

1

2,989,437

ANTI-INFLAMMATORY AND ANTI-BACTERIAL DECONGESTANT NASAL SPRAY COMPOSITIONS

Milton Wruble, Kalamazoo Township, Kalamazoo County, and Harold F. Hailman, Kalamazoo, Mich., assignors to The Upjohn Company, Kalamazoo, Mich., a corporation of Michigan
No Drawing. Filed June 8, 1955, Ser. No. 514,132
11 Claims. (Cl. 167-58)

This invention relates to a therapeutic composition, more particularly a nasal preparation containing neomycin, an anti-inflammatory corticosteroid and phenylephrine.

The mucous membrane of the major portion of the nasal cavity is composed of the superficial ciliated columnar epithelium containing the terminal portion of the ducts from secretory mucous and serous glands, the basement membrane which is a band of collagen material of variable thickness underlying the ciliated epithelium, and the submucosa lying immediately under the basement membrane which is composed of connective tissue containing the mucous and serous glands, a network of blood vessels, nerves and lymphatics. This region is the predominant site of inflammatory reactions.

A thin mucous film normally covers the exposed ciliated epithelium. The cilia moving rhythmically cause the mucous film to flow backward to the pharynx to remove foreign matter including bacteria. The intact normally functioning nasal mucosa is on the whole quite resistant to infection.

A number of factors may be implicated in the disruption of physiological integrity of the nasal mucosa. Sudden exposure to change in temperature and humidity, sensitivity to allergens (pollens, molds, bacteria), overexposure to irritants such as chemicals and smoke may contribute to changes in the mucosa and result in inflammation.

Objectively, the picture is one of vascular congestion, edema, exudation and secretory dysfunction. These changes constitute a break in the integrity of the mucosa and predispose to infection.

Swelling of the tissue which is most marked in the area of the turbinates interferes with nasal breathing and drainage from the sinuses, and causes or perpetuates itching and sneezing. Extension of inflammation into the nasopharynx may obstruct the eustachian tube to cause the accumulation of fluid and create pressure disturbances in the middle ear.

Chronic inflammation produces several types of pathological changes in the nasal mucosa. Long standing edema or repeated allergic reactions favor polyp formation. It becomes evident that prompt suppression of inflammation will not only provide the patient with welcome relief but may also prevent complications.

It is therefore an object of this invention to provide a therapeutic composition which is effective in the treatment of nasal disorders. It is also an object of this invention to provide such a composition which provides a combination of active ingredients each of which enhances and supplements the activity of the other. A further object is the provision of such a preparation which reduces local edema in certain nasal conditions and thus improves the therapeutic action of the anti-inflammatory corticosteroid and/or neomycin. A still further object is the provision of such a composition which has greater antibiotic activity than neomycin alone. A further object is the provision of a combination which interferes less with ciliary action than the individual components. Another object is the provision of such a composition which prolongs, increases, or otherwise improves the anti-inflammatory effect of the corticosteroid. A still further object is the provision of

2

such a composition which improves the vasoconstrictor action of the phenylephrine by reducing its destruction by enzymes in the nasal mucosa. A still further object is the provision of such a composition which corrects vasomotor paralysis and restores the response of the mucosa to the vasoconstrictor. A still further object is the provision of such a composition which improves the spreading and local tissue penetration of the anti-inflammatory corticosteroid when applied topically. A still further object is the provision of such a composition which suppresses the rebound effect of vasoconstrictors. A still further object of the invention is to provide such a composition which is prepared in a special emulsion base to form a stable and pharmaceutically elegant composition. Other objects will be apparent to one skilled in the art to which this invention pertains.

The foregoing and additional objects have been accomplished by the provision of a therapeutic composition comprising neomycin, an anti-inflammatory corticosteroid and phenylephrine as the essential active ingredients, in a sprayable emulsion-type vehicle, preferably containing diethylaminoethyl oleyl amide phosphate.

Essentially the composition of the present invention is prepared by dispersing the active ingredients in a vehicle suitable for nasal use. It is preferred that the vehicle be a very thin, mobile, sprayable emulsion which holds the active ingredients particularly hydrocortisone, adequately suspended for long periods of time without loss in potency and without discoloration and in which even where some settling does occur after long periods of standing, resuspension is readily attained by slight shaking.

