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REVIEW

Allergic Rhinitis: Focus on the Intranasal Route of Fluticasone Furoate

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Abstract: Fluticasone furoate is a new synthetic steroid structurally related to fluticasone propionate but with a higher affinity for the glucocorticoid receptor. It demonstrates high local efficacy and low systemic availability thus producing maximal efficacy with minimal side effects. Intranasal steroids are recommended first line treatment for allergic rhinitis in both adults and children over 2 years. The safety profile of fluticasone furoate has been evaluated in terms of its plasma concentrations, HPA axis, growth in children and bone metabolism and ocular side effects with no major side effects although further studies are warranted. The potential advantages are the new device which has been developed for delivery which is patient preferred, faster onset of action and a consistent improvement on the ocular symptoms of allergic rhinitis.

Keywords: allergic rhinitis, fluticasone furoate, intranasal steroids

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Introduction

This paper provides a concise review of the properties and clinical use, side effects of intranasal fluticasone furoate for allergic rhinitis. Medline and Cochrane databases were searched for references relating to FF, intranasal steroids and allergic rhinitis.

Pharmacology and Mechanism of Action

Properties of GC which determine their effectiveness include lipophilicity, bioavailability and receptor affinity.

Fluticasone furoate (FF) is a synthetic, lipophilic trifluorinated glucocorticoid receptor agonist. It is structurally related to fluticasone propionate with modification of the 17 alpha ester moiety of fluticasone propionate. This modification leads to enhanced affinity for the glucocorticoid (GC) receptor. FF and FP do not require de-esterification as do budesonide and ciclesonide. FF and FP have a fluoromethylthioester at the 17 beta position that is cleaved via hepatic metabolism (P450 isozyme 3A4) to inactivate any glucocorticoid that might enter the systemic circulation. The 17 alpha ester group is stable and is not cleaved from the rest of the molecule.[1]

The lipophilicity property causes greater mucosal absorption and retention increasing GC receptor exposure and also enhances plasma protein binding. The newer steroids e.g. FF, FP, mometasone furoate and ciclesonide are 3–1000 times more lipophilic than older preparations.[2]

Upon application of an intra nasal corticoid steroid to the nasal mucosa most of the drug is cleared rapidly. Approximately 70% is swallowed moving to the potential for systemic availability. Absorbed drug is either avidly bound to plasma proteins or subject to first pass metabolic inactivation in the liver thus minimising its systemic availability. First pass metabolism is via the P450 isozyme 3A4 to the 17β-carboxylic acid metabolite which has 10,000 lower GC receptor agonist potency than FF. The residual drug in the nose can be directly absorbed into the systemic circulation and will by-pass the protective hepatic first pass mechanism, however the high tissue binding of FF results in low systemic absorption.

In healthy males single or multiple intranasal doses (up to 880 ug) once daily for 7 days resulted in plasma drug levels that are below the lower limit of assay sensitivity in most cases and if measurable plasma levels were <30 pg/mL. FF is 99.4% bound to plasma protein. Absolute nasal and oral bioavailability after high doses (up to 8800 ug) is low (geometric mean 0.5%).[3]

FF is largely excreted in the faeces with only 1%–3% found in the urine. The average elimination half life is 15.1 hours.

The particular structural features of FF also enable better interaction with the amino acids within the binding site of the glucocorticoid receptor enhancing FF's affinity for the glucocorticoid receptor leading to a fast association and slow dissociation from the receptor. It has a higher receptor affinity than other commonly used corticosteroids e.g. FF > mometasone furoate > FP > beclomethasone > ciclesonide > budesonide > triamcinalone > flunisolide > dexamethaosne.[2]

All glucocorticoids exert their effect via the GC receptor by 2 means. The first, is the DNA – binding dependent mechanism whereby activated GC receptor binds directly to DNA at certain specific sites resulting in enhanced or diminished transcription of various gene products. The second is a DNA binding independent mechanism whereby the activated GC receptor interacts with transcription factors such as NFKB inhibiting the ability to enhance transcription of pro inflammatory gene products.

