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Do Spinosad or Ivermectin Have a Place in Head Lice Eradication?

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An estimated 6 million to 12 million infestations of head lice occur each year in the United States (US) among children 3 to 11 years of age.[1] Some studies suggest that girls get head lice more often than boys, probably due to more frequent head-to-head contact and length of hair. [2] African-Americans are less commonly infested with lice due to their hair shape and width.[2] In the US, infestation with head lice is most common among preschool and elementary school-age children and their household members.[1] Increased incidence of resistance with evidence that common therapies are losing their effectiveness has lead to the production of new products.[2] This article will discuss two new treatments for head lice to determine their place in therapy.

Lice are small insects that bite through the skin and survive on the blood of its host.[2] The life span of a female louse is about one month and is likely to lay about 7-10 eggs (a.k.a. nits) daily. [2] The nits are cemented to the base of host hair and hatch in eight days releasing nymphs that mature in another eight days.[2] There are three known varieties of parasitic lice affecting humans: Pediculus humanus capitis (head lice), Pediculus humanus humanus (body lice) and Phthirus pubis (pubic lice or crabs).[2] The most prevalent of the three is head lice which are found worldwide. Disease is spread through direct contact via playmates, clothing, combs, headphones, towels and beds. Head lice manifestations are not typically associated with morbidity, are not a sign of uncleanliness, and do not transmit systemic disease, although secondary streptococcal and staphylococcal pyoderma may occur.[6]

Topical pediculicides are the initial treatment of choice for head lice. The previous 2002 American Academy of Pediatrics (AAP) Head Lice Guidelines, which were updated in 2010, recommended over the counter (OTC) permethrin 1% cream rinse (Nix) as first-line topical drug of choice for head lice, followed by malathion if resistance is high.[4,5] Since then, two new drugs have been approved by the Food and Drug Administration (FDA) for the treatment of peduculosis capitis (spinosad 0.9% topical suspension and ivermectin 0.5% lotion).[6,7] In addition, oral ivermectin has been studied for treatment of head lice off-label.[8] Clinical evidence (June 2010) and The Canadian Agency for Drugs and Technologies in Health (May 2010) published comparative reviews recommending permethrin 1% as first line.[9,10]

Recommended Therapy

Permethrin (Nix) is the gold standard for the treatment of lice.[4,5] Permethrin, a FDA pregnancy category B drug, is a synthetic pyrethroid which inhibits sodium ion influx through nerve cell membrane channels in ectoparasites, resulting in delayed repolarization and resultant paralysis and death of the parasites.[11] The 1% lotion is indicated for patients > 2 months old and the 5% cream has been shown safe and effective on infants <1 month old. Pyrethroid resistance is mediated by mutation of the alpha subunit gene of the neuronal voltage-gated sodium channel, conferring decreased sensitivity of the channel to pyrethroid (knock-down resistance).[11] The most recent AAP guidelines recommend that unless resistance has been proven in the community, 1% permethrin or pyrethrins can be used for treatment of active infestations because it has such low toxicity.[5,10] None of the current pediculicides are 100% ovicidal so applying permethrin at least twice is recommended. The most common adverse events of permethrin include rash and irritation to the application site.[11]

Malathion, a prescription medication, is thought to act via cholinesterase inhibition to exert both lousicidal and ovicidal actions. It is a FDA pregnancy category B drug and is indicated in individuals >2 years old.[11] According to the AAP guidelines, malathion is only recommended in cases in which resistance to other products, like permethrin, is strongly suspected or if failure to respond to permethrin occurs.[4,5] Despite some evidence that malathion lotion is more effective for lice eradication than permethrin, it is not recommended first line due to the major concern of alcohol content which makes this drug highly flammable and at risk for causing severe respiratory depression if accidently ingested.[9,12]

