Eosinophilic esophagitis: treatment with oral viscous budesonide

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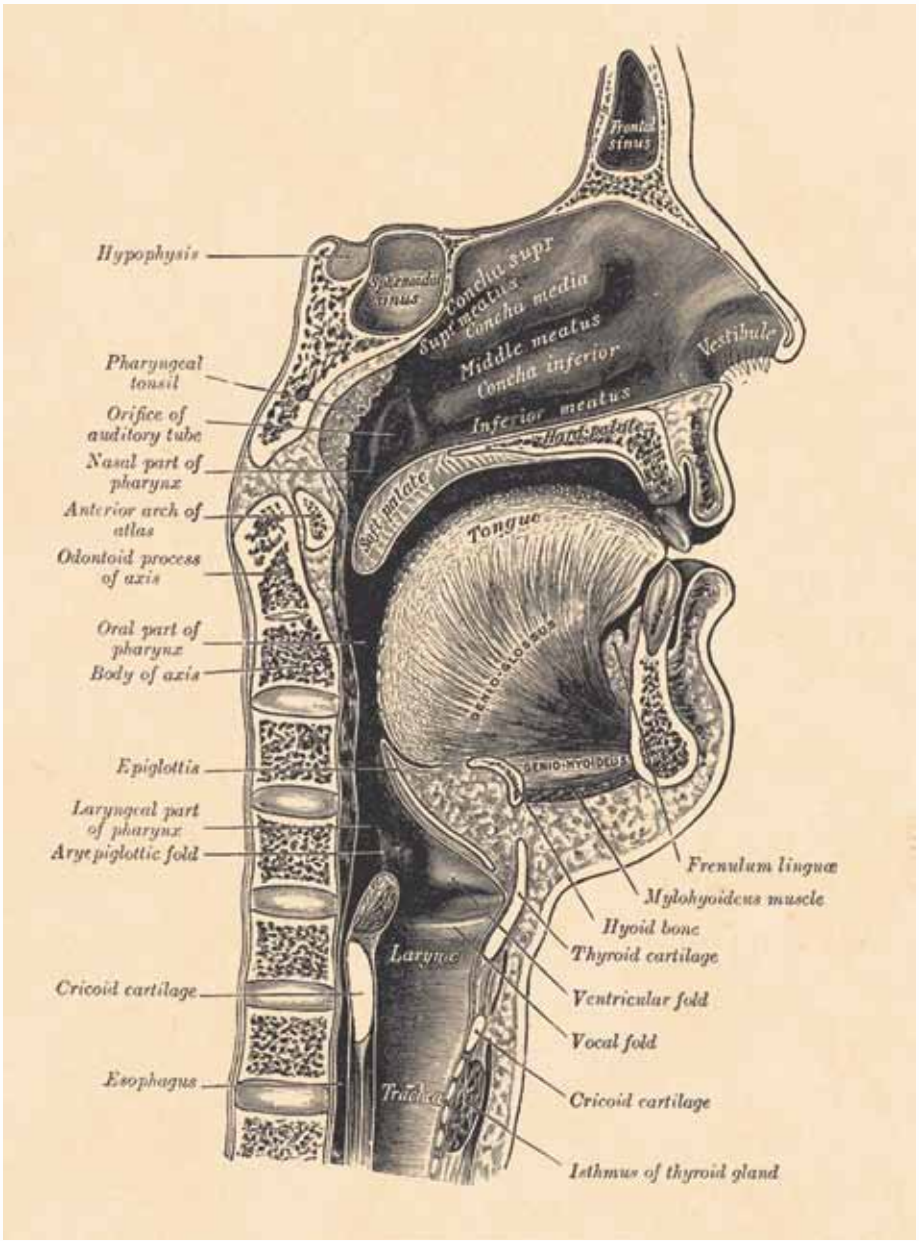
treatment with Oral Viscous Budesonide



Eyal Zur, RPh, MBA

ABSTRACT

Eosinophilic esophagitis is a clinicopathologic disease isolated to the esophagus. It is caused by immunologic reactions to ingested and inhaled allergans. Symptoms include regurgitation, vomiting, pain, anorexia, and dysphagia. Endoscopy with biopsy is currently the only reliable diagnostic test for eosinophilic esophagitis. The disease should remit with treatments of dietary exclusion, topical corticosteroids, or both. Oral viscous budesonide is one of the promising options of topical corticosteroid to treat eosinophilic esophagitis. Since there are no commercial medicines of oral viscous budesonide, it is solely a compounded medication. This article briefly discusses the properties of the disease and covers a few compounding possibilities to oral viscous budesonide.

