

Continued from previous page

Using benzoyl peroxide in the morning and a retinoid at night provides synergistic effects, but applying anything at the same time as a retinoid is likely to cause skin irritation, he added.

► **Pustules.** If pustules are present, add a twice-daily topical antibiotic (erythromycin or clindamycin), which is safe to combine with benzoyl peroxide but shouldn't be applied at the same time as a tretinoin.

Some vehicles may dry the skin, while others may feel greasy, either of which can work to the advantage of individual

patients. Rarely, clindamycin may cause diarrhea.

Acne on the back or chest often does not respond well to retinoids or benzoyl peroxide, and teenage boys often won't adhere to any topical therapy (including topical antibiotics), so systemic antibiotics may be needed before you can get them to transition to topical therapies, Dr. Lane noted. Tetracyclines are his first choice for systemic therapy, followed by erythromycin.

Systemic side effects can cause GI irritation or yeast vaginitis and may decrease the effectiveness of oral contraceptives.

Some adolescent girls with acne may

benefit from hormonal therapy, but Dr. Lane leaves this approach to the patient's primary care physician.

► **Cysts and scars.** More aggressive treatment is appropriate for acne with cysts and scars, and many of these patients will end up receiving isotretinoin from a dermatologist who can follow them carefully for numerous potential side effects.

For patients aged 18-25 years, isotretinoin therapy will get rid of acne for 10 years or longer in 30%, and 40% will have recurrent acne that responds to topical therapies or antibiotics. The odds are even better for patients aged 12-15 years, Dr. Lane said. ■

Incontinentia Pigmenti Not All That Rare

BY SHERRY BOSCHERT
San Francisco Bureau

STANFORD, CALIF. — A rare genetic disorder that usually is lethal to male babies and can leave abnormalities of the skin, eyes, and other body parts in females, may be more common than originally thought.

Incontinentia pigmenti is caused by a mutation in the IKBKG gene (also known as NEMO), which resides on the X chromosome. A genetic diagnosis can be helpful in females with suspected incontinentia pigmenti because they carry a 50:50 risk of passing the mutation on to their offspring, Dr. Louanne Hudgins said at a pediatric update sponsored by Stanford University.

Typically, blistering on the skin of a neonate or infant progresses to a wart-like rash, swirling macular hyperpigmentation, and linear hypopigmentation.

Other ectodermal-derived tissues are affected, too. Patients with incontinentia pigmenti often have patchy alopecia of the scalp, dystrophic nails, and tooth abnormalities (fewer teeth than normal or abnormal formation, such as a cone-shaped tooth). Associated eye problems are the most significant finding in survivors with incontinentia pigmenti. They often have retinal vascular proliferation, which can lead to retinal detachment.

"The mother may look completely normal or may have linear patches without as much hair" as a typical scalp, but genetic testing can identify incontinentia pigmenti in 80% of cases, said Dr. Hudgins, professor of pediatrics and chief of medical genetics at Stanford.

She and her associates used to test for incontinentia pigmenti only in girls who had all of the associated findings, and rarely made the diagnosis. More recently, however, "we've been doing the testing in kids with a few findings, and are finding the mutation. I think it's more common than we thought it was," she said. "In our genetic disorders of the skin clinic, we see as many as four or five cases per year" of incontinentia pigmenti.

Even with a presumptive diagnosis, it's important to order an ophthalmologic exam. "If this child is at risk for retinal detachment, you need to have that child followed by ophthalmology on a regular basis so you can maintain the best vision possible," she said. Dental and dermatologic evaluations also are warranted. "If they have ongoing skin problems, it's certainly a good idea to have a dermatologist follow them," said Dr. Hudgins, who reported having no conflicts of interest. ■

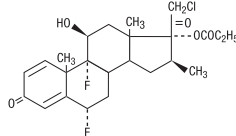
Ultravate® (halobetasol propionate ointment) Ointment, 0.05%

DESCRIPTION

Ultravate® (halobetasol propionate ointment) Ointment, 0.05% contains halobetasol propionate, a synthetic corticosteroid for topical dermatological use. The corticosteroids constitute a class of primarily synthetic steroids used topically as an anti-inflammatory and antipruritic agent.

