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Treatment Options for Head Lice in the Era of Increasing Pyrethroid Resistance

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On August 18th, a press conference was held at the 250th National Meeting and Exposition of the American Chemical Society (ACS) to describe the results of an analysis of lice samples collected from across the United States that would be presented at the meeting. The authors found that 104 out of the 109 lice populations tested expressed high levels of a genetic mutation resulting in resistance to pyrethroids, the most commonly used lice treatment.[1] While the findings were not entirely unexpected based on studies conducted over the past two decades, the documentation of resistance in 25 states, including Virginia, led to widespread coverage of the news in the lay press and increased concerns regarding the availability of effective treatments.[2]

Pyrethroid Resistance

Pyrethrins are derived from natural extracts of chrysanthemums, including *Chrysanthemum cinerariifolium* and *C. coccineum*. First used as insecticides in China as early as 1000 BC, pyrethrins produce paralysis in insects without adversely affecting mammals. Pyrethrins are excitoxins which prevent closure of voltage-gated sodium channels in axonal membranes, preventing the nerves from repolarizing. As a result, the axonal membrane is permanently depolarized, paralyzing the insect.[3]

Pyrethrins are currently marketed in combination with 4% piperonyl butoxide to improve response.[4-6] Piperonyl butoxide, an organic inhibitor of cytochrome P450 enzymes, prevents insects from breaking down pyrethrins or pyrethroids, and as a result prolongs their effectiveness. The combination is available without prescription in shampoo form as Rid® and various other brands.

Pyrethroids, synthetic analogues of pyrethrins, were developed in 1960s. A second-generation pyrethroid, permethrin, is currently one of the most frequently purchased over-the-counter (OTC) lice treatments in the United States. Permethrin was first introduced in the United States in 1986 as a prescription medication. It was approved for OTC use as a 1% lotion in 1990.[4] It has been estimated that more than $100 million is spent annually in the United States on permethrin products such as Nix®.

In the study presented at the ACS meeting, Yoon and colleagues from Southern Illinois University tested for the presence of a trio of genetic mutations, M815I, L920F, and T917I, collectively known as "knockdown" resistance (kdr) mutations. The kdr-type point mutations result in amino acid substitutions in the p-orthologous voltage-sensitive sodium channel α-subunit, resulting in desensitization of the insect's nervous system to pyrethrins and pyrethroids. Of the 30 states included in the samples tested, 25 had samples that included all three mutations, making them 100% resistant to pyrethrins and pyrethroids. The authors previously identified widespread presence of kdr mutations in samples of lice from the United Kingdom, Australia, and Uruguay, with increasing resistance observed in samples from Argentina, Brazil, the Czech Republic, Denmark, Egypt, and Israel.[1,7,8]

Treatment Options

Several alternatives exist to the use of pyrethrins and pyrethroids for children with head lice. Beginning with the approval of malathion by the Food and Drug Administration (FDA) in 1999, four prescription products have been added to the list of topical pediculicides available for use in resistant cases. Oral ivermectin, while not

approved for this use, has been shown in clinical trials to be another effective treatment option.

Malathion

Malathion, an organophosphate, is marketed as a 0.5% lotion, with a vehicle of 78% isopropyl alcohol, terpineol, dipentene, and pine needle oil (Ovide®).[4,9] Malathion is an irreversible cholinesterase inhibitor that produces an excess of acetylcholine, preventing neurons from returning to a resting state after activation and resulting in death of the insect. Terpineol, dipentene, and pine needle oil also have pediculicidal properties. The lotion is applied to dry hair, left to air dry, and washed off after 8 to 12 hours. While the FDA approved the duration necessary for optimal eradication, shorter treatment periods, as little as 20 minutes, have been shown to be as effective in clinical trials.[10] A nit comb should be used to remove dead lice and eggs after use. In two phase 3 controlled trials conducted by the manufacturer, 95% of subjects treated with Ovide® were lice-free 24 hours after treatment, compared to 60% of those who used the Ovide® vehicle without malathion. At 7 days post-treatment, 90% of the treated and 30% of the controls were still lice-free, respectively. Although most patients require just a single treatment, if lice are present 7-9 days post-treatment, a second application may be used.

