

Difluprednate in Ophthalmic Practice

Minal Patel, Deepika Singhal

Department of Ophthalmology, GMERS Medical College, Sola, Ahmedabad, Gujarat, India

Correspondence to: Deepika Singhal (deepika1103@yahoo.com)

Received: 07.08.2013 Accepted: 28.08.2013 DOI: 10.5455/njppp.2014.4.280820132

Introduction

Surgical technique in all fields of ophthalmology has reached to a very high level over the years. Despite such technical advances, surgical manipulation of anterior segment structures stimulates the release to arachidonic acid from cell membranes which triggers the production of prostaglandins and leukotrienes. These in turn lead to cellular reaction and protein leakage.

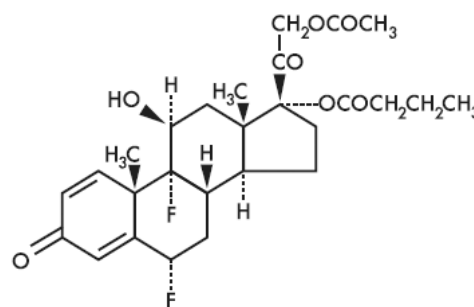
When the topical corticosteroids are used postoperatively, they inhibit the release of arachidonic acid from the cell membrane phospholipids, thus preventing the formation of leukotrienes and prostaglandins. In this way topical corticosteroids break the inflammatory cascade without the risk of systemic adverse effects.^[1] These agents are continued until the anterior chamber reaction has resolved and the blood-aqueous barrier has been reestablished.^[2]

In last few years, prednisolone acetate and betamethasone are strong steroids in use. Currently, the most widely prescribed strong topical corticosteroids in the US is prednisolone acetate 1%. While it controls inflammation effectively, it has not been shown to consistently address postoperative pain and discomfort in a large clinical trial.^[3] Chances of side effects like ocular hypertension and cataract formation are higher with these steroids. In June 2008 difluprednate ophthalmic emulsion 0.05% was approved by the US Food and Drug Administration (FDA) for the treatment of inflammation and pain associated with ocular

surgery. This was the first ophthalmic steroid approved by the FDA since 1973 as it is high in potency and has good safety profile as well as the ability to reduce postoperative pain.

Pharmacology

Difluprednate (difluoroprednisolone butyrate acetate or DFBA) is a synthetic difluorinated prednisolone derivative. The chemical name is 6 α ,9-difluoro-11 β ,17,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate (CAS number 23674-86-4). Difluprednate has a molecular weight of 508.56, and the empirical formula is C₂₇H₃₄F₂O₇. Difluprednate is represented by the following structural formula:



Originally developed for dermatologic applications, the molecule derives its potency from fluorination at the C6 and C9 positions.^[4] Its anti-inflammatory activity is further augmented by replacing the 17-hydroxyl group with butyrate. Its lipophilicity, thus corneal penetration is enhanced by substituting the 21-hydroxyl group with acetate.^[5]

Pharmacokinetics

After instilling difluprednate emulsion is rapidly deacetylated in the aqueous humor to difluoroprednisolone butyrate (DFB). DFB is drug's active metabolite and it has a similar corticosteroid activity profile.^[6] Endogenous tissue esterases then metabolize DFB to the inert metabolite hydroxyfluoroprednisolone butyrate (HFB), which limits systemic exposure to the active compound.^[7]

Indication and Usage

Difluprednate ophthalmic emulsion 0.05% is indicated for the treatment of inflammation and pain associated with ocular surgery (only FDA approved indication).

Dosage

It is used in a twice a daily or 4 times daily dosage depending upon the severity of inflammation.

Safety and Tolerability

Strong topical steroids such as dexamethasone – can lead to an IOP increase. Ocular hypertension often occurs as early as 1 week after repeat dosing.^[8] This effect can be much more pronounced in glaucomatous eyes.^[9] Increase in IOP for a longer time can lead to optic nerve damage and thus visual fields defects and possible reduction in visual acuity.

Extensive clinical testing has demonstrated that difluprednate 0.05% emulsion causes an elevation in IOP in a small minority. It was resolved in all patients after stopping the medication or with topical anti glaucoma drugs. Compared with betamethasone dosed at equal frequency, the incidence of IOP elevation was essentially equal between the two groups^[10-12], indicating an acceptable safety level.

Other known side effects of topical steroids include formation of posterior subcapsular cataracts and a predisposition to secondary ocular infections.

In many ophthalmic products Benzalkonium chloride (BAK), a quaternary ammonium detergent^[13,14] is used as a preservative. BAK breaks down cell walls by emulsifying membrane lipids^[15], which disrupts the tear film causing immunoallergic reactions^[16], and creates direct toxicity to corneal and conjunctival epithelial cells. Difluprednate ophthalmic emulsion does not contain BAK, and instead uses sorbic acid as a preservative. Sorbic acid causes little damage and irritation to the ocular surface and is recommended for use in sensitive eyes.^[17]

Clinical Use

Difluprednate is the first topical steroid indicated for the treatment of both postoperative inflammation and pain. It is also effective in treating anterior uveitis.

