New Study: Smoking Doesn't Up Skin Surgery Risk

BY DOUG BRUNK

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LAS VEGAS — The incidence of complications following skin surgery is no different in smokers, compared with nonsmokers, results from a 5-year, single-center study demonstrated.

The finding flies in the face of conventional thinking that smokers "do worse after skin surgery, that they heal slower, and that they get more infections," Dr. Anthony Dixon said at the annual meeting of the International Society for Dermatologic Surgery.

A study from 1992 suggested that smoking compromises wound repair in part because nicotine reduces blood flow to the skin and increases blood platelet aggregation, which raises the risk of microthrombosis (Am. J. Med. 1992;93:22S-4S). The author also said that carbon monoxide decreases oxygen transport and metabolism.

"But unfortunately, until now there hasn't been a long prospective trial to find out whether or not this theory is true," said Dr. Dixon of the dermatology department at Australia's Bond University in Robina, Queensland. "Many dermatologists advise patients to cease smoking for a week prior to having skin surgery. There's no evidence base for that."

He and his associates conducted an observational study of 7,224 lesions excised on 4,197 patients between July 2002 and July 2007. Dr. Dixon performed all procedures; the average patient age was 65 years, and 55% were male.

In all, there were 286 complications (3.96%). The most common complication was infection, followed by bleeding, dehiscence, and skin necrosis.

Dr. Dixon reported that the incidence of total complications was similar between smokers and nonsmokers (3.6% vs. 4.0%, respectively). The incidence of infection was 1.9% in smokers, compared with 2.2% in nonsmokers, a difference that was not statistically significant. Bleeding occurred in 0.2% of smokers and in 0.8% of nonsmokers, a difference that was also not statistically significant.

Logistic regression analysis that adjusted for age, sex, operation type, lesion diagnosis, body site location, and socioeconomic background found that smoking did not predict any complication.

Based on these findings, "we can't justify smoking cessation prior to skin surgery,"

Patients are advised to cease smoking 1 week before skin surgery. 'There's no evidence base for that.'

DR. DIXON

said Dr. Dixon, who emphasized that he and his fellow researchers "are all nonsmokers and we encourage our patients not to smoke for other health reasons. There are certainly things we try to get our patients to remember prior to surgery, but stopping smoking is not one of them."

In an interview, he acknowledged certain limitations of the study, including the fact that some of the patients may have been smokers but did not declare themselves as such. "Also, Australia has one of the lowest rates of smoking in the Western world and this may not reflect circumstances in countries with much higher smoking rates," he said.

In a separate analysis to be published in Dermatologic Surgery, he and his associates studied the same patient population to investigate the incidence of complications after skin surgery in diabetic and nondiabetic patients. Of the 4,197 patients in the study, 196 had known diabetes and 4,001 did not. The average age of diabetic patients was 72 years.

The incidence of total complications between diabetic and nondiabetic patients was the same, at 1.8%, but the incidence of infection was significantly higher in patients with diabetes (4.2%), compared with those without (2.0%). Bleeding occurred in 0.9% of diabetic patients and 0.7% of nondiabetic patients, a difference that was not statistically significant.

Logistic regression analysis that adjusted for age, sex, operation type, lesion diagnosis, body site location, and socioeconomic background found that a known history of diabetes was predictive of infection.

Dr. Dixon, who is also director of research for a group of skin cancer clinics in Australia, had no disclosures to make. ■

PROFESSIONAL BRIEF SUMMARY - See package insert for full prescribing information

CUTIVATE® LOTION, 0.05%
(fluticasone propionate lotion)

