

Implants and Connective Tissue Disease: No Link?

BY KATE JOHNSON
Montreal Bureau

One of the largest studies to examine the long-term health effects of cosmetic breast implants has found little evidence to advance the debate about whether implants are linked to connective tissue disease.

The retrospective cohort study by the National Cancer Institute was primarily designed to assess cancer occurrence and

overall mortality patterns among implant recipients.

Several published reports on that cohort showed no association between implants and subsequent risk of breast cancer or most other cancers.

However, a two- to threefold increase in the rates of respiratory and brain cancers and a four- to fivefold increase in suicide rates were found among women with implants, compared with control patients. (For references, see the NCI's fact sheet at

www.nci.nih.gov/newscenter/silicone-factsheet.)

Findings linking implants with connective tissue disorders (CTDs), however, are far less conclusive.

"Given the diagnostic complexities of these diseases, excess risks, if they exist, may be beyond detection even in a study of this size," wrote principal author Louise A. Brinton, Ph.D., of the National Cancer Institute, Rockville, Md. (Am. J. Epidemiol. 2004;160:619-27).

"The design of the study did not enable us to derive any firm conclusions, but we were able to rule out very large increased risks," she told this newspaper.

Roughly half the 7,234 breast augmentation recipients (49.7%) had received silicone implants, while about 34% received double lumen implants, about 12% received saline implants, and about 4% received other or unspecified implant types.

The 2,138 control patients were of similar age and had had other types of plastic surgery not involving silicone, such as abdominoplasty or liposuction; blepharoplasty or rhytidectomy; and rhinoplasty, otoplasty, mentoplasty, or genioplasty.

Surgeries in both groups had taken place between 1983 and 1984.

Study subjects were mailed questionnaires about demographic information, subsequent plastic surgeries, current health status, and

lifestyle factors that could affect their health.

They were asked whether they had a physician's diagnosis of a

CTD—including

rheumatoid arthritis (RA),

arthritis of another type, scleroderma, sys-

temic lupus erythematosus (SLE), Sjögren's syndrome,

Raynaud's phenomenon, fibrositis/fibromyalgia, vasculitis, chronic fatigue syndrome, or multiple sclerosis.

The study found that 4.8% of implant patients reported a diagnosis of one of four major CTDs (RA, scleroderma, SLE, or Sjögren's syndrome), compared with 2.9%

of controls, representing a relative risk of 2.0. This risk elevation was statistically significant, but after controlling for various confounding factors, the investigators concluded that the risks were not significant.

One limitation is that risk estimates were based on patient reports of their CTD diagnosis, rather than on a physician's report.

Two rheumatologists blinded to the implant status of the patients reviewed medical records to determine if each participant's history, physical examination, and radiographic and laboratory findings supported each CTD diagnosis as "likely," "unlikely," or "unable to assess."

Although the reviewers were able to access the medical records of only 30%-40% of study participants, they concluded that "most diagnoses were insufficiently supported, either because the records were incomplete or because clinical criteria were not met."

When relative risks were recalculated using only the "likely" diagnoses, the revised estimated relative risk for RA, scleroderma, and Sjögren's syndrome combined was still 2.0, and for RA alone it was 1.3, both of which were not statistically significant, given the smaller sample size.

Continued on following page

Luxiq® (betamethasone valerate) Foam, 0.12%

BRIEF SUMMARY For Dermatologic Use Only Not for Ophthalmic Use

INDICATIONS AND USAGE Luxiq is a medium potency topical corticosteroid indicated for the relief of the inflammatory and irritative manifestations of corticosteroid-responsive dermatoses of the scalp. **CONTRAINDICATIONS** Luxiq is contraindicated in patients who are hypersensitive to betamethasone valerate, to other corticosteroids, or to any ingredient in this preparation. **PRECAUTIONS** **General:** Systemic absorption of topical corticosteroids has caused reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of HPA axis suppression, hypokalemia, and glucocorticoid excess can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment. Conditions which augment systemic absorption include the application of the 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 HPA axis suppression. 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**.) If irritation develops, Luxiq 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. In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, use of Luxiq should be discontinued until the infection has been adequately controlled. **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. Avoid contact with the eyes. 2. This medication should not be used for any disorder other than that for which it was prescribed. 3. The treated scalp area should not be bandaged or 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, such as with other topical corticosteroids, therapy should be discontinued until relief is achieved. If no improvement is seen within 2 weeks, contact the physician. **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 the effect on fertility of betamethasone valerate. Betamethasone was genotoxic in the *in vitro* human peripheral blood lymphocyte chromosome aberration assay with metabolic activation and in the *in vivo* mouse bone marrow micronucleus assay. **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. There are no adequate and well-controlled studies in pregnant women. Therefore, Luxiq should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time. **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 Luxiq is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. 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. Hypothalamic-pituitary-adrenal (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. 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. **ADVERSE REACTIONS** The most frequent adverse event was burning/itching/stinging at the application site; the incidence and severity of this event were as follows:

Product	Incidence and severity of burning/itching/stinging			
	Total incidence	Mild	Moderate	Severe
Luxiq Foam n=63	34 (54%)	28 (44%)	5 (8%)	1 (2%)
Betamethasone valerate lotion n=63	33 (52%)	26 (41%)	6 (10%)	1 (2%)
Placebo Foam n=32	24 (75%)	13 (41%)	7 (22%)	4 (12%)
Placebo Lotion n=30	20 (67%)	12 (40%)	5 (17%)	3 (10%)

Other adverse events which were considered to be possibly, probably, or definitely related to Luxiq occurred in 1 patient each; these were parasthesia, pruritus, acne, alopecia, and conjunctivitis. The following additional local adverse reactions have been reported with topical corticosteroids, and they may occur rarely with Luxiq: acne, folliculitis, delayed wound healing, and intracranial hypertension. An approximately decreasing order of occurrence: irritation; dryness; folliculitis; acneiform eruptions; hypopigmentation; perioral dermatitis; allergic contact dermatitis; secondary infection; skin atrophy; striae; and miliaria. Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hypercorticism, and hypokalemia in some patients. **OVERDOSAGE:** Topically applied Luxiq can be absorbed in sufficient amounts to produce systemic effects. (See **PRECAUTIONS**.) **DOSE AND ADMINISTRATION Note:** For proper dispensing of foam, can must be inverted. For application to the scalp invert can and dispense a small amount of Luxiq onto a saucer or other cool surface. Do not dispense directly onto hands as foam will begin to melt immediately upon contact with warm skin. Pick up small amounts of foam with fingers and gently massage into affected area until foam disappears. Repeat until entire affected scalp area is treated. Apply twice daily, once in the morning and once at night. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary. Luxiq should not be used with occlusive dressings unless directed by a physician. **HOW SUPPLIED** Luxiq is supplied in 100 gram (NDC 63032-021-00) and 50 gram (NDC 63032-021-50) aluminum cans. Store at controlled room temperature 68-77°F (20-25°C). **WARNING FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING AND IMMEDIATELY FOLLOWING APPLICATION.** Keep out of reach of children. Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 120°F (49°C).

Manufactured for: Connetics Corporation, Palo Alto, CA 94303 USA

For additional information: 1-877-821-5337 or visit www.luxiq.com

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LUX® Foam, 0.05% (clobetasol propionate)