Ultravate® (halobetasol propionate cream) Cream, 0.05% contains halobetasol propionate, a synthetic corticosteroid for topical dermatological use. The corticosteroids constitute a class of primarily synthetic steroids used topically as an anti-inflammatory and antipruritic agent.

Chemically halobetasol propionate is 21-chloro-6 α , 9-difluoro-11 β , 17-dihydroxy-16 β -methylpregna-1,4-diene-3-20-dione, 17-propionate, C₂₈H₃₇ClF₂O₅. It has the following structural formula:



Halobetasol propionate has the molecular weight of 485. It is a white crystalline powder insoluble in water.

Each gram of Ultravate Ointment contains 0.5 mg/g of halobetasol propionate in a base of aluminum stearate, beeswax, pentarythritol cocoate, petrolatum, propylene glycol, sorbitan sesquioleate, and stearyl citrate.

Halobetasol propionate has the molecular weight of 485. It is a white crystalline powder insoluble in water.

Each gram of Ultravate Cream contains 0.5 mg/g of halobetasol propionate in a cream base of cetyl alcohol, glycerin, isopropyl isostearate, isopropyl palmitate, steareth-21, diazolidinyl urea, methylchlorisothiazolinone, (and) methylisothiazolinone and water.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, halobetasol propionate has anti-inflammatory, antipruritic and vasoconstrictive actions. The mechanism of the anti-inflammatory activity of the topical corticosteroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A₂ inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusive dressings with hydrocortisone for up to 24 hours have not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Human and animal studies indicate that less than 6% of the applied dose of halobetasol propionate enters the circulation within 96 hours following topical administration of the ointment or cream.

Studies performed with Ultravate indicate that it is in the super-high range of potency as compared with other topical corticosteroids.

INDICATIONS AND USAGE

Ultravate Ointment 0.05% is a super-high potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Treatment beyond two consecutive weeks is not recommended, and the total dosage should not exceed 50 g/week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in children under 12 years of age is not recommended.

As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

Ultravate Cream 0.05% is a super-high potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Treatment beyond two consecutive weeks is not recommended, and the total dosage should not exceed 50 g/week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in children under 12 years of age is not recommended.

As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

CONTRAINDICATIONS

Ultravate Ointment and Cream are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

General

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of 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.

Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free-cortisol tests. Patients receiving super potent corticosteroids should not be treated for more than 2 weeks at a time and only small areas should be treated at any one time due to the increased risk of HPA suppression.

Ultravate Ointment produced HPA axis suppression when used in divided doses at 7 grams per day for one week in patients with psoriasis. These effects were reversible upon discontinuation of treatment.

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If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. 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. For information on systemic supplementation, see prescribing information for those products.

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

If irritation develops, Ultravate Ointment or Cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing 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 anti-bacterial agent should be used. If a favorable response does not occur promptly, use of Ultravate Ointment or Cream should be discontinued until the infection has been adequately controlled.

Ultravate Ointment should not be used in the treatment of rosacea or perioral dermatitis, and it should not be used on the face, groin, or in the axillae.

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Information for Patients

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

- 1) The medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- 2) The 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, otherwise covered or wrapped, so as to be occlusive unless directed by the physician.
- 4) Patients should report to their physician any signs of local adverse reactions.

Laboratory Tests

The following tests may be helpful in evaluating patients for HPA axis suppression: ACTH-stimulation test; A.M. plasma cortisol test; Urinary free-cortisol test.

Ultravate® (halobetasol propionate cream) Cream, 0.05%

For Dermatological Use Only. Not for Ophthalmic Use.

Rx only

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

Positive mutagenicity effects were observed in two genotoxicity assays. Halobetasol propionate was positive in a Chinese hamster micronucleus test, and in a mouse lymphoma gene mutation assay *in vitro*.

Studies in the rat following oral administration at dose levels up to 50 µg/kg/day indicated no impairment of fertility or general reproductive performance.

