United States Patent Office 3,019,162 Patented Jan. 30, 1962

3,019,162

CINCHOPHEN-HYDROCORTISONE TOPICAL COMPOSITIONS

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No Drawing. Filed May 18, 1959, Ser. No. 813,678
4 Claims. (Cl. 167—58)

This invention relates to compositions containing cinchophen together with hydrocortisone or the 21-acetate thereof as the principal active ingredients, and, more particularly, to such compositions adapted for external use.

It has recently been discovered that cinchophen (2 phenylquinoline-4-carboxylic acid) is a highly active therapeutic agent in the topical treatment of erythema. Qualitatively, the action of cinchophen appears not unlike that of hydrocortisone and hydrocortisone acetate when applied topically for the relief of erythematous conditions of the skin, although their mechanisms of action may differ widely. Unexpectedly, however, cinchophen has been found to be potentiated by hydrocortisone or its 21-acetate, the combination demonstrating a synergism which significantly enhances the effectiveness of such compositions beyond that of medicaments containing either cinchophen or the steroid as the sole active ingredient.

The treatment of erythema, particularly that arising through over-exposure to the sun, has long provided a problem to which an entirely satisfactory solution has not been developed. In the typical case, treatment of a sun-induced erythema (erythema solare) with conventional emollients and commercial preparations requires that the affected area be protected from re-exposure until healing is virtually complete. Where the subject desires protection against severe burn but nevertheless wishes to acquire a tan, the problem is further complicated, for an effective screening agent comonly prevents or greatly diminishes tanning. The synergistic combination of principal active ingredients in the present compositions provides effective means for obtaining relief from severe burn and for facilitating the restoration of affected areas, as well as providing compositions which are useful in preventing the development of severe burn due to over-exposure to the sun without appreciably affecting the tanning which would normally result from such exposure.

The qualities heretofore described for the present compositions are provided by the incorporation of cinchophen and hydrocortisone or hydrocortisone acetate in synergistic concentrations as the principal active ingredients. The unexpected degree of topical effectiveness of these compounds is realized through provision of compositions containing the said principal active ingredients dispersed in a pharmaceutically acceptable dermatologic base. By "dermatologic base" is meant a vehicle or carrier suitable for application to the skin, i.e., for topical or external use. The particular pharmaceutical forms adaptable to the purposes of this invention include ointments, lotions, pastes, jellies, powders and the like, ointments and lotions normally being preferred. As employed in the specification and claims herein, the term "ointment" is intended to embrace formulations having oleaginous, absorption, water-soluble and emulsion-type bases as defined and described in "Remington's Practice of Pharmacy," 11th edition (1956), page 336, Mack Publishing Company, Easton, Pennsylvania. Of the various types of bases mentioned, the emulsion-type is preferred, the said emulsion bases being either of the water-in-oil or oil-in-water type and specifically including creams, which are solid emulsions containing a suspension or solution and are intended for external use. The term "lotions" refers to liquid suspensions or dispersions stabilized by the presence of suspending agents or surface active agents, or both, and designed for external application.

The method for the preparation of pharmaceutically acceptable formulations involves the incorporation of the principal active ingredients, together with any complementary active or supplemental ingredients, into the selected pharmaceutical form by techniques well known in the art. The amount of the principal active ingredients can be varied widely to constitute compositions which are useful in the treatment of the conditions described. However, the pronounced synergistic activity which has been demonstrated for combinations of the said principal active ingredients is to be found in particular in compositions including hydrocortisone or hydrocortisone acetate in a concentration of at least 0.2% by weight, up to a maximum consistent with economy and effectiveness, preferably no more than about 3%. The concentration of cinchophen can vary from about 0.001% to about 10% by weight, from about 0.5% to about 2% being preferred.

Various complementary active ingredients can be employed with the cinchophen-hydrocortisone or hydrocortisone acetate combinations to provide a desirable adjunctive ameliorative or therapeutic effect. Thus, local or topical anesthetics such as benzyl alcohol and menthol can be incorporated in the formulation. Likewise, such antibacterial agents and antibiotics as bacitracin, polymyxin and neomycin, and antiseptics such as hexachlorophene, phenol, the essential oils, camphor, oil of cloves, oil of eucalyptus and allantoin can be included.

