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(54) Title: ANTI-COLD KIT, ANTI-COLD PREPARATION AND USE THEREOF

(57) Abstract

Anti-cold kit and anti-cold preparation comprising a water-soluble, physiologically acceptable ascorbate and dexpanthenol. The kit may be in the form of two separate units which comprise 1) a dry, water-soluble, physiologically acceptable ascorbate, and 2) an aqueous solution of dexpanthenol, respectively, which are mixed immediately before use in order to obtain the anti-cold preparation, or it may be in the form of an anhydrous mixture of a water-soluble, physiologically acceptable ascorbate and dexpanthenol, to which water is added immediately before use in order to obtain the anti-cold preparation. The preparation is in the form of a substantially isotonic aqueous solution comprising a water-soluble, physiologically acceptable ascorbate and dexpanthenol.

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Anti-cold kit, anti-cold preparation and use thereof

Common cold is one of the world's most widespread diseases. In some countries it is estimated that about 15 % of all absence from work due to illness is caused by common cold, and although the disease is not considered to be one of the most dangerous ones, it is in any case among the most expensive for society. It is also often a precursor for other respiratory passage diseases, such as bronchitis and pneumonia.

So far there has not been found any effective remedy against cold. For a long time efforts have been made to prepare a vaccine, but these efforts have not been successful, presumably due to the particular properties of this disease. The disease which is normally called common cold, is to a great extent caused by an infection of rhino virus. Of this type of virus there are much more than 100 different variants. This virus flourishes and propagates on the mucous membranes in the nose and in the upper part of the throat and damages or destroys at the same time the mucous membranes. In contrast to the influenza virus the rhino virus does not enter into the blood. It needs a temperature of about 33°C and large amounts of oxygen, i.e. the conditions which are specifically found in the nasal cavity. These specific growth conditions are presumably the reason why a suitable vaccine has not been found so far.

It is well known that ascorbic acid (vitamin C) does have value in controlling the common cold, see Linus Pauling, "Vitamin C and the Common Cold", W.H. Freeman and Co., San Francisco, 1970.

Even the inventor has previously described the use of ascorbic acid in the form of a water-soluble salt for topical treatment of cold (see "The common cold: A New Approach", The Journal of International Research Communications, September 1973). The reason why an ordinary ascorbate solution has been found to be suitable for the treatment of cold, is presumably primarily caused by the fact that it is an effective and non-toxic reducing agent. As a consequence of this reducing property of ascorbates the conditions which are favourable for the growth of rhino virus, as mentioned above, will not be obtained.

Although the use of ascorbic acid/ascorbate has a favourable effect, this effect is of a somewhat shorter duration than what may be desired.

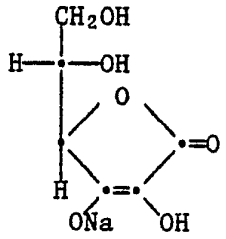
It has now been surprisingly found that addition of dexpanthenol (d-panthenol) to an ascorbate will result in a pharmaceutical preparation with unexpected and beneficial effects. This is presumably due to a synergism between ascorbate and dexpanthenol.

Topical application of the preparation according to the invention to nose, mouth or throat to a mammal in need thereof, such as a human being, results in much higher mucosal concentration of ascorbate than any oral megadose. Thus, about one milliliter of drops according to the invention if taken topically provides 1000 times greater levels of ascorbate in the nose than 15 g vitamin C orally in one dose. Additionally, the synergistic effect of the preparation according to the invention results in a desirable prolonged effect on the mucous membrane.

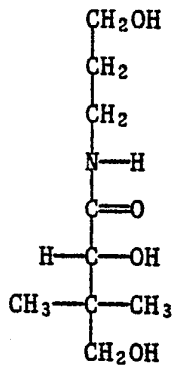
Thus it is an object of the present invention to provide an anti-cold preparation which is in the form of a substantially isotonic aqueous solution comprising dexpanthenol and a water-soluble, physiologically acceptable ascorbate.

It is a further object of the invention to provide an anti-cold kit which comprises a watersoluble, physiologically acceptable ascorbate and dexpanthenol. Furthermore the invention is directed to the use of said kit for the manufacture of said anti-cold preparation. A further object of the invention is the use of the preparation according to the invention for treatment or prophylaxis of conditions responsive to the disclosed synergistic combination of a watersoluble, physiologically acceptable ascorbate and dexpanthenol.