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DEFINITION

Eosinophilic esophagitis (EoE) represents a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.[1] It most likely represents an immunologic reaction to ingested and inhaled allergens.[2-6] The following figure shows examples of endoscopic features of EoE.

FIGURE. Endoscopic features of eosinophilic esophagitis.

Source: J Allergy Clin Immunol 2011; 128(1): 3–20.

- A: Normal esophagus
- B: Esophageal furrowing
- C: White mucosal plaques
- D: Esophageal ring trachealization (concentric rings)
- E: Small-caliber esophagus with mucosal tearing after endoscopy

PREVALENCE

Prevalence of EoE is increasing with rates now ranging from 6 to 30 cases per 100,000 individuals.[7-10] Although this may also represent increased physician-recognition, it is likely that the rise in prevalence is real and mirrors the recent increase in prevalence of atopic disorders, such as asthma.[9,11] The disease was first described in children but occurs in adults as well. In adults, this disease is more common in men than women, with a mean age of onset of 38 years.[10]

DIAGNOSIS AND SYMPTOMS

The diagnosis of EoE is dependent upon finding ≥15 eosinophils per high power field (eos/hpf) in esophageal mucosal biopsies.[12-13] Symptoms of EoE often mimic gastroesophageal reflux disease (GERD) but are often refractory to acid-suppression therapy. Symptoms include regurgitation, vomiting, pain, anorexia, and dysphagia.[11-12] Although the optimal therapy for EoE is unclear, a major concern for untreated EoE is esophageal remodeling and development of strictures, which are reported in 16% to 40% of adult patients.[14-16] A likely prerequisite of esophageal remodeling is the presence of lamina propria (LP) fibrosis, as seen under light microscopy and measured by levels of transforming growth factor-β1 (TGF β1) and phosphorylated Smad2/3.[17-19]

TREATMENT

LP remodeling associated with EoE diminishes with topical corticosteroids therapy,[17-18] and patients with specific polymorphisms in the TGF β1-promotor gene may respond better to corticosteroid therapy.[18] Treatment options for EoE are dietary restrictions including those identified by skin testing,[6] six-food elimination diet,[20] and elemental formula.[2,21] Systemic corticosteroids[22] are effective but are sel-

dom warranted , especially in emergency cases, such as severe dysphagia, hospitalization, and weight loss.[23]Topical corticosteroids, such as fluticasone propionate, administered through a metered-dose inhaler, and oral viscous budesonide suspension (OVB), can be compounded and can safely induce and maintain low esophageal eosinophil levels[24-31]; however, when discontinued, the disease almost always recurs.[32] Studies have documented topical corticosteroids short-term safety, except for local fungal infections.[1] Steroid resistance as demonstrated by the lack of histologic responsiveness and the failure to modify local esophageal gene expression has been reported.[33] Before 2007, fluticasone was primarily used. Since then, OVB has also been shown to be effective.[31,34] Moreover, there is some evidence that budesonide can reverse esophageal fibrosis.[18] The clinical recommendations for the treatment of EoE according to update consensus recommendations for children and adults by experts committee are[1]:

- Topical corticosteroid therapy should be considered in all children and adults given a diagnosis of EoE for both initial and maintenance therapy (see the Table that accompanies this article). The type and duration of steroid therapy depends on the disease severity, the patient's lifestyle, the ability of the patient to continue the medication, and family resources.
- After induction of clinicopathologic remission, topical corticosteroid therapy might need to be maintained; however, long-term therapy must be individualized for each patient.
- When topical steroids are used chronically, in addition to observing side effects, growth should be carefully monitored in children.