The present compositions typically include, in addition to the foregoing principal and complementary ingredients, such materials as emulsifying agents, solvents, antioxidants, preservatives, buffers, perfumes and bodying materials. Preferably, the compositions herein represent an emulsified base into which the active ingredients are incorporated, together with the foregoing collateral constituents, to produce an ointment, including a cream, or a lotion.

The present compositions are useful in the prevention of erythema as well as in the treatment of an established erythema. Of particular interest is their effectiveness in preventing the onset of painful erythema following exposure of human subjects to intense sunlight or artificial ultraviolet light, as well as their usefulness in treating an established erythematous condition such as sunburn of the skin. Laboratory and clinical tests have indicated that these compositions not only possess a high degree of efficacy but in addition are well tolerated. Extensive clinical studies on human subjects utilizing a mustard oil test and an ultraviolet burn test have permitted the definition of the synergistic range of the principal active ingredients of the novel compositions.

In the mustard oil test erythema is induced by exposing a number of predetermined areas on the skin of the forearms of human subjects to gauze patches saturated with mustard oil. After a specified period of time, the patches are removed and the skin is seen to be erythematous. The composition under test is applied by inunction to certain of the erythematous areas, and suitable control formulations are applied to the other areas. Each treated area is then covered with a clean gauze patch and the medication allowed to remain for a specified time. The patches are then removed and the formulations evaluated from comparative observations of the medicated and control areas.

In the ultraviolet burn test, erythema is induced by exposing the skin of the lumbar region of the back of human subjects to a sunlamp. A number of predeter-

mined areas are exposed for a specified period of time at a constant distance from the light source. Immediately following exposure, the control and medicated formulations are applied to the affected areas by inunction, and each area is covered with a gauze patch. The patches are allowed to remain for a specified time, after which they are removed and comparative observations made as before.

Results in the foregoing tests are recorded as "more effective," "equal," or "less effective" than the control.

The table below shows the results obtained on a comparison of (1) compositions containing varying amounts of cinchophen and constant amounts of hydrocortisone acetate with compositions containing only cinchophen in varying amounts, (2) compositions containing varying amounts of hydrocortisone acetate and constant amounts of cinchophen with compositions containing only cinchophen in constant amounts, and (3) compositions containing only hydrocortisone acetate with compositions containing only the base formulation. In the table, the columns designated I, II and III refer to the number of times the said compositions were found to be "more effective," "equal" or "less effective" than corresponding compositions omitting the steroid.

Percent Cinchophen	Percent Hydrocortisone Acetate	I More Effective	II Equal	III Less Effective
2.0	0.2	51	26	28
2.0	----			
1.0	0.2	12	15	8
1.0	----			
0.5	0.2	22	19	13
0.5	----			
2.0	0.1	5	2	5
2.0	----			
2.0	0.05	4	5	3
2.0	----			
---	0.2	45	58	43
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From the foregoing data it can be seen that a synergism or potentiating relationship is evidenced by the fact that lowering the concentration of cinchophen but maintaining the concentration of hydrocortisone acetate resulted in compositions which were enhanced in effectiveness by the presence of the hydrocortisone acetate. A further indication of synergism or potentiation is noted in the foregoing results which show that decreasing the amount of hydrocortisone acetate while maintaining the amount of cinchophen at a constant percentage produced a decrease or total loss of the synergistic or potentiating effect. Further confirmation of the synergism or potentiation of the said active ingredients is found in the fact that compositions containing the small amount of hydrocortisone acetate with no cinchophen in combination therewith were found to be inactive as compared to the base formulation per se. The base formulation employed was that appearing hereinafter as the formulation of Example 2, the cinchophen and hydrocortisone acetate being omitted.