In other genotoxicity testing, halobetasol propionate was not found to be genotoxic in the Ames/Salmonella assay, in the sister chromatid exchange test in somatic cells of the Chinese hamster, in chromosome aberration studies of germinal and somatic cells of rodents, and in a mammalian spot test to determine point mutations.

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 in laboratory animals.

Halobetasol propionate has been shown to be teratogenic in SPF rats and chinchilla-type rabbits when given systemically during gestation at doses of 0.04 to 0.1 mg/kg in rats and 0.01 mg/kg in rabbits. These doses are approximately 13, 33 and 3 times, respectively, the human topical dose of Ultravate Ointment and Cream. Halobetasol propionate was embryotoxic in rabbits but not in rats.

Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats, but not in rabbits.

There are no adequate and well-controlled studies of the teratogenic potential of halobetasol propionate in pregnant women. Ultravate Ointment or Cream 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 human milk. Because many drugs are excreted in human milk, caution should be exercised when Ultravate Ointment or Cream is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Ultravate Ointment or Cream in pediatric patients have not been established and use in pediatric patients under 12 is not recommended. 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 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 papilloedema.

Geriatric Use

Of approximately 850 patients treated with Ultravate® Ointment in clinical studies, 21% were 61 years and over and 6% were 71 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients; and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Of approximately 400 patients treated with Ultravate Cream in clinical studies, 25% were 61 years and over and 6% were 71 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients; and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

In controlled clinical trials, the most frequent adverse events reported for Ultravate Ointment included stinging or burning in 1.6% of the patients. Less frequently reported adverse reactions were pustulation, erythema, skin atrophy, leukoderma, acne, itching, secondary infection, telangiectasia, urticaria, dry skin, miliaria, paresthesia, and rash.

The following additional local adverse reactions are reported infrequently with topical corticosteroids, and they may occur more frequently with high potency corticosteroids, such as Ultravate Ointment. These reactions are listed in an approximate decreasing order of occurrence: folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae and miliaria.

In controlled clinical trials, the most frequent adverse events reported for Ultravate Cream included stinging, burning or itching in 4.4% of the patients. Less frequently reported adverse reactions were dry skin, erythema, skin atrophy, leukoderma, vesicles and rash.

The following additional local adverse reactions are reported infrequently with topical corticosteroids, and they may occur more frequently with high potency corticosteroids, such as Ultravate Cream. These reactions are listed in an approximate decreasing order of occurrence: folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae and miliaria.

OVERDOSAGE

Topically applied Ultravate Ointment can be absorbed in sufficient amounts to produce systemic effects (see **PRECAUTIONS**). Topically applied Ultravate Cream can be absorbed in sufficient amounts to produce systemic effects (see **PRECAUTIONS**).

DOSEAGE AND ADMINISTRATION

Apply a thin layer of Ultravate Ointment to the affected skin once or twice daily, as directed by your physician, and rub in gently and completely.

Ultravate (halobetasol propionate ointment) Ointment is a super-high potency topical corticosteroid; therefore, treatment should be limited to two weeks, and amounts greater than 50 g/wk should not be used. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Ultravate Ointment should not be used with occlusive dressings.

Apply a thin layer of Ultravate Cream to the affected skin once or twice daily, as directed by your physician, and rub in gently and completely.

Ultravate (halobetasol propionate cream) Cream is a super-high potency topical corticosteroid; therefore, treatment should be limited to two weeks, and amounts greater than 50 g/wk should not be used. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Ultravate Cream should not be used with occlusive dressings.

HOW SUPPLIED

Ultravate® (halobetasol propionate ointment) Ointment, 0.05% is supplied in the following tube sizes:

15 g (NDC 10631-102-15)

50 g (NDC 10631-102-50)

Ultravate® (halobetasol propionate cream) Cream, 0.05% is supplied in the following tube sizes:

15 g (NDC 10631-103-15)

50 g (NDC 10631-103-50)

STORAGE

Store between 15°C and 30°C (59°F and 86°F).

U.S. Patent No. 4,619,921

Manufactured by Ranbaxy Laboratories Inc.
Jacksonville, FL 32257 USA

Revised June 2008