Calciphylaxis Is 'Akin to a Myocardial Infarction'

BY BETSY BATES Los Angeles Bureau

LAS VEGAS — An evolving understanding of the pathogenesis of calciphylaxis in hospitalized patients may lead to antithrombotic treatment strategies focused on vascular occlusion as well as dialysis- and parathyroid-specific interventions.

"Calciphylaxis is a therapeutic conun-

drum and also a nightmare," said Dr. Mark D.P. Davis, professor of dermatology at the Mayo Clinic, Rochester, Minn.

We urgently need better treatment and preventive strategies," he stressed at a dermatology seminar sponsored by Skin Disease Education Foundation.

The condition's name, calciphylaxis, reflects an early belief that the introduction of a certain agent (likely during dialysis) induced calcification of vessels, a notion now disputed since the disease occurs in patients without renal insufficiency.

A more accurate name, first proposed by Dr. Patrick Dahl and associates, is the vascular calcification-cutaneous necrosis syndrome (J. Am. Acad. Dermatol. 1995;33:53-8), which better characterizes calciphylaxis as "akin to a myocardial infarction," Dr. Davis said.

Calcifications in the walls of small arterioles supplying the skin are the first

New Zealand white rabbits were treated with Retin-A Micro (tretinoin gel) microsphere, 0.1%, at doses of 0.2, 0.5, and 1.0 mg/kg/day, administered topically for 24 hours a day while wearing Elizabethan collars to prevent ingestion of the drug. There appeared to be increased incidences of certain alterations, including domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species, at 0.5 and 1.0 mg/kg/day. Similar malformations were not observed at 0.2 mg/kg/day, 3 times the maximum human systemic dose of tretinoin after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area, In a repeat study of the highest topical dose (1.0 mg/kg/day) in pregnant rabbits, these effects were not seen, but a few alterations that may be associated with tretinoin exposure were seen. Other pregnant rabbits exposed topically for six hours to 0.5 or 0.1 mg/kg/day tretinoin while restrained in stocks to prevent ingestion, din ot show any teratogenic effects at doses up to 17 times (1.0 mg/kg/day) the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, adjusted for total body surface area, but fetal resorptions were increased at 0.5 mg/kg. In addition, topical tretinoin in on Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area, the testine dimension of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area, but fetal resorptions were increased at 0.5 mg/kg. In addition, topical tretinoin in non Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area, the septical doses, however, delayed ossification of several bones occurred in rabbits. In rats, a dose-dependent increase of supernumerary ribs was observed. Oral tretinoin mas theratogenic in tasts, mice, rabbits, hamsters, and subhuman primates. Tretinoin was teratogenic in Wistar rats when given orally or topically in doses greater than 1 mg/

Teprited. Similar results have also been reported in pigtan macaques. <u>Topical</u> tretinoin in animal teratogenicity tests has generated equivocal results. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (8 times the maximum human systemic dose normalized for total body surface area). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was topically applied. Supernumerary ribs have been a consistent finding in rats when dams were treated topically or orally with retinoids.

a consistent finding in rats when dams were treated topically or orally with retinoids. There are no adequate and well-controlled studies in pregnant women. Retin-A flicos should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty human cases of temporally associated congenital mafformations have been reported during two decades of clinical use of Retin-A. Although no definite pattern of teratogenicity and no causal association has been established from these cases, five of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

significance of these spontaneous reports in terms of risk to the fetus is not known. **Non-Teratogenic Effects:** Topical tretinoin has been shown to be feotoxic in rabbits when administered 0.5 mg/kg/day (8 times the maximum human systemic dose applied topically and normalized for total body surface area), resulting in fetal resorptions and variations in ossifica-tion. Oral tretinoin has been shown to be feotoxic, resulting in skeletal variations and increased intrauterine death in rats when administered 2.5 mg/kg/day (21 times the maximum human systemic dose applied topically and normalized for total body surface area). There are, however no adequate and well-controlled studies in pregnant women. Animal Toxicity Studies: In male mice treated topically miter days of the surface days of

