Efficacy and safety of mometasone furoate nasal spray in allergic rhinitis, acute rhinosinusitis and nasal polyposis

Seasonal and perennial allergic rhinitis, acute rhinosinusitis and nasal polyposis are common inflammatory conditions of the nose and/or sinuses that produce bothersome symptoms and markedly affect patients’ quality of life [1–3]. These diseases frequently coexist, suggesting that each may be a manifestation of an inflammatory process within the continuous airway [3–5]. Clinical treatment guidelines for each of these conditions conclude that research evidence supports treatment with an intranasal corticosteroid [5–9].

One of the most extensively investigated intranasal corticosteroids for inflammatory diseases of the nose and sinuses is mometasone furoate nasal spray (MFNS). Mometasone furoate is a potent 17-heterocyclic corticosteroid formulated in an aqueous suspension such as molds or pollen [5,10]. Seasonal allergic rhinitis is an IgE-mediated response to outdoor seasonal allergens such as molds or pollen [5,10]. Perennial allergic rhinitis comprises a number of conditions that result from either continuous or intermittent exposure to allergens, most commonly indoor allergens such as dust mites, molds, insects (cockroaches) and animal dander [5,9]. Both seasonal and perennial allergic rhinitis are characterized by extensive infiltration of the nasal mucosa by inflammatory cells, such as eosinophils and basophils, as well as the release of inflammatory mediators such as histamine, prostaglandins and leukotrienes from mast cells [11].

The purpose of this review is to summarize the efficacy and safety of MFNS for seasonal and perennial allergic rhinitis, acute rhinosinusitis and nasal polyposis.

**Allergic rhinitis**

Allergic rhinitis affects approximately 13% of the American population and 17–29% of the European population, with prevalence varying widely in different regions [5,28,29,201].

One of the most extensively studied intranasal corticosteroids for these conditions is mometasone furoate nasal spray (MFNS). In more than 20 clinical trials, MFNS has been shown to reduce both objective and subjective signs of inflammation and promote rapid resolution of nasal, sinus and ocular symptoms in adults, adolescents and children. MFNS is well-tolerated and local adverse events are generally mild and self-limiting, usually resolving without discontinuation of therapy. The low systemic bioavailability (<0.1%) and high first-pass metabolism of MFNS also reduce its risk for systemic adverse events.

**Key Words:** allergic rhinitis, rhinosinusitis, nasal polyposis

**Intranasal corticosteroids**

Seasonal and perennial allergic rhinitis, acute rhinosinusitis and nasal polyposis are common inflammatory conditions of the nose and/or sinuses that produce bothersome symptoms and markedly affect patients’ quality of life. Treatment guidelines for each of these conditions recommend intranasal corticosteroids, which help to alleviate symptoms by reducing inflammation. One of the most extensively studied intranasal corticosteroids for these conditions is mometasone furoate nasal spray (MFNS). In more than 20 clinical trials, MFNS has been shown to reduce both objective and subjective signs of inflammation and promotes rapid resolution of nasal, sinus and ocular symptoms in adults, adolescents and children. MFNS is well-tolerated and local adverse events are generally mild and self-limiting, usually resolving without discontinuation of therapy. The low systemic bioavailability (<0.1%) and high first-pass metabolism of MFNS also reduce its risk for systemic adverse events.
ocular mucosa [9,12]. Although allergic rhinitis is often considered a minor condition [32,33], it can substantially impair the ability of patients to function at work [34], in social situations [7–37,201,202] or at school [38,39]. These patients also have a lower quality of life and a greater degree of depression than those without allergic rhinitis [37–40]. The losses in workplace productivity attributed to the disease in the USA, where most of the available data have been collected, are estimated to be between US$2.4 and US$4.6 billion annually [41]. In addition, direct and indirect expenditures associated with the treatment of allergic rhinitis in the USA are approximately US$1.5 billion and US$2 billion, respectively, per year [40]. Costs of treating allergic rhinitis are also reported to be high in other countries [42].

### Treatment of allergic rhinitis

Since intranasal corticosteroids are considered to be the most effective medications available for the treatment of allergic rhinitis, as stated in the guidelines, they are recommended as first-line therapy, especially in patients with moderate-to-severe, persistent symptoms and impaired quality of life: nasal congestion and/or blockage; or continuing symptoms despite treatment with histamine H1-receptor antagonists (Figure 2) [9,33,202].

Mometasone furoate nasal spray is one of the most intensively studied intranasal corticosteroids for allergic rhinitis. More than 20 clinical trials involving more than 6000 adults, adolescents and children have assessed its efficacy and safety [12–15,17,43–50]. Ten of these were randomized, double-blind, placebo-controlled trials evaluating the use of MFNS to treat the nasal symptoms of seasonal and perennial allergic rhinitis (Table 1) [12–19,51,52].

