

Tumescent Anesthesia Not Just for Liposuction

BY BETSY BATES

Los Angeles Bureau

SAN DIEGO — Physicians should think outside the liposuction box when it comes to using tumescent anesthesia in dermatologic surgery practices, Dr. Jeffrey A. Klein said at the annual meeting of the California Society of Dermatology and Dermatologic Surgery.

Excisions, Mohs surgery, lipoma removal, breast reduction, and intravascular

vein ablation all lend themselves well to the use of tumescent anesthesia, according to the discoverer of the technique.

Besides providing long-lasting and profound local anesthesia, bactericidal protection, and elevation of tissues for delicate procedures, the tumescent technique offers "exquisite hemostasis," said Dr. Klein, a dermatologic surgeon in San Juan Capistrano, Calif., who is credited with revolutionizing the safety of liposuction anesthesia by pioneering the use of dilute

concentrations of lidocaine and epinephrine in saline with sodium bicarbonate.

"I'm really impressed at how little blood loss there is," he said.

In laser and radiofrequency procedures, tumescent liposuction acts as a heat sink. For excisions or Mohs surgery on the neck or face, it can lift lesions safely away from superficial nerve branches, he pointed out.

It can be used in conjunction with dissection with blunt liposuction cannulas to separate fibrous, multilobular lipomas

from surrounding tissue so they can be easily excised. In Germany, it is being used to perform sentinel lymph node biopsies on melanoma patients.

Dr. Klein outlined examples of numerous dermatologic procedures he has performed with tumescent liposuction, from the extraction of excess glandular tissue through the nipple of a patient with male gynecomastia to the excision of a large melanoma down to fascia.

Mohs surgery of a large, recurrent basal cell carcinoma can be accomplished as "essentially a painless procedure" during which the patient remains awake, he said.

The lack of infections seen following liposuction—just 1 in more than 6,000 procedures performed by Dr. Klein—suggests that "there must be a very substantial bacteriocidal effect" of tumescent solution, he said.

Obviously, much smaller volumes of tumescent fluid are utilized in these other procedures than are needed in large liposuction cases, but the ratio of the ingredients in the formula remains the same. (See box.)

Once the area is infiltrated, "you need to allow time for detumescence to occur," said Dr. Klein.

In large abdominal liposuction cases, this process ideally should occur over the course of an hour. For smaller dermatologic surgery cases, the procedure should be delayed for at least 15-30 minutes for fluids to drain away and the architecture of the lesion to be restored.

Recovery following cases in which tumescent anesthesia is used is remarkably quick, with patients most likely able to return to work within a day, even following large excisions.

Dr. Klein noted that tumescent anesthesia has been widely adopted by other specialties and is commonly used in stem cell harvesting and vein, breast, burn, craniofacial, and rectal surgery.



Rx Only

Brief summary.

Please see full prescribing information for complete product information.

Carac Cream 0.5%

(fluorouracil cream)

FOR TOPICAL DERMATOLOGICAL USE ONLY (NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE)

INDICATIONS AND USAGE

Carac is indicated for the topical treatment of multiple actinic or solar keratoses of the face and anterior scalp.

CONTRAINDICATIONS

Fluorouracil may cause fetal harm when administered to a pregnant woman. Fluorouracil is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

No adequate and well-controlled studies have been conducted in pregnant women with either topical or parenteral forms of fluorouracil. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when fluorouracil was applied to mucous membrane areas. Multiple birth defects have been reported in the fetus of a patient treated with intravenous fluorouracil.

Animal reproduction studies have not been conducted with Carac. Fluorouracil, the active ingredient, has been shown to be teratogenic in mice, rats, and hamsters when administered parenterally at doses greater than or equal to 10, 15, and 33 mg/kg/day, respectively, [4X, 11X, and 20X, respectively, the Maximum Recommended Human Dose (MRHD) based on body surface area (BSA)]. Fluorouracil was administered during the period of organogenesis for each species. Embryolethal effects occurred in monkeys at parenteral doses greater than 40 mg/kg/day (65X the MRHD based on BSA) administered during the period of organogenesis.

Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD). DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities.

Carac is contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS

The potential for a delayed hypersensitivity reaction to fluorouracil exists. Patch testing to prove hypersensitivity may be inconclusive.

Patients should discontinue therapy with Carac if symptoms of DPD enzyme deficiency develop.

Rarely, unexpected, systemic toxicity (e.g. stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parenteral administration of fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase "DPD" activity. One case of life threatening systemic toxicity has been reported with the topical use of 5% fluorouracil in a patient with a complete absence of DPD enzyme activity. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel. Although this case was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil.

Applications to mucous membranes should be avoided due to the possibility of local inflammation and ulceration.

PRECAUTIONS

General: There is a possibility of increased absorption through ulcerated or inflamed skin.

