

# PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the  
University of Virginia Children's Hospital

---

Volume 18 Number 6

June 2012

---

## **New Options for Eradicating Resistant Head Lice**

*Marcia L. Buck, Pharm.D., FCCP, FPPAG*

Since 2009, the Food and Drug Administration (FDA) has approved three new prescription-only treatments for eradication of *Pediculus capitis*. While over-the-counter agents such as permethrin or pyrethins remain the recommendation for first-line therapy,<sup>1</sup> these new pediculicides are often more effective and may be particularly useful in difficult-to-eradicate cases or in patients with permethrin-resistant lice.<sup>2</sup> In addition to their efficacy, these agents produce limited systemic exposure and have few adverse effects, making them safer than malathion.

On April 10, 2009, the FDA approved benzyl alcohol 5% lotion for treatment of head lice in patients 6 months of age and older.<sup>3</sup> The following year, on January 18, 2010, spinosad 0.9% topical suspension was approved for adults and children 4 years of age and older.<sup>4</sup> The newest of the lice treatment, ivermectin 0.5% lotion, was approved on February 7, 2012 for use in patients 6 months of age and older.<sup>5</sup> These three new products represent three different mechanisms for eradicating lice and broaden the number of options for the management of affected children.

### Benzyl Alcohol 5% Lotion

The approval of benzyl alcohol 5% lotion (Ulesfia®, Shionogi Pharma, Inc.) represents the first time this commonly used pharmaceutical preservative has been utilized as an active ingredient. Benzyl alcohol kills lice by inhibiting their ability to close their respiratory spiracles, causing the lice to asphyxiate. It does not have ovicidal activity. The lotion vehicle contains water, mineral oil, sorbitan monooleate, polysorbate 80, carbomer 934P, and trolamine as inactive ingredients.<sup>3</sup>

Benzyl alcohol 5% lotion was studied in 628 patients 6 months of age and older prior to approval. Three phase II studies were conducted

to determine optimal dose and duration of lotion application. Two multicenter, randomized, vehicle-controlled phase III studies were conducted in patients with head lice infestation. The primary endpoint was the proportion of subjects who were lice-free 14 days after their last treatment. In the first study, 76.2% of subjects in the group receiving treatment with the benzyl alcohol 5% lotion were lice-free, compared to 4.8% of those treated with the vehicle alone. In the second study, 75% of the active treatment group were lice-free, compared to 26.2% of the group given the vehicle alone. An open-label extension trial was conducted after the two controlled trials. There were 128 subjects enrolled in this trial, including 81 treatment failures from the previous trials (68 of whom had received only the vehicle) and 47 new subjects. Fourteen days after the second treatment, 96 subjects (75%) were lice-free.<sup>3,6</sup>

Benzyl alcohol 5% lotion should be applied to dry hair, saturating the hair and scalp. The manufacturer includes guidelines for the amount of lotion to be applied based on the patient's hair length in the patient information leaflet contained in the package. The lotion is available in 4 and 8-ounce bottles, and the volume to be applied ranges from 4 ounces for short hair (0-2 inches) to 48 ounces for long hair (over 22 inches in length). After 10 minutes, the lotion should be rinsed off with water. The hair may be shampooed immediately after the lotion has been rinsed off. Use of a small-tooth comb to remove nits is recommended. If lice are still present, the treatment may be repeated in 7 days.<sup>3</sup>

As with all topical lice treatments, care should be taken to avoid getting the product in the mouth or eyes. Adverse effect data for benzyl alcohol 5% lotion were pooled from two randomized, multicenter, vehicle-controlled clinical trials and one open-label study. The most commonly reported adverse effects were pruritus (occurring

in 12% of patients), erythema (10%), pyoderma (7%), or ocular irritation (6%). Less common reactions included application site dryness, excoriation, paresthesia, or thermal burn (all < 1%). Contact dermatitis has been reported in a small number of patients using this product.<sup>3</sup>

There is minimal systemic absorption after topical administration. In a study of 19 children ranging in age from 6 months to 4 years, a 30 minute application of the lotion resulted in measurable benzyl alcohol levels in 4 of the patients (21%). Concentrations ranged from 1.63 to 2.99 mcg/mL.<sup>3,6</sup>

The use of benzyl alcohol 5% lotion is restricted to patients 6 months of age and older. Use in younger infants, particularly neonates or premature infants, could produce toxic serum concentrations as the result of impaired clearance stemming from reduced levels of alcohol dehydrogenase. Toxicity resulting from administration of IV medications containing benzyl alcohol in infants, referred to as “gaspings syndrome,” was first noted in the 1980’s. The syndrome consists of severe metabolic acidosis, a gasping respiratory pattern, hypotension, central nervous system depression, seizures, intraventricular haemorrhage, and death. Although the potential systemic exposure following a single 10 minute application of the 5% lotion is significantly lower than that reported in cases of gasping syndrome, there is enough reason for concern that the product has not been tested in and is not indicated for use in infants younger than 6 months.<sup>3,7</sup>