Esophageal dilation with or without concomitant medical or dietary therapy can provide relief of dysphagia in selected patients with EoE. In the absence of high-grade esophageal stenosis, a trial of medical or dietary therapy before performance of esophageal dilation is reasonable. For high-grade strictures, dilation before initiation of medical therapy has been well tolerated and effective. The risk of chest pain after dilation is significant and should be discussed with patients. The use of esophageal dilation as primary therapy without concomitant medical or dietary therapy does not address the underlying inflammatory process and has been inadequately studied. On the other hand, the degree to which esophageal strictures will reverse with medical or dietary therapy alone is uncertain.[1]

COMPOUNDING ORAL VISCOUS BUDESONIDE SUSPENSION/GEL

Four major versions of OVB have been used in recent clinical trials[29,31,35-36]:

TRIAL 1

Mixed budesonide nebulizer suspension 0.5 mg/2 mL (Pulmicort respule; AstraZeneca) with sucralose (Splenda; McNeil Nutrition) in a ratio of ten 1-g packets of Splenda to 1 mg budesonide to create approximately an 8-mL volume. The dosage for this trial was 1 ounce a day (8 mL), preferably at bedtime. The patients did not eat or drink for 30 minutes after drug ingestion.[31]

TRIAL 2

A dosage of one budesonide 0.5-mg respule was mixed in five 1-g packets of sucralose for a total volume of 10 mL to 15 mL, dosed at 0.5 mg twice daily.[29]

TRIAL 3

The third trial used a ratio of 1 mg budesonide in 4 mL of solution twice daily.[35]

TRIAL 4

The fourth trial reported using budesonide combined with rincinol containing polyvinylpyrrolidone (Butler) at a dose of 3 mg/10 cc twice daily.[36]

Sucralose, a substituted disaccharide, is stable at a low pH, is water-soluble, and is nonbioaccumulative. Following consumption, 85% of sucralose is excreted unchanged in feces and 15% of absorbed sucralose is excreted unchanged in urine. Sucralose does not serve as a substrate for intestinal microflora.[37] Rincinol containing polyvinylpyrrolidone is a muco-adherent that forms a thin, protective coating over oral mucosa.

Between rincinal and sucralose, compounding agents, researchers recommend sucralose for preparing viscous budesonide doses,

TABLE. Recommended Doses of Corticosteroids for Eosinophilic Esophagitis.[1]

DRUG NAME	ADMINISTRATION	DOSAGE
Topical Swallowed Corticosteroids[a]		
Fluticasone	Puffed and swallowed through a metered-dose inhaler	Adults: 440 mcg to 880 mcg 2 times daily Children: 88 mcg to 440 mcg 2 to 4 times daily (to a maximal adult dose)
Budesonide	Dosed as a viscous suspension	Older children and adults: 2 mg daily Children (<10 years): 1 mg daily
Systemic Corticosteroid[b]		
Prednisone	Oral liquid swallowed	1 mg/kg to 2 mg/kg

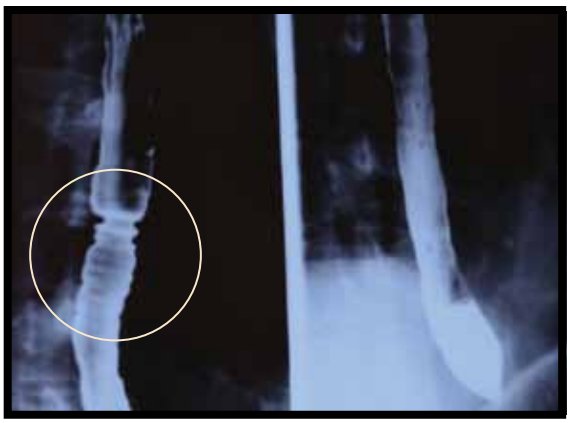
[a]Dosages shown for the topical swallowed corticosteroids are initial doses.
[b]Dosages shown for the systemic corticosteroid (prednisone) are for severe cases (e.g., small-caliber esophagus, weight loss, hospitalization).

given its wider availability, extensive studies, safety profile, and effective application in multiple randomized control trials.[38]

According to the author's experience none of the four versions of OVB are pharmaceutically successful.