### Seasonal allergic rhinitis

To evaluate the clinical efficacy and optimum therapeutic dose of MFNS, Bronsky et al. conducted a multicenter, double-blind, dose-ranging study involving 480 adults (≥18 years) with moderate seasonal allergic rhinitis [13]. Subjects were randomly assigned to treatment with one of four daily doses of MFNS (50, 100, 200 or 800 µg) or placebo for 28 days. Treatment efficacy was determined using a seven-point scale to assess severity of nasal (discharge, rhinorrhea, stuffiness/congestion, sneezing or itching) and non-nasal (eye itching, tearing, and redness and itching of ears or palate) symptoms. Within 3 days of treatment, subjects in the 50, 200 and 800 µg daily MFNS groups reported a significant (p < 0.05) reduction of symptoms. By day 7, all four doses were found to be significantly more effective than placebo (p ≤ 0.05). Since the two lower doses provided less consistent relief, the investigators concluded that 200 µg daily was the appropriate MFNS dose for alleviating the symptoms of seasonal allergic rhinitis.

A series of additional trials extended these findings across a broad range of subjects. In the double-blind, randomized, placebo-controlled trial of 121 adolescents (≥12 years) and adults carried out by Melzack et al., MFNS 200 µg daily was associated with a significant reduction in mean total morning nasal symptom scores (congestion, rhinorrhea, itching and sneezing) compared with placebo (p = 0.02) after 1 week [16]. At week 2, significant improvement was noted in the active treatment group (p = 0.029). In
addition, MFNS was associated with a significant improvement in nasal cytology, including a reduction in the numbers of eosinophils, basophils and neutrophils.

Meltzer et al. also confirmed that, when given in appropriate dosages, MFNS can alleviate the symptoms of seasonal allergic rhinitis in children as young as 6 years old [51]. This multicenter, double-blind, placebo-controlled, dose-ranging study enrolled 679 children between 6 and 11 years of age who received MFNS in doses of 25, 100 or 200 µg daily or beclomethasone dipropionate (BDP) nasal spray 84 µg twice-daily for up to 4 weeks. According to physician

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Subjects (n)</th>
<th>Age (years)</th>
<th>Treatment (duration)</th>
<th>Effect on symptoms</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>SAR studies</td>
<td></td>
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<tr>
<td>Hebert et al. (1996)</td>
<td>501</td>
<td>≥18</td>
<td>MFNS 100 µg q.d. MFNS 200 µg q.d. BDP 200 µg b.i.d. Placebo 4 weeks</td>
<td>MFNS (both doses) and BDP more effective than placebo (p ≤ 0.01)</td>
<td>[15]</td>
</tr>
<tr>
<td>Graft et al. (1996)</td>
<td>349</td>
<td>≥12</td>
<td>MFNS 200 µg q.d. BDP 168 µg b.i.d. Placebo 8 weeks</td>
<td>MFNS and BDP initiated 4 weeks before ragweed season decreased minimal symptom days versus placebo (p &lt; 0.01)</td>
<td>[14]</td>
</tr>
<tr>
<td>Bronsky et al. (1997)</td>
<td>480</td>
<td>18–65</td>
<td>MFNS 50 µg q.d. MFNS 100 µg q.d. MFNS 200 µg q.d. MFNS 800 µg q.d. Placebo 28 days</td>
<td>MFNS 200 µg q.d. and 800 µg q.d. consistently more effective than placebo (p &lt; 0.05)</td>
<td>[13]</td>
</tr>
<tr>
<td>Meltzer et al. (1998)</td>
<td>121</td>
<td>≥12</td>
<td>MFNS 200 µg q.d. Placebo 2 weeks</td>
<td>MFNS improved total nasal symptom score versus placebo (p = 0.024)</td>
<td>[16]</td>
</tr>
<tr>
<td>Meltzer et al. (1999)</td>
<td>679</td>
<td>6–11</td>
<td>MFNS 25 µg q.d. MFNS 100 µg q.d. MFNS 200 µg q.d. BDP 84 µg b.i.d. Placebo 4 weeks</td>
<td>MFNS 100 µg q.d. (p = 0.03) and 200 µg q.d. (p = 0.04) and BDP 84 µg q.d. (p &lt; 0.01) more effective than placebo</td>
<td>[51]</td>
</tr>
<tr>
<td>Berkowitz et al. (1999)</td>
<td>239</td>
<td>12–60</td>
<td>MFNS 200 µg q.d. Placebo 1 day</td>
<td>MFNS improved total nasal symptom score in 7 h versus placebo (p &lt; 0.01)</td>
<td>[12]</td>
</tr>
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<td>Gawchick et al. (2003)</td>
<td>245</td>
<td>≥12</td>
<td>MFNS 200 µg q.d. Placebo 14 days</td>
<td>MFNS improved total nasal symptom score versus placebo (p ≤ 0.017)</td>
<td>[52]</td>
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<td>PAR studies</td>
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<tr>
<td>Drouin et al. (1996)</td>
<td>427</td>
<td>≥12</td>
<td>MFNS 200 µg q.d. BDP 200 µg b.i.d. Placebo 12 weeks</td>
<td>MFNS and BDP improved total nasal symptom score versus placebo (p ≤ 0.01)</td>
<td>[17]</td>
</tr>
<tr>
<td>Mandl et al. (1997)</td>
<td>474</td>
<td>≥12</td>
<td>MFNS 200 µg q.d. FP 200 µg q.d. Placebo 12 weeks</td>
<td>MFNS and FP improved total nasal symptom score versus placebo (p &lt; 0.01)</td>
<td>[18]</td>
</tr>
<tr>
<td>Bende et al. (2002)</td>
<td>438</td>
<td>≥18</td>
<td>MFNS 200 µg q.d. BDP 128 µg q.d. BDP 256 µg q.d. Placebo 4 weeks</td>
<td>MFNS and BDP improved total nasal symptom score versus placebo (p &lt; 0.002)</td>
<td>[19]</td>
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</table>

