Intranasal Fluticasone Propionate
A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential in Allergic Rhinitis

Harriet M. Bryson and Diana Faulds
Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by: J. Bousquet, Hôpital de l'Aiguelongue, Montpellier, France; J. Dolovich, McMaster University, Hamilton, Ontario, Canada; T.A. Johannessen, Horten ENT Centre, Horten, Norway; M. Kaliner, National Institutes of Health, Bethesda, Maryland, USA; S. Lozewicz, Department of Respiratory Medicine and Allergy, St Bartholomew's Hospital, London, England; S. Makino, Dokkyo University School of Medicine, Mibu, Tochigi, Japan; H. Malmberg, Ear, Nose and Throat Clinic, Helsinki University Central Hospital, Helsinki, Finland; M. Okuda, Nippon Medical School, Tokyo, Japan; D.S. Pearlman, Colorado Allergy and Asthma Clinic, Aurora, Colorado, USA; A.S. Rebuck, Asthma Centre, The Toronto Hospital, Toronto Western Division, Toronto, Ontario, Canada; G.K. Scadding, The Royal National Throat, Nose and Ear Hospital, London, England; P. Small, The Sir Mortimer B. Davis – Jewish General Hospital, Montreal, Quebec, Canada.

Contents

Summary

1. Pharmacodynamic Properties
   1.1 Topical Anti-Inflammatory Activity
   1.2 Effects on Allergen-Induced Nasal Response
   1.3 Effects on Nasal Cytology
   1.4 Effects on Pituitary-Adrenal Function

2. Pharmacokinetic Properties

3. Therapeutic Efficacy
   3.1 Seasonal Allergic Rhinitis
      3.1.1 Dose-Finding Studies
      3.1.2 Comparisons with Placebo
      3.1.3 Comparisons with Beclomethasone Dipropionate and Flunisolide Acetonide
      3.1.4 Comparisons with Other Agents
   3.2 Perennial Rhinitis

4. Tolerability

5. Dosage and Administration

6. Place of Intranasal Fluticasone Propionate in Therapy
Summary

Synopsis

Fluticasone propionate is a potent topical anti-inflammatory corticosteroid with low systemic activity. Available pharmacodynamic data are only preliminary; however, large placebo- and drug-controlled clinical studies involving almost 4000 patients with seasonal allergic rhinitis and 1500 with perennial allergic and nonallergic rhinitis have confirmed the efficacy of intranasal fluticasone propionate in the control of nasal symptoms. Fluticasone propionate generally demonstrated similar efficacy compared with intranasal beclomethasone dipropionate, flunisolide acetonide and oral astemizole and better or a trend towards better efficacy compared with oral loratadine, terfenadine, cetirizine and intranasal sodium cromoglycate (cromolyn sodium) against nasal symptoms.

The incidence of adverse effects in association with intranasal fluticasone propionate appears to be comparable to that observed with placebo; the most frequently reported effects are nasal dryness/burning, epistaxis and headache. Consistent with its minimal systemic availability, intranasal fluticasone propionate in a dosage of up to 4 mg/day does not cause adrenal suppression.

Thus, based on early data from large clinical trials, fluticasone propionate administered once daily offers an effective and convenient treatment option in patients with seasonal and perennial allergic rhinitis, and is distinguished by its low oral bioavailability.

Pharmacodynamic Properties

Fluticasone propionate has potent topical anti-inflammatory activity coupled with low systemic activity. It has more than 9 times the anti-inflammatory activity of fluocinolone acetonide, and twice the activity of beclomethasone dipropionate in the McKenzie skin vasoconstriction assay in humans.

After allergen challenge, 2 weeks' pretreatment with intranasal fluticasone propionate 200 μg/day did not significantly inhibit the immediate increase in nasal airways resistance in atopic patients; no data concerning the possible effects of fluticasone propionate on the late and re-challenge phases of the allergic response are available.

A reduction in the number of nasal eosinophils, basophils and neutrophils has been observed in patients with seasonal allergic rhinitis after treatment with intranasal fluticasone propionate 50 to 800 μg/day administered for 2 weeks to 6 months. Further investigation revealed that the number of activated eosinophils in the nasal mucosa during the immediate allergic response was reduced after treatment with fluticasone propionate 200 μg/day, suggesting that fluticasone propionate may act by preventing eosinophil activation.

Although intravenous fluticasone propionate 2mg produced a marked reduction in plasma cortisol levels, no such effects were evident after oral administration of fluticasone propionate 16mg or after intranasal fluticasone propionate 4 mg/day for 7 days. No suppression of pituitary-adrenal function was reported after up to 12 months' treatment with intranasal fluticasone propionate 50 to 1600 μg/day in patients involved in 9 large clinical trials.

Pharmacokinetic Properties

Fluticasone propionate is poorly absorbed following oral administration. The small portion of drug which is absorbed is metabolised rapidly and has a total blood clearance (plasma clearance adjusted for packed cell volume) almost equivalent to hepatic blood flow. Thus, the hepatic extraction ratio of fluticasone propionate is almost unity, giving the drug an oral bioavailability of < 1%. For a drug intended to have only local effects, this compares favourably with budesonide (11%), flunisolide (20%) and dexamethasone and prednisolone (> 80%), as low drug bioavailability minimises systemic adverse effects. There are no investigations concerning the pharmacokinetics of intranasal fluticasone propionate.

87 to 100% of an oral dose of fluticasone propionate is excreted in the faeces, 3 to 40% as the inactive 17β-carboxylic acid metabolite.