The studies alluded to above indicate that a concentration of at least about 0.2% hydrocortisone acetate is required to potentiate the activity of cinchophen or to provide a synergistic combination of the two ingredients. The enhancement of results obtained with such combinations extends likewise to compositions in which hydrocortisone is substituted for the hydrocortisone acetate above. In general, the concentration of cinchophen in such compositions can vary from about 0.001% to about 10%, as heretofore described, from about 0.5% to about 2% being preferred.

The compositions of this invention can be best illustrated by specific examples of formulations incorporating the principal active ingredients described herein. Accordingly, the following examples are illustrative of

the novel compositions and methods for their use as contemplated in the present invention, but such examples are not to be construed as limiting the scope thereof.

Example 1

A lotion is prepared from the following ingredients:

	Percent
Stearic acid	2.5
Ethylene glycol monostearate	0.75
Heavy mineral oil	4.5
Lanolin	0.5
Methylparaben	0.1
Sorbitol, 70% solution	4.5
Magnesium aluminum silicate	0.4
Sodium hydroxide	0.5
Cinchophen	0.5
Hydrocortisone	0.2
Water, q.s.	

The lotion base is prepared from the foregoing ingredients in the usual manner and the cinchophen and hydrocortisone incorporated therein to form the completed lotion.

Substitution of hydrocortisone acetate for the hydrocortisone in the above formulation yields a lotion having similar properties.

The foregoing lotions are useful in the prevention of erythema or the treatment of an established erythematous condition when administered by inunction in the usual manner, preferably two times daily.

Example 2

A cream is prepared from the following ingredients:

	Percent
White mineral oil	5.0
Stearic acid	18.0
Propylene glycol	5.0
Potassium hydroxide	1.0
Methylparaben	0.1
Propylparaben	0.05
Perfume	0.2
Cinchophen	2.0
Hydrocortisone acetate	0.2
Water, q.s.	

The cream base is formulated in the usual manner, and the active ingredients are incorporated therein.

In the above formulation, hydrocortisone can be substituted for the hydrocortisone acetate employed therein to give a composition of similar effectiveness.

The foregoing creams are useful in the prevention and treatment of erythema when applied to the affected areas twice daily.

Example 3

An ointment is prepared from the following ingredients:

	Percent
White mineral oil	7.0
Lanolin	1.0
Ethylene glycol monostearate	3.0
Stearic acid	1.0
Cinchophen	0.5
Hydrocortisone	3.0
Water, q.s.	

The above formulation is compounded to form an ointment in the usual manner.

In the above formulation, hydrocortisone acetate can be substituted for the hydrocortisone to give an ointment of similar effectiveness.

The above ointments are applied topically by inunction in the usual manner, preferably twice daily, for the prevention of erythema or as treatment for an established erythematous condition.

Example 4

A powder is prepared from the following ingredients:

	Percent
Talc	97.8
Cinchophen	2.0
Hydrocortisone acetate	0.2

The above powder is compounded in accord with conventional practices.

Substitution of hydrocortisone for the hydrocortisone acetate above produces a powder of similar effectiveness.

The powder is preferably moistened with water and applied by inunction two times daily for the prevention of erythema or in the treatment of an established erythema.

It is to be understood that this invention is not to be limited to the exact details of operation or exact compositions shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the scope of the appended claims.

What is claimed is:

1. A composition for topical use which comprises: from about 0.5% to about 2% cinchophen and at least about 0.2% of a compound selected from the group consisting of hydrocortisone and hydrocortisone acetate, dispersed in a pharmaceutically acceptable dermatologic base.

2. A lotion comprising about 2% cinchophen and at least about 0.2% hydrocortisone acetate, dispersed in a pharmaceutically acceptable lotion base.

3. A cream comprising about 2% cinchophen and at least about 0.2% hydrocortisone, dispersed in a pharmaceutically acceptable cream base.

4. A method for the prevention and treatment of erythema which comprises: applying to the skin a composition including about 2% cinchophen and at least about 0.2% hydrocortisone acetate, dispersed in a pharmaceutically acceptable dermatologic base.

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