Lindane shampoo is FDA approved for the treatment of head lice. It is directly absorbed by parasites and ova through the exoskeleton.[4,5] It then stimulates the nervous system resulting in seizures and death of parasitic arthropods. Lindane is an FDA pregnancy category C drug. In 2003, the FDA issued a public health advisory concerning lindane that cites increased risk of neurologic side effects and death in younger patients and adults weighing less than 110 pounds.[13] According to APP guidelines, 1% lindane shampoo is no longer recommended as a treatment option because of concerns regarding the FDA health risks of central nervous system (CNS) toxicity and risk of seizure, as well as increased resistance documented in the United States.[4,5,14] With increased failures of treatment over time and the current black box warning, use of lindane has been banned in California and is considered unsafe and not as effective as other products.[15,16]

Spinosad

Spinosad, FDA approved for the treatment of lice in January of 2011, leads to insect paralysis and death by causing central nervous system excitation and involuntary muscle contractions.[17] It is thought to be both pediculocidal and ovicidal. Spinosad is a FDA pregnancy category B drug and is approved for those >4 years.[17]

The Stough et al trial was an investigator blinded, randomized controlled trial (RCT) including two identical phase III studies comparing spinosad 0.9% topical suspension without nit-combing to permethrin 1% with nit-combing for 7 days and possibly an extra 7 days if live lice were still present after first applcation.[18] A third arm with spinosad 0.9% topical suspension with nit-combing was performed but results were only reported in combination with the first spinosad arm for adverse events. The study included 1038 patients ≥6 months old with active head lice. The primary endpoint was the proportion of participants lice free at 14 days. The secondary endpoint was the proportion of patients lice free at 7 days.[18]

The primary endpoint occurred in 87.4% of the patients treated with spinosad compared to 48.3% of patients treated with permethrin (relative risk [RR] 1.93; 95% CI, 1.73 - 2.16; P<0.001). The secondary endpoint occurred in 73.4% of the patients treated with spinosad compared to 24.8% of patients treated with permethrin (RR 2.83; 95%CI, 2.39 - 3.37). Application site erythema was experienced with spinosad in 3.1% of patients compared to 6.8% of patients treated with permethrin (RR 0.45; 95% CI, 0.25 - 0.81; P=0.007). Adverse events were very similar between groups with application site erythema as the only significant difference with a higher occurrence in the permethrin group.[18]

This study was rated poor quality because it was not blinded to patient or care-giver, it was unclear if the evaluators were blinded and allocation concealment was not described.[19] In addition, withdrawals were not reported and the FDA agreed to reduce safety evaluations based upon proven safety in Phase II trials. Only the first 25 qualifying pediatric participants in each study had clinical laboratory assessments on days 0 (screening) and day 14. The safety results were not reported but the authors stated in the text there were no serious adverse events in spinosad group and three serious adverse events in permethrin group.[19] The results of this study are suspect due to lack of data. Therefore, spinosad should be further evaluated before it can be recommended over permethrin.

Ivermectin

Ivermectin lotion was FDA approved for lice in February of 2012. It is a semisynthetic anthelminthic agent that binds selectively and with strong affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells.[20] This leads to increased permeability of cell membranes to

chloride ions then hyperpolarization of the nerve or muscle cell, and death of the parasite. Ivermectin is a FDA pregnancy category C drug. The topical form is available for children ≥6 months.[20]

There are no current published studies comparing ivermectin 0.5% lotion to either permethrin or malathion, but there were two identical multi-center, randomized, double-blind, vehicle-controlled studies conducted on patients 6 months of age and older with head lice infestation. In both studies, all subjects received a single application of either ivermectin lotion or vehicle control with instructions not to use a nit comb.[22] In study 1, there were 16.2% (12/74) in the vehicle group and 76.1% (54/71) in the ivermectin group who were lice free at the end of the treatment period. In study 2, there were 18.9% (14/74) in the vehicle group and 71.4% (50/70) in the ivermectin group who were lice free at the end of the treatment period.[22] The quality of these studies cannot be evaluated and the placebo evidence does not allow a comparison to currently available therapies.