Rx Only

FOR TOPICAL USE ONLY.
NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.
INDICATIONS AND USAGE: CUTIVATE® (fluticasone propionate) Lotion is indicated for the relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 1 year of age or older. The safety and efficacy of drug use for longer than 4 weeks in this population have not been established. The safety and efficacy of CUTIVATE® Lotion in pediatric patients below 1 year of age have not been established.
CLINICAL PHARMACOLOGY: Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties.
Although fluticasone propionate has a weak affinity for the progesterone receptor and virtually no affinity for the mineralocorticoid, estrogen or androgen receptors, the clinical relevance as related to safety is unknown. Fluticasone propionate is lipophilic and has strong affinity for the glucocorticoid receptor. The therapeutic potency of glucocorticoids is related to the half-life of the glucocorticoid receptor complex. The half-life of the fluticasone propionate-glucocorticoid receptor complex is approximately 10 hours.
Pharmacokinetics: ***Absorption:*** The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.
Special Population (Pediatric): Plasma fluticasone levels were measured in patients 2 years - 6 years of age in an HPA axis suppression study. A total of 13 (62%) of 21 patients tested had measurable fluticasone at the end of 3 - 4 weeks of treatment. The mean ± SD fluticasone plasma values for patients aged under 3 years was 47.7 ± 31.7 pg/mL and 175.5 ± 243.6 pg/mL. Three patients had fluticasone levels over 300 pg/mL, with one of these having a level of 819.81 pg/mL. No data was obtained for patients < 2 years of age.
CLINICAL STUDIES: CUTIVATE® Lotion applied once daily was superior to vehicle in the treatment of atopic dermatitis in two studies. The two studies enrolled 438 patients with atopic dermatitis aged 3 months and older, of which 169 patients were selected as having clinically significant* signs of erythema, infiltration/papulation and erosion/oozing/crusting at baseline. Table 1 presents the percentage of patients who completely cleared of erythema, infiltration/papulation and erosion/oozing/crusting at Week 4 out of those patients with clinically significant baseline signs.

Table 1: Complete Clearance Rate

	CUTIVATE® Lotion	Vehicle
Study 1	9/45 (20%)	0/37 (0%)
Study 2	7/44 (16%)	1/43 (2%)