#### Spinosad

Spinosyns are natural fermentation products of a soil actinomycete bacterium, *Saccharopolyspora spinosa*. While many spinosyns have been identified, the most common are spinosyn A and spinosyn D. Spinosad, a 5:1 ratio of the two, interferes with nicotinic acetylcholine receptors in insects, causing neuronal excitation. Paralysis then results from neuromuscular fatigue. It has both pediculocidal and ovicidal activity, killing nits as well as adult lice. Spinosad is available as a 0.9% topical suspension (Natroba®, ParaPRO LLC) in a vehicle containing the following inactive ingredients: water, isopropyl alcohol, benzyl alcohol, hexylene glycol, propylene glycol, cetearyl alcohol, steralkonium chloride, cetareth-20, hydroxyethylcellulose, butylated hydroxytoluene, and FD&C yellow #6.<sup>4,8,9</sup>

The manufacturer conducted two phase III multicenter, randomized, investigator-blind, comparison studies in adults and children 6 months of age and older.<sup>10</sup> In both studies, patients were randomized to receive either

spinosad 0.9% without nit-combing or permethrin 1% with nit-combing. Each patient could be treated up to two times over the 21-day observation period. The primary endpoint was the percentage of subjects who were free of lice 14 days after their last treatment.

In the first study of 180 patients, spinosad was effective in 84.6% of patients, compared to 44.9% of the patients treated with permethrin. Similar results were found in the second trial, with 86.7% of the 83 spinosad patients responding compared to only 42.9% of the 84 patients treated with permethrin. In both studies, the results were statistically significant ( $p < 0.001$ ). The percentage of patients requiring only one treatment was also higher in the spinosad group.<sup>10</sup>

Before applying spinosad, the 4-ounce bottle should be thoroughly shaken. The suspension should be applied to dry hair, including complete coverage of the scalp. The suspension should be left on for 10 minutes and then washed off with warm water. Use of a nit-comb is not essential, but it is recommended in patients being treated with spinosad to remove dead lice and nits. If lice are seen 7 or more days after the initial treatment, a second treatment should be applied.<sup>4</sup>

Adverse effect information was also gathered in the two comparison trials. The most frequently reported adverse effects were application site erythema (in 3% of patients), ocular erythema (2%), and application site irritation (1%). These percentages were similar or lower than those reported in the permethrin group. Other less common adverse effects included application site dryness or exfoliation, alopecia, and dry skin (all < 1%). The safety and efficacy of spinosad has not been studied in children under 4 years of age.<sup>4,10</sup>

In a study of 14 children between 4 and 15 years of age, plasma spinosad concentrations were measured following application of a spinosad 1.8% suspension for 10 minutes. None of the plasma samples contained a spinosad concentration above the lower limit of detection (3 ng/mL), indicating minimal systemic exposure. Although spinosad 0.9% topical suspension contains only a small amount of benzyl alcohol, like benzyl alcohol 5% lotion, it is not recommended for use in infants less than 6 months of age.<sup>4</sup>

#### Ivermectin Lotion, 5%

The most recent addition to the market is a topical preparation of an antiparasitic drug used enterally for more than 20 years in the US. In a recent comparison trial, oral ivermectin

demonstrated efficacy in 95% of difficult-to-treat cases, including permethrin treatment failures, compared to only 85% of patients treated with topical malathion.<sup>11</sup> Topical administration of ivermectin has long been proposed as an equally effective method for lice eradication without the risks of systemic exposure, but until now there has been no commercially available preparation.<sup>12</sup>

Like other avermectins, ivermectin selectively binds to glutamate-gated chloride channels in invertebrate nerve and cell muscles which leads to increased permeability to chloride and hyperpolarization, resulting in paralysis and death. It may also bind to gamma-aminobutyric acid (GABA)-gated chloride channels, augmenting this response. Ivermectin has low affinity for mammalian ligand-gated chloride channels and limited penetration into the central nervous system, reducing its potential for toxicity. Ivermectin has little to no ovicidal activity.<sup>5,13</sup>

Ivermectin 0.5% lotion (SKLICE™, Sanofi Pasteur, Inc) is indicated for the treatment of head lice in patients 6 months of age and older.<sup>5</sup> The product contains the following inactive ingredients: water, olive oil, oleyl alcohol, Crodalan AWS (an emollient), lanolin alcohol, cyclomethicone, shea butter, sodium citrate, sorbitan tristearate, methyparaben, propylparaben, and citric acid.

