



Barbara Rinehart

JOURNAL ARTICLE

ASTHMA: INHALED CORTICOSTEROIDS

My responsibilities were:

- 🌿 Worked with agency to develop outline
- 🌿 Researched medical literature
- 🌿 Wrote manuscript for author review
- 🌿 Referenced and annotated manuscript

Mometasone furoate antagonizes AMP-induced bronchoconstriction in patients with mild asthma

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Background: Mometasone furoate (MF) is a new potent corticosteroid for use in treating asthma.

Objective: To test the lower range of the dose-response curve, effects of MF delivered by dry powder inhaler (DPI) on AMP-induced bronchoconstriction were compared with those of placebo.

Methods: In a placebo-controlled, 3-phase cross-over, single-center, double-blind study, 15 patients with mild asthma were randomized to three 2-week treatment phases (separated by 4-week washout phases) with MF DPI 50 µg twice daily, MF DPI 100 µg twice daily, or placebo. AMP challenge was performed before and at the end of each treatment phase.

Results: Thirteen patients completed all 3 phases and were included in the primary efficacy analysis. Treatment with MF DPI 50 µg twice daily or with MF DPI 100 µg twice daily significantly reduced the bronchoconstrictive response to AMP, displacing the dose-response curve to the right by 2.81 and 3.11 doubling dilutions, respectively, compared with placebo ($P < .001$). The improvement in FEV₁ over the 2-week treatment phase was significantly ($P < .033$) greater during treatment with MF DPI 50 µg or 100 µg twice daily than with placebo. Peak expiratory flow rate, wheezing scores, difficulty breathing scores, nocturnal awakenings requiring salbutamol, and puffs of salbutamol per day also indicated a greater improvement in respiratory function and symptoms of asthma with MF DPI 50 or 100 µg twice daily than with placebo. Both doses of MF DPI were well tolerated.

Abbreviations used
 BID: Twice-daily dosing
 DPI: Dry powder inhaler
 FVC: Forced vital capacity
 MF: Mometasone furoate
 PC₂₀: Provocative concentration producing a 20% fall in FEV₁
 PEF: Peak expiratory flow rate

the currently available inhaled corticosteroids have high topical potency in the lungs, as well as rapid first-pass hepatic metabolism when absorbed from the gastrointestinal tract, thus greatly reducing their systemic bioavailability relative to oral corticosteroids.²

Mometasone furoate (MF) is a highly potent topical steroid. MF has been used extensively in topical dermatologic formulations since 1987 for treating corticosteroid-responsive skin diseases.³⁻⁵ MF is also available in an aqueous nasal spray formulation for the treatment of allergic rhinitis.⁶ A new dry powder inhaler (DPI) formulation of MF is under investigation for use in treating asthma.^{7,8}

Much of the current knowledge concerning the anti-inflammatory effects of corticosteroids is based on the fact that MF has been shown to be involved in the inflammatory response in the human lung. MF has an anti-inflammatory effect on the release of proinflammatory mediators, such as interleukin-1, interleukin-6, and interleukin-8, and on the release of nitric oxide, prostaglandin G/H synthase, and matrix metalloproteinase-9.

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Holgate et al 907

bronchoconstriction was induced by AMP challenge. The effect of MF DPI 50 µg BID on AMP-induced bronchoconstriction was compared with placebo. The effect of MF DPI 100 µg BID on AMP-induced bronchoconstriction was compared with placebo.

In period and all specified for medication specified by each treatment phase (placebo wash-out period). Patients performed and received the challenge. They entered the trial. Another 4-week wash-out period followed. Patients then received the challenge and entered the last 2 weeks then entered the challenge was performed at

as performed at all visits to (FVC) and compared with Coal reference ranges.¹⁸ rate (PEFR) (in liters per use of rescue medication (puffs) assessed response to placebo.

