

Educate Parents to Back Watchful Waiting for AOM

BY CHRISTINE KILGORE

Contributing Writer

Watchful waiting for nonsevere acute otitis media can be as acceptable to parents as immediate antibiotic treatment—if parents are properly educated about the options, new study findings and survey results indicate.

Parents' satisfaction with their children's care was no different among parents whose children were randomized to re-

ceive either immediate antibiotic treatment or watchful waiting in an outcomes study of the two approaches. The parents all were educated at the study site—a pediatric clinic in Galveston, Texas—about the risks and benefits of treatment.

In a separate study, only a minority of parents who were randomly surveyed by mail about a hypothetical visit for an ear infection—without being given much information—said they would feel comfortable with a watchful waiting approach.

Most said they would feel neutral or dissatisfied with such an approach.

The studies, both of which appear in the June issue of *Pediatrics*, show that “when it’s properly explained, parents are equally satisfied with watchful waiting and antibiotic treatment [for nonsevere acute otitis media],” said Allan S. Lieberthal, M.D., who led development of the American Academy of Pediatrics’ guidelines on the diagnosis and management of acute otitis media. “Now we need tools for educating

parents within the confines of a busy pediatric office,” he said in an interview.

Investigators in the randomized study used a handheld flip chart for a 5- to 10-minute review with parents of the definition and causes of ear infections, characteristics of nonsevere and severe acute otitis media (AOM), antibiotic resistance and costs, rate of symptom response to antibiotics, and possible adverse outcomes associated with immediate treatment versus observation. Parent satisfaction was no different between a group of 111 children randomized to a watchful waiting group and 112 randomized to receive immediate antibiotics, either at day 12 or day 30 after the children were seen, reported David P. McCormick, M.D., of the University of Texas, Galveston, and his colleagues (*Pediatrics* 2005;115;1455-65).

‘When it’s properly explained, parents are equally satisfied with watchful waiting and antibiotic treatment [for nonsevere acute otitis media].’

In the survey, 5,129 parents in 16 Massachusetts communities were asked to rate their level of satisfaction “if your child’s doctor diagnosed an ear infection and recommended waiting 1 or 2 days before starting antibiotics (to see if the symptoms get better on their own).”

Of 2,054 parents who returned the survey, 34% said they would be somewhat or extremely satisfied. Another 26% indicated they would be neutral, and the remaining 40% said they would be somewhat or extremely dissatisfied, reported Jonathan A. Finkelstein, M.D., of Harvard Medical School, Boston, and his associates (*Pediatrics* 2005;115;1466-73).

Both studies were conducted before the AAP guidelines were published last year.

In addition to offering new insight into issues of parent acceptance, findings from the randomized study affirm what the guidelines say: that some children with nonsevere AOM may be observed with watchful waiting as long as they maintain nonsevere status and are kept comfortable with appropriate symptom management, Dr. Lieberthal said.

Of the children randomized to the watchful waiting group, 66% completed the study without antibiotics.

Immediate antibiotic treatment was associated with 16% fewer treatment failures—a difference that the investigators said was larger than what they “expected from [their] review of the literature”—and improved symptom control.

Antibiotic treatment also was associated, however, with increased antibiotic-related adverse events. And although immediate treatment resulted in eradication of *Streptococcus pneumoniae* carriage in the majority of children, the *S. pneumoniae* strains cultured from children in the antibiotic group at day 12 were more likely to be multidrug-resistant than were strains from the watchful waiting group,

Continued on following page

BRIEF SUMMARY

47002/Issued: December 2000

Protopic® (tacrolimus)

Ointment 0.03%
Ointment 0.1%

FOR DERMATOLOGIC USE ONLY NOT FOR OPHTHALMIC USE

INDICATIONS AND USAGE:

PROTOPIC Ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated for short-term and intermittent long-term therapy in the treatment of patients with moderate to severe atopic dermatitis in whom the use of alternative, conventional therapies are deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies.

