 11-epoxide MF and 2 additional minor degradation products. The binding affinity of 9, 11-epoxide MF for glucocorticoids receptor is 2 to 4 times higher than dexamethasone (DEX), and it has been suggested that the 9, 11-epoxide MF metabolite may contribute to systemic glucocorticoid exposure.

The liver metabolizes intranasal corticosteroids efficiently since they are high-extraction drugs with clearance values close to liver blood flow. In human hepatocytes, 2 primary metabolites (ie, 6beta-OH MF and MET1) and 2 minor metabolites have been identified. It is interesting to note that 6beta-OH MF has an affinity for the glucocorticoid receptor that is 7 times greater than DEX.

Once-daily morning administration of intranasal corticosteroids is predicted to have a minimal effect on diurnal HPAA rhythm. Endogenous cortisol levels are at their physiological nadir in the morning and the GH secretion has its peak in the late evening, so the administration of intranasal corticosteroids in the morning should not change daytime cortisol levels and the normal circadian rhythm of HPPA.

In a review of literature performed in 2008, Hochhaus et al concluded that MF-treatment did not produce demonstrable effects on HPPA even when the drug was administered at up to 20 times the recommended daily dose. Furthermore, plasma cortisol, urinary free cortisol, and 8 am plasma cortisol were similar in patients who received a single dose of oral MF, intranasal MF, or placebo. Moreover, pediatric patients showed no significant changes in mean cortisol concentrations or 24-hours urinary-free cortisol concentrations. Finally, the available data suggests that in children and adults MF has a favourable tolerability profile.

Safety
In 2007, Herman reviewed double-blind, placebo-controlled studies of once-daily administration of intranasal corticosteroids and concluded that the overall occurrence of adverse events was similar between the different intranasal steroids investigated. There was no significant suppression of serum cortisol values before or after adrenocorticotropin hormone stimulation for any of the treatment groups that used FP, TAA, or BDP. There was no statistically significant modification on markers for adrenocortical activity, bone formation, or white cell count for BUD, TAA, or MF.

Healthy volunteers treated with FP showed lower overnight urinary cortisol levels compared with placebo treatment, but no significant effects on HPAA function (24-hours plasma cortisol levels and 24-hours and fractioned urinary cortisol levels), markers of bone formation (osteocalcin levels), and white blood cells count were seen with BUD, MF, or TAA.

In 1999, Berkowitz et al assessed treatment-emergent adverse events in patients treated with MF. Adverse events considered by the investigators to be possibly or probably treatment-related were headache and pharyngitis, with severe coughing and pruritus occurring only rarely. No serious adverse effects were reported. After 5 years, Suisse et al published a population-based cohort study with nested case-control analysis of elderly patients who were administered respiratory medications (monitored for 4 years), and found no effects on the rate of hip or upper extremity fractures with intranasal corticosteroids.

Safety studies, conducted before and after 12 months of treatment with MF, have evaluated potential glaucoma and/or cataract formation, short-term lower-leg growth, and assessed the effects of MF on growth and statural growth. No significant changes from baseline in intraocular pressures or posterior subcapsular cataracts were observed at the end of the study, and no clinically-relevant changes in vital signs, electrocardiograms, clinical laboratory values or nasal examinations were reported for MF.

Even if in pediatric patients a decrease in growth velocity, adrenal suppression and growth failure have been reported receiving intranasal corticosteroids such as BDP, no effects on growth velocity and/or the function HPPA have been observed using MF nasal spray at therapeutic doses.

The use of intranasal corticosteroids could potentially increase the risk of nasal irritation, dryness, bleeding, epistaxis, septal perforations, sneezing, and coughing. However, biopsies of nasal mucosa before and after 1 year of treatment with MF in adults showed improvement of the appearance of the epithelium and reduction of the inflammatory cell infiltrate (such as eosinophils and mast cells) and no signs of mucosa atrophy.
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Finally, the incidence of adverse events in children treated with MF was comparable to that in patients treated with placebo or active control, and the most frequent adverse event was epistaxis. Pharyngitis, sneezing, and headache were mild and of short duration.

**Immunopathological Mechanisms of Action**

AR is an immunological disease mediated by immunoglobulin E (IgE) that involves inflammation of the nasal membrane after exposure to an allergen. AR involves an initial sensitization during which allergen-specific IgE binds to receptors on mast cells and basophils, followed by an allergic/inflammatory response at subsequent re-exposure to the allergen. In nasal mucosa, this process leads to cross-linking of IgE on the surface of mucosal cells, mast cells, and basophils, along with degranulation of inflammatory cells, causing the release of preformed mediators such as histamine within 5 minutes after allergen contact (early-phase response). Next (usually within 15 minutes), there is synthesis of mediators (ie, leukotrienes, prostaglandins, platelet-activating factor, and several cytokines) that produce vasodilatation, increase glandular secretions and sensory nerve stimulation leading to the immediate symptoms of AR such as sneezing, rhinorrhea, itching, and nasal congestion.

