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(72) **Inventeur/Inventor:**
JOHANNESSEN, BAARD, NO

(73) **Propriétaire/Owner:**
NETTFORSK AS, NO

(74) **Agent:** SHAPIRO COHEN LLP

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(54) **Title: METHOD OF COMBATTING HUMAN HEAD LICE**

(57) **Abrégé/Abstract:**
The invention provides a method of treatment of a human subject to combat infestation by multicellular ectoparasites with exoskeletons, in particular head lice, which method comprises topically applying to said subject a first and a second pediculicide, said first pediculicide being a carbamate or organophosphate pediculicide and said second pediculicide being a pyrethroid or pyrethrin pediculicide, characterized in that said second pediculicide is applied between 15 minutes and 12 hours after the application of said first pediculicide.

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(71) Applicant *(for all designated States except US)*: **NETTFORSK AS** [NO/NO]; Langbryggen 19, N-4841 Arendal (NO).

(71) Applicant *(for GB only)*: **COCKBAIN, Julian** [GB/GB]; 42 Southmoor Road, Oxford OX2 6RD (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **JOHANNESSEN, Baard** [NO/NO]; Nettforsk AS, Langbryggen 19, N-4841 Arendal (NO).

(74) Agents: **COCKBAIN, Julian** et al.; Dehns, St Bride's House, 10 Salisbury Square, London EC4Y 8JD (GB).

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(54) Title: METHOD OF COMBATTING HUMAN HEAD LICE

(57) Abstract: The invention provides a method of treatment of a human subject to combat infestation by multicellular ectoparasites with exoskeletons, in particular head lice, which method comprises topically applying to said subject a first and a second pediculicide, said first pediculicide being a carbamate or organophosphate pediculicide and said second pediculicide being a pyrethroid or pyrethrin pediculicide, characterized in that said second pediculicide is applied between 15 minutes and 12 hours after the application of said first pediculicide.

METHOD OF COMBATTING HUMAN HEAD LICE

FIELD OF THE INVENTION

This invention relates to a method of topical treatment of living human subjects to combat multicellular ectoparasites with exoskeletons, especially ectoparasites of the orders *Phthiraptera* (lice), *Acarina* (mites) and *Siphonaptera* (fleas), more especially *Pediculus humanus capitis* (human head lice), and to a pharmaceutical kit for use in that method.

BACKGROUND

Many humans are infested with such multicellular ectoparasites, eg ticks, fleas, mites, and lice, especially mites and lice, e.g. the head louse (*Pediculus humanus capitis*), body louse (*Pediculus humanus humanus*), the pubic louse (*Pthirus pubis*) and the scabies mite (*Sarcoptes scabiei*). Head lice, in particular, are a common problem for humans, especially school children. Effective control involves rapid and accurate detection, the use of a fine-toothed comb and the application of head lice killing chemicals, pediculicides.

Pediculicides are frequently toxic to other ectoparasites, eg the mites responsible for scabies, and thus elsewhere may also be referred to as insecticides or scabicides, etc.

The pediculicides currently available generally fall into three classes: organophosphates (eg malathion), carbamates (eg carbaryl), and pyrethroids (eg permethrin).

These pediculicides however have toxic effects. Concerns have long been expressed about organophosphate toxicity in particular, for example in relation to farm workers. Organophosphate poisoning does not require ingestion - cutaneous absorption can lead to signs of poisoning. Symptoms of organophosphate poisoning may

include excessive excessive salivation, sweating, rhinorrhea, muscle twitching, weakness, tremor, incoordination, headache, dizziness, nausea, vomiting, abdominal cramps, diarrhoea, respiratory depression, wheezing, blurred vision and more. Carbamates can cause adverse reactions such as sweating, vision blurring, incoordination and convulsions. Pyrethroids similarly can cause adverse reactions even on dermal exposure, such as excitory neurotoxicity, altered dopamine uptake, and dermatitis.

