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(54) Title: THE USE OF RETINOIDS AND THEIR DERIVATIVES TO INCREASE THE RATE OF GROWTH OF HUMAN SCALP HAIR AND TO INCREASE THE RATE OF GROWTH OF FUR IN CERTAIN FUR-BEARING ANIMALS

(57) Abstract

This invention involves the use of retinoids to increase the rate of hair growth and to prolong the anagen phase of the hair cycle.

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Title: The Use of Retinoids and Their Derivatives to Increase the Rate of Growth of Human Scalp Hair and to Increase the Rate of Growth of Fur in Certain Fur Bearing Animals.

Background of the Invention

1. Field of the Invention

This invention relates to the use of retinoids and their derivatives in order to increase the rate of growth of human scalp hair and to increase the rate of growth of fur in certain fur bearing animals.

2. Description of the Prior Art

A normal characteristic of human hair growth in most individuals is that it diminishes with age. Both the rate of growth of the hair and the length of the growing cycle are reduced. This condition is common to all individuals with rare exception and must be differentiated from true male pattern alopecia which is a distinct clinical entity associated in certain individuals with the production of the male sex hormone, testosterone and its derivatives, particularly dihydrotestosterone.

Many factors may influence the rate of hair growth including race, sex, age, region, season of the year, nutrition and hormones (Myers and Hamilton, 1951, Hamilton, 1958, Yano, 1936, Maeda, 1938, Troter, 1923, Pinkus, 1924, and Ono, 1963). In the past, many attempts have been made to alter the course of male pattern alopecia

through numerous types of treatments, all of which have proven unsuccessful. This invention does not purport to reverse total male pattern alopecia. This invention describes a treatment to increase the rate of growth of hair from growing hair follicles and from the hair follicles of certain fur bearing animals, and to prolong the growing phase of the hair cycle.

In the past, Vitamin A compounds, hereafter referred to as retinoids have been shown to be effective in treating many types of disorders including dermatological conditions such as acne and psoriasis. I have now found a new use for the retinoids in increasing the rate of hair growth and prolonging the anagen phase of the hair cycle.

In the past, Vitamin A compounds, hereafter referred to as retinoids have been shown to be effective in treating many types of disorders including dermatological conditions such as acne and psoriasis. I have now found a new use for the retinoids in increasing the rate of hair growth.

Summary of the Invention

I have discovered that retinoids particularly all trans retinoic acid and its derivativies can increase the rate of scalp hair growth in humans and that it can also be used to increase the rate of growth of fur in certain fur bearing animals and to retard molting. The choice of administration is topically by use of lotions,

ointments, creams, etc. However, administration is not limited to these means, the effect can also be obtained by the oral or systemic administration of the retinoid compounds.

Detailed Description of the Invention

This invention concerns the use of retinoids, including all trans retinoic acid and its metabolites and other retinoid compounds in order to increase the rate of scalp hair growth in humans and to increase the rate of pelt (fur) growth in certain fur bearing animals. All trans retinoic acid has been shown to cause elevated DNA synthesis in keratinocytes in cell culture. All trans-retinoic acid has been shown to cause elevated DNA synthesis in keratinocytes in cell culture. All trans-retinoic acid can also be shown to increase the turnover time of epidermal cells in cell culture experiments as well as in in vivo experiments with human subjects. I have discovered that the cells of the hair follicle including the papillae can be stimulated by retinoids including all trans retinoic acid. When tested experimentally, the retinoids caused the cells of the dermal papillae and the cells of the root sheath to incorporate more tritiated thymidine into DNA and to reproduce at a more rapid rate than untreated cells from other hair follicles. This stimulation by the retinoid compounds ultimately causes the entire hair follicle to become more activated and the mitotic index as measured by thymidine-H^3 incorporation into DNA to rise. Therefore the individual scalp hairs can be shown to grow at an increased rate and the anagen phase is prolonged.