The difficulties involved in preparing an effective, physically stable nasal preparation are considerable as witnessed by the following statement which appeared in the Journal of Allergy 25: 513 (1954):

"Unfortunately, however, as certain attempts at our hospital and elsewhere have demonstrated, particulate suspensions of hydrocortisone acetate—at least in the concentrations heretofore used—cannot be uniformly dispersed on membrane surfaces, nor do they lend themselves well to aerosolization."

Furthermore, it has been a difficult problem to prepare a stable emulsion of the viscosity required for spraying (preferably 11.3 centistokes, or 11.5 centipoises) which is capable of suspending relatively high concentrations of the insoluble hydrocortisones for long periods without agglomeration.

The phrase "anti-inflammatory corticosteroid" as used in the present specification means those adrenal cortical steroids and their derivatives which possess local anti-inflammatory activity, particularly on the mucous membranes. These corticosteroids include hydrocortisone (the preferred corticosteroid), cortisone, 9 α -fluoro-11 β , 17 α - dihydroxyprogesterone, 9 α - fluoro - 11 - keto-17 α -hydroxyprogesterone and the like.

The word "hydrocortisone" as used in the present specification means 17 α -hydroxycorticosterone and its topically active derivatives, such as the 21-esters including the acetate, the cyclopentylpropionate, and the like; the Δ^1 analogs, such as 11 β ,17 α ,21-trihydroxy-1,4-pregnadiene-3,20-dione and its esters; the 2-methyl derivatives such as 2 - methyl - 11 β ,17 α ,21 - trihydroxy - 4 - pregnene - 3,20-dione and its esters; combinations of the foregoing derivatives, such as 2-methyl-11 β ,17 α ,21-trihydroxy-1,4-pregnadiene-3,20-dione and its esters; and the like. The 2-methyl derivatives and processes for their production are disclosed in copending application Serial Number 485,318, filed January 31, 1955, now Patent No. 2,923,720.

The word "cortisone" as used in the present specification means 17 α -hydroxy-11-dehydrocorticosterone and its topically active derivatives, such as the 21-esters including

the acetate, the hemisuccinates, and the like; the Δ^1 analogs, such as 17 α ,21-dihydroxy-1,4-pregnadiene-3,11,20-trione and its esters; and the like.

The word "neomycin" as used in the present specification means the antibiotic more fully described in Waksman, "Neomycin," Rutgers University Press, 1953. It includes the various forms of neomycin (such as the B and C forms) and their therapeutically active derivatives (such as the sulfate and the hydrochloride salts).

The word "phenylephrine" as used in the present specification means 1-m-hydroxy- α -(methylaminomethyl)-benzyl alcohol and its therapeutically active salts (such as the hydrochloride salt). The compound is more particularly described in U.S. Patents 1,932,347 and 1,954,389.

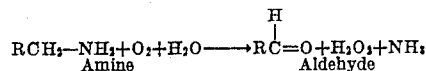
In a preferred embodiment the composition of the present invention is prepared as a nasal spray in a buffered, isotonic base having a pH which is most advantageous for use on the nasal mucosa (a pH between about 5.5 and 6.5). The preparation must be nonirritating to the nasal mucosa. The vehicle for the active ingredients is preferably an oil-in-water emulsion. The emulsion is stabilized by an emulsifying or stabilizing agent, or combination of such agents, which prevents the oil globules from coalescing for long periods of time. The oil or fat phase in the preferred embodiment of the present invention comprises glyceryl monostearate and spermaceti. The emulsifying agent in the preferred embodiment comprises polysorbate 80, U.S.P., and diethylaminoethyl oleyl amide phosphate. The diethylaminoethyl oleyl amide phosphate performs a dual function in that it also stabilizes the phenylephrine in the nasal mucosa by reducing enzyme oxidation thereof. This stabilization function applies both to the situation where phenylephrine is used alone as well as to one in which an anti-inflammatory corticosteroid and neomycin are also present in the composition. In order to minimize irritation in the nose, the emulsion is preferably made isotonic using such materials as sodium chloride and/or sodium citrate. The latter also acts as a buffer to stabilize the pH. The emulsion is preferably preserved with myristyl gamma picolinium chloride and/or sorbic acid. A humectant, preferably propylene glycol, is also desirable; this material also aids in stabilizing the emulsion. In addition to the individual contributions of the separate ingredients, the combination of ingredients in the preferred embodiment of the present invention provides a composition possessing superior therapeutic and pharmaceutical properties.