Side Effects

It may lead to formation of posterior subcapsular cataract. It can increase intraocular pressure which can damage optic nerve and can lead to visual field defects. Secondary ocular infection from pathogens including herpes simplex, perforation of the globe where there is thinning of the cornea and sclera are also not uncommon.^[18]

Ocular adverse reactions occurring in 5-15% of subjects in clinical studies included corneal oedema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis.^[18]

Use in Pregnancy

Pregnancy Category C: Difluprednate has been shown to be embryotoxic (decrease in embryonic body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal) anomalies when administered subcutaneously to rabbits and rats during organogenesis.

Difluprednate is administered topically with

minimal systemic absorption but use of it during pregnancy has not been evaluated and cannot rule out the possibility of harm, it should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo of fetus.

Use in Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production. So in nursing mothers difluprednate should be used cautiously.

Use in Pediatric Age Group

Safety and effectiveness has not been established.

Contraindication

Difluprednate is contraindicated in bacterial infection and fungal infection of the eye. It is also contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis, vaccinia and varicella.

REFERENCES

- Schimmer BP, Parker KL. Adrenocorticotrophic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: Hardman JG, Limbird LE, Gilman AG, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th Edition. New York: McGraw-Hill; 2001. p.1649-77.
- Sanders DR, Kraff M. Steroidal and nonsteroidal anti-inflammatory agents. Effects on postsurgical inflammation and blood-aqueous humor barrier breakdown. Arch Ophthalmol 1984;102(10):1453-6.
- Korenfeld M. Difluprednate: changing the landscape of ocular pharmacology. Expert Rev Ophthalmol 2008;3(6):619-25.
- Bikowski J. The position not the presence of the halogen in corticosteroids influences potency and side effects. J Drug Dermatol 2006;5(2):125-30.
- Yamaguchi M, Yasueda S, Isowaki A, Yamamoto M, Kimura M, Inada K, et al. Formulation of an ophthalmic lipid emulsion containing an anti-inflammatory steroidal drug, difluprednate. Int J Pharm 2005;301(1-2):121-8.
- Fujino A, Ohtu S, Shibata K. Studies on the metabolic fate of difluprednate (DFBA). 3. Metabolism in rats and rabbits after subcutaneous administration. Pharmacometrics 1985;29:713-23
- Tajika T, Shirasaki Y, Kimura M. Ocular distribution and metabolism after instillation of difluprednate ophthalmic emulsion in rabbits. The 2007 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO). Poster B744, Program 2654. Fort Lauderdale, FL, USA, 6-10 May 2007.
- Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics. I. The effect of dexamethasone in the normal eye. Arch ophthalmol 1963;70:482-91.
- Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics.II. The effect of dexamethasone in the glaucomatous eye. Arch ophthalmol 1963;70:492-99.
- Senju Pharmaceutical Co.,Ltd.,Osaka, Japan. Phase IIb clinical study of difluprednate 0.05% vs betamethasone 0.1% in the treatment of postoperative inflammation. April 2004. Data on file.
- Ohji M, Tano Y, Hida T. Efficacy and safety results of a phase III study of difluprednate ophthalmic emulsion 0.05% in postoperative inflammation. The 2007 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO). Poster B807, Program 3903. Fort Lauderdale, FL, USA, 6-10 May 2007.
- Ohno S, Mochizuki M, Usui M. A phase III noninferiority study of difluprednate ophthalmic emulsion 0.05% in the treatment of anterior uveitis. The 2007 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO). Poster B808, Program 3904. Fort Lauderdale, FL, USA, 6-10 May 2007.
- Baudouin C. Allergic reaction to topical eyedrops. Curr Opin Allergy Clin Immunol.2005;5:459-63.
- Price F. Do you welcome BAK? Weighing the toxicity risk. Optometric Management. 2004. Available from: URL: <http://www.optometric.com/article.aspx?articleZ71020>
- Dart J. Corneal toxicity: the epithelium and stroma in iatrogenic and factitious disease. Eye 2003;17:886-92.
- Yee RW. The effect of drop vehicle on the efficacy and side effects of topical glaucoma therapy: a review. Curr Opin Ophthalmol 2007;18:134-9.
- Abelson MB, Washburn S. The downside of tear preservatives. Rev Ophthalmol 2002;9:102-6.
- Durezol (difluprednate) Ophthalmic Emulsion. Available from: URL: www.rxlist.com/durezol-drug.htm

Cite this article as: Patel MM, Singhal D. Difluprednate in ophthalmic practice. Natl J Physiol Pharm Pharmacol 2014; 4:92-94.

Source of Support: Nil

Conflict of interest: None declared