BDP: Beclomethasone dipropionate nasal spray; b.i.d.: Twice daily; FP: Fluticasone propionate nasal spray; MFNS: Mometasone furoate nasal spray; PAR: Perennial allergic rhinitis; q.d.: Daily; SAR: Seasonal allergic rhinitis.
evaluation of total nasal symptom scores at day 8, all three dosages of MFNS and the twice-daily dosage of BDP nasal spray afforded significantly greater relief than placebo (p ≤ 0.02). At 4 weeks, both the 100 µg (p = 0.03) and 200 µg (p = 0.04) daily doses of MFNS were significantly more effective than the 25 µg daily dose. However, MFNS 200 µg daily provided no significant advantage over the 100 µg daily dose, leading the investigators to conclude that MFNS 100 µg daily is the most appropriate therapeutic regimen for children with seasonal allergic rhinitis [51].

The efficacy of MFNS in the prophylaxis of seasonal allergic rhinitis was established by Graft’s study of 349 subjects, 12 years or older with a moderate-to-severe allergy to ragweed pollen [14]. Four weeks before the predicted start of ragweed season, subjects were randomly assigned to receive MFNS 200 µg daily, BDP nasal spray 168 µg twice-daily, or placebo for 8 weeks. Subjects receiving MFNS reported a significantly higher proportion of minimal symptom days compared with placebo (p < 0.01). The MFNS group had a median duration of 27 days before experiencing a non-minimal symptom day (defined as a day when the total nasal symptom score was ≥3 on a 12-point scale), compared with a median duration of 10.5 days in the placebo group [14].

Two additional retrospective analyses of data pooled from four randomized, double-blind studies comparing MFNS 200 µg daily (n = 494) with placebo (n = 497) confirmed the efficacy of MFNS in reducing the ocular symptoms of redness, tearing and itching commonly associated with seasonal allergic rhinitis [53,54]. During a 2-week study period, MFNS significantly reduced total ocular and individual symptom scores compared with placebo (p < 0.05) [53]. Subjects with moderate-to-severe symptoms experienced a significantly greater reduction in total ocular symptoms than those taking placebo (p < 0.05).

The mechanism of action of intranasal corticosteroids in relieving ocular allergy symptoms is not well understood. It has recently been shown that a nasal–ocular reflex follows nasal challenge with antigen and probably contributes to the ocular symptoms associated with allergic rhinitis. In addition to reducing inflammation, intranasal corticosteroids may reduce ocular allergy symptoms by attenuating this reflex mechanism [55].

**Sensory perceptions of intranasal corticosteroids & compliance in allergic rhinitis**

Despite the discomfort and impairment associated with allergic rhinitis, only 20% of patients are compliant with treatment [56]. One factor contributing to the high rate of noncompliance may be sensory perception [57,58]. Since patients prefer agents that do not have any taste or scent [58]. In a multicenter, randomized, double-blind, crossover study, 100 subjects with allergic rhinitis were randomized to an alcohol- and scent-free formulation of MFNS, 200 µg daily, followed by 200 µg daily of FPNS 30 min later, or vice versa [56]. Significantly more subjects preferred MFNS to FPNS (p < 0.05), and fewer subjects reported scent or odor (immediately and 2 min after drug administration; p < 0.001), taste (immediately after drug administration; p = 0.002), and aftertaste (2 min after drug administration; p = 0.007) with MFNS than with FPNS. In addition, 47% reported that they would be more likely to comply with a MFNS regimen than with a FPNS regimen (p = 0.03) [56].
Acute rhinosinusitis

Rhinosinusitis is an inflammatory process that involves the mucosa of the nose and one or more sinuses [3,8]. It is classified as acute (symptom duration <4 weeks), subacute (symptom duration 4–8 weeks), chronic (symptom duration >8 weeks), or recurrent (>3 episodes of acute sinusitis per year) [3,8,59,60]. The European position paper on rhinosinusitis and nasal polyps also classifies acute rhinosinusitis as mild, moderate or severe, based on the total severity visual analogue scale score [3].