The late-phase response, which occurs approximately 4–24 hours after allergen exposure is characterized by recruitment of inflammatory cells from blood (ie, basophils, eosinophils, lymphocytes, and monocytes) that release additional inflammatory mediators promoting inflammation and tissue damage. This results in an increase of symptoms, particularly nasal congestion.

MF acts at multiple points in the allergic inflammation pathway. Traditionally, corticosteroids showed a large effect on the late-phase response, although Frieri et al reported that MF also has a small effect on the early-phase response. The anti-inflammatory effects of intranasal corticosteroids are mediated through inhibition of pro-inflammatory cytokines (ie, IL-1, IL-3, IL-4 and IL-5) and decrease the number of inflammatory cells. It has been documented that at least in vitro, MF is the most steroid potent inhibitor of IL-4 and IL-5 release from CD4+ cells.

IL-4 and IL-5 are T-helper cell type 2 (Th2)-secreted pro-inflammatory cytokines that regulate mast cell activation and degranulation, eosinophil differentiation, and IgE production. INF-gamma is a T-helper cell type 1 (Th1)-secreted cytokine that downregulates the effects of the Th2 cytokines. MF acts by reversing the exaggerated Th2 response that contributes to the pathophysiology of allergic disease. In a review of randomized trials evaluating eosinophil levels in nasal mucosa of patients with AR and undergoing intranasal MF-treatment or placebo for 2 weeks, Hochhaus observed that MF-subjects showed a reduction in eosinophils and basophils from baseline after 6 hours (late phase), whereas subjects treated with placebo had no significant difference in nasal eosinophil levels from baseline.

MF also inhibits expression of chemoattractant cytokines such as IL-3, IL-4 and IL-5 and is 3 to 4 times more potent than DEX or BDP in inhibiting the migration of rat eosinophils. Moreover, MF enhances eosinophil apoptosis. Lastly, activation of the adhesion-molecule system is crucial to the pathogenesis of inflammatory cell infiltration in nasal mucosa, and thus the inhibition by MF may protect against cell injury due to inflammation.

**Efficacy**

The efficacy of MF in the treatment of allergic rhinitis has been demonstrated in several clinical studies and by means of its clinical utilization. This important feature is highlighted particularly in a review performed by Italian researchers, who carried out a meta-analysis of randomized, double-blind, placebo-controlled clinical trials after a comprehensive search of the MEDLINE, LILACS, SCOPUS, and the Cochrane Library databases. By this analysis, 1534 subjects and 1464 one represented MF- and placebo-group, respectively. A significant reduction in total nasal symptom scores such as congestion, rhinorrhea, sneezing, and nasal itching was observed in the MF participants. Furthermore, the study group showed a significant reduction in total non-nasal symptom scores (ie, cough, ocular, otic, palate, ant throat complaints). This evaluation provided a level Ia evidence for the efficacy of MF in the therapy of AR vs. placebo. Finally, such topical nasal steroid is also effective in preventing the onset of symptoms in patients with AR.
Patient Preference

Good management of AR is also dependent on patient compliance and acceptance of planned treatment. Factors that may influence patient compliance to treatment include efficacy, safety, dosing regimen, patient preference, and cost-effectiveness. MF has a once-daily dosing regimen and good clinical efficacy in treatment of AR. Its rapid onset of action (within 7 hours after a single intranasal dose), as well as its once-daily dosing schedule, offer an attractive option for patients with AR. The sensory attributes of intranasal corticosteroids can influence adherence to therapy, and patients have expressed preferences considering various attributes of different nasal sprays. In 1999, Gerson et al studied the characteristics of TAA, FP, and BDP in a double-blind, crossover study of adult patients with AR and found that TAA had a lower odor strength and a more preferred odor than either BDP or FP. There were no differences in taste intensities, but patients preferred the taste of TAA over FP or BDP. TAA had also higher moistness in the nose and throat than BDP. Patient-rated overall likeability was higher for TAA than for FP. Three years later, Bachert and El-Akkad compared assessments of sensory attributes from patients with AR after a single dose administration of FP, MF, and TAA in a multicenter, randomized, double-blind, crossover study. Immediately after drug administration, TAA provided significantly better comfort during administration, less irritation, less odor strength, preferred odor, more moistness of nose and throat, milder taste, and preferred taste compared with MF. TAA had less odor strength, preferred odor, more moistness of the nose and throat, and a milder taste than FP. Two minutes after drug administration, TAA had less aftertaste than FP or MF and produced less irritation. In the same year, Gross et al comparing sensory attributes of TAA and FP, found that TAA has a greater incidence of running out of the nose and sneezing than FP, but TAA has less offensive smell and treatment-related stinging and burning than FP. In 2003, Berger et al studying the differences between FP and TAA, also found that patients treated with the latter reported less odor than those administered FP, although no significant differences were found in any other attributes. Shah et al studied the perceptions of patients and their like/dislike of sensory attributes for BUD or FP in two randomized, patient-blind, crossover studies in adult patients with AR. BUD was rated as more pleasing than FP at the recommended starting dose, as well as more pleasing than FP at one-half the recommended starting dose. Patients preferred BUD and indicated a greater overall satisfaction with the sensory features of BUD than FP. BUD had less scent or taste or aftertaste after using than FP. Patients preferred the spray force and moisture content of BUD than FP. In 2004, Stokes et al had the same overall results of Bachert and El-Akkad. TAA had less odor, less taste, less dryness of nose and throat, and less aftertaste than FP and MF. Patients had also a greater preference for the odor of TAA and greater overall likeability for TAA than FP or MF, and preferred a prescription for TAA over FP or MF. Finally, Mahadevia et al studied six sensory attributes of intranasal corticosteroids: taste, smell, aftertaste, throat rundown, nose runout, and feel of spray in nose and throat. They found that preference for sensory attributes and willingness to adhere to therapy decreased with increasing intensity, and that the most important attribute was aftertaste.

