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Insecticide resistance in head lice: clinical, parasitological and genetic aspects

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Abstract

Insecticide treatment resistance is considered to be a major factor in the increasing number of infestations by head lice. The large insecticide selection pressure induced by conventional topical pediculicides has led to the emergence and spread of resistance in many parts of the world. Possible mechanisms of resistance include accelerated detoxification of insecticides by enzyme-mediated reduction, esterification, oxidation that may be overcome by synergistic agents such as piperonyl butoxide, alteration of the binding site, e.g. altered acetylcholinesterase or altered nerve voltage-gated sodium channel, and knockdown resistance (*kdr*). Clinical, parasitological and molecular data on resistance to conventional topical pediculicides show that treatments with neurotoxic insecticides have suffered considerable loss of activity worldwide. In particular, resistance to synthetic pyrethroids has become prominent, probably because of their extensive use. As other treatment options, including non-insecticidal pediculicides such as dimeticone, are now available, the use of older insecticides, such as lindane and carbaryl, should be minimized, owing to their loss of efficacy and safety concerns. The organophosphorus insecticide malathion remains effective, except in the UK, mostly in formulations that include terpineol.

Keywords: Head lice, insecticide resistance, malathion, pyrethroids, topical pediculicide
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Introduction

Head lice infestation caused by *Pediculus humanus capitis* (De Geer) is the most prevalent human ectoparasitic disease worldwide. Head lice are haematophagous, wingless insects belonging to the order Anoplura. Head lice infestation is particularly frequent among children 3–11 years of age, and may induce skin irritation, superinfection from scratching, social stigmatization, and psychological distress [1]. The economic implications are also substantial. An increased rate of louse infestation in recent years has been reported from North and South America, Australia, and a few countries in Europe and Asia [2–4]. Unlike body lice, which are vectors for typhus, recurrent fever, and trench fever, head lice are not known to transmit human infectious pathogens. However, DNA of *Bartonella quintana*, a bacterium that causes trench fever in humans, has been detected in head lice [5–7].

Treatment relies widely on the use of topical insecticides, such as topical pyrethroids or malathion, that have been recommended as first-line treatments by some national health authorities, such as in France. Other options are available, including topical non-neurotoxic agents such as dimeticone [8], and physical methods such as bug busting, albeit with variable results [9]. Other strategies using topical plant-based compounds or essential oils require further evaluation, even though some of them are already marketed. Most of the topical pediculicidal treatments are sold over the counter. Oral treatment with ivermectin is not currently recommended as a first-line treatment, but could be useful for head louse

infestation that is unresponsive to insecticide topical treatment [10].

The large insecticide selection pressure induced by conventional pediculicides has led to the emergence and spread of resistance in many parts of the world. Resistance to insecticides may induce treatment failures, which may result in chronic infestations requiring additional and episodic treatments. Additional treatments generate costs, possible toxicity, increased inconvenience, and increased insecticide selection pressure.

Detecting insecticide resistance is not easy. The persistence of living head lice after use of a pediculicide may have several causes, including: lack of adherence of the patient to the treatment protocol; incorrect treatment (underdosing or misusing); lack of ovicidal or residual killing properties of the product, leading to self-re-infestation; re-infestation (lice re-acquired after treatment); and authentic resistance of lice to the pediculicide.

Different patterns of resistance have been described: clinical resistance (i.e. persistence of live lice 1 day after insecticide application); parasitological resistance (i.e. *ex vivo* resistance of head lice to pediculicide compounds); and genetic resistance (i.e. the presence of polymorphisms in genes associated with *ex vivo* (and clinical) resistance).

The objective of this review is to describe the current knowledge about insecticide resistance, considering clinical, parasitological and molecular data. This review will be limited to conventional topical pediculicides.

Pyrethroids

Natural pyrethrum was introduced in 1945 (Table 1), and was later replaced by synthetic derivatives called pyrethroids. Indeed, pyrethroids, including d-phenothrin and permethrin, have been registered as pediculicides since the 1970s, and have been widely available since the 1980s. These compounds have been chemically altered to provide better stability to heat and light than natural pyrethrum. Pyrethroids make up most over-the-counter insecticides sold for head lice treatment. Pyrethroids are neurotoxins that modify voltage-gated sodium channels (VGSCs) by keeping the channel open for abnormally long periods, leading to spastic paralysis and death of the lice. Pyrethroids have also a rapid effect in immobilizing insects, called knockdown, which often precedes the lethal action.