Information for the Patient: Patients using Carac should receive the following information and instructions:

- This medication is to be used as directed.
- This medication should not be used for any disorder other than that for which it was prescribed.
- It is for external use only.
- Avoid contact with the eyes, eyelids, nostrils, and mouth.
- Cleanse affected area and wait 10 minutes before applying Carac.
- Wash hands immediately after applying Carac.
- Avoid prolonged exposure to sunlight or other forms of ultraviolet irradiation during treatment, as the intensity of the reaction may be increased.
- Most patients using Carac get skin reactions where the medicine is used. These reactions include redness, dryness, burning, pain, erosion (loss of the upper layer of skin), and swelling. Irritation at the application site may persist for two or more weeks after therapy is discontinued. Treated areas may be unsightly during and after therapy.
- If you develop abdominal pain, bloody diarrhea, vomiting, fever, or chills while on Carac therapy, stop the medication and contact your physician and/or pharmacist.
- Report any side effects to the physician and/or pharmacist.

Laboratory Tests: To rule out the presence of a frank neoplasm, a biopsy may be considered for those areas failing to respond to treatment or recurring after treatment.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil. Studies with the active ingredient of Carac, fluorouracil, have shown positive effects in *in vitro* and *in vivo* tests for mutagenicity and on impairment of fertility in *in vivo* animal studies.

Fluorouracil produced morphological transformation of cells in *in vitro* cell transformation assays. Morphological transformation was also produced in an *in vitro* assay by a metabolite of fluorouracil, and the transformed cells produced malignant tumors when injected into immunosuppressed syngeneic mice.

Fluorouracil has been shown to exert mutagenic activity in yeast cells, *Bacillus subtilis*, and *Drosophila* assays. In addition, fluorouracil has produced chromosome damage at concentrations of 1.0 and 2.0 mcg/mL in an *in vitro* hamster fibroblast assay, was positive in a microwell mouse lymphoma assay, and was positive in *in vivo* micronucleus assays in rats and mice following intraperitoneal administration. Some patients receiving cumulative doses of 0.24 to 1.0 g of fluorouracil parenterally have shown an increase in numerical and structural chromosome aberrations in peripheral blood lymphocytes.

Fluorouracil has been shown to impair fertility after parenteral administration in rats. Fluorouracil administered at intraperitoneal doses of 125 and 250 mg/kg has been shown to induce chromosomal aberrations and changes in chromosome organization of spermatogonia in rats. In mice, single-dose intravenous and intraperitoneal injections of fluorouracil have been reported to kill differentiated spermatogonia and spermatocytes at a dose of 500 mg/kg and produce abnormalities in spermatids at 50 mg/kg.

Pediatric Use: Actinic keratosis is not a condition seen within the pediatric population, except in association with rare genetic diseases. Carac should not be used in children. The safety and effectiveness of Carac have not been established in patients less than 18 years old.

Geriatric Use: No significant differences in safety and efficacy measures were demonstrated in patients age 65 and older compared to all other patients.

Pregnancy: Teratogenic Effects: Pregnancy Category X: See CONTRAINDICATIONS.

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Nursing Women: It is not known whether fluorouracil is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fluorouracil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

The following were adverse events considered to be drug-related and occurring with a frequency of $\geq 1\%$ with Carac: application site reaction (94.6%) and eye irritation (5.4%). The signs and symptoms of facial irritation (application site reaction) are presented below.

Summary of Facial Irritation Signs and Symptoms - Pooled Phase 3 Studies

Clinical Sign or Symptom	Active One Week	Active Two Week	Active Four Week	ALL Active Treatments	Vehicle Treatments
	N=85	N=87	N=85	N=257	N=127
	n (%)	n (%)	n (%)	n (%)	n (%)
Erythema	76 (89.4)	82 (94.3)	82 (96.5)	240 (93.4)	76 (59.8)
Dryness	59 (69.4)	76 (87.4)	79 (92.9)	214 (83.3)	60 (47.2)
Burning	51 (60.0)	70 (80.5)	71 (83.5)	192 (74.7)	28 (22.0)
Erosion	21 (24.7)	38 (43.7)	54 (63.5)	113 (44.0)	17 (13.4)
Pain	26 (30.6)	34 (39.1)	52 (61.2)	112 (43.6)	7 (5.5)
Edema	12 (14.1)	28 (32.2)	51 (60.0)	91 (35.4)	6 (4.7)

During clinical trials, irritation generally began on day 4 and persisted for the remainder of treatment. Severity of facial irritation at the last treatment visit was slightly below baseline for the vehicle group, mild to moderate for the 1 week active treatment group, and moderate for the 2 and 4 week active treatment groups. Mean severity declined rapidly for each active group after completion of treatment and was below baseline for each group at the week 2 post-treatment follow-up visit.