Oral ivermectin is FDA approved for strongyloidiasis of the intestinal tract. The use of oral ivermectin (400 mcg/kg in 3 mg tablets on days 1 and 8) for off-label head lice treatment was compared to a single application of malathion 0.5% lotion in a double-blind RCT.[21] The study only included patients 2 years and older that had previously failed either permethrin or malathion within the 2-6 week prior. It was pre-established as a non-inferiority study at absolute risk reduction (ARR) of 5% for the primary outcome of proportion of patients lice free at day 15. The secondary outcome was lice free on day 29.[21]

The primary outcome occurred in 95.2% of the patients treated with oral ivermectin compared to 85% of patients treated with malathion lotion (RR 1.12; 95%CI, 1.07 - 1.17; P<0.001).[21] The secondary outcome occurred in 96.2% of the patients treated with ivermectin compared to 87.4% of patients treated with malathion (RR 1.10; 95% CI, 1.06 - 1.15; P<0.001). In addition, 1.76% ivermectin and 1.21% malathion patients withdrew from the study due to adverse events (RR 1.46; 95% CI, 0.47 - 4.56). The ivermectin patients discontinued due to impetigo, nausea or vomiting, gastroenteritis and convulsions. The malathion patients discontinued due to rash or urticaria and gastroenteritis.[21]

The study met non-inferiority, but even though there was a response of 95.2% in the ivermectin group compared to 85% in the malathion group, it did not establish superiority because the lower CI dropped below 5% (ARR 10.2%; 95% CI, 4.6 - 15.7). Withdrawals due to adverse events were not appreciably different.[21] This was a good quality study because it was blinded, the treatment allocation was concealed, and it included an intention to treat analysis. [19] Oral ivermectin can be considered a second-line treatment option for head lice in those patients 2 years of age and older that have failed previous treatments.

Challenges

Increased resistance to permethrin 1% has been documented in the United States approaching 50% with different resistance rates dependent on geographical location.[23] Criteria for documenting resistance is based on correct use of a product and is generally accepted as the presence of lice two to three days after a treatment or after two treatments for a pediculicidal agent like permethrin or malathion.[24] Recent trials have monitored allele frequencies and identified mutations.[25,26] Not one mutation has been shown to cause all resistant occurrences.

Place in therapy

There is limited data from two poor quality RCTs that the use of topical spinosad is superior to permethrin for treatment of head lice not resistant to permethrin. Safety data was not reported. Topical ivermectin was evaluated only against placebo so comparisons to permethrin cannot be made. One small RCT trial concluded oral ivermectin was non-inferior to topical malathion for treatment resistant head lice. Until more evidence is available permethrin is recommended first line with malathion as an alternative in cases where resistance is high or permethrin fails to effectively treat head lice.[23] Table 1 summarizes the products discussed.

Table 1. Formulation, directions for use, and adverse effects of each agent.[27,28]

Agent	Formulation	Directions for use	Adverse effects	Retail Cost
Permethrin (Nix)	1% cream rinse, 5% cream	Apply after shampooing, leave on 10 minutes, rinse. Retreat in 7-10 days if live lice are seen	Local irritation	$20, $60
Malathion (Ovide)	0.5% lotion	Apply to dry hair, leave on 8-12 hours, rinse. Repeat in 7-10 days if live lice are seen	Flammable vehicle	$185
Lindane	1% shampoo, lotion	Apply to dry hair, leave on 4 minutes, rinse. No re-treatment	CNS toxicity, increased seizure risk	$125, $85
Spinosad (Natroba)	0.9% topical suspension	Apply to dry hair, leave on for 10 minutes, rinse.	Local irritation	$220
Ivermectin (Sklice)	0.5% lotion	Apply to dry hair, leave on 10 minutes, rinse.	Local irritation	$250
Ivermectin (Stromectol)	3mg, 5mg tablets (off label)	200mcg/kg/dose; repeat in 7-10 days	Headache, dizziness, nausea	$33 (6 tabs)

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