The etiology of rhinosinusitis may be viral, bacterial or allergic [4,8]. Acute rhinosinusitis is usually caused by a viral infection that, in some cases, may be complicated by a secondary bacterial infection [4,8,61,62]. Symptoms of acute rhinosinusitis resolve without the use of antibiotics in most patients [59,63]. One study reports that only 38% of adults presenting with symptoms of acute rhinosinusitis may actually have bacterial rhinosinusitis [63]. Perennial allergic rhinitis may also be a predisposing factor to acute rhinosinusitis, since allergic rhinitis contributes to rhinosinusitis in up to 30% of patients with acute maxillary rhinosinusitis and up to 80% of patients with chronic rhinosinusitis [4]. American and European guidelines for the diagnosis and treatment of acute rhinosinusitis provide algorithms to improve treatment outcomes (Figures 3 & 4) [3,8,9,62,64].

The main clinical characteristics of acute rhinosinusitis include nasal congestion, facial pain and/or pressure, rhinorrhea, postnasal drainage, headache and cough. The four signs and symptoms most predictive of acute bacterial rhinosinusitis include purulent nasal discharge, maxillary tooth or facial pain (especially unilateral), unilateral maxillary tenderness and worsening of symptoms after initial improvement [3,62,64]. Computed tomography is currently the preferred radiographic modality to confirm acute rhinosinusitis [8].

Annual crude prevalence rates of acute rhinosinusitis in the USA range from 14 to 16% of adults [203]. Definitive prevalence rates are lacking owing to inconsistencies in the definition of acute rhinosinusitis, and because not all patients with the disease seek professional care [61]. Still, the economic burden of this disease is high; total annual costs related to acute rhinosinusitis as either a primary or secondary diagnosis were estimated to be US$5.93 billion in one American study [66].

**Treatment of acute rhinosinusitis**

The rationale for the use of intranasal corticosteroids in acute rhinosinusitis resides in their anti-inflammatory properties. By reducing inflammation, intranasal corticosteroids foster drainage and increased aeration of the sinuses [3,5,6,8]. The use of intranasal corticosteroids as adjuncts to antibiotic therapy for acute bacterial rhinosinusitis is considered appropriate for patients who do not respond to initial treatment, have concomitant nasal polyposis, or are experiencing marked mucosal edema [3,8,64]. Treatment of acute bacterial rhinosinusitis with antibiotics and intranasal corticosteroids also hastens clearance of bacteria, decreases the frequency and severity of disease recurrence [6] and reduces the duration of infection [43,67,68].

Many recent studies support the benefits of intranasal corticosteroids as adjuncts to antimicrobial therapy in acute bacterial rhinosinusitis, and three randomized, multicenter, placebo-controlled studies have demonstrated that MFNS alleviates the course of acute bacterial rhinosinusitis (Table 2) [20–23]. In one study, Meltzer et al. compared a 21-day regimen of amoxicillin/clavulanate with or without MFNS in 407 subjects, 12 years or older with acute rhinosinusitis confirmed by CT scan of the paranasal sinuses [20]. The addition of MFNS to the antibiotic significantly (p < 0.01) reduced mean total symptom scores and individual symptom scores, including congestion and facial pain, during days 1–15 (p ≤ 0.01), and headache (p < 0.01), congestion (p < 0.01) and purulent rhinorrhea (p ≤ 0.05) during days 16–21.

In a similar study by Nayak et al. in 2002, 967 subjects 12 years or older with moderate-to-severe acute rhinosinusitis confirmed by CT scan received amoxicillin/clavulanate for 21 days with MFNS 200 µg twice-daily, MFNS 400 µg twice-daily, or placebo [21]. Addition of either the 200 µg (p = 0.014) or 400 µg (p = 0.017) regimen of MFNS produced a significantly greater improvement in the total symptom score than placebo. MFNS also reduced nasal stuffiness/congestion (200 µg, p = 0.01; 400 µg, p = 0.025), facial pain (200 µg, p = nonsignificant [NS]; 400 µg, p = 0.008), postnasal drip (200 µg, p = 0.038; 400 µg, p = NS), and rhinorrhea (200 µg, p = NS; 400 µg, p = 0.045).

