

Drugs Tied to Abscess Risk After Appendectomy

BY JAY CHERNIAK

Children who received diphenhydramine or ranitidine after undergoing surgery for perforated appendicitis had a significantly higher risk of a postoperative abscess than did children who received neither drug, according to a review of 98 patients at a single center.

Patients given either drug had a 70%-

80% greater risk of an abscess 5 days after appendectomy, regardless of antibiotic regimen, and patients given both drugs had a fourfold greater risk of an abscess, investigators reported. Diphenhydramine blocks the H₁ receptor and is often given after appendectomy to induce sleep or to relieve pruritus caused by narcotics. Ranitidine blocks the H₂ receptor and is given to prevent gastritis caused by ketorolac, an NSAID analgesic.

Dr. Shawn D. St. Peter and his colleagues at Children's Mercy Hospital, Kansas City, Mo., reviewed the records of all 98 children (mean age, about 8.6 years) who had surgery for perforated appendicitis at the hospital between April 2005 and November 2006.

During postoperative care, providers ordered medications from a standardized list that included ranitidine and diphenhydramine. Ranitidine was ordered by

someone other than the surgeon—either a resident or nurse practitioner—and when it was ordered, it was given within 24 hours following surgery. Diphenhydramine could be ordered on an as-needed basis. Narcotics were given to every patient, and ketorolac and ondansetron also could be ordered.

A total of 24 children received ranitidine, 17 were given diphenhydramine, 16 were administered both medications, and 41 received neither. "No differences existed in patient or operative variables in those given [ranitidine or diphenhydramine], compared with those receiving no doses," the authors said.

The results showed that children given only ranitidine or diphenhydramine had abscess rates of 17% and 18%, whereas those not given either drug had

Children who were given ranitidine or diphenhydramine after surgery for perforated appendicitis had abscess rates of 17% and 18%, vs. 10% for those given neither.

a 10% rate. The differences were significant for both medications, reported Dr. St. Peter and his colleagues (*Arch. Surg.* 2010;145:143-6). Patients who received both drugs had an abscess rate of 44%.

There were no significant differences in other outcomes, including hospital stay and wound infections. No correlations were found between abscess rates and the administration of ketorolac, naloxone, or ondansetron.

"These data represent the first clinical evidence, to our knowledge, that both H₁- and H₂-receptor antagonism may adversely affect postoperative abscess formation," the researchers wrote.

In an interview, Dr. St. Peter said that they felt these data were "real because we could find nothing about the patients that justified use of ranitidine or diphenhydramine that would correlate with the patient being sicker and thus this is why they had the higher abscess rate."

In an invited critique, Dr. Stephanie F. Heller and Dr. Michael G. Sarr wrote that the study shows the two drugs "have adverse effects that presumably attenuate several aspects of the inflammatory response. This concept has been unappreciated previously but is argued convincingly by [Dr.] St. Peter and colleagues" (*Arch. Surg.* 2010;145:147).

"What have we gleaned from this study? We should (1) not use 'prophylactic' H₂-receptor antagonists; [and] (2) use another sleeping pill, but only if absolutely needed," wrote Dr. Heller and Dr. Sarr, who are both with the surgery department of the Mayo Clinic, Rochester, Minn.

Disclosures: Dr. St. Peter and his colleagues, as well as Dr. Heller and Dr. Sarr, disclosed no financial conflicts of interest.

Acanya Gel

(Clindamycin Phosphate 1.2% and Benzoyl Peroxide 2.5%)

ACANYA® Gel
(clindamycin phosphate 1.2% and benzoyl peroxide 2.5%)

Brief summary. Please see full prescribing information for complete product information.

INDICATIONS AND USAGE

ACANYA Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older.

The safety and efficacy of this product in the treatment of any other disorders have not been evaluated.

DOSAGE AND ADMINISTRATION

Apply a pea-sized amount of ACANYA Gel to the face once daily. Use of ACANYA Gel beyond 12 weeks has not been evaluated.

ACANYA Gel is not for oral, ophthalmic, or intravaginal use.

CONTRAINDICATIONS

ACANYA Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

WARNINGS AND PRECAUTIONS

Colitis

Systemic absorption of clindamycin has been demonstrated following topical use of clindamycin. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. When significant diarrhea occurs, ACANYA Gel should be discontinued.

Severe colitis has occurred following oral and parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death.

Studies indicate 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. Stool cultures for Clostridium difficile and stool assay for C. difficile toxin may be helpful diagnostically.

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 C. difficile colitis.

Ultraviolet Light and Environmental Exposure

Minimize sun exposure following drug application. (See NONCLINICAL TOXICOLOGY.)

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trial may not reflect the rates observed in practice. Because clinical trials are also conducted under widely varying conditions, adverse reactions observed in the clinical trials of a drug cannot always be directly compared to rates in the clinical trials of another drug. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse reactions that appear to be related to drug use and for approximating rates.

The following selected adverse reactions occurred in less than 0.2% of patients treated with ACANYA Gel: application site pain (0.1%); application site exfoliation (0.1%); and application site irritation (0.1%).