BRIEF SUMMARY For Dermatologic Use Only Not for Ophthalmic Use

INDICATIONS AND USAGE LUX Foam is a super-potent topical corticosteroid indicated for short-term topical treatment of the inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp, and for short-term topical treatment of mild to moderate plaque-type psoriasis of non-scalp regions excluding the face and intertriginous areas. Treatment beyond 2 consecutive weeks is not recommended and the total dosage should not exceed 50 g per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. In a controlled clinical trial, no statistically significant differences were seen between adrenergic following 14 days of LUX Foam therapy. (See **ADVERSE REACTIONS**.) Use in children under 12 years of age is not recommended. **CONTRAINDICATIONS** LUX Foam is contraindicated in patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation. **PRECAUTIONS** **General:** Clobetasol propionate is a super-potent topical corticosteroid that has been shown to suppress the adrenals at 7.0 g of LUX Foam per day. Lesser amounts of LUX Foam were not studied. Systemic absorption of topical corticosteroids has caused reversible adrenal suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hypokalemia, and glucocorticoid excess can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment. Conditions which augment systemic absorption include the application of more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of adrenal suppression. 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. 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, LUX 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. In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, use of LUX Foam should be discontinued until the infection has been adequately controlled. **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 and should not be used longer than the prescribed time period. It is for external use only. Avoid contact with the eyes. 2. This medication should not be used for any disorder other than that for which it was prescribed. 3. The treated area should not be bandaged or 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 adrenal 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 clobetasol propionate. Clobetasol propionate was non-mutagenic in three different test systems: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay and the *E. coli* WP2 fluctuation test. Studies in the rat following subcutaneous administration of clobetasol propionate at dosage levels up to 0.05 mg/kg per day for 18 months exhibited an increase in the number of resorptions and pre-embryonic loss in the first 10 days of living litters 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 in laboratory animals. Clobetasol propionate has not been tested for teratogenicity by the topical route; 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 those levels tested down to 0.05 mg/kg. These doses are approximately 1.4 and 0.04 times, respectively, the human topical dose of LUX based on body surface area comparisons. Abnormalities 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 LUX 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. LUX Foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Use of LUX Foam should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.** **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 LUX Foam is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness of LUX Foam in pediatric patients have not been established; therefore, use in children under 12 years of age 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. Pediatric patients are therefore 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. Adrenal 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. **General Use:** Clinical studies of LUX Foam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **ADVERSE REACTIONS** In a controlled pharmacokinetic study, 5 of 13 subjects experienced reversible suppression of the adrenals at anytime during the 14 days of LUX Foam therapy to at least 20% of the body surface area. Of the 13 subjects studied, 1 of 9 with psoriasis were suppressed after 14 days and all 4 of the subjects with atopic dermatitis had abnormal cortisol levels indicative of adrenal suppression of some time after starting therapy with LUX Foam. LUX Foam is not indicated for non-scalp atopic dermatitis, as the safety and efficacy of LUX Foam in non-scalp atopic dermatitis has not been established. Use in children under 12 years of age is not recommended. Systemic absorption of topical corticosteroids has produced reversible adrenal suppression, manifestations of Cushing's syndrome, hypercorticism, and hypokalemia in some patients. (See **PRECAUTIONS**.) In a controlled clinical trial (1984 subjects) with LUX Foam, in subjects with psoriasis of the scalp, there were no localized adverse reactions reported in the LUX Foam treated subjects. In two controlled clinical trials (360 subjects) with LUX Foam in subjects with psoriasis of non-scalp regions, localized adverse events that occurred in the LUX Foam treated subjects included application site burning/itching/dryness (10%), application site dryness (1%), and other (10%). In the LUX Foam treated subjects with other topical corticosteroid formulations, the most frequently reported local adverse reactions have included burning, stinging, irritation, pruritus, erythema, folliculitis, cracking and fissuring of the skin, numbness of the fingers, skin dryness, and testicular atrophy (10%). The following additional local adverse reactions have been reported with other topical corticosteroids, but they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids such as LUX Foam. These reactions are listed in an approximate decreasing order of occurrence: dryness; hypopigmentation; acneiform eruptions; hypopigmentation; perioral dermatitis; allergic contact dermatitis; secondary infection; skin atrophy; striae; and miliaria. Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hypercorticism, and hypokalemia in some patients. **OVERDOSAGE:** Topically applied LUX Foam can be absorbed in sufficient amounts to produce systemic effects. (See **PRECAUTIONS**.) **DOSE AND ADMINISTRATION Note:** For proper dispensing of foam, hold the can upside down and depress the actuator. LUX Foam should be applied to the affected area twice daily, once in the morning and once at night. Invert the can and dispense a small amount of LUX Foam (up to a maximum of a golf-ball-size dollop or one and a half capfuls) into the cap of the can, onto a saucer or other cool surface, or to the lesion, taking care to avoid contact with the eyes. Dispensing directly onto hands is not recommended (unless the hands are the affected area), as the foam will begin to melt immediately upon contact with warm skin. When applying LUX Foam to a hair-bearing area, move the hair away from the affected area so that the foam can be applied to each affected area. Pick up small amounts with fingers and gently massage into affected area until the foam disappears. Repeat until entire affected area is treated. Apply the smallest amount possible that sufficiently covers the affected area(s). No more than one and a half capfuls of foam should be applied to each application. Do not apply foam to face or intertriginous areas. Use of LUX Foam on a super-high-potency area, such as the face, should be limited to 2 consecutive weeks and amounts greater than 50 g per week should not be used. Use in pediatric patients under 12 years of age is not recommended. Unless directed by a physician, LUX Foam should not be used with occlusive dressings. **HOW SUPPLIED** LUX Foam is supplied in 100 gram (NDC 63032-021-00) and 50 gram (NDC 63032-021-50) aluminum cans. Store at controlled room temperature 68-77°F (20-25°C). **WARNING FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING AND IMMEDIATELY FOLLOWING APPLICATION.** Keep out of reach of children. Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 120°F (49°C).

