

Patients Are Seeking Less-Invasive Fat Removal

BY DOUG BRUNK
San Diego Bureau

LAS VEGAS — Tumescence liposuction may be the current preferred method for removing unwanted fat, but laser lipolysis and other minimally invasive innovations may be the next frontier in body contouring.

"The toned body look is the new fashion statement and the reflection of youth," said Dr. Mark Nestor at the annual meet-

ing of the International Society for Dermatologic Surgery. "Our patients are scared off by liposuction. They are looking for safe and effective minimally invasive treatments, not only for the face, but for removing unwanted fat."

What's more, he said, tumescence liposuction "is certainly technique dependent. Some people are wonderful at it; others are not as good."

One minimally invasive device for body contouring currently on the market is the

Smartlipo (Cynosure Inc.), a 1064-nm and 1320-nm Nd:YAG laser, which requires a small incision to accommodate a 1- to 2-mm cannula and 300- or 600-mcm fiber that will heat and disrupt fat cells.

Cleared by the Food and Drug Administration in November 2006, the device is used in conjunction with tumescence solution and requires local anesthesia. Its photothermal and photomechanical effects cause coagulation of tissue, which results in skin tightening, said Dr. Nestor, a der-

matologist who practices in Aventura, Fla. Hemostasis of blood vessels causes less bleeding and bruising, compared with traditional liposuction.

"You're heating the fat, but you're also dragging it behind the dermis," he explained. "Because of that, you're causing collagen remodeling and tightening."

Smartlipo's 1064-nm wavelengths are broadly absorbed by hemoglobin, and the energy delivered is distributed homogeneously into fat, "so it's very good at coagulation," he said. "You get enhanced hemostasis and you get healing."

The 1320-nm wavelengths are absorbed by water and the energy delivered is localized at the tip of the laser, "so you get a lot of fat disruption."

The combination of both wavelengths "tends to work the best," Dr. Nestor said,

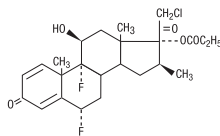
Ultravate® PAC (halobetasol propionate ointment) Ointment, 0.05%

For Dermatological Use Only. Not for Ophthalmic Use.

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.

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, pentaerythritol cocoate, petrolatum, propylene glycol, sorbitan sesquioleate, and stearyl citrate.

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. Studies performed with Ultravate Ointment 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.

CONTRAINDICATIONS

Ultravate Ointment is 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.

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 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 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.

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.

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. 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 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 is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Ultravate Ointment 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 papilledema.

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.

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.

OVERDOSAGE

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

DOSAGE 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.

HOW SUPPLIED

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

50 g (NDC 10631-110-01)

STORAGE

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

RANBAXY

Jacksonville, FL 32257 USA



"Our patients are scared off by liposuction. They are looking for safe and effective" procedures.

DR. NESTOR

by allowing for safer, more even and efficient energy delivery. In his clinical experience, patients usually require a single treatment but may require a touch-up for optimal results.

Another system he discussed is the LipoSonix (Medicis Inc.), which has not been cleared by the FDA but is available for use in Europe. This device uses a transducer to focus high-intensity ultrasound within adipose tissue at depths up to 13 mm without harming the skin or underlying tissues and organs.

The transducer is automatically scanned over a relatively large area of skin for ease of use and to ensure uniform energy deposition, "similar to the way a pattern generator works in a cosmetic laser system," Dr. Nestor said.

The transducer scans out a defined volume of tissue, creating what he called "a controlled injury zone." Chemotactic signals "then draw macrophages to the site of the injury, where they engulf lipid and cellular debris and carry it away through the lymphatics," Dr. Nestor said. This results in a reduction of the volume of the treated tissue.

The cellular debris eventually gets absorbed through the liver, and the process does not appear to cause spikes in triglycerides or cholesterol.

LipoSonix "is very precise and sophisticated, and it's easy to use," Dr. Nestor said. "This is a very exciting technology and becoming a prototype for high-energy cellulite removal using ultrasound."

Dr. Nestor disclosed that he has received equipment discounts from Cynosure, and has also received fees for speaking and consulting on behalf of the company. He also disclosed being a member of Medicis's scientific advisory board. He has also received fees for speaking engagements and research conducted on behalf of the company. ■