A water-soluble, physiologically acceptable ascorbate is e.g. an alkali metal ascorbate, such as sodium or potassium ascorbate, or an ascorbate such as calcium ascorbate, zinc ascorbate or ammonium ascorbate. An alkali metal ascorbate is preferred, especially preferred is sodium ascorbate of the formula



The correspoding iso-ascorbates are included as well. Dexpanthenol, also known as D-panthenol, is (R)-2,4-dihydroxy-N-(3-hydroxypropyl)-3,3-dimethylbutaneamide of the formula



Instead of dexpanthenol it is also possible to use dl-panthenol, but this results in a somewhat reduced effect.

The kit and the preparation comprise an ascorbate as defined hereinbefore and dexpanthenol as the essential active ingredients, in a preferred embodiment as their only active ingredients.

The ascorbate and dexpanthenol should be used in a molar ratio of about 5:1 to 1:5, preferably of about 2:1 to 1:2, most preferably in about the same molar amounts. It is possible to use an excess of one or the other component in the preparation, since the components also separately have a favourable effect on their own. However, the preparation must be essentially isotonic, it must be non-irritating and compatible with the tissue and have a pH close to that which is normally found in the nose (mouth, throat). An isotonic solution is generally defined as a solution being isoosmotic with a 0,9 % sodium chloride solution. Preferably, the instant essentially isotonic preparation may be slightly hypertonic, but generally the tonicity of the preparation is equivalent to a 0,9 % sodium chloride solution or in the range of a 0.9 % sodium chloride solution. The pH of nasal secretion is slightly alkaline (pH between 8 and 9). Accordingly the pH of the preparation is preferably about neutral, e.g. about pH 6 to 7.

Having in mind the condition of isotonicity of the preparation it is preferred to use solutions which comprise about 3 % by weight of dexpanthenol and an equimolar amount of ascorbate. In case sodium ascorbate is used, a preferred preparation comprises about 3 % by weight of sodium ascorbate and about 3 % by weight of dexpanthenol.

The preparation may also contain isotonicity or pH regulating additions and acceptable flavouring agents and preserving agents.

For adjusting isotonicity preferably sodium chloride may be used. pH-regulating additions are buffers, e.g. borate buffers, or preferably phosphate buffers. Suitable preserving agents are e.g. methyl- or propyl-p-hydroxy-benzoate, chlorobutanol or, being preferred, benzalkoniumchloride. Flavouring agents or artificial

sweeteners may be present, such as banana extract (especially for children), anis, menthol, or pineapple. These ingredients are optional and, if present, are present in small amounts.

In case that free ascorbic acid is used, the addition of a basic salt, such as e.g. sodium carbonate, is essential to have a pH of the preparation near to neutral.

Neither oil nor glycerine nor any other substance which would interfere with the movement of the cilia of the nasal tissue should be present in the preparation.

Freshly prepared preparations have a redox potential rH (derived according to Clark's formula) of 15.5 whereas the mucus of the nose has an average rH of 23-24 (For details see example 4). Accordingly the preparation of the present invention lowers the redox potential in the nose which is beneficial in that a lower potential is detrimental to the growing conditions of the common cold viruses.

Experiments were therefore carried out in order to determine the duration of action of the preparation of the invention:

One ml of the nosedrops was applied to each nostril of a test person. After 1, 2, 5, 9, 12, 15 and 24 hours, nose washings were taken in the following way:

Physiological saline solution (3 ml) was introduced into each nostril from a pipette, the subject being in a sitting position with the head tilted backwards - none of the fluid being swallowed. The fluid was then collected in a glass container, the subject leaning forwards and blowing it out. This was repeated twice. The combined washings thus obtained were transferred to a 100 ml flask and 5 ml of each of the following reagents were added:

R.1: 2 % aqueous solution of potassium ferricyanide,
R.2: 4 % aqueous solution of ferric chloride.