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"We were relying on self-reports of these conditions that even rheumatologists have a hard time diagnosing, and ... many of these conditions are extremely rare. So we ended up with very small numbers, and it was really not possible to either confirm or refute whether there is an association," said Dr. Brinton.

The investigators note that their observations of selection and reporting biases underscore the complexities of evaluating the relationship of implants and CTDs.

"Thus, future studies designed to resolve the question of a possible association

between breast implants and rheumatoid arthritis or other CTDs would need to be very large and include well-validated and documented cases and unbiased assessments of exposure," they said.

"There were a lot of methodological problems with this study, and the authors did a good job of outlining them," commented Diana Zuckerman, Ph.D., president of the National Center for Policy Research for Women & Families, a Washington-based nonprofit group. "This is the latest of several red flags warning women that the risks of breast implants have not been adequately studied," she said in an interview. ■

Fingerpricking Tied to Necrosis

Fingerprick sites should be inspected regularly for skin necrosis in diabetic patients who have peripheral vascular disease, said Olivier Giannini, M.D., and Michael Mayr, M.D., of the University Hospitals of Basel (Switzerland).

The physicians reported the case of a 59-year-old diabetic man who was hospitalized for amputation of the lower right leg because of severe arterial occlusive disease. While recovering from the surgery, the patient took fingerprick blood samples to monitor his blood sug-

ar. Within a few days, multiple small, well-circumscribed areas of skin necrosis around the fingerprick sites quickly progressed to full necrosis of the distal phalange, despite treatment with iloprost infusions, the investigators said (Lancet 2004;364:980).

Regular inspection of these sites may prevent such deterioration. If it does develop, capillary blood samples could be drawn from the thenar eminence, rather than the fingertips, they added.

—Mary Ann Moon

Herb Takers' Risk of Bleeding Is Uncertain

NEW YORK — Herb-using individuals who are at risk of bleeding should be advised to use caution, despite uncertainty about the actual degree of risk that may be involved, Adrian Fugh-Berman, M.D., said at a meeting on botanical medicine sponsored by Columbia University and the University of Arizona.

"Actual, theoretical, and fanciful herbal adverse events and interactions infest the medical literature," said Dr. Fugh-Berman of Georgetown University, Washington.

Given the level of uncertainty, it is prudent to check international normalized ratio (INR) of anticoagulated patients 7-14 days after starting any herbal, dietary supplement, or weight-loss regimen. By the same token, all herbs and supplements should be discontinued 2 weeks before surgery, she said.

Many herbs contain coumarins, most of which are benign. Some inhibit platelet aggregation in vitro, but few have been associated with actual bleeding episodes.

In one study, a 10-g dose of ginger decreased platelet aggregation 4 hours later, and a case was reported in which a 76-year-old woman developed nosebleeds and showed changes in INR after eating dried ginger and drinking tea made from it for several weeks. But three clinical studies found that up to 4 g of fresh ginger daily had no effect on bleeding.

Garlic oil has been shown to decrease platelet aggregation for up to 6 hours, and two cases of excessive postsurgical bleeding have been reported in which patients had consumed garlic-laden meals the night before.

"Tell patients not to consume meals heavy in garlic within a few days of surgery," Dr. Fugh-Berman advised.

Ginkgolide B, a component of *Ginkgo biloba*, is a known platelet aggregation factor antagonist, and the herb, alone or with analgesics, has been associated with intracranial bleeding events.

Clinical studies, however, found that one standardized ginkgo preparation (EGb761) had no effect on hemostasis, coagulation, or fibrinolysis in healthy men, and another (Bio-Biloba) did not change INR in patients who had been stabilized on warfarin.

—Carl Sherman



before

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after



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