

Severity Assessment Bolsters Dermatitis Treatment

BY DOUG BRUNK
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LA JOLLA, CALIF. — How has your sleep been? When's the last time your skin was totally clear? Those are the two questions Dr. Lawrence F. Eichenfield asks his atopic dermatitis patients.

"It's amazing how families don't tell you about sleep disturbance unless you ask," he said at a meeting sponsored by Rady Children's Hospital and the American Academy

of Pediatrics. "At least 20% of families say they've lost sleep because of their child's scratching. . . . I view sleep disturbance as a marker for out-of-control disease."

Another way to gauge the severity of disease is to ask patients or their parents when the last time the patient's skin was totally clear as well as asking how the skin has been over time, so that you can assess the skin between office visits.

He also makes it a point to ask about the quantity and use of topical corticosteroids

and other medications. "I want to know if they're using 30 g, 50 g, or even 90 g of medication a month so I can let them know whether I'm worried about the quantity of use or not," said Dr. Eichenfield, chief of pediatric and adolescent dermatology at Rady Children's Hospital and the University of California, San Diego.

The first phase of treating atopic dermatitis is what he termed "induction therapy," or getting the disease under control. He recommends a course of topical cor-

ticosteroids for 1-3 weeks, "depending on how bad it is" as a first line of treatment. Three products have received Food and Drug Administration approval for use in patients as young as 3 months of age: desonide nonethanolic foam (Verdeso, Stiefel Laboratories Inc.), desonide aqueous gel (Desonate, SkinMedica Inc.), and fluocinolone acetonide oil (Derma-Smoother, Hill Dermaceuticals Inc.).

"Generally, we use 'strength as needed' to get the disease under control," said Dr. Eichenfield, who was involved in clinical studies of the topical agents but has no financial interest in their manufacturers.

Another option is generic topical corticosteroids. "It's nice that I can send my patients to Wal-Mart or Target and for \$4 they can get 80 g of triamcinolone 0.1% ointment," he commented.

Using wet wraps—an intensive therapy applying steroids under hydrated gauze wraps, covered by dry wraps—for 3-4 days yields the same results as using topical corticosteroids for 2-3 weeks, he said.

Dr. Eichenfield uses topical calcineurin inhibitors (TCIs) as second-line agents in patients with persistent or frequently re-

Clindagel®

(clindamycin phosphate gel)
topical gel, 1%

Brief Summary

For External Use

INDICATIONS AND USAGE: Clindagel® is indicated for topical application in the treatment of acne vulgaris. In view of the potential for diarrhea, bloody diarrhea and pseudomembranous colitis, the physician should consider whether other agents are more appropriate. (See CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS.)

CONTRAINDICATIONS: Clindagel® is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin, a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

WARNINGS: Orally and parenterally administered clindamycin has been associated with severe colitis, which may result in patient death. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin.

Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool culture for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

When significant diarrhea occurs, the drug should be discontinued. Large bowel endoscopy should be considered to establish a definitive diagnosis in cases of severe diarrhea.

Antiperistaltic agents, such as opiates and diphenoxylate with atropine, may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of oral and parenteral therapy with clindamycin.

PRECAUTIONS

General: Clindagel® should be prescribed with caution in atopic individuals.

Drug Interactions: Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenicity of a 1% clindamycin phosphate gel similar to Clindagel® was evaluated by daily application to mice for two years. The daily doses used in this study were approximately 3 and 15 times higher than the human dose of clindamycin phosphate from 5 milliliters of Clindagel®, assuming complete absorption and based on a body surface area comparison. No significant increase in tumors was noted in the treated animals. A 1% clindamycin phosphate gel similar to Clindagel® caused a statistically significant shortening of the median time to tumor onset in a study in hairless mice in which tumors were induced by exposure to simulated sunlight.

Genotoxicity tests performed included a rat micronucleus test and an Ames Salmonella reversion test. Both tests were negative. Reproduction studies in rats using oral doses of clindamycin hydrochloride and clindamycin palmitate hydrochloride have revealed no evidence of impaired fertility.

