TITLE OF THE INVENTION

PREVENTION OF GLUCOCORTICOID-INDUCED SKIN ATROPHY

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a method for the prevention of glucocorticoid-induced skin atrophy by the topical administration of retinoids.

Description of the Prior Art

The most widely prescribed drugs to treat dermatologic disease are glucocorticosteroids. Approximately 50% of prescriptions written by dermatologists are for topical glucocorticosteroids. Since the introduction of these substances in the early 1950's for dermatologic disease, topical corticosteroid therapy continues to be the mainstay for the management of a broad spectrum of inflammatory dermatoses. Although systemic corticosteroids are often required in some dermatologic diseases, topical treatment is preferred in most responsive cases because it causes fewer systemic adverse effects.

Topical corticosteroids are generally most effective in the treatment of acute and chronic dermatoses such as seborrheic or atopic dermatitis, contact dermatitis of the irritant or allergic type, localized neurodermatitis, anogenital pruritus and psoriasis.

Individual topical corticosteroid preparations vary in anti-inflammatory potency and clinical efficacy. Therapeutic efficacy of a particular steroid can often be enhanced by increasing the concentration or by using occulsive dressings. Topical corticosteroids may be grouped according to relative anti-inflammatory potency. Still activity may vary considerably depending upon the vehicle, the site of application, disease, the individual patient, and whether or not an occlusive dressing is used.

Although some dermatoses may require therapy with a potent corticosteroid initially, treatment with hydrocortisone, betamethasone, dexamethasone, methylprednisolone, or prednisolone, is often

sufficient and is less likely to cause adverse reactions. Although fluorinated corticosteroids are generally potent and efficacious, fluorination is not essential for increased anti-inflammatory potency (e.g., hydrocortisone valerate has greater anti-inflammatory activity than does betamethasone or dexamethasone). Potent corticosteroids are customarily used for severe or resistant dermatoses such as psoriasis and chronic neurodermatitis. Dermatoses such as discoid lupus erythematosus, lichen planus, granuloma annulare, and psoriasis of palms, soles, elbows and knees or psoriatic plaques usually require potent corticosteroids.

In general, topical application of corticosteroids does not produce systemic side reactions, although abnormal laboratory tests may occur, viz., decreased adrenal production of cortisol. However, systemic corticosteroid side effects may occur when the drugs are used on large areas of the body, for prolonged periods of time, with an occlusive dressing, and/or in infants and children. These include Cushing's disease, acne, osteoporosis, etc.

Potent topical corticosteroids often cause dermatologic side effects. These are most likely to occur in intertriginous and facial areas and are most severe with fluorinated corticosteroids, especially on the face where steroids are rapidly absorbed. Local corticosteroid side effects occur most frequently with occlusive dressings, especially with prolonged therapy.

Local side effects have become more frequent with the clinical use of newer and more potent glucocorticosteroidal analogs. The most common adverse reaction is skin atrophy, i.e., a thinning of the epidermis and dermis accompanied by telangiectasia and striae. Minimal trauma to atrophic skin may also produce purpuric lesions. Other dermatologic side effects include acneiform eruption, pruritus, hypertrichosis, rosacea-like eruptions on the face, perioral dermatitis, burning or stinging sensation, folliculitis, and hypopigmentation. Skin ulceration has occurred in patients with impaired circulation. Because of the high prevalence and seriousness of skin atrophy, it would be very valuable to have

available a preparation which was anti-inflammatory but did not cause skin thinning or striae; the latter is a permanent scar.

Topical retinoids such as tretinoin (all-trans-retinoic acid) have been used by dermatologists for almost twenty years. For example, tretinoin is used topically in the treatment of acne vulgaris, primarily grades I-III, in which comedones, papules, and pustules predominate.

In concentrations of 0.1% to 0.3%, tretinoin has been used successfully in the treatment of other skin conditions such as psoriasis, ichthyosis congenita, Darie's disease, epidermolytic hyperkeratosis, senile comedones, senile keratosis, trichostasis, flat warts and basal cell carcinomas.

SUMMARY OF THE INVENTION

The present invention is directed to a method for preventing glucocorticoid-induced skin atrophy. The method comprises the topical administration of retinoids. The retinoids may be any natural and/or synthetic analog which possess the biological activity of vitamin A.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to the use of retinoids for the prevention of glucocorticoid-induced skin atrophy, a side effect of prolonged topical glucocorticoid therapy for dermatological diseases.