*Clinically significant was defined as having moderate or severe involvement for at least two of the three signs (erythema, infiltration/papulation, or erosion/oozing/crusting) in at least 2 body regions. Patients who had moderate to severe disease in a single body region were excluded from the analysis.
CONTRAINDICATIONS: CUTIVATE® Lotion 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 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. Patients applying a potent 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 cosyntropin ($ACTH_{1•24}$) stimulation testing.
Forty-two pediatric patients (4 months to < 6 years of age) with moderate to severe atopic eczema who were treated with CUTIVATE® Lotion for at least 3-4 weeks were assessed for HPA axis suppression and 40 of these subjects applied at least 90% of applications. None of the 40 evaluable patients suppressed, where the sole criterion for HPA axis suppression is a plasma cortisol level of less than or equal to 18 micrograms per deciliter after cosyntropin stimulation. Although HPA axis suppression was observed in 0 of 40 pediatric patients (upper 95% confidence bound is 7.2%), the occurrence of HPA axis suppression in any patient and especially with longer use cannot be ruled out. In other studies with fluticasone propionate topical formulations, adrenal suppression has been observed.
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 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. 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).
Fluticasone propionate Lotion, 0.05% may cause local cutaneous adverse reactions (see ADVERSE REACTIONS).
Fluticasone propionate lotion contains the excipient imidurea which releases traces of formaldehyde as a breakdown product. Formaldehyde may cause allergic sensitization or irritation upon contact with the skin.
If irritation develops, CUTIVATE® Lotion 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 antibacterial agent should be used. If a favorable response does not occur promptly, use of CUTIVATE® Lotion should be discontinued until the infection has been adequately controlled.
CUTIVATE® Lotion should not be used in the presence of preexisting skin atrophy and should not be used where infection is present at the treatment site. CUTIVATE® Lotion should not be used in the treatment of rosacea and perioral dermatitis.
Laboratory Tests: The cosyntropin ($ACTH_{1•24}$) stimulation test may be helpful in evaluating patients for HPA axis suppression.
Carcinogenesis, Mutagenesis, and Impairment of Fertility: No studies were conducted to determine the photoco-carcinogenic potential of CUTIVATE® Lotion.
In an oral (gavage) mouse carcinogenicity study, doses of 0.1, 0.3 and 1 mg/kg/day fluticasone propionate were administered to mice for 18 months. Fluticasone propionate demonstrated no tumorigenic potential at oral doses up to 1 mg/kg/day (less than the MRHD in adults based on body surface area comparisons) in this study.
In a dermal mouse carcinogenicity study, 0.05% fluticasone propionate ointment (40 µl) was topically administered for 1, 3 or 7 days/week for 80 weeks. Fluticasone propionate demonstrated no tumorigenic potential at dermal doses up to 6.7 µg/kg/day (less than the MRHD in adults based on body surface area comparisons) in this study.
Fluticasone propionate revealed no evidence of mutagenic or clastogenic potential based on the results of five in vitro genotoxicity tests (Ames assay, *E. coli* fluctuation test, *S. cerevisiae* gene conversion test, Chinese hamster ovary cell chromosome aberration assay and human lymphocyte chromosome aberration assay) and one in vivo genotoxicity test (mouse micronucleus assay).
No evidence of impairment of fertility or effect on mating performance was observed in a fertility and general reproductive performance study conducted in male and female rats at subcutaneous doses up to 50 µg/kg/day (less than the MRHD in adults based on body surface area comparisons).
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.
Systemic embryofetal development studies were conducted in mice, rats and rabbits. Subcutaneous doses of 15, 45 and 150 µg/kg/day of fluticasone propionate were administered to pregnant female mice from gestation days 6 – 15. A teratogenic effect characteristic of corticosteroids (cleft palate) was noted after administration of 45 and 150 µg/kg/day (less than the MRHD in adults based on body surface area comparisons) in this study. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 15 µg/kg/day (less than the MRHD in adults based on body surface area comparisons).
Subcutaneous doses of 10, 30 and 100 µg/kg/day of fluticasone propionate were administered to pregnant female rats in two embryofetal development studies (one study administered fluticasone propionate from gestation days 6 – 15 and the other study from gestation days 7 – 17). In the presence of maternal toxicity, fetal effects noted at 100 µg/kg/day (less than the MRHD in adults based on body surface area comparisons) included decreased fetal weights, omphalocele, cleft palate, and retarded skeletal ossification. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 10 µg/kg/day (less than the MRHD in adults based on body surface area comparisons).
Subcutaneous doses of 0.08, 0.57 and 4 µg/kg/day of fluticasone propionate were administered to pregnant female rabbits from gestation days 6 – 18. Fetal effects noted at 4 µg/kg/day (less than the MRHD in adults based on body surface area comparisons) included decreased fetal weights, cleft palate and retarded skeletal ossification. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 0.57 µg/kg/day (less than the MRHD in adults based on body surface area comparisons).
Oral doses of 3, 30 and 300 µg/kg/day fluticasone propionate were administered to pregnant female rabbits from gestation days 8 – 20. No fetal or teratogenic effects were noted at oral doses up to 300 µg/kg/day (less than the MRHD in adults based on body surface area comparisons) in this study. However, no fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY).
Fluticasone propionate crossed the placenta following administration of a subcutaneous or an oral dose of 100 µg/kg tritiated fluticasone propionate to pregnant rats.
There are no adequate and well-controlled studies in pregnant women. During clinical trials of CUTIVATE® Lotion, women of childbearing potential were required to use contraception to avoid pregnancy. Therefore, CUTIVATE® Lotion 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 CUTIVATE® Lotion is administered to a nursing woman.
Pediatric Use: CUTIVATE® Lotion may be used in pediatric patients as young as 1 year of age. The safety and efficacy of CUTIVATE® Lotion in pediatric patients below 1 year of age have not been established.
Forty-two pediatric patients (4 months to < 6 years of age) with moderate to severe atopic eczema who were treated with CUTIVATE® Lotion for at least 3-4 weeks were assessed for HPA axis suppression and 40 of these subjects applied at least 90% of applications. None of the 40 evaluable patients suppressed, where the sole criterion for HPA axis suppression is a plasma cortisol level of less than or equal to 18 micrograms per deciliter after cosyntropin stimulation. Although HPA axis suppression was observed in 0 of 40 pediatric patients (upper 95% confidence bound is 7.2%), the occurrence of HPA axis suppression in any patient and especially with longer use cannot be ruled out.
In other studies with fluticasone propionate topical formulations, adrenal suppression has been observed. CUTIVATE® (fluticasone propionate) Cream, 0.05% caused HPA axis suppression in 2 of 43 pediatric patients, ages 2 and 5 years old, who were treated for 4 weeks covering at least 35% of the body surface area. Follow-up testing 12 days after treatment discontinuation, available for 1 of the 2 patients, demonstrated a normally responsive HPA axis.
HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include low plasma cortisol levels to an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.
In addition, local adverse events including cutaneous atrophy, striae, telangiectasia, and pigmentation change have been reported with topical use of corticosteroids in pediatric patients.
Geriatric Use: A limited number of patients above 65 years of age have been treated with CUTIVATE® Lotion in US and non-US clinical trials. Specifically only 8 patients above 65 years of age were treated with CUTIVATE® Lotion in controlled clinical trials. The number of patients is too small to permit separate analyses of efficacy and safety.
ADVERSE REACTIONS: In 2 multicenter vehicle-controlled clinical trials of once-daily application of CUTIVATE Lotion by 196 adult and 242 pediatric patients, the total incidence of adverse reactions considered drug related by investigators was approximately 4%. Events were local cutaneous events, usually mild and self-limiting, and consisted primarily of burning/stinging (2%). All other drug-related events occurred with an incidence of less than 1% and inclusively were contact dermatitis, exacerbation of atopic dermatitis, folliculitis of legs, pruritus, pustules on arm, rash, and skin infection (0 vs. 1%).
Per Table 2, the actual number/(per cent) of drug-related events for the CUTIVATE Lotion group (N=221) versus the vehicle group (N=217), respectively, were burning/stinging 4/(2%) vs. 3/(1%); contact dermatitis 0/(0) vs. 1(<1%); exacerbation of atopic dermatitis 0/(0) vs. 1/(<1%); folliculitis of legs 2/(<1%) vs. 0/(0); pruritus 1/(<1%) vs. 1/(<1%); pustules on arm 1/(<1%) vs. 0/(0); rash 1/(<1%) vs. 2/(<1%); and skin infection 0/(0) vs. 3/(1%).
The incidence of drug-related events on drug compared to vehicle (4% and 5%, respectively) was similar. Events as per Table 3 were local, cutaneous, and inclusively were dry skin, 3 events (7%); stinging at application sites, 2 events (5%); and excoriation, 1 event (2%).
In an open-label study of 44 pediatric patients applying CUTIVATE® Lotion to at least 35% of body surface area twice daily for 3 or 4 weeks, the overall incidence of drug-related adverse events was 14%. Events as per Table 3 were local, cutaneous, and inclusively were dry skin (7%), stinging at application site (5%), and excoriation, 1 event (2%).