Since head lice infestation is a particular problem for school children, there is thus a need for a head lice treatment with reduced exposure to pyrethroids and organophosphates. Coadministration of both a pyrethroid and an organophosphate has been proposed by Mazars in FR-A-2793112 which describes a device which produces an aerosol simultaneously from a first solution containing an organophosphate (eg malathion) and a second solution containing a pyrethroid (eg permethrin). We have found however that dermal exposure to these pediculicides may be reduced without compromising efficacy by staggered application of an organophosphate or carbamate and of a pyrethroid, preferably in that order. Thus, the staggered administration according to the invention is more concerned with reducing exposure of the human subject to potentially toxic chemicals than with overcoming ectoparasite resistance to pediculicides.

SUMMARY OF EMBODIMENTS OF THE INVENTION

Thus viewed from one aspect the invention provides a method of killing ectoparasites while resident on a surface of a body of a human, comprising contacting said ectoparasites with a first and with a second pediculicide, said first pediculicide being a carbamate or organophosphate pediculicide and said second pediculicide being a pyrethroid or pyrethrin pediculicide, wherein said second pediculicide is

applied between 15 minutes and 12 hours after the application of said first pediculicide.

Viewed from another aspect the invention provides a pyrethroid or pyrethrin pediculicide for use in treatment of humans by a method according to the present invention. Viewed from another aspect the invention provides an organophosphate or carbamate pediculicide for use in treatment of humans by a method according to the present invention.

Viewed from a further aspect the invention provides a kit comprising in separate containers a first topical pediculicide composition containing a carbamate or organophosphate pediculicide and a second topical pediculicide composition containing a pyrethroid or pyrethrin pediculicide, and printed instructions for the use of said compositions by the time-staggered application of the first topical pediculicide composition followed by the second topical pediculicide composition between 15 minutes and 12 hours after the application of the first pediculicide composition.

Viewed from a still further aspect the invention provides the use of a pyrethroid or pyrethrin pediculicide for the preparation of a first topical pediculicide composition and use of an organophosphate or carbamate pediculicide for the preparation of a second topical pediculicide composition, the first topical pediculicide composition and the second topical pediculicide composition for time-staggered topical application to a human subject to combat infestation by multicellular ectoparasites with exoskeletons.

The time period between application of the two pediculicides is preferably 20 minutes to 4 hours, more preferably 30 minutes to 3 hours, especially about 2 hours.

Viewed from a still further aspect the invention provides a pyrethroid or pyrethrin pediculicide for use in treating ectoparasites that have been exposed previously to an organophosphate or carbamate, wherein

exposure of the ectoparasites to the organophosphate or carbamate occurred between 15 minutes and 12 hours previously.

Viewed from a still further aspect the invention provides Use of a pyrethroid or pyrethrin in the treatment of ectoparasites that have been exposed previously to an organophosphate or carbamate, wherein exposure of the ectoparasites to the organophosphate or carbamate occurred between 15 minutes and 12 hours previously.

Treatment of head lice according to the invention, which may be to kill lice present in the hair or to kill any lice which it is thought might be present in the hair, is preferably combined with combing of the hair with a fine-toothed comb, eg a "nit comb". Such combs have long been widely available but in a preferred embodiment of the invention such a comb is included in the kit of the invention which preferably comprises a package containing such a comb, the two pediculicide compositions and instructions, eg printed on the package or enclosed within the package as an insert. Combing may be effected before, during or after the method of the invention, preferably after, and preferably repeatedly. Combing is best effected when the hair is wet and particularly when the hair has been treated with a conditioner.

The two pediculicide compositions may take any convenient topical application form, eg solution, cream, gel, cream rinse, dispersion, powder, lotion, spray, unguent, etc. Preferably however at least one of the compositions is a shampoo, ie a surfactant containing composition, or cream rinse. It is particularly preferred that the later applied composition is a shampoo or cream rinse.

In an especially preferred embodiment, the first-applied composition is an organophosphate-containing gel or solution, eg one containing an alcohol such as isopropanol, or a physiologically tolerable carbamate

formulation, eg a lotion, and the later applied composition is a pyrethroid-containing shampoo or cream rinse. Permethrin shampoos are frequently actually cream rinses (conditioners).