CONTRAINDICATIONS:

PROTOPIC Ointment is contraindicated in patients with a history of hypersensitivity to tacrolimus or any other component of the preparation.

PRECAUTIONS:

General

Studies have not evaluated the safety and efficacy of PROTOPIC Ointment in the treatment of clinically infected atopic dermatitis. Before commencing treatment with PROTOPIC Ointment, clinical infections at treatment sites should be cleared.

While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with PROTOPIC Ointment may be associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum. In the presence of these infections, the balance of risks and benefits associated with PROTOPIC Ointment use should be evaluated.

In clinical studies, 33 cases of lymphadenopathy (0.8%) were reported and were usually related to infections (particularly of the skin) and noted to resolve upon appropriate antibiotic therapy. Of these 33 cases, the majority had either a clear etiology or were known to resolve. Transplant patients receiving immunosuppressive regimens (e.g., systemic tacrolimus) are at increased risk for developing lymphoma; therefore, patients who receive PROTOPIC Ointment and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, discontinuation of PROTOPIC Ointment should be considered. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans (see ADVERSE REACTIONS), PROTOPIC Ointment shortened the time to skin tumor formation in an animal photocarcinogenicity study (see Carcinogenesis, Mutagenesis, Impairment of Fertility). Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

The use of PROTOPIC Ointment may cause local symptoms such as skin burning (burning sensation, stinging, soreness) or pruritus. Localized symptoms are most common during the first few days of PROTOPIC Ointment application and typically improve as the lesions of atopic dermatitis heal. With PROTOPIC Ointment 0.1%, 90% of the skin burning events had a duration between 2 minutes and 3 hours (median 15 minutes). Ninety percent of the pruritus events had a duration between 3 minutes and 10 hours (median 20 minutes). The use of PROTOPIC Ointment in patients with Netherton's Syndrome is not recommended due to the potential for increased systemic absorption of tacrolimus. The safety of PROTOPIC Ointment has not been established in patients with generalized erythroderma.

Information for Patients (See patient package insert)

Patients using PROTOPIC Ointment should receive the following information and instructions:

1. Patients should use PROTOPIC Ointment as directed by the physician. PROTOPIC Ointment is for external use only. As with any topical medication, patients or caregivers should wash hands after application if hands are not an area for treatment.
2. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using PROTOPIC Ointment.
3. Patients should not use this medication for any disorder other than that for which it was prescribed.
4. Patients should report any signs of adverse reactions to their physician.
5. Before applying PROTOPIC Ointment after a bath or shower, be sure your skin is completely dry.

Drug Interactions

Formal topical drug interaction studies with PROTOPIC Ointment have not been conducted. Based on its minimal extent of absorption, interactions of PROTOPIC Ointment with systemically administered drugs are unlikely to occur but cannot be ruled out. The concomitant administration of known CYP3A4 inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, or *in vivo* clastogenicity assays performed in mice. Tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes. Reproductive toxicology studies were not performed with topical tacrolimus.

Pregnancy:

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of topically administered tacrolimus in pregnant women. The experience with PROTOPIC Ointment when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

There are no adequate and well-controlled studies of systemically administered tacrolimus in pregnant women. Tacrolimus is transferred across the placenta. The use of systemically administered tacrolimus during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. PROTOPIC Ointment should be used during pregnancy only if the potential benefit to the mother justifies a potential risk to the fetus.

Nursing Mothers

Although systemic absorption of tacrolimus following topical applications of PROTOPIC Ointment is minimal relative to systemic administration, it is known that tacrolimus is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from tacrolimus, 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

PROTOPIC Ointment 0.03% may be used in pediatric patients 2 years of age and older. Two phase 3 pediatric studies were conducted involving 606 patients 2-15 years of age: one 12-week randomized vehicle-controlled study and one open-label, 1 year, long-term safety study. Three hundred and thirty (330) of these patients were 2 to 6 years of age.