Because of the flammability of the Ovide® vehicle, parents and care providers should be cautioned to avoid using blow dryers or heated styling instruments after application. There should be no smoking or open flames near a patient being treated. Application of malathion may result in skin irritation or stinging in up to 10% of patients. Cases of second degree burns have also been reported after use, but appear to be rare. If skin irritation occurs, the area should be washed immediately. If the lotion comes into contact with the eyes, the eyes should be immediately flushed with water. The adult who will be applying the lotion should also understand the need to thoroughly wash his/her hands after completing the application. Malathion is approved for use in children 6 years of age and older and is contraindicated in patients less than 2 years of age.[11]

Benzyl alcohol

In 2009, the FDA approved benzyl alcohol 5% lotion (Ulesfia®) for the treatment of head lice in children 6 months of age and older.[12,13] Unlike the other treatments described, benzyl alcohol is not a pediculicide; it acts by suffocating the lice upon contact. The lotion is applied to dry hair until it is thoroughly saturated, left on for 10 minutes, and then washed out. Ulesfia® is sold as an 8 oz. bottle or in a package of two bottles and a lice removal comb. The manufacturer provides a wide variety of parent resources in both English and Spanish at http://www.ulesfialotion.com/hcp_index.html, including a chart of the amount of lotion that should be applied based on the length of the patient's hair. A child with short hair (2-4 inches) will require one 8 oz. bottle, while a child with long hair of 22 inches or more will require up to 6 bottles. A second treatment may be applied after 7 days, if needed.

Two phase 3 randomized, double-blind, vehicle-controlled trials were conducted in a total of 628 children prior to marketing.[12,13] In the first trial, 76.2% of patients treated with benzyl alcohol were lice-free 14 days after treatment, compared to 4.8% in the group treated with the vehicle alone ($p < 0.001$).[12] In the second study, the results were 75% and 26.2% ($p < 0.001$). An open-label extension study of the previous two studies was conducted in 128 patients, including 81 treatment failures from the vehicle-alone group. The overall treatment success rate was 92.2% one day after treatment and 75% at 14 days. In addition, more patients had a reduction in pruritus after benzyl alcohol than the vehicle (52.5% versus 31.3% in trial 1 and 78.8% versus 55.5% in trial 2, $p < 0.001$). Reduction in skin excoriation and resolution of pyoderma were also significantly higher in the benzyl alcohol group than in the vehicle group.

The pooled adverse effect data reported in the two controlled studies, along with an open-label study, included pruritus (in 12% of patients), erythema (10%), pyoderma (7%), and eye irritation upon inadvertent exposure (6%), reactions that are often associated with infestation.[12] No serious adverse effects were reported. Intravenous administration of benzyl alcohol has been associated with fatal neonatal gasping syndrome; as a result of the potential risk for transdermal absorption, this product is contraindicated in infants less than 6 months of age.

Benzyl alcohol 5% lotion offers a distinctly different mechanism of action from other lice treatments. It is well tolerated and has been shown to have little risk for adverse effects. In addition, the use of benzyl alcohol may avoid the development of resistance.

Spinosad

Spinosad was approved by the FDA in 2011 as a 0.9% suspension (Natroba®).[14] The suspension contains spinosyn A and spinosyn D, natural

fermentation products of the soil actinomycete bacterium, *Saccharopolyspora spinosa*, in a 5:1 ratio. Spinosyns are both ovicidal and pediculicidal. They interfere with nicotinic acetylcholine receptors in insects, causing neuronal excitation followed by paralysis. Spinosad is applied to dry hair, saturating the scalp, left in place for 10 minutes and then rinsed out. Although the use of a nit comb is not necessary, it may be helpful to remove the dead nits and lice. While most patients require only one treatment, a second application may be done 7 days after the initial treatment if lice are still seen.

The efficacy of spinosad was evaluated in two randomized, active-controlled trials with permethrin 1%.[14] A total of 1,038 children and adults were treated. In the first trial, 84.6% of the patients treated with spinosad remained lice-free at 14 days post-treatment, compared to 44.9% of the permethrin group ($p < 0.001$). Similar results were observed in the second trial, with 86.7% of spinosad patients remaining lice-free, compared to only 42.9% of permethrin patients ($p < 0.001$).

Spinosad is generally well tolerated; the most frequently reported adverse effects with its use include erythema (in 3% of patients), ocular erythema (2%), and application site irritation (1%).[14] Similar rates of these adverse effects were reported in the permethrin-treated group. Rare serious adverse effects include skin exfoliation, alopecia, and dry skin (all in less than 1% of patients). Spinosad is approved for use in children 4 years of age and older. The product contains benzyl alcohol, so as with Ulesfia®, it is contraindicated in children less than 6 months of age.

