Head Lice Resistance Rendering OTCs Ineffective

Brought to you by ParaPRO with contributions from
Dr. J. Marshall Clark, PhD

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Dr. Clark is a professor in the Department of Veterinary & Animal Sciences at the University of Massachusetts, Amherst and director of the Massachusetts Pesticide Analysis Laboratory. Dr. Clark has spent the majority of his career at UMass Amherst, joining the university shortly after receiving his PhD in entomology with a specialty in environmental toxicology from Michigan State University in 1981.

Dr. Clark has over 400 publications including more than 200 peer-reviewed articles and 38 book chapters, predominantly in the areas of insect/invertebrate toxicology, vertebrate toxicology, and environmental chemistry.

Prior to receiving his PhD, Dr. Clark earned an MS in entomology, specialty in insecticide toxicology and a BS in zoology from the University of Wisconsin-Madison. He is a Fellow of the AGRO Division of the American Chemical Society and the Entomological Society of America.

Dr. Clark is an educational consultant on the topic of head lice, supported by ParaPRO, LLC.

Overview

Resistance—A Natural Phenomenon of Evolution

Human head lice still represent a sizable portion of one of the longest and most prevalent parasitic infestations of humans. Its effects on families and communities are both economic and social. In the past 10 years, significant progress has been made in the study of head lice and the information generated has led to a number of new developments for their control. The in vitro rearing of head lice has allowed the establishment of insecticide-susceptible and -resistant reference strains, which have allowed more formal descriptions of pediculicide resistance, its underlying mechanisms, and the detection and monitoring of resistance.

Pediculosis capitis, or head lice infestations, is a worldwide problem that affects predominantly children aged 3 to 11 years old, but can affect people of any age.[1] In the US, pediculosis capitis affects approximately 8% of school-aged children, with 2.6 million households affected and the costs of pediculosis capitis estimated at >$1 billion USD per year.[2]

Over the past 70 years, control of pediculosis capitis has been largely dependent upon the availability of natural and synthetic insecticides starting with DDT (1943), natural pyrethrins (1945), the organochlorines (1960), organophosphorous insecticides (1971), carbamates (carbaryl, 1977) and synthetic pyrethroids (permethrin, phenothrin, 1992).[3] In the United States, the pyrethrins/

pyrethroids have dominated the over-the-counter (OTC) market. Insecticide resistance to currently used pediculicides, including permethrin, synergized pyrethrins, organochlorines, and organophosphorous agents, has occurred worldwide and is certainly contributing to increased incidences of pediculosis capitis.[4-7] Resistance is an acquired trait that an insect develops over time through selective pressure created by prolonged use of insecticides. Due to resistance, we need to understand the biological mechanisms leading to resistance and identify new target sites, in order to develop and implement novel control and resistance management strategies.

Knockdown Resistance is Well Established in the United States

> **"Early studies suggested that resistance to pyrethroids and pyrethrins insecticides is caused by a genetic resistance mechanism, known as knockdown resistance or *kdr*[10-13]"**

Pyrethroids and pyrethrins are neurotoxic to lice. They both act by targeting neuronal voltage-sensitive sodium channels leading to hyperexcitation of the nervous system due to the influx of sodium ions, which causes membrane depolarization. This action ultimately leads to paralysis and death.[8,9] Agents containing pyrethroids and pyrethrins are readily available over-the-counter and because of their extensive use have resulted in resistance at a concerning level. Early studies suggested that louse resistance to pyrethroids and pyrethrins is caused by a genetic resistance mechanism, known as knockdown resistance or *kdr*, where mutations cause amino acid substitutions in voltage-sensitive sodium channels, leading to target site insensitivity.