The flask was then filled to the mark with distilled water. The mixing of R.1 and R.2 forms a brown colour, but the presence of any reducing agent will render the solution blue, due to the formation of the Berlin blue colour. The intensity of the blue colour was measured using a Lovibond tintometer (cell width 1/2 inch.) and Table 1 gives the experimental results. The measurements were made 3 minutes after adding the reagents. The values obtained are in direct proportion to the reducing power of the nose washings and are thus an indication of the activity of the solutions as antioxidants i.e. of their effectiveness in changing the oxidation-reduction potential of the mucous membrane of the nose. Only the blue colour intensity has been reported in Table 1. It should be noted that this method can be only approximate for measuring the reducing ability, since much of the reducing power remains in the mucus which is too thick to be expelled with the nose washings.

Table 1

Lovibond Readings Washings	8.2	7.1	5.2	3.5	1.5	0.9	0
Hours	1	2	5	9	12	15	24

It is apparent from Table 1 that the antioxidant activity of the nosedrops is of reasonably long duration. In the cases tested, it was found that the application of the drops three to five times daily was sufficient to maintain a considerable change in the oxidation-reduction potential.

It has been found most suitable to pre-formulate the preparation as a kit of two separate units, wherein one unit contains a dry, water-soluble physiologically acceptable ascorbate, such as sodium ascorbate, suitably in a glass bottle equipped with a pipette. An aqueous solution of dexpanthenol is kept in another unit, such as a glass bottle. Immediately before use the contents of the two units are mixed, for instance by pouring an aqueous solution of dexpanthenol into the glass bottle containing the starting ascorbate. The amount of starting ascorbate and of dexpanthenol must be

adjusted so that the resulting solution becomes essentially isotonic. Instead of a glass bottle equipped with a pipette it is for instance also possible to use a compressable bottle which may be used by administering the preparation in the form of a spray. The reason why it is desirable to keep the active ingredients of the preparation in two separate units which are mixed immediately before use, is that the final preparation has a limited durability since it is easily exposed to the oxygen of the air. However, the dry starting ascorbate is stable, and this is also the case with dexpanthenol either in neat form or in solution. Even the final preparation is stable for 30 days, such that stability of the preparation can be guaranteed to the user for one week. This has been affirmed by analyzing the preparations according to the invention with respect to pH and redox-potential over a period of 30 days. The properties of the preparation remain within the beneficial ranges discussed hereinbefore over a period of time which is sufficient for the therapy of a cold.

The preparation may also be prepared from a kit comprising calculated weighed amounts of the neat active ingredients, ascorbate and dexpanthenol, without the presence of water. This kit will be stable for a prolonged time, and a suitable amount of distilled water is added thereto immediately before use, whereby there is obtained a solution which may be used directly. The final preparation may also be kept in frozen condition.

The new preparation may be used as a prophylactic agent or after a cold has broken out. It is suitably used as a prophylactic agent, for instance after a cold epidemic has broken out, and it will then to a considerable extent prevent those who have been treated with the preparation, from catching a cold.

Furthermore the new kit and preparation may be beneficial and/or prophylactic against dust or polluted air, and may be used as an antiallergic or antihistaminic agent, e.g. for mammmals, especially human beings, suffering from hey fever.

The preparation has been successfully tested on several individuals, who have either not caught a cold even if they have been in an environment with much cold, or who have rapidly recovered after having caught a cold. A larger systematic test was carried out in a military camp in which all the voluntary test persons were of approximately the same age and were exposed to approximately the same conditions. A group of the test persons received a preparation containing the described components, (see example 1), while another group only received a placebo preparation, in each case about 1 ml (20 to 30 drops) in each nostril about 5 times daily. None of the test persons knew whether they received the placebo preparation or a preparation containing the active components.

After the treatment period all the test persons presented a written report in which they could state whether the cold was "completely cured", "improvement", or "no improvement".

The results were as follows:

	Number of test persons			
	Completely cured	Improvement	No improvement	Total
Treated	86	83	10	179
Placebo	3	6	36	45

As will be seen, in the treated group "completely cured" or "improvement" was obtained for 169 of the test persons, i.e. about 94 %, while the corresponding value for those who had only received a placebo preparation, was about 20 % (9 test persons of a total of 45).