The author's formula for OVB is included with this article. Xanthan gum was chosen as the suspending, thickening, and mucoadhesive agent. Xanthan gum is a high-molecular-weight polysaccharide gum. It contains D-glucose, D-mannose, and D-glucuronic acid. It is soluble in hot or cold water. Its solutions are neutral to litmus. Xanthan gum is used in pharmaceutical manufacturing as a suspending, stabilizing, thickening, and emulsifying agent. It is also used similarly in the food industry. Suspensions of crushed tablets or insoluble powders made with xanthan gum were reported to be in better quality, improved consistency, and, therefore, preferable to those made with tragacanth.

The stability was generally good and only a small number of drugs had been found to be incompatible (amitriptyline, tamoxifen, and verapamil). Solutions of xanthan gum demonstrate maximum stability at pH values between 4 and 10. Xanthan gum was found to be a suitable suspending vehicle for delivering antispasmodics topically along the length of the esophagus in patients with esophageal spasm.[39] In the formulation included, the concentration of xanthan gum is 2%, yielding a viscous stable gel. The budesonide used in the formulation is well suspended and homogenous due to a very efficient mixing method with an electronic mortar and pestle (EMP). Adding two kinds of sweeteners and flavor makes the preparation palatable with reasonable expectation for good compli-



THE LEFT SIDE SHOWS MULTIPLE RINGS ASSOCIATED WITH EOSINOPHILIC ESOPHAGITIS AFTER A BARIUM SWALLOW OF THE ESOPHAGUS.

ance by patients. Glycerin adds to the formula's adhesiveness and sweetness properties. Packaging the preparation in amber syringes allows the patient an easy way to measure the dose, no waist of the viscous gel, and protection from light.

CONCLUSION

Larger studies of adults with promising results are needed to recommend OVB as first-line therapy for EoE. Since there is no commercial medicine for OVB, the responsibility to supply this medicine lies with compounding pharmacists world wide. The long-term safety profile of budesonide in the treatment of EoE should also be established. The dosage of budesonide may need to be adjusted seasonally according to symptom variation. For treatment-refractory patients, a trial of OVB can be attempted before proceeding with esophageal dilatation, hopefully to avoid it. In the interim, OVB is an excellent alternative to swallowed fluticasone propionate for treating patients with EoE, and it may be the first-choice treatment in some patients.[38]

Rx BUDESONIDE ORAL VISCOUS GEL 2 MG/8 ML

For 240 mL (1-month supply)

Budesonide		0.06 g
Xanthan gum		4.8 g
Saccharin sodium		0.18 g
Stevia		0.18 g
Sodium benzoate		0.45 g
Glycerin		23.6 mL
Edetate disodium		0.24 g
Flavor	qs	
Purified water	qs	240 mL

METHOD OF PREPERATION

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Triturate, thoroughly, in a mortar and pestle all the powders except the xanthan gum.
4. Add the glycerin gradually with constant stirring to prepare an homogenous mixture.
5. Pour the mixture into an appropriate graduate.
6. Add the purified water and flavor to 234 mL.
7. Spread the xanthan gum on top of the graduate ***without mixing*** and add purified water to final volume.
8. Pour the mixture from step 7 into an electronic mortar and pestle 500-mL jar.
9. Select the "suspension>2%" program and allow the machine to finish the preparation.
10. Fill four 60-mL amber syringes with the gel and cap it.
11. Package and label

PACKAGING

Package in capped 60-mL amber syringes.

LABELING

Keep out reach of children. Refrain eating and/or drinking 1 hour after using the medicine. For oral use. Use only as directed.

STABILITY

A beyond-use date of up to 30 days can be used for this preparation.

USE

Swallow 8 mL of the gel before bed time. Refrain eating and/or drinking 1 hour after using the medicine.

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