The most common adverse events associated with PROTOPIC Ointment application in pediatric patients were skin burning and pruritus (see ADVERSE REACTIONS). In addition to skin burning and pruritus, the less common events (< 5%) of varicella zoster (mostly chicken pox), and vesiculobullous rash were more frequent in patients treated with PROTOPIC Ointment 0.03% compared to vehicle. In the long-term 1 year safety study involving 255 pediatric patients using PROTOPIC Ointment, the incidence of adverse events, including infections, did not increase with increased duration of study drug exposure or amount of ointment used. In 491 pediatric patients treated with PROTOPIC Ointment, 3(0.6%) developed eczema herpeticum. Since the safety and efficacy of PROTOPIC Ointment have not been established in pediatric patients below 2 years of age, its use in this age group is not recommended.

Geriatric Use

Twenty-five (25) patients ≥ 65 years old received PROTOPIC Ointment in phase 3 studies. The adverse event profile for these patients was consistent with that for other adult patients.

ADVERSE REACTIONS:

No phototoxicity and no photoallergenicity was detected in clinical studies of 12 and 216 normal volunteers, respectively. One out of 198 normal volunteers showed evidence of sensitization in a contact sensitization study.

In three randomized vehicle-controlled studies and two long-term safety studies, 655 and 571 patients respectively, were treated with PROTOPIC Ointment.

The following table depicts the adjusted incidence of adverse events pooled across the 3 identically designed 12-week studies for patients in vehicle, PROTOPIC Ointment 0.03%, and PROTOPIC Ointment 0.1% treatment groups, and the unadjusted incidence of adverse events in two one year long-term safety studies, regardless of relationship to study drug.

Incidence Of Treatment Emergent Adverse Events

	12-Week, Randomized, Double-Blind, Phase 3 Studies				Open-Label Studies (up to 1 year)		
	12-Week Adjusted Incidence Rate (%)				0.1% Tacrolimus Ointment Incidence (%)		
	Adult		Pediatric		Adult	Pediatric	
	Vehicle n=212	0.03% Tacrolimus Ointment n=210	0.1% Tacrolimus Ointment n=209	Vehicle n=116	0.03% Tacrolimus Ointment n=118	n=316	n=255
Skin Burning [†]	26	46	58	29	43	47	26
Pruritus [†]	37	46	46	27	41	25	25
Flu-like symptoms [†]	19	23	31	25	28	22	35
Allergic Reaction	8	12	6	8	4	22	15
Skin Erythema	20	25	28	13	12	12	9
Headache [†]	11	20	19	8	5	10	18
Skin Infection	11	12	5	14	10	11	11
Fever	4	4	1	13	21	2	18
Infection	1	1	2	9	7	14	8
Cough Increased	2	1	1	14	18	3	15
Asthma	4	6	4	6	6	5	16
Herpes Simplex	4	4	4	2	0	12	5
Eczema Herpeticum	0	1	1	0	2	2	0
Pharyngitis	3	3	4	11	6	5	10
Accidental Injury	4	3	6	3	6	4	12
Pustular Rash	2	3	4	3	2	6	8
Folliculitis [†]	1	6	4	0	2	11	2
Rhinitis	4	3	2	2	6	5	5