The exact impact of pyrethroid resistance on effective control is not known. Pyrethroid resistance in head louse populations appears to be widespread in various countries, but varies in intensity and is not yet uniform [11]. In 1983, the reported clinical efficacy in a study from Panama was optimal [12] (Table 2). Clinical and parasitological resistance to pyrethroids was first reported in France (1994), on the basis of a randomized controlled trial [13]. In this study, the clinical efficacy of d-phenothrin was only 39% at day 7 (Table 2), which probably reflected an already well-established resistance to pyrethroids by head lice in the study sites. The subsequent main clinical studies, conducted mostly in the USA and the UK, are summarized in Table 2. Clinical efficacy assessed on day 7 following application of the compound ranged from 10% [9] to 79.5% [14].

TABLE 1. Main topical formulations of insecticides available for the treatment of *Pediculus capitis*

Drug	Class	Year introduced	Formulation
Natural pyrethrum	Pyrethrins	1945	Spray 1%, piperonyl butoxide (Spray-Pax)
Permethrin	Synthetic pyrethroid	1992	Lotion 0.5% (Nix) Shampoo 0.3%, piperonyl butoxide Cream rinse 1%
Phenothrin	Synthetic pyrethroid	1992	Liquid 0.5% in an aqueous base Lotion 0.2% Mousse 0.5%
Malathion	Organophosphorus	1971	Liquid 0.5% in an aqueous base Lotion 0.5% in an alcoholic base, terpineol, and pine needle oil (Ovide; Prioderm)
Carbaryl	Carbamate	1977	Carbaryl 1% in an aqueous base (Carylderm)
Lindane	Organochlorine	1960	Shampoo 1%

Meanwhile, parasitological resistance was reported from Europe (Czech Republic [15], the UK [16], and Denmark [17]), Israel [18], the USA [3,19–21], Argentina [22,23], Japan [24], and Australia [25]. It should be stressed that resistance detection with bioassay-based methods is often difficult [26]. The lack of standardization of bioassays makes it difficult to compare results from different studies [27]. In addition, the slower kill times or knockdown responses for permethrin, for example, that were observed in bioassays were not necessarily synonymous with clinical failure, as the insecticide killed all of the lice, albeit more slowly, at the end of the test. In clinical practice, longer exposures could result in relatively good efficacy, even on 'resistant' head lice.

The molecular events that govern the resistance to pyrethroids have been at least partly elucidated. Early reports indicated that permethrin resistance in head lice was mostly conferred by the recessive *kdr* trait [20]. Three point mutations (M815I, T917I, and L920F) in the VGSC α-subunit gene associated with permethrin-resistant phenotypes were suggested to be responsible for *kdr*-type resistance [28]. Sequence analyses of cloned cDNA fragments and genomic

TABLE 2. Efficacy of topical insecticides for the treatment of *Pediculus capitis* in main clinical trials

