

Dimeticone-Based Pediculicides: A Physical Approach to Eradicate Head Lice

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Abstract: Resistance of head lice to insecticides with a neurotoxic mode of action, such as permethrin and malathion, is increasing in incidence and geographic extent. As a consequence, physically acting pediculicidal products have emerged. Dimeticones are synthetic silicone oils of low surface tension and can therefore coat most surfaces, thus also killing head lice (*Pediculus humanus capitis*) by physical means. Considering this mode of action, the development of head lice resistance in the future is very unlikely. In this review, *ex vivo* and clinical evidence on the efficacy of dimeticones against head lice is presented. Besides the high adulticidal and excellent ovicidal *ex vivo* efficacy, clinical efficacy of high concentrated dimeticone has been shown. We conclude that dimeticone-based products are a safe and effective option for those patients who prefer not to use pediculicides with a neurotoxic mode of action, especially in areas where resistances of head lice against permethrin and malathion-based products have been reported, or are suspected.

Keywords: Dimeticone, head lice, pediculosis, physical mode of action, treatment.

INTRODUCTION

Lice have been parasitizing man for many thousands of years [1], and still today head lice infestations are a common problem not only in resource-poor settings, but also in developed market economies [2, 3]. Throughout the world, prevalence of pediculosis even seems to have increased in the recent years [3].

Since ancient times, humans apply topical products for the treatment of pediculosis, and since the beginning of the 20th century, chemical topical pediculicides have been extensively used. However, some of these compounds are highly toxic, such as dichlorodiphenyltrichloroethane (DDT) and lindane - the latter has only recently been taken from the European market as a pediculicide. In addition, resistance to pediculicides with a neurotoxic mode of action, such as permethrin and malathion, is increasing in occurrence and geographic extent [4-9]. This has led to the search for new, more effective compounds with a better safety (non-toxic) profile and which are less susceptible for the development of insecticide resistance. In this context, several physically acting pediculicidal products have emerged as alternative treatments, with the silicone oil dimeticone at the forefront [10-16].

Dimeticones (synonyms: polydimethylsiloxanes; dimethylpolysiloxanes) are polymers considered non-toxic and physiologically inert to humans. They are synthetic silicone oils of low surface tension and can therefore coat most surfaces. These liquids consist of a silicon-oxygen chain with methyl side groups, molecular formula: $(C_2H_6OSi)_n$. The chain length (n) of the polymers determine the molecular weight and viscosity, as well as the creeping and spreading properties.

Dimeticones of different viscosities and concentrations are used for example in contact lenses, cookware, bandages, breast implants, lubricating oils, topically as shampoos and hair conditioners, orally as anti-flatulent products, and recently in topical head lice products.

MODE OF ACTION OF DIMETICONES AGAINST HEAD LICE

Two studies have shown that dimeticone kills head lice by physical means [17, 18]. A physical mode of action is of outstanding importance, as in this case the development of resistance of head lice against the compound is very unlikely. However, both studies disagree in relation to asphyxiation of lice as the cause of death. Böckeler & Richling (2008) claimed that the high concentrated (92%) two-phase dimeticone product NYDA[®] was capable of entering the tracheal system, with subsequent asphyxiation of lice [18]. The silicone oil would coat the louse surface and enter the entire respiratory tract, thereby blocking spiracles and tracheae. They observed that this dimeticone product even filled the head tracheae and fine tracheal branches,

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displacing air and blocking oxygen supply of the louse's central nervous system. The authors further noticed that the lice were immobilized within one minute and that this was strongly correlated with the time of the influx of dimeticone into the head tracheae. In contrast to these observations, Burgess (2009) argued that dimeticones had a high oxygen permeability and, based on his studies on a 4% dimeticone/96% cyclomethicone product (Hedrin[®], marketed in other countries as EtoPril[®], Pouxit[®], Piky[®], Neositrin[®] or XTLuis[®]), suggested that this dimeticone lotion was killing lice by entering spiracles and tracheae of lice, which would lead to disruption of water management, subsequent osmotic stress and gut rupture [17, 19]. He observed weight loss in untreated lice, as compared to lice treated with 4% dimeticone, indicating inhibition of water loss in treated lice. Forty-five until 280 min after treatment, lice treated with 4% dimeticone lost 6% weight, as compared to 35% weight loss in an untreated control group [17].

