

VERBATIM

'What has tended to happen in vulvar diseases is that tumors and neoplasms have been gynecologically handled, and skin rashes have been dermatologically handled. What we are trying to do is to get rid of the notion of gynecological disease or dermatologic disease to say that it is vulvar disease.'

Dr. Peter J. Lynch on diagnosing vulvar disease, p. 47

Thrombosis, Not Bleeding, Poses Greater Surgery Concern

BY JEFF EVANS
Senior Writer

WASHINGTON — Bleeding during or after superficial cutaneous surgery may provoke more worry from both patients and their clinicians, but thrombotic events actually have greater consequences and are harder to detect, Dr. Clark C. Otley said at the annual meeting of the

American Academy of Dermatology.

Bleeding "almost never causes a permanent disability," but a thrombotic complication that occurs after stopping a patient's blood thinner perioperatively "is much more serious and underappreciated because they're going to go to an ER for their stroke and you may never know about it," said Dr. Otley, who is a professor of dermatology at the Mayo Clinic, Rochester, Minn.

Based on the results of a survey of dermatologic surgeons, Dr. Otley found that 72% of them believed that they could tell if a patient was taking a blood thinner based on how the patient "oozed" intraoperatively.

In another study, however, with 110 patients undergoing cutaneous excisional surgery, Dr. Otley and his colleagues found that blinded dermatologic surgeon

observers were able to determine if patients were taking a blood-thinning agent with a sensitivity of only 14% and a false-positive rate of 16% (Plast. Reconstr. Surg. 2002; 110:98-103).

In another blinded study of

100 patients undergoing coronary artery bypass graft who were taking a placebo or aspirin, cardiac surgeons were correct about the patients' blood thinner status only 51% of the time.

"I would argue that, objectively, you really can't tell whether somebody [is] on a blood thinner," he said.

Of 11 studies that have evaluated patient risk of hemorrhage while on blood thinners, 10 have found no increased risk of severe hemorrhagic complications.

In the one conflicting study of 21 patients, warfarin complications such as persistent bleeding, hematoma, infection, and graft loss occurred (Aesthetic Plast. Surg. 2002;26:483-5).

In a member survey of the American College of Mohs Micrographic Surgery and Cutaneous Oncology, 168 surgeons reported 46 patients who had thrombotic events within a 3-day period before or after stopping a blood thinner, including three deaths.

This yielded a rate of 1 thrombotic event per 12,816 operations, or 1 of every 6,219 operations in which warfarin was discontinued and 1 of every 21,448 when aspirin was not used (J. Am. Acad. Dermatol. 2003;48:233-7).

Another more recent study reported thrombotic complications in 126 patients, including 15 deaths.

"Medically necessary blood thinners should, in general, be continued if there aren't countermending variables that indicate a need to stop them," Dr. Otley commented. ■

NEW **Olux-E™**
(clobetasol propionate)
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References: 1. Data on file [011], Connetics Corporation.
2. Data on file [NDA], Connetics Corporation.

BRIEF SUMMARY

Rx Only

FOR TOPICAL USE ONLY

NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE

INDICATIONS AND USAGE

Olux-E Foam is indicated for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years of age or older (see PRECAUTIONS). Treatment should be limited to 2 consecutive weeks and patients should not use greater than 50 grams per week (see DOSAGE AND ADMINISTRATION).

Patients should be instructed to use Olux-E Foam for the minimum amount of time necessary to achieve the desired results (see PRECAUTIONS).

Use in pediatric patients under 12 years of age is not recommended because of numerically high rates of hypothalamic-pituitary-adrenal (HPA) axis suppression seen in patients under 12 years of age (see PRECAUTIONS: Pediatric Use).

CONTRAINDICATIONS

Olux-E Foam is contraindicated in patients who are hypersensitive to clobetasol propionate or to any ingredient in this preparation.

WARNINGS

The propellant in Olux-E Foam is flammable. Avoid fire, flame or smoking during and immediately following application.

PRECAUTIONS

General: **Olux-E Foam has been shown to suppress the HPA axis.**

Systemic absorption of topical corticosteroids has caused reversible adrenal suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses because of their larger skin surface to body mass ratios (see PRECAUTIONS: Pediatric Use).

Conditions which increase systemic absorption include the application of more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Therefore, patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of adrenal suppression (see laboratory tests below). If adrenal suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids.

In a study evaluating the potential for HPA axis suppression, using the cosyntropin stimulation test, Olux-E Foam demonstrated adrenal suppression after two weeks of twice daily use in patients with atopic dermatitis of at least 30% body surface area (BSA). The proportion of subjects twelve years of age and older demonstrating HPA axis suppression was 16.2% (6 out of 37). In this study HPA axis suppression was defined as serum cortisol level ≤ 18 mcg/dL 30-min post cosyntropin stimulation. The laboratory suppression was transient; in all subjects serum cortisol levels returned to normal when tested 4 weeks post treatment.

Patients with acute illness or injury may have increased morbidity and mortality with intermittent HPA axis suppression. Patients should be instructed to use Olux-E Foam for the minimum amount of time necessary to achieve the desired results (see INDICATIONS AND USAGE).