Ivermectin

Topical ivermectin 0.5% lotion (Sklice®) was approved by the FDA in 2012 for the treatment of lice in children 6 months of age and older.[15] It has pediculicidal, but not ovicidal, activity. Ivermectin binds to glutamate-gated and gamma-aminobutiric acid-gated chloride channels in invertebrate nerves and muscle cells. The result is an increase in chloride ion permeability, resulting in hyperpolarization, paralysis and death of the lice. Ivermectin has a low affinity for mammalian ligand-gated chloride channels and limited penetration into the central nervous system, lessening the risk for toxicity.

Ivermectin lotion should be applied to dry hair and the scalp, left on for 10 minutes and then rinsed off. A single treatment is typically adequate, since the eggs that hatch after treatment are paralyzed and unable to feed. A nit comb may be used to remove the dead lice and nits following treatment.

The efficacy of topical ivermectin lotion was established in two randomized, double-blind vehicle-controlled studies.[16] A total of 765 patients 6 months of age and older were enrolled in these multicenter studies. There were significantly more patients in the ivermectin group that were lice-free on post-treatment day 2 (94.9% versus 31.1% in the vehicle group), on day 8 (85.2% versus 20.8%), and on day 15 (73.8% versus 17.6%), $p < 0.001$ for each comparison. The ivermectin-treated group also had a significantly greater reduction in pruritus, skin excoriation, and erythema than the controls. The most commonly reported adverse effects after ivermectin application include skin dryness, dandruff, a sensation of burning skin, and eye irritation or redness, all in < 1% of patients.[15]

Oral ivermectin is not approved by the FDA for the treatment of head lice, but has been compared to topical treatments in several clinical trials.[17-19] In a 2010 study conducted in Egypt, 80 children with head lice were randomized to oral ivermectin (a single dose of 200 mcg/kg) or a single application of malathion 0.5% lotion.[17] Cure rates were similar between the treatments, with 77.5% of the ivermectin group and 87.5% of the malathion group being lice-free at day 8, 92.5% versus 95% on day 15, and 75% versus 80% on day 29, with all differences not statistically significant. Both treatments were well tolerated. In the ivermectin group, two patients had worsening pruritus which resolved within three days without additional treatment. A similar study comparing an oral ivermectin dose of 400 mcg/kg to malathion 0.5% lotion found that ivermectin was more effective (95.2% of patients lice-free versus 85% in the malathion group).[18]

A second study conducted in Egypt in 2014 compared topical 1% ivermectin versus oral ivermectin (200 mcg/kg) in 62 children.[19] At 1 week post-treatment, 88% of the children in the topical group were lice-free, compared to 45% in the oral ivermectin group ($p = 0.002$). At 2 weeks, following retreatment when necessary, complete eradication of lice was documented in 90% of patents in the topical group and 97% given oral ivermectin ($p = 0.3$). At 4 weeks, all patients treated with topical ivermectin remained lice-free, versus 97% of the oral ivermectin group ($p = 0.3$). Adverse effects were similar in both groups, consisting of transient skin irritation, headache, dizziness, nausea, vomiting, and muscle pain. The authors concluded that both routes of administration were effective, but

topical application of ivermectin was more likely to result in lice eradication and a faster resolution of pruritus. Based on these studies and the greater potential for toxicity with systemic exposure, oral ivermectin should be reserved for patients failing other treatment options.

Cost of Treatment

The prices of the prescription treatments for head lice vary among retailers. Several manufacturers offer rebates or coupons for their products on their websites. A comparison of current prices is provided in Table 1, based on data compiled from retail pharmacies on the website GoodRx (http://www.goodrx.com/).

Table 1. Cost Comparison

Product	Size	Cost
Permethrin (Rid®)	60 mL	$9-20
Pyrethrins/Piperonyl butoxide (Nix®)	60 mL	$8-20
Malathion (Ovide®)	59 mL	$98-$200
Benzyl alcohol (Ulesfia®)	240 mL	$60-65
Spinosad (Natroba®)	120 mL	$100-198
Ivermectin (Sklice®)	120 mL	$280-300
Oral ivermectin	2-8 mg	$10-20

Summary

It is estimated that over 6 million cases of head lice occur in the United States each year. While the use of topical OTC treatments and physical nit removal remain first-line therapies, the increasing frequency of pyrethroid resistance has led to the need for pediatric health care providers to be aware of alternative treatments. A number of agents are available, but caution should be used in selecting the appropriate agent based on patient age and the presence of underlying medical conditions.

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