Since intranasal corticosteroids are an effective adjunctive therapy for acute bacterial rhinosinusitis, they may have potential as monotherapy for acute uncomplicated rhinosinusitis [69]. A third study, by Meltzer et al. in 2005, investigated the use of MFNS as monotherapy in 981 subjects 12 years or older with acute uncomplicated rhinosinusitis lasting for 7 days or more but 28 days or less; those with acute bacterial
Mometasone furoate nasal spray
Drug Evaluation

This study compared MFNS 200 µg once- or twice-daily for 15 days with amoxicillin alone or placebo alone. MFNS 200 µg twice-daily was superior to both placebo alone (p < 0.001) and amoxicillin monotherapy (p = 0.002) in improving symptom scores. In another study, MFNS monotherapy was also shown to provide a significantly greater improvement in patients’ health-related quality of life [22].

Fokkens et al., on behalf of the European Academy of Allergology and Clinical Immunology, recommends that adults with mild symptoms of acute rhinosinusitis lasting less than 5 days receive treatment, such as analgesics or decongestants, aimed at symptomatic relief, while patients with moderate symptoms persisting or increasing in severity after 5 days should receive intranasal corticosteroids [3]. In patients with severe acute rhinosinusitis, antibiotic therapy and intranasal corticosteroids are recommended (Figure 4) [3]. Current American treatment guidelines are similar [8]. Infection with resistant pathogens should be considered in severe cases if symptoms do not improve after 3–5 days of antibiotic treatment [8,62,69].

Nasal polyposis
Nasal polyposis is estimated to affect approximately 2.7–4% of the population [3,9,70]. Its prevalence increases to 7–15% in patients with asthma and to 36–96% in patients with aspirin sensitivity [3]. Symptoms include nasal obstruction, congestion, purulent nasal discharge and postnasal drip [71]. More than 75% of patients also have an impaired sense of smell [72]. These symptoms have a marked impact on quality of life, interfering with physical, social and normal daily activities. The symptoms can also cause sleep disorders and headaches, as well as impair patients’ moods and their psychological well-being [73].

Nasal polyposis is characterized by an eosinophil-dominated inflammation of unknown cause and is often associated with asthma, aspirin sensitivity or cystic fibrosis [9,71]. One possible mechanism for the development of nasal polyposis involves bacterial colonization of the nasal cavity, causing the synthesis and release of enterotoxins that act as superantigens to stimulate the local immune system [74]. A hallmark of bilateral nasal polyposis, which is observed in approximately 90% of adults with the condition, is a mixed cellular infiltrate with predominant eosinophilia [75]. Increased levels of inflammatory mediators, such as interleukin-5 [76], eotaxin [77] and eosinophil cationic protein [78] are also present.

Treatment of nasal polyposis
Treatment objectives for nasal polyposis include reducing or eliminating polyps, opening the nasal airway, improving or restoring sense of smell and preventing recurrence. Surgical removal of polyps, with or without medical therapy, for more severe cases and medical therapy for mild-to-moderate cases are the usual treatment regimens [79]. Although endoscopic surgery has been shown to be effective for reducing polyp size and temporarily improving nasal blockage [80–82], one randomized, controlled study in 2001 reported

Figure 3. Algorithm for differentiating viral and bacterial acute rhinosinusitis.
CT: Computed tomography; ENT: Ear, nose and throat. Adapted with permission from [62].

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that medical treatment alone with oral or topical corticosteroids appeared to be sufficient to treat most of the symptoms of nasal polyposis [81]. Another study by Benitez and colleagues found that subjects with severe nasal polyposis had a significant improvement in their symptoms with a short course of oral corticosteroids followed by intranasal corticosteroids [83]. In addition, the postsurgical recurrence rate for nasal polyposis after 2 years is reported to be as high as 60% in some studies [84–86]. At this time, the benefits of surgery over medical therapy have not been established [81,82].

Treatment with intranasal corticosteroids reduces the eosinophil-associated inflammation of polyposis, thereby helping to control symptoms and reduce polyp size [9,24–25,81,87]. Fokkens et al. and the European Academy of Allergology and Clinical Immunology, as well as other authors, concluded that intranasal corticosteroids are generally effective for improving symptoms and decreasing polyp size, although little improvement in sense of smell was reported [3,88–90].