During clinical trials, patients were assessed for local cutaneous signs and symptoms of erythema, scaling, itching, burning and stinging. Most local skin reactions increased and peaked around week 4 and continually decreased over time reaching near baseline levels by week 12. The percentage of patients that had symptoms present before treatment, the maximum value recorded during treatment, and the percent with symptoms present at week 12 are shown below.

Local Skin Reactions—Percent Patients with Symptoms Present. Combined Results from the Two Phase 3 Trials (N = 773)

	Before Treatment (Baseline)			Maximum During Treatment			End of Treatment (Week 12)		
	Mild	Mod*	Severe	Mild	Mod*	Severe	Mild	Mod*	Severe
Erythema	22	4	0	25	5	<1	15	2	0
Scaling	8	<1	0	18	3	0	8	1	0
Itching	10	2	0	15	2	0	6	<1	0
Burning	3	<1	0	8	2	0	2	<1	0
Stinging	2	<1	0	6	1	0	1	<1	0

*Mod=Moderate

DRUG INTERACTIONS

Erythromycin

ACANYA Gel should not be used in combination with topical or oral erythromycin-containing products due to its clindamycin component. *In vitro* studies have shown antagonism between erythromycin and clindamycin. The clinical significance of this *in vitro* antagonism is not known.

Concomitant Topical Medications

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.

Neuromuscular Blocking Agents

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

USE IN SPECIFIC POPULATIONS

Pregnancy Category C

There are no well-controlled trials in pregnant women treated with ACANYA Gel. It also is not known whether ACANYA Gel can cause fetal harm when administered to a pregnant woman. ACANYA Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproductive/developmental toxicity studies have not been conducted with ACANYA Gel or benzoyl peroxide. Developmental toxicity studies of clindamycin performed in rats and mice using oral doses of up to 600 mg/kg/day (240 and 120 times amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) or subcutaneous doses of up to 200 mg/kg/day (80 and 40 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) revealed no evidence of teratogenicity.

Nursing Mothers: It is not known whether clindamycin is excreted in human milk after topical application of ACANYA Gel. 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 use ACANYA Gel while nursing, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of ACANYA Gel in pediatric patients under the age of 12 have not been evaluated. Clinical trials of ACANYA Gel included patients 12-17 years of age.

Geriatric Use

Clinical studies of ACANYA Gel did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity and impairment of fertility testing of ACANYA Gel have not been performed.

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered topically twice per week for 20 weeks induced skin tumors in transgenic Tg.AC mice. The clinical significance of this is unknown.

Carcinogenicity studies have been conducted with a gel formulation containing 1% clindamycin and 5% benzoyl peroxide. In a 2-year dermal carcinogenicity study in mice, treatment with the gel formulation at doses of 900, 2700, and 15000 mg/kg/day (1.8, 5.4, and 30 times amount of clindamycin and 3.6, 10.8, and 60 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ACANYA Gel based on mg/m², respectively) did not cause any increase in tumors. However, topical treatment with a different gel formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats. In an oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900 and 3000 mg/kg/day (1.2, 3.6, and 12 times amount of clindamycin and 2.4, 7.2, and 24 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ACANYA Gel based on mg/m², respectively) for up to 97 weeks did not cause any increase in tumors. In a 52-week dermal photocarcinogenicity study in hairless mice, (40 weeks of treatment followed by 12 weeks of observation), the median time to onset of skin tumor formation decreased and the number of tumors per mouse increased relative to controls following chronic concurrent topical administration of the higher concentration benzoyl peroxide formulation (5000 and 10000 mg/kg/day, 5 days/week) and exposure to ultraviolet radiation.

Clindamycin phosphate was not genotoxic in the human lymphocyte chromosome aberration assay. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *S. typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

Fertility studies have not been performed with ACANYA Gel or benzoyl peroxide, but fertility and mating ability have been studied with clindamycin. 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 ACANYA Gel, based on mg/m²) revealed no effects on fertility or mating.

HOW SUPPLIED

ACANYA Gel (clindamycin phosphate 1.2% and benzoyl peroxide 2.5%) is supplied as a kit containing the following components:

Components	NDC#	Net Weight
Benzoyl Peroxide Gel	NDC 59987-101-25	40g
Clindamycin Phosphate Solution	NDC 59987-101-24	10g

Admixing Instructions

Prior to dispensing, add the clindamycin phosphate solution in the bottle to the benzoyl peroxide gel and stir with the provided spatula until homogenous (at least 1 1/2 minutes).

ACANYA Gel (admixed) can be stored at room temperature up to 25°C (77°F) for 2 months. Place a 2-month expiration date on the label immediately following admixing.

Storage and Handling

Store at 25°C (77°F). Protect from freezing. Keep out of the reach of children. Keep jar tightly closed.

RX Only

Marketed by CORIA Laboratories, a division of Valeant Pharmaceuticals North America, Aliso Viejo, CA 92656

Manufactured by Contract Pharmaceuticals Limited Niagara, Buffalo, NY 14213

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References: 1. Thiboutot D, Zaenglein A, Weiss J, Webster G, Calvarese B, Chen D. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: assessment of efficacy and safety in 2813 patients. *J Am Acad Dermatol.* 2008;59:792-800. 2. Data on file, CORIA Laboratories. 3. Acanya Gel package insert, CORIA Laboratories.

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