The concentrations of the various active ingredients are important, particularly in the preferred embodiments of present invention. The amounts of the active ingredients used depend primarily upon the therapeutic activity of each ingredient. For example, the concentrations of the corticosteroid used would preferably vary from 0.05 percent for 2-methyl-11 β ,17 α ,21-trihydroxy-1,4-pregnadiene-3,20-dione to 2.5 percent for hydrocortisone acetate. (All percentages are weight by volume unless otherwise specified.) An adequate concentration of neomycin is about 0.5 percent, although it is preferred to use an additional 0.1 percent to compensate for losses during manufacture and storage. There can be considerable variation of this amount without impairing the therapeutic effectiveness of the combination. Similarly, the concentration of phenylephrine preferably varies from 0.1 percent to one percent, especially 0.25 percent. The concentration of the fat or oil in the emulsion preferably ranges from two to four percent. Of the total composition 0.03 to 0.3 percent is preferably diethylaminoethyl oleyl amide phosphate. The desirable concentration of polysorbate 80 U.S.P. in the emulsion ranges from 0.25 to 1.5 percent, preferably 0.5 percent. Although considerable variation of these concentrations is possible, the best results are obtained within the preferred limits given.

In preparing the composition of the present invention, the micronized corticosteroid can be dispersed in the aqueous phase before the emulsification step. Where the

corticosteroid shows some decomposition at the emulsification temperature it is preferably dispersed in the emulsion after it is cooled either before, or at the same time as, the addition of the phenylephrine and neomycin. The neomycin and phenylephrine are always added after the temperature has been lowered since they are unstable to the heat required during emulsification. For aqueous dispersions of corticosteroids which are difficult to wet, e.g., 11 β ,17 α -dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione, the preferred emulsion form of the composition of the present invention is even more important in forming a satisfactory, physically stable suspension.

Phenylephrine tends to oxidize in the presence of amine oxidase, an enzyme found in the nasal mucosa. The therapeutic effectiveness of phenylephrine is adversely affected by such oxidation. One of the advantages of the composition of the present invention is its tendency to stabilize phenylephrine in the presence of amine oxidase. The following table shows the effect of neomycin, hydrocortisone acetate, hydrocortisone alcohol, and the vehicle alone on the rate of oxidation of phenylephrine by amine oxidase. The source of the enzyme used in the test was guinea pig liver. The rate of oxidation was measured manometrically. The reaction measured can be illustrated by the following formula:



TABLE

Phenyl- eph- rine, mg.	Neo- mycin, mg.	Hydro- cort. Ac., mg.	Hydro- cort. Alc., mg.	Vehicle, ml.	Nose Spray, ml.	mm. ¹ O ₂ / hour
1.25						71
1.25					0.5	34
1.25		7.5				74
1.25			7.5			68
1.25	2.5					71
1.25	2.5	7.5				80
1.25	2.5		7.5			74
1.25					0.5	86
1.25						39
1.25				0.5		71
1.25				0.5		52
1.25						53
1.25						71
1.25				0.5		10
1.25						10
1.25				0.5		62
1.25				0.5		49
1.25	2.5	7.5		0.5		53
					0.5	42

¹ No enzyme.

The data show that additions of neomycin, hydrocortisone alcohol or acetate, alone or in combination had little or no inhibitory effect on the oxidation of phenylephrine by amine oxidase. The vehicle inhibited the oxidation of phenylephrine by 21 and 27 percent in different experiments. The rate of oxidation of the phenylephrine was still lower when the whole composition was tested than when the various ingredients were added separately. The reason for this is unknown.