Pregnancy: Teratogenic effects—Pregnancy Category B

Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin phosphate, clindamycin hydrochloride and clindamycin palmitate hydrochloride. These studies revealed no evidence of fetal harm. The highest dose used in the rat and mouse teratogenicity studies was

Rx only

equivalent to a clindamycin phosphate dose of 432 mg/kg. For a rat, this dose is 84 fold higher and for a mouse 42 fold higher, than the anticipated human dose of clindamycin phosphate from Clindagel® based on a mg/m² comparison. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether clindamycin is excreted in human milk following use of Clindagel®. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, 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.

Pediatric Use: Safety and effectiveness in children under the age of 12 have not been established.

Geriatric Use: The clinical study with Clindagel® did not include sufficient numbers of patients aged 65 and over to determine if they respond differently than younger patients.

ADVERSE REACTIONS: In the one well-controlled clinical study comparing Clindagel® and its vehicle, the incidence of skin and appendages adverse events occurring in ≥1% of the patients in either group is presented below:

Body System/Adverse Event	Number (%) of Patients	
	Clindagel® QD N=168	Vehicle Gel QD N=84
Skin and appendages disorders		
Dermatitis	0 (0.0)	1 (1.2)
Dermatitis contact	0 (0.0)	1 (1.2)
Dermatitis fungal	0 (0.0)	1 (1.2)
Folliculitis	0 (0.0)	1 (1.2)
Photosensitivity reaction	0 (0.0)	1 (1.2)
Pruritus	1 (0.6)	1 (1.2)
Rash erythematous	0 (0.0)	0 (0.0)
Skin dry	0 (0.0)	0 (0.0)
Peeling	1 (0.6)	0 (0.0)

Orally and parenterally administered clindamycin has been associated with severe colitis, which may end fatally.

Cases of diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral formulations of clindamycin and rarely with topical clindamycin (see WARNINGS). Abdominal pain and gastrointestinal disturbances, as well as gram-negative folliculitis, have also been reported in association with the use of topical formulations of clindamycin.

OVERDOSE: Topically applied Clindagel® may be absorbed in sufficient amounts to produce systemic effects (see WARNINGS).

Reference: 1. Shalita AR, Myers JA, Krochmal L, Yaroshinsky A. The safety and efficacy of clindamycin phosphate foam 1% versus clindamycin phosphate topical gel 1% for the treatment of acne vulgaris. *J Drugs Dermatol.* 2005;4(1):48-56.

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DR. EICHENFIELD

current atopic dermatitis. He noted that use of TCIs has dropped about 50% since the FDA issued a black box warning in 2005 concerning the potential for oncogenesis.

"There have been no further data confirming any true risk associated with the use of these medicines topically," he noted. "There have been multiple negative studies showing generally very low blood levels of these topical agents when used appropriately."

The second phase in treating atopic dermatitis is maintenance therapy. With severe cases, Dr. Eichenfield prefers clearly defined regimens; in some patients this may be intermittent topical corticosteroids, in others TCIs intermittently or daily, and in some a mixture of corticosteroids, TCIs, and nonsteroidal barrier creams.

The last phase in treatment is "stepped maintenance," in which the agent or agents are decreased as tolerated. "That is the time to step backward in frequency of application of medications," he advised. "A slow withdrawal of medications allows you to titrate how little is needed to keep the skin in good shape, the patient not itchy, and the family sleeping through the night."

Dr. Eichenfield disclosed that he has been a clinical investigator in trials conducted by Amgen Inc., Astellas Pharma Inc., Ferndale Laboratories Inc., Galderma Laboratories, Graceway Pharmaceuticals, Hill Dermaceuticals Inc., Johnson & Johnson, Novartis Pharmaceuticals Corp., and Medicis Pharmaceutical Corp. He stated that he has no relevant financial interest in any of the companies. ■