Mometasone furoate nasal spray is the first intranasal corticosteroid to be approved by the USA FDA for the medical treatment of nasal polyposis [24]. Results of the first large-scale clinical studies of MFNS for nasal polyposis were published in 2005 and 2006. Three 4-month, multicenter, randomized, placebo-controlled clinical trials enrolled 354, 310 and 298 patients, respectively [24–26], to evaluate the efficacy and safety of 200 µg daily and 200 µg twice-daily dosing of MFNS. The twice-daily regimen of MFNS was chosen to help overcome the possible obstruction of drug distribution by polyps. In all three studies, subjects receiving either dosage of MFNS experienced significantly greater improvement than those receiving placebo in the reduction of the size and extent of endoscopically verified bilateral nasal polyps, as well as in congestion/obstruction, loss of sense of smell, anterior rhinorhea and postnasal drip (Figure 5) [24–26]. A statistically significant improvement with both doses of MFNS was observed within the first month of treatment and continued
The twice-daily dosing regimen of MFNS was superior to the once-daily dosing formulation for improving the symptoms of congestion and obstruction \((p = 0.039)\) \([24–26]\).

In one study, the overall change in bilateral polyp grade score with MFNS represented a clinically significant reduction of approximately \(30\%\) relative to baseline \([24]\). Since reducing polyp size is thought to be a slow process, this degree of improvement in 4 months is noteworthy. Incremental improvements in polyp grade continued throughout the course of the study, suggesting that treatment with MFNS should be maintained to achieve a full response. Response to MFNS did not vary with the size of the polyps. In addition, \(57\%\) of patients receiving MFNS \(200 \mu g\) twice-daily were considered to be improved based on its effect on polyp grade and congestion/obstruction score, compared with \(43\%\) of patients receiving MFNS \(200 \mu g\) daily and \(34\%\) of patients receiving placebo \([24]\).

The significant improvement in loss of sense of smell associated with MFNS contrasts with previous studies regarding endoscopic surgery or other intranasal corticosteroids, in which sense of smell did not improve \([84,91–94]\). Comparisons between medical and surgical treatment indicate that surgery has very little effect on hyposmia or anosmia \([81]\), supporting the importance of medical therapy in treating this symptom \([24]\).

For many patients, loss of sense of smell is one of the most disturbing symptoms of nasal polyposis \([95]\), and its return is therefore an important therapeutic goal. However, change in sense of smell may be more subjective than other symptoms, which may account for the observed placebo effect in many studies \([27]\). Importantly, the improvement in sense of smell seen with MFNS therapy corresponds to the increased improvement in polyp grade scores over time \([24,26,27]\).

A recent analysis of the onset of symptomatic effect of MFNS \(200 \mu g\) twice-daily revealed a rapid improvement in most symptoms of nasal polyposis from within 24 h after the first dose to within 5 days of initiating therapy \([27]\). Subjects receiving this dose of MFNS experienced statistically significant \((p < 0.05)\) improvement compared with placebo at day 2 for anterior rhinorrhea, day 3 for nasal congestion, day 5 for postnasal drip and day 13 for sense of smell. Peak nasal inspiratory flow also improved significantly at day 2 \((p = 0.031)\) \([27]\). The rapid onset of action of MFNS in nasal polyposis may be due to the high topical potency of the drug in inhibiting the synthesis and release of

### Table 2. Summary of clinical studies of MFNS for the treatment of acute rhinosinusitis.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Subjects (n)</th>
<th>Age (years)</th>
<th>Treatment (duration)</th>
<th>Effect on symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meltzer et al. (2000)</td>
<td>407</td>
<td>(\geq 12)</td>
<td>ACP 875 mg b.i.d. + MFNS 400 (\mu g) b.i.d. or placebo 21 days</td>
<td>ACP + MFNS significantly better than ACP + placebo ((p \leq 0.01)) ([20])</td>
</tr>
<tr>
<td>Nayak et al. (2002)</td>
<td>967</td>
<td>(\geq 12)</td>
<td>ACP 875 mg b.i.d. + MFNS 200 (\mu g) b.i.d. or MFNS 400 (\mu g) b.i.d. or placebo 21 days</td>
<td>ACP + MFNS (both doses) significantly better than ACP + placebo ((p \leq 0.017)) ([21])</td>
</tr>
<tr>
<td>Meltzer et al. (2005)</td>
<td>981</td>
<td>(\geq 12)</td>
<td>Amoxicillin 500 mg t.i.d. 10 days or MFNS 200 (\mu g) q.d. 15 days or MFNS 200 (\mu g) b.i.d. 15 days or placebo</td>
<td>MFNS 200 (\mu g) b.i.d. significantly better than placebo ((p &lt; 0.001)) or amoxicillin ((p = 0.002)); MFNS 200 (\mu g) q.d. significantly better than placebo ((p = 0.018)) ([23])</td>
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ACP: Amoxicillin/clavulanate potassium; b.i.d.: Twice daily; MFNS: Mometasone furoate nasal spray; q.d.: Daily; t.i.d.: Three-times daily.
proinflammatory cytokines such as IL-1, IL-5, IL-6 and TNF [13,27,96]. Similar to the previous studies, the treatment effect of MFNS for all symptoms persisted for at least 4 months [24,26,27] and increased with the duration of therapy [27]. This improvement in symptom scores corresponds to the increased improvement in polyp grade scores over time.