The stability of the phenylephrine in the composition of the present invention is due to one of the ingredients in Tegacid Regular, the trade name for an emulsifying agent available from the Goldschmidt Chemical Corp., New York, N.Y., containing glyceryl monostearate and diethylaminoethyl oleyl amide phosphate. The latter material is almost entirely responsible for this stability. Diethylaminoethyl oleyl amide phosphate is prepared by reacting equivalent amounts of oleyl diethylaminoethyl amide and phosphoric acid in aqueous solution. The diethylaminoethyl oleyl amide phosphate in Tegacid Regular consists mainly of



Tegacid Regular contains approximately five percent by

5

weight of diethylaminoethyl oleyl amide phosphate, the balance being almost entirely glyceryl monostearate.

Clinical trial in humans has shown that the composition of the present invention provides good to excellent results in the following conditions: nasal polyps, allergic rhinitis, acute sinusitis, chronic sinusitis, acute nasopharyngitis, chronic maxillary sinusitis, asthma due to sinus infection, basomotor rhinitis, hay fever, pollinosis, and the like.

The following examples are illustrative of the processes and compositions of this invention and are not to be construed as limiting.

Example 1

44,000 milliliters of the composition of the present invention is prepared from the following types and amounts of ingredients:

	Grams
Myristyl gamma picolinium chloride	10.3
Powdered neomycin sulfate	283
Phenylephrine hydrochloride, U.S.P.	110
Sodium chloride, U.S.P.	44
Sodium citrate, U.S.P.	198
Propylene glycol, U.S.P.	440
Spermaceti, U.S.P.	440
Tegacid Regular (Goldschmidt)	660
Polysorbate 80, U.S.P.	220
Micronized hydrocortisone acetate	660
Water for injection, sufficient to make up 44,000 mls.	

25,000 milliliters of sterile water at a temperature of approximately ninety degrees centigrade is transferred to a sterile, calibrated, stainless steel mixing tank fitted for rapid agitation. While agitating, a hot mixture of spermaceti, Tegacid, and polysorbate 80 is added aseptically. Rapid agitation is continued until the temperature of the emulsion is approximately 38 degrees centigrade. Sterile aqueous solutions of myristyl gamma picolinium chloride, neomycin, phenylephrine, sodium chloride, sodium citrate and propylene glycol, and sterile micronized hydrocortisone acetate are added aseptically. This is mixed thoroughly for approximately two hours. Sterile water is added to bring the composition up to volume and the whole is milled through a sterile colloid mill. The composition is assayed for hydrocortisone acetate, phenylephrine hydrochloride, neomycin, pH, particle size and sterility. Fifteen milliliters of the suspension-emulsion is filled into each sterile plastic squeeze bottle.

Example 2

Following the procedure of Example 1, a composition containing hydrocortisone free alcohol at a concentration of 0.5 percent is prepared by substituting 220 grams thereof for the hydrocortisone acetate in the formula given.

Example 3

Following the procedure of Example 1, a composition containing 11 β ,17 α -dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione at a concentration of 0.1 percent is prepared by substituting 44 grams thereof for the hydrocortisone acetate in the formula given.

A concentration of 0.05 percent is prepared by substituting 22 grams.

Example 4

Following the procedure of Example 1, a composition containing 2-methyl-11 β ,17 α -dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione at a concentration of 0.05 percent is prepared by substituting 22 grams thereof for the hydrocortisone acetate in the formula given.

Example 5

Following the procedure of Example 1, a composition containing 17 α ,21-dihydroxy-1,4-pregnadiene-3,11,20-trione at a concentration of 0.1 percent is prepared by substituting 44 grams thereof for the hydrocortisone acetate in the formula given.

6

Example 6

15,000 milliliters of the composition of the present invention is prepared from the following types and amounts of ingredients:

	Grams
Micronized hydrocortisone acetate	225
Polysorbate 80, U.S.P.	75
Sodium chloride U.S.P.	15
Sodium citrate gran., U.S.P.	67.5
Myristyl gamma picolinium chloride	3.5
Glyceryl monostearate NF	214
Diethylaminoethyl oleyl amide phosphate	11
Spermaceti, U.S.P.	150
Propylene glycol, U.S.P.	150
Neomycin sulfate powder	96
Phenylephrine hydrochloride, U.S.P.	37.5
Sorbic acid	7.5
Deionized water, sufficient to make up 15,000 mls.	

