

Endemic Dengue Hemorrhagic Fever Surfaces

BY JOHN R. BELL
Associate Editor

SAN ANTONIO — What is likely the first-ever case of dengue hemorrhagic fever to originate within Texas occurred last year among residents of the border area of South Texas, as did three endemic cases of classic dengue fever.

Physicians should consider dengue when diagnosing any resident of that region who presents with fever, an epi-

demologist from the Texas Department of State Health Services reported.

Allison Abell, Ph.D., reported 18 dengue cases—three in the absence of recent international travel—in residents of greater Brownsville, Tex., found in 2005 by the Border Infectious Disease Surveillance project, a joint surveillance program of the United States and Mexico.

Her team had identified the patients via blood samples taken during home visits to 20 persons identified as at risk based on re-

ports of undifferentiated fever, at least one IgM-positive test result, and patient questionnaires.

The team also conducted interviews and environmental assessments during those visits; notably, 3 of the 18 dengue cases were in people who denied having traveled to any foreign country in the last 3 months. Even more worrisome was that one of those three patients developed dengue hemorrhagic fever, rather than the less-severe classic dengue fever seen in the other 17.

That case apparently “represents the first classically presented case of [dengue hemorrhagic fever] with transmission within Texas,” Dr. Abell said at a meeting of the Southwest Conference on Diseases in Nature Transmissible to Man. A prior case of dengue hemorrhagic fever appeared with unusual symptoms several years ago, she noted. Untreated dengue hemorrhagic fever has a mortality of around 50%, but treatment reduces the rate to roughly 5%, she added.

Moreover, three asymptomatic household contacts of the 18 patients tested IgM-positive for dengue, and one denied any recent foreign travel, Dr. Abell reported. Of the 18 cases, 14 were in residents of the Brownsville area, directly across the border from Matamoros, Mexico.

Although dengue fever is not rare in persons returning to the United States from dengue-endemic regions abroad, endemic cases with the United States have been

rare since the end of World War II, according to the Centers for Disease Control and Prevention. Only a few indigenous dengue cases have occurred here in the last few years, most of them in Texas. (Hawaii reported 15 cases in 2001-2002.) However, dengue infection is not nationally notifiable, and reporting is passive; thus, incidence might be underreported, the CDC noted.

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Dr. Abell and her colleagues identified environmental risk factors for 15 of the 18 dengue patients by visiting their homes. Dengue is transmitted by the *Aedes aegypti* mosquito and occurs in four serotypes. Objects that collect rainwater, such as pet dishes and toys, were present outside the homes of 9 of the 15 patients (60%). Unmounted tires were present on the property of six patients (40%). And five patients (33%) had windows without screens at their homes. About half the patients reported rarely or never using insect repellent, and two-thirds reported never wearing protective clothing during outdoor activities, Dr. Abell said.

Clinical symptoms reported were sudden onset of fever and headache, often with retroorbital pain, as well as muscle and joint pain, rash, and bleeding in some cases. Almost all patients were Hispanic, and slightly more than half were female. “The most common risk factor really was travel,” with 15 of the 18 reporting recent travel to Mexico, Dr. Abell noted at the meeting, held in conjunction with the International Conference on Diseases in Nature Communicable to Man.

Overall, Texas has reported fewer than 10 cases per year of dengue in the last decade, Dr. Abell reported, with the exception of 1999, when an outbreak of 66 cases, including 2 probably indigenous cases, hit the border town of Laredo. ■

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Duac® Topical Gel

(clindamycin, 1% - benzoyl peroxide, 5%)

For Dermatological Use Only.
Not for Ophthalmic Use.

Rx Only

INDICATIONS AND USAGE

Duac Topical Gel is indicated for the topical treatment of inflammatory acne vulgaris.

Duac Topical Gel has not been demonstrated to have any additional benefit when compared to benzoyl peroxide alone in the same vehicle when used for the treatment of non-inflammatory acne.