A further testing was carried out mainly at the Training Center of the Royal Norwegian Air Force at Kjevik in Southern Norway and also at the University of Oslo.

The subjects were asked to apply the nosedrops according to the invention into both nostrils so that they could clearly feel it trickling down the back of the nasal cavity and into the throat. A small amount was also sprayed into the mouth cavity, over the palate, and in the throat, so that the mucous membranes of the upper respiratory tract were well moistened with the solution. The subjects were asked to report on special forms the effects of the drops.

The preparation (but not the placebo) was also used as a prophylactic during military manoeuvres in the mountains in the winter of 1985. Although the soldiers slept in snow caves where the temperature was well below freezing point (between -15 and -30°C.), none of the participants developed a cold during the manoevres which lasted for about 12 days. In previous years more than 50 % of the soldiers had developed a cold during same type of manoeouvres.

In both the experiments - at the Training Center at KJEVIK and at the University of OSLO - no undesirable side effects were observed.

357 subjects participated in the tests, 295 receiving the preparation and 62 receiving placebo drops. All subjects reported on the effects of the drops.

The clinical tests give the following results showing the distribution of subjects in the two groups, - the group relative to treatment and the placebo-group - having reference to the category and results of treatment and showing the significant level of difference between the two groups:

Number of treatments

	No common cold symptoms after treatment:	Improvement during treatment	No improvement during treatment	Total	Significant level of difference from the placebo-treated group
(A)	110(44.7 %)	120(48.8 %)	16(6.5 %)	246	$p < 0.0001$
	230	(93.5 %)			
(B)	31(63.2 %)	16(32.6 %)	2(4 %)	49	$p < 0.0001$
	47	(95.9 %)			
(C)	141(47.8 %)	136(46.1 %)	18(6.1 %)	295	$p < 0.0001$
	277	(93,9 %)			
(D)	4(6.5)	13(21 %)	45(72.6 %)	62	
	17	(27.5 %)			

Explanation:

(A): Group at Training Center KJEVIK
(B): Group at University of OSLO
(C): Combined groups KJEVIK and OSLO
(D): Group treated with Placebo (isotonic sodium chloride solution)

Comparison of the results shows a highly significant difference between the group treated with the isotonic solution of dexpanthenol and sodium ascorbate and the group receiving the placebo. It is clear that, in the former group, there was a far greater proportion of subjects who indicated either that they had no symptoms of the common cold after treatment or that there was an improvement during the treatment.

Example 1: 3.16 g (0.0155 moles) of dexpanthenol are dissolved in 100 ml distilled water, and the solution is filled into a 100 ml bottle. In another 100 ml bottle 3.05 g (0.0155 moles) sodium

ascorbate are charged. The content in the two bottles is stable for a long time.* Immediately before use the dexpanthenol solution is filled into the bottle containing the solid sodium ascorbate which dissolves. The resulting solution represents an essentially isotonic preparation ready for use.

*(Tests have been conducted for a period of up to 18 months and no instability has been observed)

Example 2: The same amounts as above of the two starting materials are mixed and kept in a sterile bottle. The same amount (100 ml) of sterile, distilled water is added immediately before use and results in a clear solution.

Example 3: After mixing 0.9 g sodium ascorbate (dry substance) with the attached 30 ml solution of stabilized buffered dexpanthenol in water the final mixture has the following composition:

0.900 g sodium ascorbate
0.900 g dexpanthenol
0.030 g NaH_2PO_4
0.003 g Na_2HPO_4
0.003 g benzalkoniumhydrochloride.

This preparation of 30 ml has a pH of 6.5. Stability is guaranteed for 1 week.

Example 4: Measurement of pH and redox potential

All the measurements of pH and redox potential were performed on an ORION Research Microprocessor pH/millivolt meter Model 811. The measurements were made at room temperature (24° - 25°C) and the following electrodes were used:

1) For pH: An ORION Research pH combination electrode.
2) For redox potential: Platinum/silver chloride ORION analyzer Model 96 - 98.

The rH was derived according to Clark's formula:

$$rH = \left(\frac{E_{ref} + E}{E_N} + pH\right) \cdot 2 \qquad (E_h = E_{ref} + E)$$

E_h = redox potential against Standard Hydrogen Electrode

E_{ref} = standard potential of reference electrode.