In lice, *kdr* is due to 3-point mutations in the α-subunit gene of the voltage-sensitive sodium channel (M815I, T917I, and L920F).[10] In the presence of these 3 mutations, the hyperexcitation of the nervous system due to the influx of sodium ions does not occur.[11] The lack of hyperexcitement prevents paralysis and death of the louse. In a 2012 study, 98.7% of the sequenced lice were homozygous for the three kdr mutations.[12] This high frequency of *kdr* mutations suggests that increased insecticide selection pressure due to the overuse of pyrethrins and pyrethroids has occurred. The fact that the *kdr* mutations were homozygous in so many lice also suggests that they are widespread and susceptible alleles at the three loci are rare.

> **"... a 2016 clinical report, which demonstrated an increase in the frequency of *kdr* gene mutations to 98.3% in lice collected from 138 collection sites (rural and metropolitan) in 48 states[13]"**

The *kdr* resistance to pyrethrins and pyrethroids has had a dramatic impact on the therapeutic effectiveness of products containing them as noted in a 2016 clinical report, which demonstrated an increase in the frequency of *kdr* gene

mutations to 98.3% in lice collected from 138 collection sites (rural and metropolitan) in 48 states (Alaska and West Virginia were not included). The increased frequency of *kdr* mutations correlated well with the decrease effectiveness of the over-the-counter products containing permethrin seen in a number of clinical studies.[13]

Other Resistance Issues

Malathion, a phosphorodithioate-type organophosphorus insecticide, is an indirect nerve toxin that acts by inhibiting acetylcholinesterase activity in vivo.[14] Inhibiting acetylcholinesterase prevents the efficient hydrolysis of the neurotransmitter acetylcholine, resulting in overstimulation of postsynaptic effector organs, such as muscles, causing paralysis and death. Malathion was removed from the market in the United States twice due to issues with flammability, odor, and prolonged application time but was reintroduced in 1999.[15]

"In Europe, widespread malathion resistance has been reported.[16] Current levels of resistance to malathion-containing products in the United States have not been reported.[17]"

In Europe, widespread malathion resistance has been reported.[16] Current levels of resistance to malathion-containing products in the United States have not been reported.[17] This difference may be due, in part, to formulation differences between that used in Europe versus the United States and likely[18] due to the lack of recent clinical studies determining resistance levels to this insecticide. Studies on malathion-resistant lice from the UK have shown that enhanced malathion carboxylesterase activity is the major cause of resistance.[19] It is likely that similar findings will occur with continued used of malathion-containing products in the United States.

Lindane, an organochlorine insecticide, is a direct nerve toxin, which induces hyperexcitability accompanied by convulsions by blocking the gamma-aminobutyric acid-gated chloride channel, ultimately leading to paralysis and death of lice. Resistance to lindane has been reported for many years[3]. Its potential toxicity, label restrictions and the availability of safer and more effective alternatives have limited lindane's use[19].

Potential Impact of Resistance on Pediculicides, Now and in The Future

In states, regions, or countries where resistant lice are common, many patients find themselves self-treating numerous times with over-the-counter pediculicides

before seeking treatment from a physician or healthcare professional.[21]

Overexposure of over-the-counter pyrethroids and pyrethrin's as well as prescription organophosphorus (malathion) and organochlorine (lindane) agents, beyond their recommended application frequencies, as determined from their labels, can induce many known side effects ranging from headaches, dizziness, and nausea; to muscle tremors, slow heart rate, and abdominal pain; to neurotoxicity, reproductive toxicity, and to hepatotoxicity, respectively.[20]

"New pediculicides need to be safe to humans, rapidly eliminate live lice and viable eggs, show no cross-resistance to other products, and be easily used and affordable.[15]"

As new pediculicides are introduced into the marketplace, it is imperative that we understand how lice may develop resistance or cross-resistance to these compounds. It's also imperative that the molecular mechanisms mediating resistance be identified for effective resistance monitoring and management. New pediculicides need to be safe to humans, rapidly eliminate live lice and viable eggs, show no cross-resistance to other products, and be easily used and affordable.[15]

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