Scanning electron microscopy studies have shown that deposits of dimeticone formed a coating inside the spiracle, or even blocked the entire spiracle opening (in the case of 4% dimeticone) [17] and that the cuticle was coated by dimeticone, also entering the stigmata (92% dimeticone) [18]. In conclusion, independent to the different modes of action described, both dimeticone products kill lice by physical means.

LABORATORY AND CLINICAL EVIDENCE

Ex Vivo Adulticidal Efficacy

We have recently performed two standardized *ex vivo* studies on adult head lice from Brazil, showing that a product based on dimeticone in a high concentration (92%) has an excellent efficacy [20, 21]. In both studies, after 20 min contact time, lice treated with the commercial two-phase dimeticone product NYDA[®] showed no or only minor vital signs already after 5 minutes, and this effect persisted at all observation points within 24 hours (100% efficacy). In addition, another two-phase dimeticone product ("NYDA[®] sensitive") was tested, a similar product without fragrances. Efficacy was similar to the first product containing fragrances [20]. Low-concentration 4% dimeticone/96% cyclomethicone (Hedrin[®]) produced a mortality of 74% after 6 hours; some lice that showed no or minimal vital signs few minutes after application, recovered after several hours, which was allocated to the reduced contact time of 20 min, as compared to clinical application of several hours [21]. In these studies, the efficacy of 1% malathion (100%) was similar to high concentration dimeticone, but efficacy of 0.5% permethrin (two products of 0.5% alcoholic solution and 1% aqueous lotion) ranged from 76% to 96% 10 min until 6 hours after application of products, and pyrethrum extract did not show satisfactory efficacy [20, 21]. In fact, a study assessing available OTC products in Brazil found varying efficacy of permethrin-based products and suggested that the formulation would influence efficacy, but that permethrin-resistance may also occur in this area [22]. A recent study determining knockdown resistance gene mutations has shown the presence of permethrin-resistant lice collected in this Brazilian study area [23], which may be responsible for the low efficacy observed for permethrin products with a neurotoxic mode of action, in the comparative studies.

Ex Vivo Ovicidal Efficacy

Ovicidal efficacy of head lice products is often not known, as in clinical studies this can only be assessed indirectly e.g. by the number of premature stages (nymphs) found on a head several days after treatment, indicating inefficacy against eggs. In addition, most laboratory-based studies on ovicidal efficacy rely on eggs collected from infested individuals [24, 25], and thus study conditions are not standardized, nor is the exact age of eggs known.

A recent study has filled this gap, by using a standardized approach [26]. Efficacy against two different groups of eggs was assessed after 60 min of incubation in dimeticone products, as compared to other pediculicides on the market: young eggs (1-2 days after oviposition), and mature eggs (9-11 days after oviposition). Two silicone products containing high concentrations of dimeticone, namely NYDA[®] (mixture of two dimeticones of different viscosities in a total concentration of 92%) and Jacutin[®] Pedicul Fluid (100% pure dimeticone) had high ovicidal efficacy against young eggs (100% and 97.7%, respectively) [26]. The two-phase dimeticone significantly outperformed the pure dimeticone against mature eggs (94.9% vs 73.7% efficacy). The two-phase formula in NYDA[®] (one dimeticone with high viscosity, another with low viscosity and high volatility) may contribute to increased efficacy, as compared to the single dimeticone of high viscosity in Jacutin[®]. Dimeticone of low viscosity may function due to its creeping and spreading properties as a vehicle for the other dimeticone component of higher viscosity, thus facilitating entry into spiracles of lice [18].