E_N = value of electrode slope VS temperature. Nernst potential.

For the electrode system used in this study the values are:

$$rH = \left(\frac{244 + MV}{59.2} + pH\right) \cdot 2$$

MV = Millivolt measured at reference (Platinum/silver chloride) electrode.

Patent claims

1. Anti-cold kit, characterized in that it comprises a water-soluble, physiologically acceptable ascorbate and dexpanthenol.

2. Anti-cold kit according to claim 1, characterized in that it comprises a water-soluble, physiologically acceptable ascorbate and dexpanthenol as its only active ingredients.

3. Anti-cold kit according to claim 1, characterized in that it is in the form of two separate units which comprise

1) a dry, water-soluble, physiologically acceptable ascorbate, and
2) an aqueous solution of dexpanthenol, respectively,

which are mixed immediately before use.

4. Anti-cold kit according to claim 1, characterized in that it comprises an anhydrous mixture of a water-soluble, physiologically acceptable ascorbate and dexpanthenol, to which water is added immediately before use.

5. Anti-cold kit according to claim 1, characterized in that it comprises additionally a buffer and/or a preserving agent.

6. Anti-cold kit according to claim 3, characterized in that one of those two units comprises an aqueous solution of dexpanthenol which is about 3 % by weight and the other unit comprises about the same molar amount of a dry, water-soluble, physiologically acceptable ascorbate.

7. Anti-cold kit according to claim 6, characterized in that it comprises additionally a buffer and/or a preserving agent.

8. Anti-cold kit according to claim 3, characterized in that the ascorbate is sodium ascorbate.

9. Anti-cold preparation, characterized in that it is in the form of a substantially isotonic aqueous solution comprising dexpanthenol and a water-soluble, physiologically acceptable ascorbate.

10. Anti-cold preparation according to claim 9, characterized in that it comprises a water-soluble, physiologically acceptable ascorbate and dexpanthenol as its only active ingredients.

11. Anti-cold preparation according to claim 9, characterized in that it comprises additionally a buffer and/or a preserving agent.

12. Anti-cold preparation according to claim 9, characterized in that the ascorbate and dexpanthenol are present in a molar ratio of about 5:1 to 1:5.

13. Anti-cold preparation according to claim 9, characterized in that the ascorbate and dexpanthenol are present in about the same molar amounts.

14. Anti-cold preparation according to claim 13, characterized in that dexpanthenol is present in about 3 % by weight.

15. Anti-cold preparation according to claim 9, characterized in that the ascorbate is sodium ascorbate.

16. Anti-cold preparation according to claim 9, characterized in that it comprises about 3 % by weight of sodium ascorbate and about 3 % by weight of dexpanthenol.

17. Anti-cold preparation according to claim 9, characterized in that it consists of an aqueous solution of about 3 % by weight of sodium ascorbate and about 3 % by weight of dexpanthenol.

18. Anti-cold preparation according to claim 9, characterized in that it consists of an aqueous solution of about 3 % by weight of sodium ascorbate, about 3 % by weight of dexpanthenol and a buffer and/or a preserving agent.

19. The use of an anti-cold kit as defined in claim 1 for the manufacture of an anti-cold preparation as defined in claim 9 characterized by mixing the ingredients or dissolving them in water.

20. The use of an aqueous preparation as defined in claim 9 for the treatment or prophylaxis of cold by topical administration in nose, mouth or throat to a mammal in need thereof.

21. The use of an aqueous preparation as defined in claim 9 for the treatment or amelioration of allergic conditions by topical administration in nose, mouth or throat to a mammal in need thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 87/00203

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 31/375; // (A 61 K 31/375, 31:16)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	Rote Liste, 1974, Editio Cantor, (Aulendorf/ Württ., DE), see no 67049 B, "Orisan"	1-21
P,X	WO, A 86/06629 (POSTLEY, John E.) 20 November 1986 see page 3, lines 10-19, summary	1-21

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* Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16th July 1987	10 AUG 1987
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. VAN MOL

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/EP 87/00203 (SA 16858)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 28/07/87

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A- 8606629	20/11/86	AU-A-	5906986	04/12/86
		EP-A-	0221998	20/05/87