Otitis Media	4	0	1	6	12	1	7
Sinusitis [†]	1	4	2	8	3	3	7
Diarrrhea	3	3	4	2	5	4	6
Urticaria	3	3	6	1	1	5	5
Lack of Drug Effect	1	1	0	1	1	10	2
Bronchitis	0	2	2	3	3	3	6
Vomiting	0	1	1	7	6	1	5
Maculopapular Rash	2	2	2	3	0	4	3
Rash [†]	1	5	2	4	2	2	5
Abdominal Pain	3	1	1	2	3	1	5
Fungal Dermatitis	0	2	1	3	0	2	6
Gastroenteritis	1	2	2	3	0	4	2
Alcohol Intolerance [†]	0	3	7	0	0	6	0
Acne [†]	2	4	7	1	0	2	4
Sunburn	1	2	1	0	0	4	4
Skin Disorder	2	2	1	1	4	1	4
Conjunctivitis	0	2	2	2	1	4	2
Pain	1	2	1	0	1	4	3
Vesiculobullous Rash [†]	3	3	2	0	4	2	2
Lymphadenopathy	2	2	1	0	3	2	3
Nausea	4	3	2	0	1	1	2
Skin Tingling [†]	2	3	8	1	2	2	1
Face Edema	2	2	1	2	1	3	1
Dyspepsia [†]	1	1	4	0	0	1	4
Dry Skin	7	3	3	0	1	0	1
Hyperesthesia [†]	1	3	7	0	0	3	0
Skin Neoplasm							
Benign ^{††}	1	1	1	0	0	2	3
Back Pain [†]	0	2	2	1	1	3	1
Peripheral Edema	2	4	3	0	0	2	1
Varicella Zoster/ [†]							
Herpes Zoster ^{††}	0	1	0	0	5	1	3
Contact Dermatitis	1	3	3	3	4	1	1
Asthma	1	2	3	0	0	2	1
Pneumonia	0	1	1	2	0	1	2
Eczema	2	2	2	0	0	3	0
Insomnia	3	4	3	1	1	1	0
Exfoliative Dermatitis	3	3	1	0	0	0	2
Dysmenorrhea	2	4	4	0	0	0	2
Periodontal Abscess	1	0	1	0	0	3	0
Myalgia [†]	0	3	2	0	0	1	0
Cyst [†]	0	1	3	0	0	0	0

[†] May be reasonably associated with the use of this drug product

^{††} Four cases of chicken pox in the pediatric 12-week study; 1 case of "zoster of the lip" in the adult 12-week study; 7 cases of chicken pox and 1 case of shingles in the open-label pediatric study; 2 cases of herpes zoster in the open-label adult study.

^{†††} Generally "warts".

Other adverse events which occurred at an incidence greater than or equal to 1% in any clinical study include: alopecia, ALT or AST increased, anaphylactoid reaction, angina pectoris, angioedema, anorexia, anxiety, arrhythmia, arthralgia, arthritis, bilirubinemia, breast pain, cellulitis, cerebrovascular accident, cheilitis, chills, constipation, creatinine increased, dehydration, depression, dizziness, dyspnea, ear pain, ecchymosis, edema, epistaxis, exacerbation of untreated area, eye disorder, eye pain, furunculosis, gastritis, hernia, hyperglycemia, hypertension, hypoglycemia, hypoxia, laryngitis, leukocytosis, leukopenia, liver function tests abnormal, lung disorder, malaise, migraine, neck pain, neuritis, palpitations, paresthesia, peripheral vascular disorder, photosensitivity reaction, procedural complication, routine procedure, skin discoloration, sweating, taste perversion, tooth disorder, unintended pregnancy, vaginal moniliasis, vasodilatation, and vertigo.

OVERDOSAGE:

PROTOPIC Ointment is not for oral use. Oral ingestion of PROTOPIC Ointment may lead to adverse effects associated with systemic administration of tacrolimus. If oral ingestion occurs, medical advice should be sought.

DOSAGE AND ADMINISTRATION:

ADULT
PROTOPIC Ointment 0.03% and 0.1%

Apply a thin layer of PROTOPIC Ointment 0.03% or 0.1% to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis.

The safety of PROTOPIC Ointment under occlusion which may promote systemic exposure, has not been evaluated. PROTOPIC Ointment 0.03% and 0.1% should not be used with occlusive dressings.

PEDIATRIC PROTOPIC Ointment 0.03%

Apply a thin layer of PROTOPIC Ointment 0.03% to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis. The safety of PROTOPIC Ointment under occlusion, which may promote systemic exposure, has not been evaluated. PROTOPIC Ointment 0.03% should not be used with occlusive dressings.