A pronounced placebo effect occurred in this study, particularly for the end points of nasal congestion/obstruction and sense of smell, and increased over time [27]. Such an effect, observed in many studies of nasal polyposis [24,26,27], may be attributable to the inactive components of MFNS. Thus, the use of placebo groups remains important for future trials of nasal polyposis [26,27].
Mometasone furoate may thus offer patients with nasal polyposis a therapeutic option that can reduce or delay the need for surgery by effectively relieving the symptoms of this disease [24]. Once-daily dosing of MFNS appears to be as effective as twice-daily dosing across this population as a whole, except for nasal congestion and obstruction. Individual subject response should determine the optimal dosing regimen [24]. Further studies are necessary to determine the lasting effect of MFNS on the continued resolution of nasal symptoms associated with nasal polyposis, since maximal reduction in polyp size may take several months to achieve [24,27,89].

**Safety of MFNS**

- **Local adverse events**
  In clinical studies involving both adults and children, the incidence of adverse events is generally similar in patients receiving MFNS in doses ranging from 50 to 800 µg daily, and is comparable to those receiving placebo. Local adverse events in patients from all age groups are mild in intensity and self-limiting, and resolve without discontinuation of therapy [12–19,51,52,97]. The most common local adverse events include epistaxis (ranging from blood-tinged mucus to bleeding) and headache [12–15,17–19,51,52,98]. A multicenter, open-label, 12-month study of changes in nasal histopathology reported that MFNS did not lead to changes in epithelial thickness or focal metaplasia, suggesting that long-term treatment is not associated with nasal atrophy [99].

- **Systemic safety**
  The possible routes of systemic exposure with intranasal corticosteroids include absorption of the locally deposited dose through the nasal mucosa or absorption of a potentially swallowed dose through the gastrointestinal tract [100]. Some clinicians are reluctant to prescribe intranasal corticosteroids, particularly for pediatric patients, owing to concerns regarding possible systemic effects, including impairment of the normal response to stress, growth retardation due to suppressed cortisol levels, formation of cataracts and osteoporosis [101,102]. However, use of intranasal corticosteroids has not been associated with serious side effects.

One indication of an agent’s potential for systemic adverse events is its bioavailability, which depends partly on its absorption across the highly vascular nasal mucosa [103]. The degree of systemic absorption depends on its lipophilicity. Thus, intranasal corticosteroids with lower systemic bioavailability, such as MFNS, fluticasone furoate and fluticasone propionate, are highly lipophilic, whereas those with higher bioavailability, such as flunisolide, beclomethasone dipropionate and budesonide, are less lipophilic [103,104]. Systemic bioavailability is also partly determined by the degree of first-pass hepatic metabolism, which is generally favorable with intranasal corticosteroids [101]. When used at recommended doses, MFNS has a systemic concentration of less than 0.5%, which is equal to or lower than that reported for other intranasal corticosteroids (Table 3) [100,102–105].

Studies of the systemic safety of MFNS reveal no effect on hypothalamic–pituitary–adrenal (HPA)-axis function in adults, as assessed by the measurement of cortisol levels. In a placebo-controlled, randomized, parallel-group study of 24 adult volunteers, eight received MFNS, administered at single doses of 1, 2 and 4 mg; none experienced clinical symptoms of HPA-axis suppression [48]. Effects on the plasma cortisol concentration curve, urinary free cortisol, and 8 am plasma cortisol were similar to placebo at all doses of MFNS. These findings reveal that even when given in doses up to 20-times the projected clinical dose, MFNS does not affect cortisol secretion. In another study involving 27 adults with perennial allergic rhinitis, randomized to MFNS 200 µg daily or triamcinolone acetonide 220 µg daily for 3 weeks, there were no differences between the two drugs in values obtained at baseline and at 3 weeks in systemic bioactivity markers, including plasma and urine cortisol levels [106]. In a third study of MFNS in nasal polyposis, no significant differences in 24-h urinary free cortisol were found over the treatment period among the MFNS 200 µg twice-daily, MFNS 200 µg daily or placebo groups [24]. Suppressed cortisol levels impair the normal response to stress and can retard growth rate in children [107]. However, studies of MFNS in children have not demonstrated that it produces any relevant absorption. In a randomized, evaluator-masked, placebo-controlled study of 96 children