Unique structural features of FF lead to its enhanced safety and efficacy. The fluticasone backbone and the 17 alpha furoate ester are important for glucocorticoid receptor binding with diminished binding at other steroid receptors. The 17 beta substitution is cleaved with hepatic metabolism to inactivate the molecule prior to its entry into the systemic circulation.

There are numerous desirable features of FF including its potency as an anti-inflammatory agent mediated by its effects on NFKB. It is long acting because of its greater tissue retention. It has specific steroid hormone receptors cell activity because of its particular structural features thus diminishing side effects produced by binding to other steroid binding sites. Because of its structure it has minimal availability to the systemic circulation. This is in part due to its very high degree of protein binding in the

circulation as well as the very effective inactivation via cleavage of the 17 beta moiety during first pass metabolism.

Numerous *in vitro* studies have demonstrated the mechanisms by which FF has the greater affinity and greater efficacy as a topically active glucocorticoid:[1,2]

1. Anti inflammatory activity: NFKB activates many inflammatory cytokine pathways. Glucocorticoids inhibit NFKB mediated gene transcription. Thus NFKB reporter assays can be used to measure anti inflammatory activity of various glucocorticoids *in vitro*. In such assays both FF and mometasone furoate has shown greater potency than the other commonly available topical corticosteroids.
2. Anti inflammatory effects in an animal model: FF has significantly greater inhibitory activities on lung eosinophilia in an experimental rat model of ovalbumin – induced respiratory allergic eosinophilia. It also demonstrated a long anti inflammatory duration of action in this model.
3. Fallic activity of binding to the glucocorticoid receptor: There are similarities between the ligand – binding domains of receptors within the steroid hormone receptor family so ligands for the glucocorticoid receptor often have affinity for other steroid receptors e.g. oestrogen, androgen and mineral low corticoid receptors. FF as well as FP, have highly selective profile for the glucocorticoid receptor compared to the other steroid hormone receptors and this selectivity is significantly better than seen with mometasone furoate, budesonide and ciclesonide. This is a function of its particular structural attribute.
4. Retention in respiratory tissue: Prolonged retention within the tissue of the target organ is a desirable property of topically applied glucocorticoids as this enhances the opportunity for pharmacological action and also reduces the risk of systemic availability. In an experimental model using monolayers of human lung epithelium FF has been shown to bind to a greater degree than other topical steroids. Whatsmore the rate of transport from the tissue was lower than that seen with other molecules.
5. Protective affects on airway epithelial barrier: Glucocorticoids can enhance the repair potential of damage cells and reduce the affects of a variety of cellular insults. This is done via the induction of certain anti inflammatory proteins which result from glucocorticoid receptor activation.

Safety Profile

Safety has been assessed in three domains: effect on the HPA axis, bone metabolism and growth as well as ocular side effects.

Plasma FF concentrations were undetectable in the majority of subjects and variably detectable (>10 pg/mL) in the minority.[4] In children FF was detectable (>10 pg/mL) in about 10% with evidence of a dose response effect

Evaluation of the HPA axis in children was assessed by 24 hour urinary cortisol with no significant differences between placebo and FF 55 or 110 ug daily doses.[5]

Effects on growth measurements can be determined by knemometry (knee to heel length) and stadiometry (height). For FF only a very short 2 week study in 53 children has been described and showed no detrimental effects on knemometry compared with placebo.[6] The asthma literature on the adverse effects of inhaled steroids has documented adverse effects for beclomethasone, FP and budesonide, but it is acknowledged that effects on final height may be insignificant.[8] A Cochrane review in this area only considered biochemical markers of bone turnover, bone density and development of fractures which is more applicable to an older population and concluded that over 2–3 years there was no increased fracture rates or reduction in bone density but that high dose ICS could cause increased bone turnover the clinical significance of which was unclear.[10] Given that topical steroids are frequently long term therapies maintained for decades more studies are needed to examine long term safety in both adult and paediatric populations.