Personal Best Peak Flow for measuring PEF and tests recorded morning and evening inhalations, asthma (eg, cough), number of nocturnal awakenings, asthma medications.

the change in log₁₀PC₂₀ secondary efficacy variables (eg, response to nocturnal awakenings) were scored as 0 = none; 1 = increase with my normal daily able, interfered with most of the treatment visits of each test level of symptoms with treatment phase with use of the improved, 3 = no change.

instructed to withhold medication, 6 hours; oral anti-24 hours; intranasal anti-48 hours. Patients were to exercise or cold air exposures for at least 2 hours before the challenge and were to refrain from ingestion of coffee, tea, and alcohol for at least 6 hours before the challenge. AMP challenge

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Holgate et al 908

ID	MF DPI 100 µg BID
	0.635
	1.719
	1.084
	1.069 ± 0.119
	-22.3
	-10.2

≤ .001
 ≤ .001
 = .57)

MF DPI 100 µg BID	No.	Mean
	13	3.158
	13	0.343 ± 0.070*
	13	4.364
	12	0.122 ± 0.073
	13	435.4
	9	49.4
	13	0.330
	9	-0.156
	13	0.455
	9	-0.323
	13	0.091
	9	-0.033
	12	0.393
	9	-0.337
	13	2.596
	9	-1.558

*Only FEV₁ and FVC were statistically significant.

and response to

patient recorded changes in scores, morning difficulty asthma-related nocturnal awakenings, and use of salbutamol were numerically better during treatment with MF DPI than during treatment with placebo (Table II) but were not analyzed for statistical significance. Evening wheezing, coughing, and difficulty breathing scores showed results similar to the

Holgate et al 911

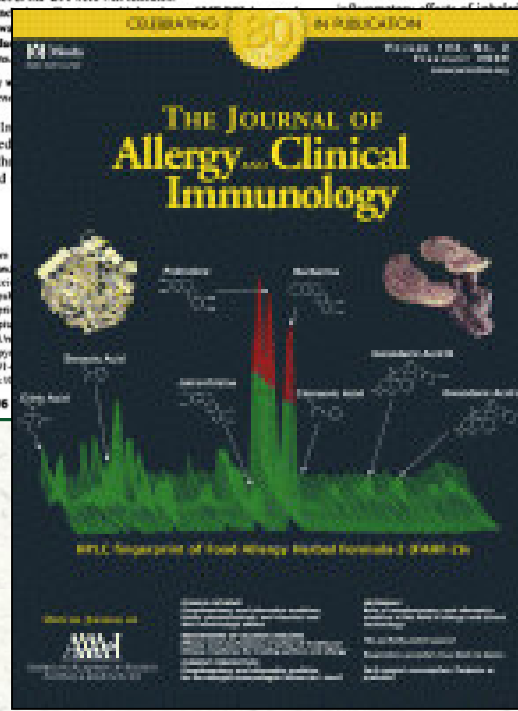
efficacy and safety of 21-34. of inhaled corticosteroids (Nasonex) (1998;137:51-53). A. Ellis CN, Ginn JD, et al: Inhaled corticosteroids in the treatment of bronchitis: a meta-analysis. *Am J Respir Crit Care Med* 1999;160:1000-1005.

study during the first the second treatment patients completed all 3 uded in the primary analy-

µg BID or MF DPI 100 µg the bronchoconstrictor th treatment with placebo. means, these increases in th MF DPI 50 µg BID or significantly greater ($P < .05$) treatment with placebo no significant differences onse based on AMP challenge during treatment with MF DPI 50 µg BID (Table I).

Subsequent to bronch challenge following 12,580-4. Dose-response effect of inhaled MF on airway hyper-responsiveness in mild asthma. *Am Rev Respir Dis* 1999;160:1000-1005.

report of Working Party of the British Society for Allergy and Clinical Immunology. *Br J Clin Pharmacol* 1999;48:1-10.



controlled study of patients with mild asthma.

target of therapy. *J Allergy Clin Immunol* 1998;102:517-22.