A major problem in influencing hair growth is to obtain good percutaneous absorption of the active compounds. Another problem is the accurate measurement of hair growth to substantitate the results of the testing. All trans-retinoic acid and its derivatives and the other retinoid compounds have been shown to give excellent percutaneous absorption and to be very active on the keratinizing cells of the skin, including the hair follicle. Furthermore, a relatively recent method which gives excellent results has been used to measure the rate of hair growth. This method was devised by Saitoh, M. et al and utilizes microcapillary tubes which are graduated using 0.2 mm graduations. (a reproduction of the photograph of the instruments utilized for this method is enclosed.)

As used herein, the term retinoid denotes retinol, retinal, retinyl esters as well as retinoic acid and its esters, derivatives and normal metabolites. The terminal group may be oxidized, reduced esterified, etc. The alkali metal (sodium, potassium, etc) and alkaline earth metal (magnesium, clacium, etc) salts are also included herein.

The pharmaceutical or cosmetic or veterinary preparations of the present invention can be prepared by the conventional techniques for the preparation of lotions, creams, conditioners or shampoos for the scalp or veterinary preparations for pelts. Included also are preparations which can be administered orally and compounds which can be added to animal feeds.

In addition to the active retinoids of this invention, the

various preparations can contain any conventional pharmaceutically acceptable or cosmetically acceptable inert or pharmacodynamically active additives. For example, the lotions may be prepared using various forms of alcohols or other solubilizers such as glycols, or esters. The conditioners may contain the normally acceptable commerically produced compounds such as cetyl alcohol, ceteareth-5,-20 hydrantoins, hydrolyzed animal protein, glycol stearate, amodimethicone, paraffin, mineral oil, etc. (These are only given as examples, and are not meant to be inclusive.) The topical compounds may also contain various oils including essential fatty acids and other polyunsaturated fatty acids and their derivatives, and compounds such as hormones, including progesterone, estradiols, thyroid, etc.

The topically applied lotions, creams, and conditioners, etc will vary according to the standard art with regard to the amounts of other hydrophilic and hydrophobic containing ingredients including emulsifiers, so that either an oily, semi-oily or oil free product may be obtained. The shampoos may contain any of the conventionally used detergents or soaps and any other compounds used by those familiar with the art. Oil based shampoos are included in these formulations.

The oral preparations may be tablets, liquids, capsules, etc. The pharamaceutically acceptable substances commonly used as preservatives, stabilizers, moisture retainers, emulsifiers, etc. can be present in these preparations. Conventionally acceptable antioxidants such as tocopherols, N-methyl a-tocopheramine, butylated hydroxyanisole and butylated hydroxytoluene, can be also incorporated in

the preparations described in this invention.

The dosages in which the retinoids are administered can be varied eith the route of administration and the requirement s of the subjects.

The topical treatments may consist of lotions, creams, conditioners, shampoos, oil treatments, etc with from 0.001 to 2% by weight of all trans-retinoic acid or derivatives, or other retinoids, as the preferred dosages in the described compositions.

The oral pharmaceutical preparations may be·admininstered at a daily dose of from 0.25 mg to 2 mg per kilogram of body weight. These can be also incorporated into animal chow in the case of fur bearing animals ,in the case of dogs or cats or other pet food or in the case of bird seed for moulting bidrds.

In order to examine the specific action of the retinoids in increasing the rate of hair growth, several types of experiments were performed. The microcappillary method was used in each case to measure the rate of hair growth.

In Table I is described the results of studies using male and female subjects. The all trans-retinoic acid was applied topically or as described in the table and the microcappillary method was used to assess hair growth rates. (see separate pages for TABLES).

In Table II is described the results of studies using male and female subjects. The ethyl ester of all transretinoic acid was applied topically or as described in the table and a control non-treated area was utilized for comparison.

In fur bearing animals, the rate of fur growth, length of hair, thickness of hair and molting season are controlled by many factors including season, light (wavelength) periodicity, temperature, hormonal factors and nutrition. Controlling all of these variables is impossible however, animals were selected and areas over the hind quarters were shaved in 2 inch diameter circular areas. In some of the animals the areas were treated topically with all-trans-retinoic acid and in other animals the retinoid was administered orally in animal chow. Some of the animals served as their ouwn controls, using treated and non-treated areas.