Opthalmological assessment by fundoscopic and slit lamp examination as well as intra-ocular pressures have been measured up to 52 weeks and showed no significant increases in intra-ocular pressure or posterior subcapsular cataracts (FF 0.33% versus placebo 0.5%).[4] A shorter 12 week study showed similar results in children aged 2–11 years.[5]

Indications for Use

The place of topical glucocorticoids in treatment guidelines for allergic rhinitis

Advantages of FF as a treatment modality for allergic rhinitis include:

- Excellent efficacy and safety profile.
- Unique features of its device.
- Patient acceptability—no taste or smell, no post nasal drip, once daily usage.
- Management of the ocular component.

Numerous trials show that FF is effective in the treatment of nasal and ocular symptoms and also quality of life scores for seasonal and perennial allergic rhinitis compared with placebo.[5,11–13] However it is interesting to note that, like asthma, topical steroids do not result in symptom improvement in all subjects suggesting a steroid nonresponsive phenotype which in lower airways disease may be due to noneosinophilic patterns of inflammation.

Early studies in allergic rhinitis did not focus on the concomitant benefits of intranasal GC on ocular symptoms but this has been addressed in more recent studies. Ocular symptom improvement begins within 2 days of starting treatment. INCS seem to be as effective as oral antihistamines in reducing symptoms of allergic conjunctivitis. It is expected that this is a class effect of GC although this view has recently been challenged.[14,15]

Ocular symptoms in allergic rhinitis occur both as a result of direct allergen contact with conjunctivae and also as a result of a parasympasthetically mediated nasal ocular reflex. Baroody et al[16] demonstrated that FF applied to the nasal mucosa can inhibit the ocular effects that result from a localised nasal antigen challenge. They devised an experiment in subjects with seasonal allergic rhinitis to demonstrate the existence of a nasal ocular reflux. They were able to show that a unilateral nasal challenge with antigen led to sneezing and a nasonasal reflex that increased with repetitive challenges demonstrating the phenomenon of priming. Ocular responses also increased after each nasal allergen challenge supporting the existence of a nasal ocular reflex response and priming. These responses were inhibited by the application of FF intranasally. In addition, eosinophils in nasal scrapings were also reduced by application of FF. Thus via the mechanisms of reduction in allergic inflammation and a reduction in the nasal ocular reflex FF is able to exert its effect locally in the nose to reduce the ocular symptoms associated with allergic rhinitis. The studies performed by Baroody et al[16] were done with FF but this is likely to be a mechanism applicable to other intranasal steroids sprays.

Surveys of patient groups have shown that they dislike certain characteristics of nasal sprays. This includes the sensation of medication running down the back of the throat, its unpleasant taste and its smell or odour. Other features highlighted in patient focus groups include the fact that the spray does not provide 24 hour symptom relief and does not relieve symptoms quickly enough. There are numerous complaints about the devices that have been available including the length of the nozzle and the difficulty in administering such sprays to children. Opaque bottles are criticised because patients cannot tell when a refill is needed.[12]

The device developed for the administration of FF does address some of these deficiencies and in particular includes a window whereby patients can check how much solution is left in their bottles as well as having a much shorter nozzle for ease of administration. The device is side actuated which is easier for some patients to use. The FF formulation is tasteless and odourless and the volume is small enough so that the sensation of liquid running down the back of the throat has been minimised. These are examples of design features in both the device and the medication that now address many of the deficiencies highlighted by patients themselves.

Indications for use

Fluticasone furoate has the following market approval. The FDA in the USA approved FF (Veramyst) from April 2007 for the treatment of seasonal and perennial allergic rhinitis in adults and children greater than or equal to 2 years. Approval in Australia for FF (Avamys) was given by the TGA in 2008 for the same indication and age range as in the USA. The European Union approved FF (Avamys) in 2008 and Japan (Allermist) in 2009.