Compound	Study site	Year	Number of patients	Cure rate Day 7 (%)	Cure rate Day 14 (%)	References
Permethrin creme rinse 1%	Panama	1983	29	100	97	Taplin 1986 [12]
d-Phenothrin lotion 0.3%	France	1992	98	39		Chosidow 1994 [13]
Permethrin creme rinse 1%	USA	1996–1999	39		79.5	Hipolito 2001 [14]
Phenothrin lotion 0.5%	UK	2003	125	78		Burgess 2005 [58]
Permethrin creme rinse 1%	USA	Reported in 2004	22	55		Meinking 2004 [59]
Permethrin creme rinse 1%	UK	Reported in 2005	40	10		Hill 2005 [9]
Permethrin creme rinse 1%	USA	Reported in 2007	10		50	Meinking 2007 [38]
Malathion lotion 0.5%	UK	Reported in 1981	108		98	Maunder 1981 [48]
Malathion lotion 0.5%	Canada	Reported in 1984	29	93		Mathias 1984 [49]
Malathion lotion 0.5%	France	1992	95	95		Chosidow 1994 [13]
Malathion lotion 0.5%	UK	Reported in 2000	40	78		Roberts 2000 [56]
Malathion lotion 0.5% (Ovide)	USA	Reported in 2007	28		100	Meinking 2007 [38]
Malathion lotion 0.5%	UK, Ireland, France, Israel	2004	327	90		Chosidow 2010 [10]
Malathion lotion 0.5% (Ovide)	USA	Reported in 2004	41		98	Meinking 2004 [59]
Aqueous malathion 0.5%	UK	Reported in 2005	30	17		Hill 2005 [9]
Aqueous malathion 0.5%	UK	2006	29	34.5		Burgess 2007 [8]
Malathion gel 0.5%	USA	Reported in 2007	51		100	Meinking 2007 [38]
Lindane lotion 0.5%	UK	Reported in 1981	97		91	Maunder 1981 [48]
Lindane shampoo 1%	UK	Reported in 1981	57		86	Maunder 1981 [48]
Lindane shampoo 1%	Panama	1983	30	67	43	Taplin 1986 [12]
Lindane shampoo 1%	Canada	Reported in 1984	33	88		Mathias 1984 [49]
Carbaryl lotion 0.5%	UK	Reported in 1981	81		100	Maunder 1981 [48]
Carbaryl shampoo 0.5%	UK	Reported in 1981	64		97	Maunder 1981 [48]

DNA fragments from individual louse samples confirmed that all of the mutations exist *en bloc* as a resistant haplotype. Further experiments using site-directed mutagenesis at the corresponding amino acid sequence positions of the house fly *para*-orthologous VGSC α-subunit (*Vssc1WT*) gene and heterologous coexpression with the sodium channel auxiliary subunit of house fly (Vsscβ) in *Xenopus* oocytes showed that the T917I mutation was the main cause of permethrin resistance in head lice via a *kdr*-type nerve insensitivity mechanism [23].

The frequency of the resistant *kdr*-like haplotype is extremely variable, according to geographical area. A recent study reported a resistant *kdr*-like allele frequency of 0.00 for lice from Ecuador, Papua New Guinea, South Korea, and Thailand [29], whereas lice from Uruguay, the UK and Australia had a frequency of 1.00. Values ranging from 0.11 to 0.97 were found for Brazil, Denmark, the Czech Republic, Egypt, and Israel. A study published in 2003 reported a resistant *kdr*-like allele frequency ranging from 0.33 to 1.00 in California, Florida, and Texas [11]. Other studies have also reported variable frequencies: 0.07 in Japan [30], 0.44 in Wales, UK [31], 0.93 in France [32], 0.95 in Denmark [17], and 0.97 in Canada [33]. Indeed, the widespread use of pyrethroids may have been a key factor in the selection of homozygous resistant lice. A recent article suggested that lice from countries that have easy access to pyrethroid-based pediculicides may have higher levels of *kdr* mutant alleles [29].

The high prevalence of *kdr* mutant alleles has to be interpreted with caution, as the T917I and L920F mutations in the *kdr* gene may not be correlated with treatment failure in prospective studies. Thus, a recent study including a limited number of lice in Germany reported that the presence of *kdr* mutant alleles did not correlate with clinical failure of pyrethroids [34]. Further clinical trials are required to document the relevance of *kdr* genotyping as predictive of the clinical outcome of pyrethroid treatment.

Monooxygenase activity may also be partially responsible for resistance to pyrethroids. Increased monooxygenase activity was associated with resistance to permethrin in a study by Gonzalez Audino *et al.* [35], using biochemical methods. In this study, piperonyl butoxide (PBO) significantly enhanced the toxicity of permethrin in four colonies of head lice, suggesting that this enzymatic system was responsible for a proportion of pyrethroid resistance. Indeed, the addition of PBO slows the biotransformation of pyrethrum and pyrethroids by partially inhibiting insects' cytochrome P450 enzymes, which significantly improves their effectiveness. Thus, PBO is a compound included in the formulation of some pediculicides containing pyrethrins [26]. Permethrin resistance did not appear to be associated with glutathione-*S*-transferase activity in a study conducted in Israel [36].