In fur bearing animals, the guard hairs and the pile hairs differ in thickness, length and growth rate. In the rabbits studied, the guard hairs averaged 34 mm and the pile hairs 30 mm in length. The effect of topical application of all trans-retinoic acid was to increase the rate of new hair growth. An effect on the non-shaved fur bearing areas treated with topical all trans retinoic acid in lotion form, was a decrease in the sheading or molting of fur. The mean rate of hair (fur) growth from treated shaved areas was 0.3 mm/day for 3 rabbits (mean) while in non-treatment shaved areas it averaged 0.2 mm per day (mean of 3 rabbits).

The effect could also be demonstrated in domestic cats and dogs; the same type of experimental procedures were used. The most striking effect in long haired dogs and cats was the retardation of molting or hair sheading. Long haired dogs and cats tended to retain more hair in the anagen phase and there was approximately 50 % less sheading during the treatment periods. Both methods of administration were satisfactory. Either topical lotion or cream treatment or systemic treatment by inclusion in animal chow was satisfactory. The daily dosage for animals was 20mg per kilogram per day in chow or 10 to 15 mg applied topically.

Commerically important fur bearing animals were also used for experimentation. Two male minks were closely clipped over the back hind quarters The animals were treated on one hind quarter and the other was used a the control. The cappillary method for measuring hair growth was used for these studies. The animals were treated by two different methods. The animals were either fed the retinoid in their chow or they were administered the retinoid topically . The daily dose was 20 mg per kg body weight per day in animal chow or 5 mg. per day applied topically. . The results of these experiments showed that the rate of growth of new pelt was increased approximately 30 % by the retinoid treatment.

Experiments using birds (canaries and parakeets) showed that inclusion of the all trans retinoic acid or the ethyl ester of all trans retinoic acid in bird food at a dosage of 30 mg. per kilogram bird weight per day retarded the molting process.

The following Examples illustrate the present invention. The methods of administration may vary by lotion, cream, ointment, pill, supplement to chow,coating for seeds, etc. These Examples are only meant to be illustrative and do not limit the mode of administration nor the ingredients which can be admixed to the present invention, nor the amounts which may be used.

Example I

Lotion formulation for the topical administration	% wt to wt
Active ingredient: all trans retinoic acid	0.1
Ethanol	q.s. to 100.0
Propylene glycol	5.0
Butylated hydroxytoluene	0.1
Safflower oil	1.0
α-tocopherol acetate	0.5

Example II

Cream Conditioner for Topical Administration

Active ingredient: All trans-retinoic acid or all trans-retinoyl acetate	1.0
Distilled water	q.s. to 100.0
Cetrimonium Chloride	5.0
cetyl alcohol	4.0
Ethanol	4.0
Butylated hydroxytoluene	1.0
hydrolyzed animal protein	0.5
methylparaben, propylparaben	0.1

Example III

All trans retinoic acid 0.1 gram is dissolved in 10 ml of acetone, and the solution admixed with 90 g of USP grade hydrophilic ointment to a uniform consistency; one gram of butylated hydroxytoluene is added. The water washable cream ointment thus prepared consists of 0.1 % active ingredient.

Example IV

Tablets for oral administration

Active ingredient: all trans retinoic acid or all trans retinoic acid ethyl ester or acetate	25 mg.
Lactose	52 mg
Cornstarch	20 mg
Microcrystalline cellulose	40 mg
Talc	2.5 mg
Magnesium stearate	0.5 mg

The active ingredient was mixed with lactose and granulated using a corn starch paste. The remainder of the above adjuvants was then admixed therein and the mass was tableted. The tablets were then tableted. The tablets were then coated with a water-soluble or water-swellable lacquer.

The same formulation can also be used and gelatin can be added to make beadlets. These beadlets are then coated with a lacquer. The beadlets and animal chow can be mixed to the desired dosage level.

The above formulation can also be used in the powdered form for mixing with bird seed and the bird seed can then be sprayed with lacquer.

Liquids, syrups or other formulations can be made consistent with the pharmaceutical art.