If irritation develops, Olux-E Foam should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a *failure to heal* rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing. If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Olux-E Foam should be discontinued until the infection has been adequately controlled.

Olux-E Foam should not be used in the treatment of rosacea or perioral dermatitis, and should not be used on the face or the groin, axillae, or other intertriginous areas.

Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Unless directed by the prescriber, it should not be used on the face, or in skin-fold areas, such as the underarms or groin. Avoid contact with the eyes or other mucous membranes. Wash hands after use.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged, wrapped, or otherwise covered so as to be occlusive unless directed by the physician.
4. Patients should report any signs of local or systemic adverse reactions to the physician.
5. Patients should inform their physicians that they are using Olux-E Foam if surgery is contemplated.
6. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.
7. Patients should not use more than 50 grams per week of Olux-E Foam, or an amount greater than 21 capfuls per week (see DOSAGE AND ADMINISTRATION).

Laboratory Tests: The cosyntropin (ACTH₁₋₂₄) stimulation test may be helpful in evaluating patients for HPA axis suppression.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Clobetasol propionate was non-mutagenic in four different test systems: the Ames test, the mouse lymphoma test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* WP2 fluctuation test. In the *in vivo* mouse micronucleus test a positive finding was observed at 24 hours, but not at 48 hours, following oral administration at a dose of 2000 mg/kg.

Studies in the rat following subcutaneous administration of clobetasol propionate at dosage levels up to 0.05 mg/kg per day revealed that the females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

Clobetasol propionate has not been tested for teratogenicity when applied topically; however, it is absorbed percutaneously, and when administered subcutaneously, it was a significant teratogen in both the rabbit and the mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.

Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. These doses are approximately 1.4 and 0.04 times, respectively, the human topical dose of Olux-E Foam based on body surface area comparisons. Abnormalities seen included cleft palate and skeletal abnormalities.

In rabbits, clobetasol propionate was teratogenic at doses of 0.003 and 0.01 mg/kg. These doses are approximately 0.02 and 0.05 times, respectively, the human topical dose of Olux-E Foam based on body surface area comparisons. Abnormalities seen included cleft palate, cranioschisis, and other skeletal abnormalities.

There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. Olux-E Foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Because many drugs are excreted in human milk, caution should be exercised when Olux-E Foam is administered to a nursing woman.

Pediatric Use: Use in pediatric patients under 12 years of age is not recommended.

After two weeks of twice daily treatment with Olux-E Foam, 7 of 15 patients (47%) aged 6 to 11 years of age demonstrated HPA axis suppression. The laboratory suppression was transient; in all subjects serum cortisol levels returned to normal when tested 4 weeks post treatment.

In 92 patients from 12 to 17 years of age, safety was similar to that observed in the adult population. Based on this data, no adjustment of dosage of Olux-E Foam in adolescent patients 12 to 17 years is warranted.

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during and/or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

Geriatric Use: A limited number of patients at or above 65 years of age have been treated with Olux-E Foam (n = 58) in US clinical trials. While the number of patients is too small to permit separate analysis of efficacy and safety, the adverse reactions reported in this population were similar to those reported by younger patients. Based on available data, no adjustment of dosage of Olux-E Foam in geriatric patients is warranted.

ADVERSE REACTIONS

In controlled clinical trials involving 821 subjects exposed to Olux-E Foam and Vehicle Foam, the pooled incidence of local adverse reactions in trials for atopic dermatitis and psoriasis with Olux-E Foam was 1.9% for application site atrophy and 1.6% for application site reaction. Most local adverse events were rated as mild to moderate and they were not affected by age, race or gender. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The following additional local adverse reactions have been reported with topical corticosteroids: folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, irritation, striae, and miliaria. They may occur more frequently with the use of occlusive dressings and higher potency corticosteroids, such as clobetasol propionate. Cushing's syndrome has been reported in infants and adults as a result of prolonged use of topical clobetasol propionate formulations.

OVERDOSAGE

Topically applied Olux-E Foam can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Apply a thin layer of Olux-E Foam to the affected area(s) twice daily, morning and evening. For proper dispensing of foam, shake the can, hold it upside down, and depress the actuator. Dispense a small amount of foam (not more than a dollop the size of a golf ball) and gently massage the medication into the affected areas (excluding the face, groin, and axillae) until the foam is absorbed. Avoid contact with the eyes.

Treatment should be limited to 2 consecutive weeks and patients should not use greater than 50 grams per week or an amount greater than 21 capfuls per week.

Therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Unless directed by a physician, Olux-E Foam should not be used with occlusive dressings.

HOW SUPPLIED

Olux-E (clobetasol propionate) Foam, 0.05% is supplied in 100 g (NDC 63032-101-00) and 50 g (NDC 63032-101-50) aluminum cans.

Store at controlled room temperature 68–77°F (20–25°C).

FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING AND IMMEDIATELY FOLLOWING APPLICATION. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or store at temperatures above 120°F (49°C).

Avoid contact with eyes or other mucous membranes.

Keep out of reach of children.

Manufactured for:

Connetics Corporation
Palo Alto, CA 94304 USA

For additional information, visit www.Olux-E.com.

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