Rx only

Astellas Pharma US, Inc.
Deerfield, IL 60015-2548
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Varicella Vaccine Was Effective During Outbreak

BY KEVIN FOLEY
Senior Writer

Varicella vaccination was found to be highly effective during an outbreak of varicella among elementary school children in Utah, reported Maryam B. Haddad of the Centers for Disease Control and Prevention, Atlanta, and associates.

The outbreak occurred from October 2002 until February 2003 in two schools, one with 597 students (school A) and another with 952 students (school B). Most parents returned a questionnaire about their children's health. Parents who reported varicella symptoms in their children were interviewed, their children's vaccination records were verified, and they were asked to submit any existing lesions for polymerase chain reaction (PCR) testing.

"Health care providers should verify the vaccination status of older children who are not subject to a school-entry requirement and might remain susceptible during adulthood," Ms. Haddad and associates recommended.

During the outbreak, 57 unvaccinated and 26 vaccinated children were reported to have varicella, with 17 more cases

among household contacts, they said. PCR analysis found wild-type varicella in five unvaccinated and three vaccinated children (specimens from two other vaccinated children were insufficient for testing). Nine unvaccinated children with varicella reported that it was a second occurrence of the disease.

In school A, 27% of the 66 unvaccinated children acquired varicella, while only 4% of the 223 vaccinated children did. In school B, 41% of the 74 unvaccinated chil-

dren reported varicella, while only 5% of the 348 vaccinated children did (Pediatrics 2005;115:1488-93).

The varicella vaccine overall was 87% effective. It was 90% effective against moderate or severe disease in school A and 99% effective in school B. Among the nine unvaccinated children with a history of varicella, the attack rate was 0.4% in school A and 1.4% in school B. Mild varicella was more common among vaccinated children (69%) than unvaccinated children (15%).

Risk factors for breakthrough varicella included a history of eczema (3.8 times greater risk), time since vaccination (relative risk 3.0 if vaccinated 5 or more years before the outbreak), and age at vaccination (relative risk 2.6 if vaccinated at age 18 months or less). Among the 163 children vaccinated 5 or more years before the outbreak, children vaccinated at age 18 months or less were 9.3 times more likely than those vaccinated after age 18 months to develop breakthrough varicella. ■

Continued from previous page

the investigators reported.

"Watchful waiting seems to be an alternative that is acceptable to parents, reduces the number and cost of antibiotic prescriptions, and reduces the percent of multidrug-resistant bacteria colonizing the nasopharynx of children after an episode of AOM," Dr. McCormick and his associates said. Regardless of the intervention, children who had received antibiotics within the previous 30 days were more than twice as likely to fail treatment as those who had not recently received antibiotics.

In addition to parent education, key factors for implementation of a watchful waiting strategy include access to follow-up care, management of AOM symptoms, and a method to classify AOM severity, the investigators said.

Dr. McCormick and his colleagues assessed AOM severity based on four factors: parental perception of severity, otoscopic examination, body temperature, and tympanogram scores. However, "in retrospect," they reported, they "could have obtained the same results"—identifying 87% of the nonsevere cases identified with the four-factor scoring system—by using a two-factor scoring system that omitted body temperature and tympanogram.

"Most children with AOM are afebrile at the time of diagnosis as a result of antipyretic medication," they said, adding that "practicing clinicians rarely use the tympanogram to make a diagnosis of AOM."

Dr. Lieberthal, cochair of the AAP's subcommittee on management of AOM and professor of pediatrics at the University of Southern California, Los Angeles, said the issue of how to most accurately and uniformly assess AOM severity is still unresolved. "We still need a validated scoring system." ■

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Reference: 1. Meinking TL, Entzel P, Villar ME, Vicaria M, Lemard GA, Porcelain SL. Comparative efficacy of treatments for pediculosis capitis infestations. *Arch Dermatol.* 2001;137:287-292.

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