12,000 milliliters of deionized water is heated in a suitable container to 70–75 degrees centigrade. Sodium chloride, sodium citrate and myristyl gamma picolinium chloride and sorbic acid are dissolved therein. Polysorbate 80 and propylene glycol are added. The hydrocortisone acetate is dispersed thoroughly therein. The glyceryl monostearate, diethylaminoethyl oleyl amide phosphate and spermaceti are added. While stirring thoroughly, the temperature is maintained at about 75 degrees centigrade for thirty minutes before cooling to room temperature. The neomycin sulfate and phenylephrine are then dissolved therein. Deionized water is added to make up a volume of 15,000 milliliters and the whole is stirred thoroughly.

In addition to the unexpected advantages shown by the compositions of this invention for many nasal conditions, a number of troublesome ear inflammations have also been treated with marked success.

Other antibacterial agents can also be added advantageously to any of the above compositions, such as one or more of polymyxin B sulfate about 2000 units per milliliter of emulsion, gramicidin about 0.005 percent, erythromycin about one percent, and a sulfonamide such as sodium sulfacetamide about five percent or 4-aminomethylbenzenesulfonamide hydrochloride about five percent.

An antihistamine, such as 1-(p-chlorophenyl)-1-(2-pyridyl)-3-dimethylaminopropane gluconate about 0.25 percent and 2-[(2-dimethylaminoethyl)(p-methoxybenzyl)amino] pyrimidine hydrochloride about 0.3 percent, can also be added to any of the formulations of this invention.

It is to be understood that the 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.

We claim:

1. A nasal spray composition comprising an anti-inflammatory adrenocorticosteroid, neomycin, and phenylephrine in a liquid vehicle suitable for nasal use.

2. A nasal spray composition comprising hydrocortisone, neomycin, and phenylephrine as the essential active ingredients and diethylaminoethyl oleyl amide phosphate as an emulsifier-stabilizer in an aerosol-type liquid vehicle.

3. A nasal spray composition comprising hydrocortisone acetate, neomycin sulfate, 1-phenylephrine hydrochloride, a preservative, and a humectant in an isotonic, aerosol-type oil-in-water emulsion.

4. A nasal spray composition comprising hydrocortisone acetate, neomycin sulfate, 1-phenylephrine hydrochloride, spermaceti, propylene glycol, polysorbate 80, U.S.P., glyceryl monostearate, and diethylaminoethyl

oleyl amide phosphate in an isotonic, aqueous, aerosol-type vehicle.

5. A nasal spray composition comprising from about 0.05 to 2.5 percent of an anti-inflammatory adrenocorticosteroid, about 0.6 percent neomycin, about 0.1 to one percent phenylephrine, and about 0.03 to 0.3 percent diethylaminoethyl oleyl amide phosphate in an isotonic, aerosol-type oil-in-water emulsion.

6. The composition of claim 5 wherein the oil phase comprises glyceryl monostearate and spermaceti.

7. The composition of claim 5 wherein the anti-inflammatory adrenocorticosteroid is hydrocortisone.

8. The composition of claim 5 wherein the anti-inflammatory adrenocorticosteroid is hydrocortisone acetate.

9. The composition of claim 5 wherein the anti-inflammatory adrenocorticosteroid is 11 β ,17 α -dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione.

10. The composition of claim 5 wherein the anti-inflammatory adrenocorticosteroid is 2-methyl-11 β ,17 α -dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione.

11. The composition of claim 5 wherein the anti-inflammatory adrenocorticosteroid is 17 α ,21-dihydroxy-1,4-pregnadiene-3,11,20-trione.

References Cited in the file of this patent

UNITED STATES PATENTS

2,684,946	Schmitz	July 27, 1954
2,730,483	Mast	Jan. 10, 1956
2,786,835	Pinson	Mar. 26, 1957
2,801,202	Poetsch	July 30, 1957

OTHER REFERENCES

- "Neosone," Modern Drugs, January 1953, p. 293.
 Conn: Current Therapy, 1952, Saunders, Phila., Pa., p. 494.
 Herrmann et al.: Deut. med. Wochschr., 74, 928-931 (1949).
 Schwartz et al.: "Surface Active Agents and Detergents," vol. II, 1958, p. 227 footnotes.