The results of patient preference studies show that the recommended once-daily starting doses of BUD and TAA were preferred by adults over FP and MF. BUD appeared to have less aftertaste than FP, and TAA appeared to have less aftertaste than either FP or MF. BUD and TAA had very similar inert ingredients: they lack phenylethyl alcohol, which is present in MF and FP and may cause unpleasant sensations (such as burning or stinging in the nose). Phenylethyl alcohol has a floral scent, and BUD and TAA were rated as having less scent or odor, and a more preferred odor than MF or FP. Recently, a new scent-free formulation of MF has been marketed.

The number of sprays per nostril for both BUD and FP in adolescent and pediatric patients is 1 puff per nostril to obtain the recommended starting dose. For TAA and MF, the number of puffs is 2 per nostril for adolescent patients and 1 per nostril in pediatric patients (less than 12 years). BUD has the lowest spray volume and the least number of sprays per nostril of all the once-daily intranasal corticosteroids.

Place in Therapy

Due to their high efficacy for controlling nasal symptoms, intranasal corticosteroids are recommended as first-line prescription treatment for
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moderate-to-severe cases of SAR and PAR.\textsuperscript{3,69,70} Several double-blind, placebo-controlled trials assessing the efficacy of intranasal corticosteroids such as MF have shown that once-daily administration is well tolerated and more effective than placebo in the treatment of SAR, although there are few differences in efficacy and tolerability among the once-daily intranasal corticosteroids.\textsuperscript{14}

Furthermore, the safety and efficacy of MF in the prophylaxis and treatment of SAR and PAR in adults has been studied.\textsuperscript{46} A dose of 100 or 200 µg once-daily is effective in relieving moderate-to-severe symptoms of SAR and PAR in patients older than 12 years.\textsuperscript{71,72} When administrated about 4 weeks before the onset of the ragweed season, MF is also effective and well-tolerated in the prophylactic treatment of SAR.\textsuperscript{58}

A dose of 100 µg once-daily is the optimal dosage, considering efficacy and safety, for children from 3 to 11 years of age with SAR or PAR. This dosage provides greater symptomatic relief, is well tolerated, and has a low potential for systemic effects because plasma concentrations of MF in children were virtually undetectable.\textsuperscript{46}

**Conclusions**

Mometasone furoate nasal spray is an intranasal corticosteroid that has a number of qualities that are important in achieving nasal selectivity with minimal systemic adverse effects. Data from clinical, animal, and in vitro studies indicate that MF has pharmacokinetic and pharmacodynamic characteristics that make it well suited for intranasal administration. Furthermore, the efficacy and safety profiles in clinical use are consistent with its pharmacokinetic and pharmacodynamic properties. Lipophilic MF in a suspension-based delivery system has a long nasal residence time and rapid hepatic clearance, with a high protein binding rate that contributes to a very low systemic bioavailability. No evidence of growth retardation has been observed at the recommended dose, and no evidence of HPAA suppression in adults or children has been seen. MF is an intranasal corticosteroid that is well tolerated, effective and safe in treatment of SAR and PAR in adults and children. MF is also good for prophylactic treatment of SAR, starting 2–4 weeks before allergen season.

Patient adherence and acceptance of treatment regimen are also important factors as intranasal corticosteroids have particular sensory attributes. Since MF is available in an aqueous formulation without alcohol, with less nasal mucosa irritation and aftertaste and no scent/odor, patients may show greater compliance to treatment.

**Disclosure**

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