RESULTS USING ALL TRANS RETINOIC ACID

TABLE I

Subject Sex	Age	Dosage	Form of Dosage	Treatment Time	mm/day Control Rate	mm/day Treatment Rate of Growth
M	36	10 mg/ day	Topical Lotion	21 days	0.3	0.45
M	38	60 Mg/ day	oral	14 days	0.21	0.25
M	24	10 mg	Topical	10 days	0.35	0.49
F	35	10 mg	Topical	30 days	0.39	0.50
F	41	60 mg	Oral	28 days	0.36	0.39
F	63	10 mg	Topical	21 days	0.28	0.38

RESULTS USING ALL TRANS RETINOIC ACID ETHYL ESTER

TABLE II

Subject Sex	Age	Dosage per day	Form of Dosage	Treatment Time	mm/day Control Rate	mm/day Treatment Rate of Growth
M	31	10 mg	Topical	21 days	0.25	0.31
M	68	10 mg	Topical	20 days	0.21	0.29
M	38	70 mg	Oral	21 days	0.30	0.32
F	36	10 mg	Topical	22 days	0.34	0.46
F	42	10 mg	Topical Cream	19 days	0.31	0.40
F	66	50 mg	Oral	20 days	0.28	0.29

11/1

Table III
RESULTS USING ALL TRANS RETINALDEHYDE
(Commerically available- for synthesis
see Merck Index)

Subject Sex	Age	Dosage	Form of Dosage	Treatment Time	mm/day Control Rate	mm/day Treatment Rate of Growth
M	36	10 mg/ day	Topical	21 days	0.30	0.35
M	38	10 Mg/ day	Topical	14 days	0.23	0.32
M	24	10 mg	Topical	10 days	0.35	0.40
F	35	10 mg	Topical	30 days	0.39	0.45
F	41	10 mg	Topical	28 days	0.31	0.35
F	63	10 mg	Topical	21 days	0.28	0.41

TABLE IV

RESULTS USING RETINOIC ACID METABOLITES (i.e. 4-hydroxy and 4-keto)

(Can be prepared by enzymatic methods; synthesis known)
Ref: Archives of Biochemistry and Biophysics, 199 p.374-383(1980)

Subject Sex	Age	Dosage per day	Form of Dosage	Treatment Time	Control Rate	Treatment Rate of Growth
M	31	10 mg	Topical	21 days	0.25	0.31
M	68	10 mg	Topical	20 days	0.21	0.28
M	38	10 mg	Topical	21 days	0.34	0.35
F	36	10 mg	Topical	22 days	0.34	0.41
F	42	10 mg	Topical —	19 days	0.39	0.48
F	66	10 mg	Topical	20 days	0.28	0.36

TABLE V 11/2

RESULTS USING OXIDATION PRODUCTS OF RETINOIC ACID i.e. 8-(2,66-trimethyl-3-oxocyclohex-1-anyl)-2,6-dimethyl -6- hydroxoctatrienal prepared by enzymatic methods (Biochimica Biophysica Acta, 627; 270-275 (1980)

Subject Sex	Age	Dosage	Form of Dosage	Treatment Time	Control Rate mm/day	Treatment Rate of Growth mm/day
M	36	10 mg/ day	Topical	21 days	0.30	0.35
M	38	10 Mg/ day	Topical	14 days	0.21	0.24
M	24	10 mg	Topical	10 days	0.35	0.35
F	35	10 mg	Topical	30 days	0.39	0.45
F	41	10 mg	Topical	28 days	0.36	0.38
F	63	10 mg	Topical	21 days	0.28	0.27

TABLE VI

RESULTS USING DEHYDRORETINOLS (PIKE LIVER OIL) AND THEIR STEREOISOMERS (SEE MERCK INDEX FOR SPECIFICATIONS) AND OXIDATION PRODUCTS INCLUDING ALDEHYDES AND ACIDS EXTRACTED FROM

Subject Sex	Age	Dosage per day	Form of Dosage	Treatment Time	mm/day Control Rate	mm/day Treatment Rate of Growth
M	31	10 mg	Topical	21 days	0.25	0.41
M	68	10 mg	Topical	20 days	0.21	0.25
M	38	10 mg	Topical	21 days	0.30	0.34
F	36	10 mg	Topical	22 days	0.34	0.34
F	42	10 mg	Topical	19 days	0.31	0.32
F	66	10 mg	Topical	20 days	0.28	0.29