Table 4: Adverse Events Occurring in ≥ 1% of Patients from Either Arm from Controlled Clinical Trials (n=438)

Body System	CUTIVATE® Lotion N = 221	Vehicle Lotion N = 217
Any Adverse Event	77 (35%)	82 (38%)
Skin		
Burning and Stinging	4 (2%)	3 (1%)
Pruritus	3 (1%)	5 (2%)
Rash	2 (<1%)	3 (1%)
Skin Infection	0	3 (1%)
Ear, Nose, Throat		
Common Cold	9 (4%)	5 (2%)
Ear Infection	3 (1%)	3 (1%)
Nasal Sinus Infection	2 (<1%)	4 (2%)
Rhinitis	1 (<1%)	3 (1%)
Upper Respiratory Tract Infection	6 (3%)	7 (3%)
Gastrointestinal		
Normal Tooth Eruption	2 (< 1%)	3 (1%)
Diarrhea	3 (1%)	0
Vomiting	3 (1%)	2 (<1%)
Lower Respiratory		
Cough	7 (3%)	6 (3%)
Influenza	5 (2%)	0
Wheeze	0	3 (1%)
Neurology		
Headache	4 (2%)	5 (2%)
Non-Site Specific		
Fever	8 (4%)	8 (4%)
Seasonal Allergy	2 (<1%)	3 (1%)

During the clinical trials, eczema herpeticum occurred in a 33-year-old male patient treated with CUTIVATE® Lotion. Additionally, a 4-month-old patient treated with CUTIVATE® Lotion in the open-label trial had marked elevations of the hepatic enzymes AST and ALT. Reported systemic post-marketing systemic adverse events with CUTIVATE® Cream and CUTIVATE® Ointment have included: immunosuppression/Pneumocystis carinii pneumonia/leukopenia/thrombocytopenia; hyperglycemia/glycosuria; Cushing syndrome; generalized body edema/blurred vision; and acute urticarial reaction (edema, urticaria, pruritus, and throat swelling). A causal role of CUTIVATE® in most cases could not be determined because of the concomitant use of topical corticosteroids, confounding medical conditions, and insufficient clinical information.
The following local adverse reactions have been reported infrequently with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, hypertrichosis, and miliaria. Also, there are reports of the development of pustular psoriasis from chronic plaque psoriasis following reduction or discontinuation of potent topical corticosteroid products.
OVERDOSAGE: Topically applied CUTIVATE® Lotion can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).
DOSAGE AND ADMINISTRATION: CUTIVATE® Lotion may be used in adult and pediatric patients 1 year of age or older. The safety and efficacy of CUTIVATE® Lotion in pediatric patients below 1 year of age have not been established (see PRECAUTIONS: Pediatric Use).
Atopic Dermatitis: Apply a thin film of CUTIVATE® Lotion to the affected skin areas once daily. Rub in gently.
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. The safety and efficacy of drug use for longer than 4 weeks have not been established. CUTIVATE® Lotion should not be used with occlusive dressings or applied in the diaper area unless directed by a physician.
HOW SUPPLIED: CUTIVATE® Lotion is supplied in:
120mL bottle (NDC 0462-0434-04)

Store between 15° and 30°C (59° and 86°F). Do not refrigerate.
Keep the container tightly closed.

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