Thirty-one patients (12% of those treated with Carac in the Phase 3 clinical studies) discontinued study treatment early due to facial irritation. Except for three patients, discontinuation of treatment occurred on or after day 11 of treatment.

Eye irritation adverse events, described as mild to moderate in intensity, were characterized as burning, watering, sensitivity, stinging and itching. These adverse events occurred across all treatment arms in one of the two Phase 3 studies.

Summary of All Adverse Events Reported in $\geq 1\%$ of Patients in the Combined Active Treatment and Vehicle Groups - Pooled Phase 3 Studies

Adverse Event	9721 and 9722 Combined				
	Active One Week	Active Two Week	Active Four Week	ALL Active Treatments	Vehicle Treatments
	N=85	N=87	N=85	N=257	N=127
	n (%)	n (%)	n (%)	n (%)	n (%)
Body as a whole					
Headache	7 (8.2)	6 (6.9)	12 (14.1)	25 (9.7)	15 (11.8)
Common Cold	3 (3.5)	2 (2.3)	3 (3.5)	8 (3.1)	3 (2.4)
Allergy	4 (4.7)	0	2 (2.4)	6 (2.3)	3 (2.4)
Infection Upper Respiratory	0	2 (2.3)	1 (1.2)	3 (1.2)	2 (1.6)
Musculoskeletal					
Muscle Soreness	0	0	0	0	2 (1.6)
Respiratory					
Sinusitis	5 (5.9)	0	1 (1.2)	6 (2.3)	6 (4.7)
Skin & Appendages					
Application Site Reaction	78 (91.8)	83 (95.4)	82 (96.5)	243 (94.6)	85 (66.9)
Irritation Skin	78 (91.8)	83 (95.4)	82 (96.5)	243 (94.6)	83 (65.4)
Special Senses					
Eye Irritation	1 (1.2)	0	2 (2.4)	3 (1.2)	0
Senses	6 (7.1)	4 (4.6)	6 (7.1)	16 (6.2)	6 (4.7)
Eye Irritation	5 (5.9)	3 (3.4)	6 (7.1)	14 (5.4)	3 (2.4)

Adverse Experiences Reported by Body System:

In the Phase 3 studies, no serious adverse event was considered related to study drug. A total of five patients, three in the active treatment groups and two in the vehicle group, experienced at least one serious adverse event. Three patients died as a result of adverse event(s) considered unrelated to study drug (stomach cancer, myocardial infarction, and cardiac failure).

Post-treatment clinical laboratory tests other than pregnancy tests were not performed during the Phase 3 clinical studies. Clinical laboratory tests were performed during conduct of a Phase 2 study of 104 patients and 21 patients in a Phase 1 study. No abnormal serum chemistry, hematology, or urinalysis results in these studies were considered clinically significant.

DOSAGE AND ADMINISTRATION

Carac cream should be applied once a day to the skin where actinic keratosis lesions appear, using enough to cover the entire area with a thin film. Carac cream should not be applied near the eyes, nostrils, or mouth. Carac cream should be applied ten minutes after thoroughly washing, rinsing, and drying the entire area. Carac cream may be applied using the fingertips. Immediately after application, the hands should be thoroughly washed. Carac should be applied up to 4 weeks as tolerated. Continued treatment up to 4 weeks results in greater lesion reduction. Local irritation is not markedly increased by extending treatment from 2 to 4 weeks, and is generally resolved within 2 weeks of cessation of treatment.

OVERDOSE

Ordinarily, topical overdosage will not cause acute problems. If Carac is accidentally ingested, induce emesis and gastric lavage. Administer symptomatic and supportive care as needed. If contact is made with the eye, flush with copious amounts of water.

HOW SUPPLIED

Cream - 30 gram tube NDC 0066-7150-30

Store at Controlled Room Temperature 20 to 25°C (68 to 77°F) [see USP].

Prescribing Information as of December 2003(a).

Keep out of the reach of children.

Rx Only

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Manufactured by:

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Horsham, PA 19044 USA

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Small-Volume Tumescent Recipe

A 100-mL formulation of tumescent local anesthesia (TLA) consists of approximately 0.25% lidocaine and epinephrine 1:400,000. To prepare this formulation, use:

- ▶ 100-mL bag of sodium chloride 0.9%.
- ▶ 300 mg lidocaine and 0.3 mg epinephrine (30 mL of 1% lidocaine with epinephrine 1:100,000).
- ▶ 3 mEq sodium bicarbonate (3 mL of 8.4% sodium bicarbonate).

On the day of surgery, a nurse prepares and labels the bag of TLA immediately after the patient arrives. For safety reasons, TLA should never be mixed 1 or more days before the day of surgery. Every bag of TLA should be well labeled at the time of its preparation.

Source: Dr. Klein