There are, however no adequate and well-controlled studies in pregnant women. Animal Toxicity Studies: In male mice treated topically with Retin-A Micro (tretinoin gel) microsphere 0.1%, at 0.5, 2.0, or 5.0 mg/kg/day tretinoin (2, 8, or 21 times the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area) for 90 days, a reduction in testicular weight, but with no pathological changes were observed at the two highest doses. Similarly, in female mice there was a reduction in ovarian weights, but without any underlying pathological changes, at 5.0 mg/kg/day (21 times the maximum human dose). In this study there was a dose-related increase in the plasma concentration of tretinoin 4 hours after the first dose. A separate toxi-cokinetic study in mice indicates that systemic exposure is greater after topical application to unrestrained animals than to restrained animals, suggesting that the systemic toxicity observed is probably related to ingestion. Male and female dogs treated with Retin-A Micro (tretinoin gel) microsphere, 0.1%, at 0.2, 0.5, or 1.0 mg/kg/day tretinoin (5, 12, or 25 times the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area, respectively) for 90 days showed no evidence of reduced testicular or ovarian weights or pathological changes.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Retin-A Micro (tretinoin gel) microsphere, 0.1% or 0.04%, is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established. Geriatric Use: Safety and effectiveness in a geriatric population have not been established. Clinical studies of Retin-A Micro did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. ADVERSE REACTIONS:

ADVERSE REACTIONS: The skin of certain sensitive individuals may become excessively red, edematous, blistered, or crusted. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the medication should be adjusted to a level the patient can tolerate. However, efficacy has not been established for lower dosing frequencies. True contact allergy to topical tretinoin is rarely encountered. Temporary hyper- or hypopig-mentation has been reported with repeated application of tretinoin. Some individuals have been reported to have heightened susceptibility to sunlight while under treatment with tretinoin. **OVERDOSAGE:** Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, is intended for topical use only. If medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. Oral ingestion of large amounts of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A. **Rx** only. Rx only.

Patent Nos.: 4,690,825; 5,145,675 & 5,955,109

OrthoNeutrogena[®]

Distributed by: OrthoNeutrogena DIVISION OF ORTHO-MCNEIL PHARMACEUTICAL, INC Los Angeles, CA 90045

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06DD0123 7/06 RETIN-A MICRO® is a registered trademark of Ortho-McNeil Pharmaceutical, Inc MICROSPONGE® is a registered trademark of Cardinal Health, Inc., Dublin, OH. evidence of the disorder. The resultant clots then trigger skin infarctions, just as a blockage of a vessel leads to a myocardial infarction.

Treatment strategies at Mayo focus on vascular occlusion, along with management of hypercalcemia (with low calcium dialysate and sodium thiosulfate in dialysis patients), hyperphosphatemia (with phosphate binding agents), hyperparathyroidism (with cinacalcet and bisphosphonates), and pain.

"We ... feel it's very important to treat vascular occlusions and eliminate these luminal thromboses causing this cutaneous infarct," he said. "One way to treat an existing clot is to use thrombolytic agents.

Several Mayo Clinic patients have been treated in this fashion with infused tissue plasminogen activator (tPA) at doses 1/10 of those used to treat a myocardial infarction. Because of concern over bleeding, patients are admitted for the 2week procedure, he said.

"We have had some success and are presently reviewing our experience with this approach," Dr. Davis said.

Anticoagulant medications, including heparin, low-molecular-weight heparin, and warfarin, are also used in calciphylaxis patients "so they don't further clot."

Dr. M.R. (Pete) Hayden, a calciphylaxis researcher who has published several studies on sodium thiosulfate as a possible treatment for calciphylaxis, said in an e-mail message that he is "looking forward excitedly to future papers" on the anticoagulant approach from Dr. Davis and Mayo researchers.

"Indeed, thrombolytic agents may be an important adjunctive intervention along with calcium-chelating agents and phosphate binding agents in appropriate patients because there are so many precipitating variables important to the development of calciphylaxis," wrote Dr. Hayden, research professor of internal medicine in the division of endocrinology, diabetes, and metabolism at the University of Missouri, Camdenton campus.

Other interventions have not fared as well. A comprehensive review of 64 patients treated at the Mayo Clinic failed to find any survival benefit for parathyroidectomy, despite case studies and series suggesting the surgery is beneficial (J. Am. Acad. Dermatol. 2007;57:365-6).

Debridement was associated with a 1year survival rate of 62%, compared with 27% survival rates in patients who failed to undergo the procedure. Because surgical and mechanical debridement are difficult to perform in patients with this "excruciatingly painful" disease, painless debridement using maggots and ultrasound is being utilized at Mayo to good effect, Dr. Davis said.

A population-based study conducted in the Rochester, Minn., area found an incidence of 4.5 cases per million people, per year. About 1% of patients with chronic renal failure and 4% of dialysis patients reportedly have the disease.