Retinoids have been defined narrowly as comprising simply vitamin A (retinol) and its derivatives, such as vitamin A aldehyde (retinal) and vitamin A acid (retinoic acid), which comprise so-called natural retinoids. However, subsequent research has resulted in a much larger class of chemical compounds that are deemed retinoids due to their biological similarity to vitamin A and its derivatives. Compounds useful in the present invention include all natural and/or synthetic analogs of vitamin A or retinol-like compounds which possess the biological activity of vitamin A in the

skin. These include: regulation of epithelial cell differentiation of keratinocytes in the epidermis; stimulation of new collagen synthesis in the dermis, and production of new blood vessels (angiogenesis). Accordingly, as used herein for purposes of the present invention, the term "retinoid" will be understood to include any of the foregoing compounds. Examples of suitable retinoids in the present invention are set forth in Table I, although it will be understood that the invention is not limited thereto.

TABLE I

all-trans-retinoic acid
13-cis-retinoic acid

(all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid ethyl ester

(all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid

N-ethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenamide

(E,E)-9-(2,6-dichloro-4-methoxy-3-methylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid ethyl ester

7,8-didehydroretinoic acid

(E,E)-4-[2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadienyl]benzoic acid

(E)-4-[4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatrienyl]benzoic acid

(all-E)-3,7-dimethyl-(3-thienyl)-2,4,6,8-nonatetraenoic acid

(E,E,E)-3-methyl-7-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2,4,6-octatrienoic acid

(E)-6-[2-(2,6,6-trimethyl-1-cyclohexen-1-yl)ethenyl]-2-naphthalenecarboxylic acid

TABLE I (cont'd)

(E,E,E)-7-(2,3-dihydro-1,1,3,3-tetramethyl-1H-inden-5-yl)-3-methyl-2,4,6-octatrienoic acid

(E)-4-[2-(2,3-dihydro-1,1,3,3-tetramethyl-1H-inden-5-yl)-1-propenyl]benzoic acid

(E)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl-1-propenyl]benzoic acid

(E)-4-[2-(5,6,7,8-tetrahydro-3-methyl-5,5,8,8-tetramethyl-2-naphthalenyl-1-propenyl]benzoic acid

(E)-1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-(1-methyl-2-phenylethenyl)naphthalene

6-(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-naphthyl)-2-naphthalenecarboxylic acid

(E)-6-[2-(4-(ethylsulfonyl)phenyl]-1-methylethenyl]-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)ethynyl]benzoic acid

(E)-2-(1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl)-1-[4-tetrazol-5-yl)phenyl]-1-propene

(E)-4-[2-(5,6,7,8-tetrahydro-7-hydroxy-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzyl alcohol

Also encompassed within the term "retinoid" are geometric and stereoisomers of the retinoids.

A pharmaceutical composition containing a retinoid as the active ingredient in intimate admixture with a pharmaceutical carrier can be prepared according to conventional pharmaceutical compounding techniques, such as those known for topical application of all-trans-retinoic acid. The carrier may take a wide variety of physical forms such as creams, dressings, gels, lotions, ointments or liquids. The retinoid will be present in an amount from about 0.00001% by weight to about 0.3% by weight, depending

on the potency of the retinoid. A suitable topical retinoid preparation in a gel vehicle is Retin-A™, which contains 0.01% to 0.1% by weight of active ingredient, produced by Ortho Pharmaceutical Corporation. The retinoid may be employed in combination with a glucocorticoid in the same vehicle.

The retinoid may be applied topically before application of the glucocorticoid, simultaneously with the application of the glucocorticoid, or after the application of the glucocorticoid.

The following example describes the invention in greater particularity, and is intended to be a way of illustrating but not limiting the invention.

EXAMPLE

Glucocorticosteroid-induced skin atrophy was evaluated in albino SKH-hairless-1 mice. The glucocorticoid, dexamethasone (0.1%, 0.05%, 0.01%) or vehicle (alcohol:propylene glycol, 70/30 v/v) was applied topically (100 µl) to the dorsal flanks of hairless mice in the morning. In the afternoon, a retinoid, all-trans-retinoic acid (0.025%), or vehicle was applied topically (100 µl) to the previously treated site. The dexamethasone and all-trans-retinoic acid were administered five consecutive days for two weeks and four consecutive days during the third week. Approximately 24 hours after the final application, double skin-fold thickness measurements of the treated sites were taken with an electronic digital caliper having an accuracy of ±0.03 mm. The results are shown in Table II.