Malathion

Malathion, a neurotoxic organophosphorus insecticide, binds irreversibly to acetylcholinesterase when converted to its oxon form, inhibiting its function, and causing spastic paralysis and death of the lice. Malathion is used in 0.5% formulations, which kill lice rapidly (within 20 min), even though the duration of application recommended by the FDA and

French health authorities is approximately 8 h. Malathion was removed from the US market in 1990 (Prioderm; Purdue Frederick Company, Norwalk, CT, USA) and in 1994 (Ovide; Medicis Pharmaceutical Corporation, Lakewood, NJ, USA), owing to problems related to prolonged application time, flammability, odour, and low sales. Ovide was re-introduced into the US market in 1999, because of the decreased efficacy reported for other insecticides, such as organochlorines and pyrethroids [37]. Malathion remained continuously on the market in Europe during the same period. Malathion is available only as a prescription product in the USA.

Head lice seem to have developed less resistance to malathion than to pyrethroids. In the early 1990s in France, 0.5% malathion lotion showed higher ovicidal and pediculicidal activity than 0.3% d-phenothrin lotion in a randomized controlled trial [13]. A more recent randomized, investigator-blinded study reported the same higher efficacy of 0.5% malathion, either in gel or in Ovide lotion, than of 1% permethrin (Nix, Creme Rinse) [38]. Ovide lotion contains 0.005 g of malathion per millilitre in a vehicle of isopropyl alcohol (78%), terpineol, dipentene, and pine needle oil. Interestingly, 30-min, 60-min or 90 min applications of 0.5% malathion gel were as effective as 8-h to 12-h applications of Ovide lotion. Using malathion with shorter application times may contribute to lowering the insecticide selection pressure and reducing residual concentrations, which may result in delayed emergence and spread of resistance.

Resistance to malathion was first reported in France [39], and then in the UK [2], Australia [25], and Denmark [17]. The effectiveness of malathion in a single-blind, randomized study in the UK was poor, showing cure rates of only 17% (n = 30) [9]. Low levels of malathion resistance were reported in 2004 in head lice collected from Florida and southern California [40]. The difference in efficacy observed between European countries and the USA may be related to its continuous use in Europe during the past 30 years, in contrast to the USA, and/or variations in formulations marketed in the respective continents [41]. Ovide formulation, which is available only in the USA (an equivalent formulation, Prioderm, is available in other countries), remains effective against head lice, even those collected in countries in which proven resistance to other malathion formulations has been found. Ovide vehicle (Ovide formulation without malathion) was first determined to have significant pediculicidal action, probably because of the isopropanol and terpenes that are included in this formulation [42]. Ovide formulation contains α-terpineol in its vehicle, which has its own insecticide effect according to a report of Downs *et al.* [43]. This 'combination' may have prevented the emergence and spread of resistance in the USA.

No mechanisms for malathion resistance have been formally reported in head lice. In a variety of insects, malathion resistance is mainly attributed to elevated esterases. Esterases may contribute to resistance by rapid hydrolysis of insecticides to their inactive forms or/and by sequestration. Using bioassays and biochemical methods, Gao *et al.* [44] found that esterases, particularly a carboxylesterase, were involved in the metabolism of malathion in a head louse strain collected from Bristol, UK, and may be involved in resistance. Malathion-resistant cases from the UK were proposed to be linked to modified acetylcholinesterase [2,41,45]. Other putative mechanisms of malathion resistance in other insects involved elevated metabolism by cytochrome P450 monooxygenases, glutathione-*S*-transferases, and phosphotriesterases [44]. In addition, synergist studies linked malathion-resistant head lice from the USA to multiple-resistance mechanisms [40]. In a study performed in 2000 in schoolchildren from Wales, Thomas *et al.* [31], using biochemical methods, did not find any increased activity of microsomal monooxygenases and total esterases. Gao *et al.* [44] did not report altered activities of phosphotriesterases, glutathione-*S*-transferases, or acetylcholinesterase.

As a firmly established and unambiguous mechanism of resistance is currently lacking, no molecular marker of malathion resistance is currently available. Consequently, *ex vivo* tests (bioassays) and clinical surveys are required to study the efficacy of malathion.