The efficacy and safety of ivermectin 0.5% lotion were studied in two phase III multicenter randomized, double-blind, vehicle-controlled studies.<sup>5</sup> A total of 289 subjects 6 months of age and older were enrolled. As in the studies for the previously described agents, the primary endpoint was the proportion of subjects lice-free at day 14. In the first study, 54 of the 71 treated subjects (76.1%) were lice-free, compared to only 12 of the 74 subjects (16.2%) given only the vehicle. Similar results were obtained in the second study, with 71.4% of the 70 treated subjects and 18.9% of the 74 controls free of lice at 14 days.

Ivermectin lotion should be applied to dry hair in an amount sufficient to cover the hair and scalp. The lotion should be left on for 10 minutes, then rinsed off with warm water. Use of a nit comb is not necessary, but may be helpful to remove dead lice and nits. The individual applying the lotion should carefully wash his or her hands after coming into contact with the lotion. To date, ivermectin 0.5% lotion has only been studied as a single treatment.<sup>5</sup>

Adverse effect data were pooled from 379 adult and pediatric patients treated in the premarketing clinical trials.<sup>5</sup> The most commonly reported adverse effects (all occurring in less than 1% of patients) included: conjunctivitis, eye irritation or redness, dry skin, dandruff, or a skin burning sensation). Accidental ingestion may result in headache, dizziness, nausea, vomiting, diarrhea, rash, pruritus, edema, paresthesias, or shortness of breath.

The pharmacokinetic profile of topical ivermectin was evaluated in 20 infants and children (ages 6 months to 3 years) taking part in the premarketing clinical trials.<sup>5</sup> The mean maximum plasma ivermectin concentration was  $0.24 \pm 0.23$  ng/mL, much lower than the concentrations achieved with oral administration. Ivermectin has not been studied in infants less than 6 months of age because of the potential for increased topical absorption in this population and the risk for systemic toxicity.

#### Cost Comparison

The cost for most over-the-counter lice treatments is approximately \$9-\$15. A 2-ounce bottle of malathion 0.5% lotion (Ovide®), the traditional prescription agent for hard-to-treat lice, is typically over \$150.<sup>14,15</sup> The manufacturer provides a \$50 rebate with the package to help offset the cost. Benzyl alcohol 5% lotion (Ulesfia®) sells for approximately \$60 per 4-ounce bottle, with the final cost determined by the number of bottles needed ranging from one to six to provide a full treatment. The manufacturer offers a \$25 coupon on their website at [www.ulesfialotion.com](http://www.ulesfialotion.com). Spinosad (Natroba®) costs approximately \$240 for a 4-ounce bottle. Information on the cost of ivermectin 0.5% lotion (SKLICE™) is not yet available.

#### Summary

Three new topical treatments for the eradication of head lice have been approved by the FDA since 2009. These prescription-only products, with their different mechanisms of action, are targeted at difficult to treat or resistant cases. All have been shown to be more effective than placebo and all have relatively mild adverse effect profiles. Comparison studies are lacking, with only spinosad having been tested against permethrin. While they are expensive and not likely to be needed for most children with head lice, these agents provide new options when traditional therapies do not provide complete eradication or are not tolerated.

#### **References**

1. Frankowski BL, Bocchini JA, Council on School Health and Committee on Infectious Diseases. Clinical report- head lice. *Pediatrics* 2010;126:392-403.