RESULTS USING ALL TRANS RETINOYL ACETATE

TABLE VII

Subject Sex	Age	Dosage	Form of Dosage	Treatment Time	mm/day Control Rate	mm/day Treatment Rate of Growth
M	36	10 mg/ day	Topical Lotion	21 days	0.30	0.45
M	38	60 Mg/ day	oral	4 days	0.21	0.2 0
M	24	10 mg	Topical	10 days	0.35	0.41
F	35	10 mg	Topical	30 days	0.39	0.39
F	41	60 mg	Oral	2 days	0.30	0.30
F	63	10 mg	Topical	21 days	0.28	0.39

TABLE VIII

RESULTS USING ALL-TRANS-RETINAMIDE

Subject Sex	Age	Dosage per day	Form of Dosage	Treatment Time	mm/day Control Rate	mm/day Treatment Rate of Growth
M	31	10 mg	Topical	21 days	0.25	0.30
M	68	10 mg	Topical	20 days	0.21	0.20
		RESULTS USING 7-RETINOIC ACID AND 9-RETINOIC ACID				
F	36	10 mg	Topical	22 days	0.34	0.40
F	42	10 mg	Topical Cream	19 days	0.31	0.41

What is claimed is:

1. A method for increasing the rate of growth of hair and prolonging the anagen phase of the hair cycle by topically or orally administering to a mammal, a retinoid or a pharmaceutically acceptable ester, ether, or salt thereof, in an amount effective for the purpose.

2. The method of Claim 1 wherein the retinoid is all trans retinoic acid, or all trans retinaldehyde, or all trans retinoyl acetate, or other suitable esters or salts of retinoic acid.

3. The method of Claim 1 wherein the retinoid is selected from the group consisting of the stereoisomers of vitamin A acid, or vitamin A_2 acid, vitamin A acid, vitamin A acid, 5,6 epoxy-vitamin A acid, dehydrovitamin A acid or the aldehydes, alcohols, esters, ethers or salts of the above mentioned compounds.

4. The method of Claim 1 wherein the retinoid is a naturally occuring metabolite of vitamin A acid such as 4-hydroxy retinoic acid, 4-keto retinoic acid, 4-oxo-retinoic acid, 5,8,oxy-retinoic acid or 7-cis 3 dehydroretinol or retinoic acid, 7-trans-9-cis-11-trans-13-trans-5'-hydroxy-retinoic acid, or 8-(2,6,6-trimethyl-3-oxocyclohex-1-enyl)-2,6-dimethyl-6-hydroxyoctatrienal or stereoisomers of the above mentioned compounds, or aldehydes or derivatives such as esters or salts thereof.

5. The method of Claim 1 wherein the compound is a carotenoid such as crocetin or crocin or its naturally occuring metabolites.

6. The method of Claim 1 wherein the mammal is a human and the hair is scalp hair.

7. The method of Claim 1 wherein the animal is a fur bearing animal and the retinoids also prevent or retard molting or shedding.

8. The method of Claim 1 wherein the retinoid concentration in the topical lotion, cream, ointment, conditioner or shampoo is between 0.001 to 5% by weight.

9. The method of Claim 1 wherein the retinoid compositions are given orally in a dosage of between 0.25 to 20 mg/kg of body weight of a mammal.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US81/00338

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

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

Int. Cl.[3] A61K 7/06; A61K 31/215

U.S. Cl. 424/70; 424/305

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/70, 305

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	US, A, 3,759,978 18 September 1973, column 10, lines 27-34	1-9
X	US, A, 3,931,279, 6 January 1976, column 2, lines 38-70	1-9
X	US, A, 3,954,835, 4 May 1976, column 6, lines 27-47	1-9

* Special categories of cited documents: [15]

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"X" document of particular relevance

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
7 July 1981	16 JUL 1981
International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/US	Dale R. Ore

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