The recommended dose in adults is 2 sprays (27.5 ug) each nostril daily which is a total dose of 110 ug with half the dose in children (2–11 years).

Table 1. Comparative bioavailability of intranasal steroids.

Corticosteroid	Route	Rec daily dose	Bioavailability (%)
Prednisolone	Oral	10000 ug (10 mg)	82
Triamcinolone	Intranasal	220	46
Beclomethasone	Intranasal	336	44
Budesonide	Intranasal	128	31
Mometasone	Intranasal	200	0.46
Fluticasone	Intranasal	200	0.42
Ciclesonide	Intranasal	200	Undetectable <25 pg/mL

Side Effects

Generally FF is well tolerated, data from pooled clinical trails in over 1000 adult and paediatric subjects showed a similar rate of side effects to placebo. Fewer than 3% withdrew from therapy as a result of side effects. Adverse events with a frequency over >1% and a higher incidence than placebo were headache (9% versus 7%), epistaxis (6% versus 4%), pharyngolaryngeal pain (2% versus 1%), nasal ulceration (1% versus <1%) and back pain (1% versus <1%).[11] Long term (12 month studies) of 605 subjects highlighted epistaxis as the only more frequent adverse event compared with placebo (20% versus 8%).[4,5]

Are There Advantages for this Particular Drug ?

The unique features of FF i.e. increased lipohilicity and greater GC receptor avidity result in lower systemic availability which can be important for children in whom steroid side effects are of concern particularly in the context of the potential long term use. Also it is important in those who use multiple routes of steroid therapy and of relevance here is the fact up to 80% of asthmatics suffer from rhinitis.

Bioavailability is comparable with FP and mometasone furoate and ciclesonide but significantly less than older GC preparations (Table 1) and for this reason should be preferred. Safety data examining effects on the HPA axis and growth rates in children have shown variable results and studies have not undertaken head to head comparisons between different steroids. However reductions in growth rates in children have been documented with intranasal beclomethasone but not with FP, mometasone and FF.[17–19] The additive effect of intranasal and inhaled steroids also needs to be considered.

In terms of clinical efficacy there is only one comparative trail of FF (110 mcg once daily) with another intranasal steroid namely FP (200 mcg twice daily), this showed similar efficacy and tolerability of the 2 drugs with a faster onset of action of FF.[13] Additionally a recent review suggests that FF may be the most consistently effective INCS for ocular symptoms,[15] but in some patients monotherapy with INCS may not be sufficient to control ocular symptoms. Meltzer et al[12] compared FF with FP in allergic rhinitis and found that after a single dose FF was preferred in terms of sensory attributes (odor, taste, after taste, post nasal drip and nose run off). It was suggested that this could result in greater medication compliance.

Conclusion

FF is a novel synthetic steroid which has a similar profile to mometasone and FP. Current data indicates that FF is an effective and safe therapy for allergic rhinitis, it may have an advantage in the treatment of concurrent seasonal allergic conjunctivitis and preliminary data indicate that it may have a more rapid onset of action.

It is delivered in a side actuated hand held device which is preferred by patients. At this stage it is expensive which can be an important consideration for many patients.

Declarations of interest

JR participated on the GSK Avamys Advisory Board, Australia in 2007–9, Novartis Xolair Advisory Board 2008–2009 and has participated in GSK, Novartis, Schering Plough, Novatech funded clinical trails.

CK participated on the GSK Avamya advisory Board, Australia in 2007–9, Novartis Xolair Advisory Board Australia 2008–2009 and has participated

in GSK, Schering plough, Novartis funded clinical trials.

Abbreviations

FF, Fluticasone Furoate; GC, Glucocorticoid; FP, Fluticasone propionate; NFKB, nuclear factor kappa beta; INCS, Intranasal corticosteroids.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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