A 4% dimeticone/96% cyclomethicone product (Hedrin[®]/EtoPril[®]) did not show efficacy against young or mature eggs in this study (0% and 0.3%, respectively). The reasons for the observed difference in ovicidal efficacy as compared to the two high concentration dimeticone products are not clear. A much higher rate of inhibited hatching was suggested in a recent clinical trial of 4% dimeticone [15]. These authors observed 22% and 33% of study participants with recently hatched nymphs a few days after topical treatment and thus assumed an ovicidal efficacy. However, the presence of nymphs in 100% was assumed in untreated participants, which does not reflect the real clinical situation, and probably led to an overestimation of the ovicidal effect [15].

In the abovementioned *ex vivo* ovicidal study, 0.5% permethrin (alcoholic solution) and 0.3% pyrethrum showed some efficacy against young eggs (45.1% and 17.0%, respectively), but both failed to kill mature eggs (0% efficacy). Previous studies have claimed a high ovicidal effect of 1% permethrin [25], whereas other authors reported low efficacy of permethrin and pyrethrum against eggs [27-29]. These observations may be due to different product formulations, differing methodological approaches, and also resistance patterns of lice and embryos [27]. A residual effect has been claimed to be responsible for "ovicidal efficacy" with residual permethrin on hairs killing newly hatched nymphs [30, 31], but this has not been assessed in the comparative ovicidal study, and there are no adequate studies to confirm this assumption.

Clinical Evidence

Several randomized comparative trials have shown clinical efficacy of low and high concentrated dimeticone products against head lice infestations [15, 16, 19, 32]. In a randomized comparative trial, we studied 145 children and teenagers in Brazil [16]. After nine days, the cure rate for those treated with a two-phase product containing a concentration of dimeticone of 92% (NYDA[®]) was 97%, as compared to 68% for those treated with a 1% permethrin product (aqueous lotion) [16]. Cure rate in the dimeticone group was independent of intensity of infestation: in participants with heavy infestations (≥ 5 lice found at visual inspection before intervention), cure rate was 97.1% in the dimeticone group, but decreased in the permethrin group (57.5%). Cosmetic acceptability was significantly better in individuals treated with dimeticone, as compared to the permethrin group. Two product-related adverse events were mild ocular irritations after direct contact of dimeticone with eyes, which resolved quickly.

Two other randomized studies from the UK revealed efficacy of 70% of 4% dimeticone/96% cyclomethicone (Hedrin[®]), as compared to 75% in patients treated with a 0.5% phenothrin product [19] and 33.3% in patients receiving treatment with 0.5% malathion [32]. More recently, Kurt *et al.* (2009) [15] achieved cure rates of 91.7% with Hedrin[®] and of 83.3% with a new formulation (4% dimeticone + 2% nerolidol in cyclomethicone) in a controlled trial involving 72 participants (14 days after treatment). In this trial performed in Turkey, cure rates were considerably higher than in the two previous trials from the UK [19, 32]. The difference in efficacy may be attributed to lower intensity of infestation in Turkey, differences in study design, and higher community-based engagement. However, as two dimeticone-based products were compared, comparisons with neurotoxic acting pediculicides cannot be made in the Turkish study.

SAFETY OF DIMETICONES

Toxicity

Dimeticones are commonly used in shampoos, conditioners, body lotions and similar products, and are safe for topical use [10, 33, 34]. As they are physiologically inert, they are not absorbed in the intestine or metabolized, and after oral ingestion they are eliminated unaltered in faeces. Therefore dimeticone is used orally as active ingredient in anti-flatulence products even for newborns and toddlers. In the animal model, no teratogenic, genotoxic or carcinogenic effects were observed after topical and oral application. The oils do not have any skin irritating, or sensitizing properties, and topical use in humans can be considered as safe [33].

Inflammability

One concern with the use of dimeticones against head lice has been its claimed inflammability. In fact, many pediculicidal products are inflammable, and most producers alert this in their package leaflets. Inflammable products include pyrethrum and permethrin-based compounds, malathion-based compounds, plant-based products, and the dimeticone-based products. Some compounds may not be inflammable by itself, but may facilitate burning of hair after application [35]. In addition, many pediculicides with a

neurotoxic mode of action are based on an alcoholic solution which enhances inflammability.