CONTRAINDICATIONS

Duac Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or 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 *Clostridium 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.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms, including fungi. If this occurs, discontinue use of this medication and take appropriate measures.

Avoid contact with eyes and mucous membranes.

Clindamycin and erythromycin containing products should not be used in combination. *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

Information for Patients: Patients using Duac Topical Gel should receive the following information and instructions:

1. Duac Topical Gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should not use any other topical acne preparation unless otherwise directed by their physician.
4. Patients should report any signs of local adverse reactions to their physician.
5. Duac Topical Gel may bleach hair or colored fabric.
6. Duac Topical Gel can be stored at room temperature up to 25°C (77°F) for up to 2 months. Do not freeze. Keep tube tightly closed. Keep out of the reach of small children. Discard any unused product after 2 months.
7. Before applying Duac Topical Gel to affected areas, wash the skin gently, rinse with warm water, and pat dry.
8. Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced squamous cell skin tumors in transgenic TgAC mice in a study using 20 weeks of topical treatment.

Genotoxicity studies were not conducted with Duac Topical Gel. Clindamycin phosphate was not genotoxic in *Salmonella typhimurium* or in a rat micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *Salmonella typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Studies have not been performed with Duac Topical Gel or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g Duac Topical Gel, based on mg/m²) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Animal reproduction studies have not been conducted with Duac Topical Gel or benzoyl peroxide. It is also not known whether Duac Topical Gel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Duac Topical Gel should be given to a pregnant woman only if clearly needed.

Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) revealed no evidence of teratogenicity.

Nursing Women: It is not known whether Duac Topical Gel is secreted into human milk after topical application. 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 of this product in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS

During clinical trials, all patients were graded for facial erythema, peeling, burning, and dryness on the following scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The percentage of patients that had symptoms present before treatment (at baseline) and during treatment were as follows:

	Local reactions with use of Duac Topical Gel % of patients using Duac Topical Gel with symptom present Combined results from 5 studies (n = 397)					
	Before Treatment (Baseline)			During Treatment		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	28%	3%	0	26%	5%	0
Peeling	6%	<1%	0	17%	2%	0
Burning	3%	<1%	0	5%	<1%	0
Dryness	6%	<1%	0	15%	1%	0

(Percentages derived by # subjects with symptom score/# enrolled Duac subjects, n = 397).

HOW SUPPLIED

Duac® (clindamycin, 1% - benzoyl peroxide, 5%) Topical Gel is available in a 45 gram tube - NDC 0145-2371-05.

Prior to Dispensing: Store in a cold place, preferably in a refrigerator, between 2°C and 8°C (36°F and 46°F). Do not freeze.

Dispensing Instructions for the Pharmacist: Dispense Duac Topical Gel with a 60 day expiration date and specify “Store at room temperature up to 25°C (77°F). Do not freeze.”

Keep tube tightly closed. Keep out of the reach of small children.

U.S. Patent Nos. 5,466,446, 5,446,028, 5,767,098, and 6,013,637
Patent Pending



Stiefel Laboratories, Inc.
Coral Gables, FL 33134

833185 Rev. 0504

REFERENCES: 1. Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. *Am Acad Derm.* 1997;37:590-595. 2. Tangheiti EA, Gold MH. A Two-center patient preference study comparing two benzoyl peroxide/clindamycin gels in acne vulgaris patients. Presented at: 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005; New Orleans, LA. Poster 108. 3. Tangheiti EA, Abramovits W, Solomon B, et al. Tazarotene versus tazarotene plus clindamycin/benzoyl peroxide in the treatment of acne vulgaris: a multicenter, double-blind, randomized parallel group trial. Presented at: 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005; New Orleans, LA. Poster 147. Duac is a registered trademark of Stiefel Laboratories, Inc. Your Choice is Clear, Make the Clear Choice, and Research in Dermatology are trademarks of Stiefel Laboratories, Inc.