The organophosphate pediculicide used according to the invention may be any organophosphate with ectoparasite killing effect which is physiologically tolerable on dermal application. Examples of such compounds include malathion, parathion, dichlorvos, chlorpyrifos, chlorthion, trichlorphon, methyl parathion, and fenchlorphos. The use of malathion however is preferred. Where a carbamate pediculicide is used, this may be any carbamate with ectoparasite killing effect which is physiologically tolerable on dermal application. One examples of such a compound is carbaryl. The use of an organophosphate however is preferred.

For treatment of head lice in particular, the organophosphate or carbamate is preferably present in the pediculicide composition at a concentration of 0.02 to 0.4% wt, especially 0.04 to 0.2% wt, particularly about 0.1% wt. The remaining components of the composition may be conventional components for topical compositions and may be present in conventional amounts, eg water, alcohols, gelling agents, surfactants, fragrances, etc.

The pyrethroid or pyrethrin pediculicide used according to the invention may be any pyrethroid or pyrethrin with ectoparasite killing effect which is physiologically tolerable on dermal application. Examples of such pyrethroid compounds, which are generally preferred relative to the pyrethrins, include permethrin, phenothrin, cypermethrin, pyrethrin and deltamethrin. The use of permethrin however is preferred. The pyrethrins, if used, may for example be derived from natural sources such as the chrysanthemum plant. However, where pyrethrins are used, it is preferred also to use a synergist (as discussed below).

For treatment of head lice in particular, the pyrethroid or pyrethrin is preferably present in the pediculicide composition at a concentration of 0.2 to 3% wt, especially 0.5 to 2% wt, particularly about 1% wt. The remaining components of the composition may be conventional components for topical compositions and may be present in conventional amounts, e.g. water, alcohol, gelling agents, surfactants, fragrances, etc.

For treatment of other ectoparasites, the pediculicide contents of the compositions may be adjusted appropriately. Thus, for example, for treatment of scabies (where the compositions will generally be applied in cream, gel or lotion form, especially cream form), the pediculicide contents may be up to five times the preferred contents recited above for head lice.

It is especially preferred that one or both of the pediculicide compositions, especially the pyrethroid or pyrethrin composition, should contain a monooxygenase inhibitor as a synergist for the pyrethroid/pyrethrin, eg piperonyl butoxide. It is also preferred that one or both of the pediculicide compositions should contain an abrasive, eg silicate or diatoms, to assist in disrupting the exoskeleton of the ectoparasite.

In the method of the invention, the pediculicides may be applied to any surface of the body, especially hair bearing surfaces, and preferably the head. Application may be preceded by, accompanied by or followed by washing and/or rinsing. Particularly preferably, the application of the later composition is followed by rinsing. Desirably the organophosphate or carbamate composition is left in contact with the hair for 15 minutes to 12 hours, especially 20 minutes to 4 hours, more preferably 30 minutes to 3 hours, most preferably about 2 hours. The pyrethroid composition is preferably left in contact with the skin and hair for 5 minutes to several hours, eg 15 to 30 minutes, depending on the nature of the formulation used. A cream formulation would typically be left in contact with the

skin and hair for up to 12 hours before washing, while a shampoo would typically be used by washing the hair for about 10 minutes followed by rinsing with water. The method of the invention may if necessary be repeated, eg after 7 to 10 days, but for a single case of infestation a single performance of the method will generally be sufficient.

The organophosphate or carbamate compositions used in the method of the invention generally contain lower concentrations of the organophosphate or carbamate component than is conventional for treatment for head lice and form a further aspect of the invention. Thus viewed from this further aspect the invention provides a topical pediculicide composition comprising a physiologically tolerable carrier and from 0.02 to 0.4% wt, preferably 0.04 to 0.2% wt, especially about 0.1% wt, of an organophosphate or carbamate pediculicide, preferably a composition in gel, cream, shampoo or solution form.

