

Patch Testing Reveals Top Allergens in Children

Using the same allergen concentrations for testing children as used in adults found safe and effective.

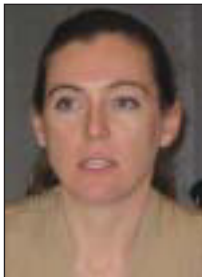
BY BRUCE JANCIN

MAUI, HAWAII — The first two multicenter studies of patch testing conducted in American children have established that the same ubiquitous allergens responsible for most allergic contact dermatitis in U.S. adults are similarly prevalent and clinically relevant in the pediatric population.

The two studies demonstrated that comprehensive patch testing in children using the same allergen concentrations as in adults is both safe and efficacious, Dr. Sharon E. Jacob said at the annual Hawaii dermatology seminar sponsored by Skin Disease Education Foundation.

One study was conducted by the North American Contact Dermatitis Group (NACDG).

The study involved 391 children—including 144 younger than 13 years old—



and 9,670 adults with recalcitrant dermatitis who were patch tested using all or part of the 65-antigen NACDG screening series. Fifty-one percent of the children and 54% of adults proved to have at least one positive patch test deemed clinically relevant, meaning that the offending allergen caused the patient's symptoms (Arch. Dermatol. 2008;144:1329-36).

'Children with clinically relevant patch test results show significant improvement with allergen avoidance.'

DR. JACOB

Dr. Jacob was the lead investigator in the other study, in which 65 children (aged 1-18 years) with recalcitrant dermatitis were patch tested. Of the children, 50 (77%) had one or more positive patch tests considered clinically relevant (Pediatr. Dermatol. 2008;25:520-7).

Both studies were retrospective and involved referral populations.

Until these two studies were published last year, American physicians were reliant upon European and Asian data re-

garding patch testing and allergic contact dermatitis (ACD) in children.

As it turns out, however, many of the top causes of pediatric ACD internationally proved to be the same allergens that came to the fore in the two U.S. studies, noted Dr. Jacob, a pediatric dermatologist at the University of California, San Diego.

For example, nickel was the No. 1 cause of pediatric ACD internationally. It was also the top cause in Dr. Jacob's study, where it accounted for 18% of cases, and in the NACDG study, in which 26% of children were found to have ACD due to nickel.

Thimerosal was No. 4 internationally, No. 2 in Dr. Jacob's study, and No. 3 in the NACDG study. Balsam of Peru (*Myroxylon pereirae*) was No. 5 abroad, No. 3 in Dr. Jacob's study, and No. 7 in the NACDG series.

All told, 8 of the top 10 allergens causing ACD in the international pediatric study were in the top 15 in Dr. Jacob's study, and 7 of the international top 10 were concordant among U.S. adults and children in the NACDG study.

Dr. Jacob has synthesized the key findings of the two U.S. studies to compile a list of the top pediatric ACD allergens in the United States. (See below.)

She urged her colleagues to consider patch testing all children with recalcitrant dermatitis that clears only with super-potent topical or oral corticosteroids. Dermatitis on the hands or eyelids is particularly suggestive of ACD. The testing often yields a big clinical payoff.

"Children with clinically relevant patch

test results show significant improvement with allergen avoidance," she said.

Yet patch testing of children is vastly underutilized in the United States, Dr. Jacob continued, in part because there is no patch test that is FDA approved for use in patients younger than 18 years. Also, there is a widespread myth that

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ACD is rare in children, supposedly because their immune systems are naive and they have fewer chemical exposures. However, studies demonstrate ACD accounts for about 20% of all childhood dermatitis.

The paucity of pediatric patch testing in the United States was highlighted in a postmarketing survey by Allerderm, which makes the TRUE (Thin-layer Rapid Use Epicutaneous) test.

In a series of 3,200 TRUE test reports during a recent 2-year period, only 93 (3%) were for patients under 19 years of age.

Dr. Jacob disclosed that she is on the speakers bureaus for Astellas Pharma, Inc. and Coria Laboratories, and has received research grants from Allerderm.

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BRIEF SUMMARY

(see package insert for full prescribing information)

Atralin™ (tretinoin) gel 0.05%

For topical use only

INDICATIONS AND USAGE

Atralin Gel is a retinoid indicated for topical treatment of acne vulgaris.

Important Limitations of Use

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Skin Irritation

The skin of certain individuals may become dry, red, or exfoliated while using Atralin Gel. 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 altogether. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued. Mild to moderate skin dryness may also be experienced if so, use of an appropriate moisturizer during the day may be helpful.

Tretinoin has been reported to cause severe irritation on eczematous or sunburned skin and should be used with caution in patients with these conditions.

Topical over-the-counter acne preparations, concomitant topical medication, medicated cleansers, topical products with alcohol or astringents, when used with Atralin Gel, should be used with caution. [See Drug Interactions (7)]

Ultraviolet Light and Environmental Exposure Unprotected exposure to sunlight, including sunlamps, should be minimized during the use of Atralin Gel. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products of at least SPF 15 and protective clothing over treated areas is recommended when exposure cannot be avoided.

Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.

Fish Allergies

Atralin Gel contains soluble fish proteins and should be used with caution in patients with known sensitivity or allergy to fish. Patients who develop pruritus or urticaria should contact their health care provider.

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two randomized, controlled trials, 674 subjects received treatment for up to 12 weeks with Atralin Gel [see Clinical Studies (14)]. In these studies, 50% of the subjects who were treated with Atralin Gel reported one or more adverse reactions; 30% of the subjects reported treatment-related adverse reactions. In the vehicle group, 29% of the 487 randomized subjects reported at least one adverse reaction; 5% of the subjects reported events that were treatment-related.