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RETIN-A MICRO (tretinoin gel) microsphere, 0.1% and 0.04%

FOR TOPICAL USE ONLY. NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

Brief Summary Retin A Micro[®] (tretinoin gel) microsphere, 0.1% and 0.04% is a formulation containing 0.1% or 0.04%, by weight, tretinoin for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/glycol dimethacrylate crosspolymer porous microspheres (MICROSPONGE[®] System) to enable inclusion of the active ingredient, tretinoin, in an aqueous

gel. IMPORTANT NOTE: This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary has been prepared by deleting information from the complete prescribing information such as certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information before prescribing the product.

Detore prescribing the product. INDICATIONS AND USAGE: Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, is indicated for topical application in the treatment of acne vulgaris. The safety and efficacy of the use of this product in the treatment of other disorders have not been established. CONTRAINDICATIONS: This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

reactions to any ingredients is no PRECAUTIONS:

General:

- General: The skin of certain individuals may become excessively dry, red, swollen, or blistered. If the degree of irritation warrants, patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use all together. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued. Excessive skin dryness may also be experienced; if so, use of an appropriate emollient during the day may be helpful.
- during the day may be helpful. Unprotected exposure to sunlight, including sunlamps, should be minimized during the use of Retin -A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Use of sunscreen products (SPF 15) and protective clothing over treated areas are recommended when exposure cannot be avoided. Muchter externee auth on wind or end, along muy be irrition to patients under treatment.
- Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.
- Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, should be kept away from the eyes, the mouth, paranasal creases of the nose, and mucous membranes.
 Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.
- Information for Patients: A Patient Information Leaflet has been prepared and is included with each package of Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%.

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Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 91-week dermal study in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squa-mous cell carcinomas and papillomas in the treatment area were observed in some female mice. These concentrations are near the tretinoin concentration of these clinical formulations of tretinoin, cutaneous squa-mous cell carcinomas and papillomas in the treatment area were observed in some female mice. These concentrations are near the tretinoin concentration of these clinical formulations (0.04% and 0.1%). A dose-related incidence of liver tumors in male mice was observed at those same doses. The maximum systemic dose associated with the administered 0.017% and 0.035% formulations are 0.5 and 1.0 mg/kg/day, respectively. These doses are two and four times the maximum human systemic dose applied topically, when normalized for total body surface area. The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose (MTD) of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice. There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was administered lopically to mice (0.1 times the maximum human systemic dose applied topically is defined as 1 gram of Retin-A Micro (tretinoin gel) microsphere, 0.1% applied daily to a 50 kg person (0.02 mg tretinoin/kg body weight). Dermal carcinogenicity testing has not been performed with Retin-A Micro (tretinoin gel) microsphere, 0.1% applied daily to a 50 kg person (0.02 mg tretinoin/kg body weight).

Dermal carcinogenicity testing has not been performed with Retin-A Micro (tretinoin gel) microsphere, 0.04% or 0.1%.

microsphere, 0.04% or 0.1%. Studies in hairless albino mice suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect has been confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretionin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial utraviolatic readiation converse. ultraviolet irradiation sources.

The mutagenic potential of tretinoin was evaluated in the Ames assay and in the *in vivo* mouse micronucleus assay, both of which were negative.

micronucleus assay, both of which were negative. The components of the microspheres have shown potential for genetic toxicity and teratogenesis. EGDMA, a component of the excipient acrylates copolymer, was positive for induction of structural chromosomal aberrations in the *in vitro* chromosomal aberration assay in mammalian cells in the absence of metabolic activation, and negative for genetic toxicity in the Ames assay, the HGPRT forward mutation assay, and the mouse micronucleus assay.

HGPRT forward mutation assay, and the mouse micronucleus assay. In dermal Segment I fertility studies of another tretinoin formulation in rats, slight (not statisti-cally significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (4 times the maximum human systemic dose applied topically, and normalized for total body surface area), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day (2 times the maximum human systemic dose applied topically and normalized for total body surface area) and above were observed. In oral Segment I and Segment III studies in rats with tretinoin, decreased survival of neonates and topical dose normalized for total body surface area).

Dermal fertility and perinatal development studies with Retin-A Micro (tretinoin gel) microsphere, 0.1% or 0.04%, have not been performed in any species.

Pregnancy: Teratogenic Effects: Pregnancy Category C.

In a study of pregnant rats treated with topical application of Retin-A Micro (tretinoin gel) microsphere, 0.1%, at doses of 0.5 to 1 mg/kg/day on gestation days 6-15 (4 to 8 times the maximum human systemic dose of tretinoin normalized for total body sur-face area after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%) some alterations were seen in vertebrae and ribs of offspring. In another study, pregnant