2. Gur I, Schneeweiss. Head lice treatments and school policies in the US in an era of emerging resistance: a cost-effectiveness analysis. *Pharmacoeconomics* 2009;27:725-34.
3. Ulesfia<sup>®</sup> lotion prescribing information. Shionogi Pharma, Inc., December 2010. Available at [https://www.ulesfialotion.com/ulesfia/hcp/prescribing\\_information/Ulesfia\\_Prescribing\\_Information.pdf](https://www.ulesfialotion.com/ulesfia/hcp/prescribing_information/Ulesfia_Prescribing_Information.pdf) (accessed 5/24/12).
4. Natroba<sup>®</sup> topical suspension prescribing information. ParaPRO, LLC, January 2011. Available at [www.natroba.com](http://www.natroba.com) (accessed 5/24/12).
5. SKLICE<sup>™</sup> lotion prescribing information. Sanofi Pasteur Inc., February 2012. Available at [www.products.sanofi.us/Skllice/Skllice.pdf](http://www.products.sanofi.us/Skllice/Skllice.pdf) (accessed 5/24/12).
6. Meinking TL, Villar ME, Vicaria M, et al. The clinical trials supporting benzyl alcohol lotion 5% (Ulesfia): a safe and effective topical treatment for head lice (pediculosis humanus capitis). *Pediatr Dermatol* 2010;27:19-24.
7. Lovejoy FH. Fatal benzyl alcohol poisoning in neonatal intensive care units: a new concern for pediatricians. *Am J Dis Child* 1982;136:974-5.
8. McCormack PL. Spinosad: in pediculosis capitis. *Am J Clin Dermatol* 2011;12:349-53.
9. Villegas, Breitzka RL. Head lice and the use of spinosad. *Clin Ther* 2012;34:14-23.
10. Stough D, Shellabarger S, Quiring J, et al. Efficacy and safety of spinosad and permethrin crème rinses for pediculosis capitis (head lice). *Pediatrics* 2009;124:e3789-e395.
11. Chosidow O, Giraudeau B, Cottrell J, et al. Oral ivermectin versus malathion lotion for difficult-to-treat head lice. *New Engl J Med* 2010;362:896-905.
12. Topical application of ivermectin for human ectoparasites. *Am J Trop Med Hyg* 1995;53:652-3.
13. Strycharz JP, Berge NM, Alves AM, et al. Ivermectin acts as a posteclosion nymphicide by reducing blood feeding of human head lice (Anoplura: Pediculidae) that hatched from treated eggs. *J Med Entomol* 2011;48:1174-82.
14. Department of Pharmacy Services, University of Utah Hospital. New drug bulletin: spinosad (Natroba – ParaPRO). April 20, 2011. Available at [http://healthcare.utah.edu/pharmacy/bulletins/NDB\\_224.pdf](http://healthcare.utah.edu/pharmacy/bulletins/NDB_224.pdf) (accessed 5/24/12).
15. Cole SW, Lundquist LM. Spinosad for treatment of head lice infestation. *Ann Pharmacother* 2011;45:954-8.

### **Correction**

There are two corrections to the March 2012 issue of *Pediatric Pharmacotherapy* (Volume 18, Number 3). On the first page, the study by Cohen should state that the "...rate of placebo response was highest in studies for depression, followed by those for anxiety and then those for OCD." In addition, the third reference was cited incorrectly; the correct reference is provided below.

Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA* 2007;297:1683-96.

### **Formulary Update**

The Pharmacy and Therapeutics Committee did not meet this month; their next meeting will be in June.

## **Pharmacology Literature Update**

### **Codeine Genetic Markers**

After the identification of the role of maternal genetic variation in producing codeine toxicity in breastfeeding infants, there has been considerable interest in the ability to predict this risk. The authors of this paper evaluated the impact of polymorphisms in CYP2D6, UGT2B7, p-glycoprotein (ABCB1), mu-opioid receptor (OPRM1), and catechol-O-methyltransferase (COMT) genes in 111 breastfeeding women and symptoms of CNS depression in the women or their infants. Their model revealed that a combination of the maternal risk genotypes of CYP2D6 and ABCB1 was significantly associated with symptoms of toxicity in the infants and their mothers (odds ratio 2.68; 95% CI 1.61-4.48). These genetic markers predicted 87% of the cases of CNS depression, with a sensitivity of 80% and a specificity of 87%. Sistonen J, Madadi P, Ross CJ, et al. Prediction of codeine toxicity in infants and their mothers using a novel combination of maternal genetic markers. *Clin Pharmacol Ther* 2012;91:692-9.

### **Off-label Prescribing in Children**

The extent and risks of off-label prescribing in the pediatric population are the focus of this concise review. The authors note that rates of off-label drug use vary from as little as 10% to as much as 65% in hospitalized infants and children, with the highest proportion of off-label prescribing occurring in neonates. They also discuss current initiatives to increase pediatric medication research and provide recommendations for prioritizing future research, to focus on medication dosing in neonates and frequently prescribed therapeutic classes such as analgesics and cardiovascular agents. Kimland E, Odland V. Off-label drug use in pediatric patients. *Clin Pharmacol Ther* 2012;91:796-801.

*Contributing Editor: Marcia Buck, Pharm.D.*

*Editorial Board: Kristi N. Hofer, Pharm.D.*

*Clara Jane Snipes, R.Ph.*

*Susan B. Cogut, Pharm.D.*

*If you have comments or suggestions for future issues, please contact us at Box 800674, UVA Health System, Charlottesville, VA 22908 or by e-mail to [mlb3u@virginia.edu](mailto:mlb3u@virginia.edu). This newsletter is also available at <http://www.medicine.virginia.edu/clinical/departments/pediatrics/education/pharm-news>*