Lindane

Lindane (γ-hexachlorocyclohexane) is a non-aromatic organochlorine insecticide. When body lice developed widespread resistance to DDT in the 1950s, owing to *kdr*, lindane, an insecticide that acts on the γ-aminobutyric acid-gated chloride channel and not on the VGSC, was introduced, and quickly became the treatment of choice for head and body lice. Before the introduction of pyrethroids, lindane was the most widely used pediculicide in the USA [46]. Available only by prescription as a 1% shampoo, lindane has neurotoxic properties resulting in the death of the insect by overstimulation of its central nervous system. However, it has only low ovicidal activity (30–50% of eggs are not killed) [47].

Resistance has been reported worldwide for many years [16,46]. Cure rates assessed on day 14 following application of the 0.5% lotion or 1% shampoo varied from 43% to 91% in the 1980s [12,48,49] (Table 2).

One per cent lindane shampoo was the least effective pediculicide tested in a study that compared lindane, malathion, pyrethrin and permethrin efficacy against treatment-resistant

and treatment-sensitive lice collected in Florida and Panama, respectively. After 3 h of exposure, only 17% and 61% of lice from Florida and Panama, respectively, were dead [21]. However, lindane was still effective in 1999 in South Korea, where another *in vitro* study revealed a success rate of 93% [50].

There are concerns that the poor efficacy of lindane will result in reapplication and overuse that increase the risk of adverse events, some of which may be serious, including cases of severe seizures in children. Owing to potential neurotoxic effects, especially when applied on the whole body surface area of lesional skin (i.e. scabies) [51] and poor effectiveness in practice [52], lindane is no longer recommended by the American Academy of Pediatrics, the Medical Letter, or the Stafford Report 2008 update, UK. The use of lindane has been banned in California. Finally, recommendations range from using it with extreme caution to withdrawing it from the market completely [21]. The European Union prohibited the use of lindane as an insecticide by the end of 2007.

Carbaryl

Carbaryl, introduced in 1977, is a carbamate insecticide that acts by reversibly inhibiting acetylcholinesterase, leading to spastic paralysis and death. It is used in 0.5–1% lotions or shampoos. Its clinical efficacy was reported as being total in 1981 [48], and ranged from 78% to 92% in 1991 [53,54]. A study performed in 1998 reported two therapeutic failures (n = 18) with 1% carbaryl lotion in Leeds, UK [45]. Exposure of head lice to concentrations ranging from 0.8 to 3.2 g per 100 mL of carbaryl showed decreased efficacy, and an enzymatic study showed an altered response of acetylcholinesterase to carbaryl of head lice from this region [45]. Since 1995, it has been available only on prescription, because of concerns about possible carcinogenic effects. One per cent carbaryl in aqueous formulation is still recommended by the guidelines based on the Stafford Report 2008 update, but it is no longer manufactured in the UK.

Conclusions

A major factor resulting in increasing numbers of head lice infestations is insecticide treatment resistance. Resistance is an acquired trait that an insect pest develops over time through selective pressure created by prolonged use of insecticides. Some pediculicides have already become ineffective, and others are likely to meet the same fate. Over the years, different insecticides have been used to control lice, and resistance patterns vary between countries and between regions within a country. Ideally, the choice of treatment should depend on local resistance patterns, but information about resistance is rarely available. Therefore, molecular markers, such as *kdr*-like polymorphisms, may be useful because they allow the processing of large numbers of insect from many populations in relatively short periods of time. Unfortunately, such molecular markers are presently lacking for organophosphorus insecticides, and clinical trials remain the reference standard for the survey of resistance to malathion.

There is strong evidence that head louse populations are continuing to develop resistance. Unnecessary and excessive use of pediculicides is frequent. The availability of many over-the-counter pediculicides makes resistance management by moderation and/or rotations/mixtures difficult, if not impractical. When control fails, the usual strategy is to use a different insecticide, preferably of another class, for the next course of treatment. Unfortunately, the number of available conventional pediculicides is shrinking, as indicated by the foreseeable elimination of lindane and carbaryl. Pyrethroids have become much less effective, and even malathion resistance is probably evolving upon increased use, as shown in the UK.

As shown by some recent clinical trials, the use of non-insecticidal pediculicides, such as dimeticone lotion, may be an effective treatment [8,55]. However, no one can guarantee that head lice will not develop other forms of resistance to these non-insecticidal pediculicides in the future. In addition, alternative treatments, such as dimeticone or bug busting, still have controversial results in comparison with insecticides in randomized controlled trials [9,56,57].

Transparency Declaration

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