There were no serious, treatment-related adverse reactions reported by subjects in any of the treatment groups.

Selected adverse reactions that occurred in at least 1% of subjects in the two studies combined, are shown in Table 1 (below). Most skin-related adverse reactions first appear during the first two weeks of treatment with Atralin Gel, and the incidence rate for skin-related reactions peaks around the second and third week of treatment. In some subjects the skin-related adverse reactions persist throughout the treatment period.

Table 1. Number of Subjects with Selected Adverse Reactions (Occurring in At Least 1% of Subjects)

Event	Atralin Gel (n = 674)	Vehicle Gel (n = 487)
Dry Skin	109 (16%)	8 (2%)
Peeling/Scaling/Flaking Skin	76 (12%)	7 (1%)
Skin Burning/ Stinging	53 (8%)	8 (2%)
Erythema	47 (7%)	1 (<1%)
Pruritus	11 (2%)	3 (1%)
Pain of Skin	7 (1%)	0 (0%)
Sunburn	7 (1%)	3 (1%)

DRUG INTERACTIONS

When treating with Atralin Gel, caution should be exercised with the use of concomitant topical medication, medicated or abrasive soaps and cleansers, products that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices, or lime. Particular caution should be exercised with the concomitant use of topical over-the-counter acne preparations containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid. Allow the effects of such preparations to subside before use of Atralin Gel is begun.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with Atralin Gel. Atralin Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Atralin Gel at doses of 0.1, 0.3 and 1 g/kg/day was tested for maternal and developmental toxicity in pregnant Sprague-Dawley rats by dermal application. The dose of 1 g/kg/day was approximately 4 times the clinical dose assuming 100% absorption and based on body surface area comparison. Possible tretinoin-associated teratogenic effects (craniofacial abnormalities [hydrocephaly], asymmetrical thyroid variations in ossification), and increased supernumerary ribs were noted in the fetuses of Atralin Gel treated animals. These findings were not observed in control animals. Other maternal and reproductive parameters in the Atralin Gel treated animals were not different from control. For purposes of comparison of the animal exposure to human exposure, the clinical dose is defined as 2 g of Atralin Gel applied daily to a 50-kg person.

Oral tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters and nonhuman primates. Tretinoin was teratogenic in Wistar rats when given orally in doses greater than 1 mg/kg/day (approximately 8 times the clinical dose based on body surface area comparison). In the cynomolgus monkey, fetal malformations were reported for doses of 10 mg/kg/day, but none were observed at 5 mg/kg/day (approximately 80 times the clinical dose based on body surface area comparison), although increased skeletal variations were observed at all doses.

Dose-related increases in embryolethality and abortion also were reported. Similar results have also been reported in pigtail macaques.

Topical tretinoin in a different formulation has generated equivocal results in animal teratogenicity tests. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (approximately 8 times the clinical dose assuming 100% absorption and based on body surface area comparison). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day (approximately 160 times the clinical dose assuming 100% absorption and based on body surface area comparison) was topically applied. Supernumerary ribs have been a consistent finding in rats when dams were treated topically or orally with retinoids.

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. Cases of temporally associated congenital malformations have been reported with use of other topical tretinoin products. The significance of these spontaneous reports in terms of risk to the fetus is not known.

Nonteratogenic effects on fetuses: Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 20 times the clinical dose based on a body surface area comparison.

Topical tretinoin has been shown to be fetotoxic in rabbits when administered in doses 8 times the clinical dose based on a body surface area comparison.

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 Atralin Gel is administered to a nursing woman.

Pediatric Use Safety and effectiveness in children below the age of 10 have not been established.

A total of 381 pediatric subjects (aged 10 to 16 years), treated with Atralin Gel were enrolled into the two clinical studies. Across these two studies, comparable safety and efficacy were observed between pediatric and adult subjects.

Geriatric Use Safety and effectiveness in a geriatric population have not been established. Clinical studies of Atralin Gel did not include any subjects over age 65 to determine whether they respond differently than younger subjects.

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Found in Zippers and Chocolate, Top Contact Allergen in Children Named

The top allergens causing ACD in children are as follows:

► **Nickel and cobalt.** These two allergens are listed jointly because they're mined together in iron ore and often cosensitize. Nickel, named the American Contact Dermatitis Society's "Allergen of the Year" for 2008, will be the target of a planned major U.S. initiative to reduce environmental nickel release.

The effort is now being organized along the lines of the successful European directive, which has sharply reduced cases of ACD. Nickel is found in many metal objects, including jeans snaps, zippers, paper clips, coins, keys, jewelry, and orthodontic braces.

► **Neomycin.** The No. 2 contact allergen in U.S. adults for the last 30 years, this antibiotic is also a cause of ACD in kids.

► **Balsam of Peru and fragrance mix.** This combination contact allergen is widely utilized to impart flavors in food products as well as for scent.

► **Formaldehyde and quaternium-15.** A common preservative,

formaldehyde is a major cause of systemic allergic reactions. It is released by quaternium-15.

► **Potassium dichromate.** Cement, leather, and watch straps are the sources most often implicated in pediatric ACD.

► **Colophony.** This allergen often is present in adhesives, cosmetics, and paper.

► **Lanolin.** This alcohol extraction of sheep sebum is used as an emulsifier and emollient. It is found in cosmetics, creams, leather, and other products.

► **Carbamates.** Commonly causing ACD, carbamates are used as accelerators in rubber.

► **Para-phenylenediamine.** Watch out for this in temporary tattoos.

► **Sorbitan sesquiolate.** An emulsifier increasingly used to enhance penetration of topical medications, including corticosteroids. It's also present in many diaper balms.

► **Disperse dyes.** These are found in clothing and diapers.

Source: Dr. Jacob