Compositions containing malathion and an alcohol, eg isopropanol, are especially preferred.

One or both of the pediculicide compositions may advantageously contain a further pediculicide, e.g. selected from the chloronicotinyl (eg imidacloprid), phenylpyrazole (eg fipronil), oxadiazine (eg indoxacarb), pyrazole (eg chlorfenapyr), or organochlorine (eg lindane) classes.

The pediculicide compositions are preferably packaged in plastic tubes, single-use sachets, or glass vials.

The method and kit of the invention may also be used in the treatment of other ectoparasites, eg fleas, ticks, other lice (eg *Pediculus humanus humanus* and *Phtirus pubis*) and mites. Scabies which results from infestation by the mite *Sarcoptes scabiei*, is one condition in particular that can be treated.

Where the ectoparasite infestation, eg scabies, is associated with hair-free areas of the skin, topical

application will be to the affected area and optionally to areas deemed to be at risk of infestation. This of course applies to all treatments according to the invention.

While in the method of the invention it is most preferable to administer the pyrethroid/pyrethrin after the organophosphate/carbamate, administration in the reverse order can be beneficial and forms a further, though less preferred, aspect of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The invention will now be described further with reference to the following non-limiting Examples.

Example 1

Organophosphate Gel composition

Malathion in concentrated solution in isopropanol is added at 0.1% wt to a commercially available hair gel, e.g. Essentials Hair Gel from The Boots Company plc.

Example 2

Pyrethroid Shampoo Composition

Permethrin is added at 1% wt to a commercially available shampoo, e.g. Head & Shoulders from Proctor & Gamble, or cream rinse/conditioner.

Example 3

Head lice treatment kit

A kit is prepared comprising a paper box, a vial containing 30 mL of the composition of Example 1, a vial containing 30 mL of the composition of Example 2, and an insert carrying instructions for use.

Example 4

Scalp Treatment

About 25 ml of the gel of Example 1 is massaged into the hair and scalp of a lice-infested schoolchild. After 30 minutes the hair is rinsed. After a further ninety minutes the hair is wetted and about 25 ml of the shampoo of Example 2 is rubbed into the hair to create a lather. The hair is rinsed after 10 minutes. The following day the hair is combed wet with a nit comb.

Example 5

Trial

A 10 year old girl had for over 4 months used a 0.5% solution of malathion (Prioderm (Trade Mark) lotion from Mundipharma) to combat head lice without any significant clinical effect. This subject then used a 1% malathion shampoo (Prioderm (Trade Mark) shampoo from Mundipharma) for 30 minutes, washed her hair with water, then used a 1% permethrin shampoo (Nix (Trade Mark) shampoo (actually a cream rinse rather than strictly speaking a shampoo)from ACO HUD) for 10 minutes. This treatment was repeated after 7 days and head lice infestation was cured.

Claims

1. A kit comprising in separate containers a first topical pediculicide composition containing a carbamate or organophosphate pediculicide and a second topical pediculicide composition containing a pyrethroid or pyrethrin pediculicide, and printed instructions for the use of said compositions by the time-staggered application of the first topical pediculicide composition followed by the second topical pediculicide composition between 15 minutes and 12 hours after the application of the first pediculicide composition.

2. The kit as claimed in claim 1 wherein the first topical pediculicide composition comprises a physiologically tolerable carrier and from 0.02 to 0.4% wt of the carbamate or organophosphate pediculicide.

3. The kit as claimed in claim 1 or 2 wherein the first topical pediculicide composition is in gel, cream, shampoo or solution form.

4. A pyrethroid or pyrethrin pediculicide for use in treating ectoparasites that have been exposed previously to an organophosphate or carbamate, wherein exposure of the ectoparasites to the organophosphate or carbamate occurred between 15 minutes and 12 hours previously.

5. Use of a pyrethroid or pyrethrin in the treatment of ectoparasites that have been exposed previously to an organophosphate or carbamate, wherein exposure of the ectoparasites to the organophosphate or carbamate occurred between 15 minutes and 12 hours previously.