TABLE II

Glucocorticosteroid-Induced
Skin Atrophy Study

Treatment			Double Skin-Fold Thickness
A.M.	P.M.	N	X mm ± S.E.
Vehicle	Vehicle	8	0.934 ± 0.086
0.1% Dexamethasone	Vehicle	6	0.587 ± 0.035*
0.05% Dexamethasone	Vehicle	8	0.725 ± 0.038*
0.01% Dexamethasone	Vehicle	8	0.911 ± 0.052**
0.1% Dexamethasone	0.025% all-trans-retinoic acid	7	0.837 ± 0.075**
0.05% Dexamethasone	0.025% all-trans-retinoic acid	6	0.917 ± 0.091**
0.01% Dexamethasone	0.025% all-trans-retinoic acid	8	0.933 ± 0.103**
Vehicle	0.025% all-trans-retinoic acid	8	1.059 ± 0.122**

* Statistically different from vehicle control ($p < 0.05$)
** Not statistically different from vehicle control ($p > .05$)

The results shown in Table II clearly demonstrate that the administration of all-trans-retinoic acid prevents the skin atrophy induced by topical glucocorticoid therapy.

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CLAIMS

1. Products containing a corticosteroid in a topically administerable pharmaceutically acceptable carrier and a retinoid in a topically administerable pharmaceutically acceptable carrier as a combined preparation for simultaneous, separate or sequential use in treating dermatologic disease.

2. The combined preparation of claim 1 which comprises a mixture of the cortcosteroid and the retinoid in a topically administerable pharmaceutically acceptable carrier.

3. The combined preparation of claim 1 or claim 2, wherein the corticosteroid is a glucocorticoid.

4. The combined preparation of claim 3, wherein the glucocorticoid is dexamethasone.

5. The combined preparation of any one of claims 1 to 4, wherein the retinoid comprises from 0.00001% to 0.3% by weight of the product containing it.

6. The combined preparation of any one of claims 1 to 5, wherein the retinoid possesses the biological activity of vitamin A.

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7. The combined preparation of any one of claims 1 to 6, wherein the retinoid is all-trans-retinoic acid, 13-cis-retinoic acid, (all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid ethyl ester, (all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid, N-ethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenamide, (E,E)-9-(2,6-dichloro-4-methoxy-3-methylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid ethyl ester, 7,8-didehydroretinoic acid, (E,E)-4-[2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadienyl]benzoic acid, (E)-4-[4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatrienyl]benzoic acid, (all-E)-3,7-dimethyl-(3-thienyl)-2,4,6,8-nonatetraenoic acid, (E,E,E)-3-methyl-7-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2,4,6-octatrienoic acid, (E)-6-[2-(2,6,6-trimethyl-1-cyclohexen-1-yl)ethenyl]-2-naphthalenecarboxylic acid, (E,E,E)-7-(2,3-dihydro-1,1,3,3-tetramethyl-1H-inden-5-yl)-3-methyl-2,4,6-octatrienoic acid, (E)-4-[2-(2,3-dihydro-1,1,3,3-tetramethyl-1H-inden-5-yl)-1-propenyl]benzoic acid, (E)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl-1-propenyl]benzoic acid, (E)-4-[2-(5,6,7,8-tetrahydro-3-methyl-5,5,8,8-tetramethyl-2-naphthalenyl-1-propenyl]benzoic acid, (E)-1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-(1-methyl-2-phenylethenyl)naphthalene, 6-(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-naphthyl)-2-naphthalenecarboxylic acid, (E)-6-[2-(4-(ethylsulfonyl)phenyl]-1-methylethenyl]-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene, 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-ethynyl]benzoic acid, (E)-2-(1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl)-1-[4-tetrazol-5-yl)phenyl]-1-propene, or (E)-4-[2-(5,6,7,8-tetrahydro-7-hydroxy-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzyl alcohol.

8. The combined preparation of claim 7, wherein the retinoid is all-trans-retinoic acid.

9. The combined preparation of claim 7, wherein the retinoid is 13-cis-retinoic acid.

10. The combined preparation of claim 7, wherein the retinoid is (E)-4-[4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatrienyl]benzoic acid, 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-ethynyl]benzoic acid, or (E)-4-[2-(5,6,7,8-tetrahydro-7-hydroxy-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]-benzyl alcohol.

11. Use of a retincid as defined in any one of claims 1 and 6 to 10 in the preparation of a topically administerable medicament for use in the prevention of corticosteroid-induced skin atrophy.

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