Several media reports from the Netherlands, France, UK and Denmark on severe burns have raised the issue on inflammability of dimeticone-based products [36-39]. For example, a five year-old girl from UK suffered from severe burns on face, head and neck after applying Hedrin[®] and playing with a lighter [39]. In another UK case, a 15 year-old boy played with a cigarette lighter after application of this 4% dimeticone/96% cyclomethicone lotion, and set fire on his hair [38]. In the Netherlands, a case of severe burn has been reported, as a man treated with this product came into proximity with the open flame of a gas water heater [36]. As a result of these incidents, in Hedrin[®] labelling has been included a warning statement: "Hair should be kept away from naked flames, cigarettes and other sources of ignition while treatment with Hedrin[®] is underway. Hedrin[®] is not water-based and will not prevent hair from burning".

All available reports of fire accidents with dimeticone-based products refer to this product containing 4% dimeticone and 96% cyclomethicone. Cyclomethicone is highly volatile and easily inflammable, and it can be assumed that the driving force for the accidents may be the cyclomethicone compound. There are no accidents reported from the use of high concentration dimeticone products, such as pure dimeticone (Jacutin[®]), silicone-based products containing plant compounds (Itax[®]), or the two-phase dimeticone NYDA[®] containing 92% dimeticone. The manufacturer of NYDA[®], who had included a warning statement on inflammability since its marketing in 2006, confirmed that after more than 2 millions of doses sold, no such incidents have been reported (Pohl-Boskamp GmbH & Co. KG; personal communication).

However, care should always be taken when using inflammable head lice products. Similar to other inflammable cosmetic products such as hair spray and perfumes, contact to cigarettes or open flames should always be avoided during treatment.

OUTLOOK

The number of available alternative head lice products to insecticides with a neurotoxic mode of action, such as compounds proven or claimed to be physically active (dimeticone, benzyl alcohol, oxyphthirine[®], isopropyl myristate), plant-based products or spinosad (a fermented product derived from the bacterium *Saccharopolyspora spinosa*) has been increasing in the last years. However, for many products formal efficacy testing has not been done, or has shown low efficacy [40]. Thus, we have previously suggested that government regulatory agencies should require standardized *ex vivo* pediculicidal tests and that only products causing high mortality of lice in these tests should be licensed for sale [40].

In addition, development of insect resistance is possible with products that do not kill head lice by physical means, and testing should be repeated in predetermined intervals. For example, the fruit fly *Bactrocera oleae* has already developed resistance against spinosad (which was commercially introduced in agriculture in 1997), even before the product has been marketed against pediculosis [41].

In this context, high-concentrated dimeticones can be considered an excellent option in head lice management. There is sufficient evidence proving high efficacy. Considering their ovicidal and pediculicidal efficacy, good safety profile and the physical mode of action that makes the development of resistance unlikely, the emergence of high concentration dimeticones can be considered a new era of head lice treatment. Dimeticone products are now established on the market and are commercialized in an increasing number of countries. For example, NYDA[®] is currently marketed in 12 European countries as well as in Turkey, Russia and the United Arabian Emirates. Jacutin[®] is marketed in Germany and Austria. The product containing 4% dimeticone (marketed as Hedrin[®], EtoPril[®], Pouxit[®], Piky[®], Neositrin[®] or XTLuis[®]) is currently available in 30 countries throughout the world (for a complete list of countries see: <http://www.hedrin.co.uk/Hedrin-in-country.html>). Itax[®] and Paramitex[®], two products containing a mixture of dimeticones and plant-based products, are available only in a limited number of European countries, and efficacy data of these compounds have not yet been published.

In conclusion, dimeticone-based products are a safe and effective alternative for those patients who prefer not to use pediculicides based on classical insecticides with a neurotoxic mode of action. They can also be regarded as a rescue therapy when traditional products failed to eradicate the lice due to resistance patterns. It can be speculated that in the next few years the physically acting pediculicides, with an unlikely risk of development of resistance, will drive out of the market the classical insecticides.

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