<table>
<thead>
<tr>
<th>Intranasal corticosteroid</th>
<th>Bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flunisolide</td>
<td>49</td>
</tr>
<tr>
<td>Beclomethasone dipropionate</td>
<td>44</td>
</tr>
<tr>
<td>Budesonide</td>
<td>34</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>0.42</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>0.46</td>
</tr>
<tr>
<td>Fluticasone furoate</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Data taken from [100,102,103,105].
Mometasone furoate nasal spray

Drug Evaluation

Executive summary

- Mometasone furoate is a potent 17-heterocyclic corticosteroid formulated in an aqueous suspension for intranasal application with a metered-dose, manual pump nasal spray.
- Mometasone furoate nasal spray (MFNS) is safe and effective for the treatment and prophylaxis of seasonal allergic rhinitis and the treatment of perennial allergic rhinitis, nasal polyposis, and as an adjunct to antibiotics for acute bacterial rhinosinusitis, as well as monotherapy for acute uncomplicated rhinosinusitis.

Allergic rhinitis

- When administered to patients with seasonal or perennial allergic rhinitis, MFNS reduces nasal congestion, rhinorrhea, nasal itching, sneezing and postnasal drainage, as well as the ocular symptoms of itching, redness and tearing.

Acute rhinosinusitis

- The rationale for using intranasal corticosteroids in acute rhinosinusitis resides in their anti-inflammatory properties.
- The administration of MFNS together with an antibiotic significantly reduces the symptoms of acute bacterial rhinosinusitis, including purulent rhinorrhea, nasal congestion, postnasal drip, headache, facial pain and cough.
- MFNS has been found to be an effective monotherapy in cases of uncomplicated acute rhinosinusitis that are usually secondary to a viral infection; its use could decrease the overuse of antibiotics in this disease.

Nasal polyposis

- Nasal polyps are benign growths that develop in the nose and sinuses, causing obstruction and interfering with breathing. They often lead to impairment or loss of sense of smell.
- MFNS has been shown to reduce nasal polyp size, but a longer duration of therapy than that used for acute rhinosinusitis may be required.
- MFNS 200 µg twice-daily significantly improves nasal congestion/obstruction, rhinorrhea, postnasal drip and sense of smell in nasal polyposis.
- It has a rapid onset and provides lasting relief of most of the major symptoms of nasal polyposis within 2–5 days of initiating therapy.
- Local adverse events associated with MFNS in patients from all age groups are mild in intensity, self-limiting and usually resolve without discontinuation of therapy.

Conclusion

Extensive clinical evidence has confirmed that MFNS is a highly effective treatment for common inflammatory disorders of the upper respiratory tract. Multiple clinical studies have consistently revealed that MFNS rapidly alleviates the symptoms of seasonal allergic rhinitis, perennial allergic rhinitis and nasal polyposis. MFNS is also important in the treatment of acute rhinosinusitis, as monotherapy in uncomplicated cases, or as an adjunct to antibiotics in documented cases of acute bacterial rhinosinusitis.

The safety profile of MFNS is well-established. Local adverse events tend to be mild-to-moderate and resolve without discontinuation of treatment. No systemic adverse events have been reported in adults or children. In summary, extensive clinical testing has demonstrated that MFNS is a safe and effective therapeutic option for the prophylaxis and treatment of seasonal allergic rhinitis and the treatment of perennial allergic rhinitis, acute rhinosinusitis and nasal polyposis.

Future perspective

Current clinical investigations with MFNS are providing substantial evidence regarding its efficacy in reducing the ocular symptoms of allergic rhinitis. Numerous clinical studies have found that MFNS is not associated with ocular-related adverse events, such as the development of glaucoma or subcapsular cataracts. They also indicate that MFNS could be a primary treatment for both the nasal and ocular symptoms of allergic rhinitis, possibly eliminating the need for patients to use separate medications for the two symptoms. In addition, MFNS has demonstrated an improved quality of life in patients with allergic rhinitis by increasing their quality of sleep and workplace productivity.

Mometasone furoate nasal spray has been recommended as an adjunct to antibiotics for
acute bacterial rhinosinusitis. By using MFNS in acute rhinosinusitis, inappropriate antibiotic use will be decreased, leading to lower costs and, most importantly, reduced bacterial resistance to antibiotics. MFNS has also been shown to reduce nasal polyp size and improve the troubling associated symptoms of nasal congestion/obstruction and loss of sense of smell. It has a rapid onset of action and provides lasting relief, thereby reducing or delaying the need for nasal polyp surgery. Future studies are needed to determine if MFNS prophylaxis is necessary to prevent the recurrence of nasal polyposis.

Financial & competing interests disclosure
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Bibliography


31 Howarth PH: Mediators of nasal blockage. Allergy 52(Suppl. 40), 12–18 (1997).


