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LOBELINE AEROSOL DILATING
MEDICAMENT

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This invention relates to medical compositions for use in aerosol therapy, especially for opening or enlarging the passages in the respiratory system; and it relates particularly to synergistic compositions comprising as primary and essential ingredients a procaine salt and a lobeline salt, or a cocaine salt and a lobeline salt.

Aerosol therapy has become very important in the treatment of respiratory diseases or pathological conditions, e. g., in the treatment of bronchitis, tuberculosis, asthma, and the like, and also in the treatment of other diseases or pathological conditions by absorption of drugs through the respiratory system and transport of the drugs to other parts of the body by means of the blood circulatory system.

An important problem confronting the art of aerosol therapy is the dilation (enlargement) of the respiratory passages so that aerosols may penetrate to the innermost regions or passages in the lungs, and to provide maximum surface or absorption area for absorbing the drugs.

In accordance with the invention, there are provided pneumo-dilating therapeutic agents suitable for administration in the form of aerosols, for relieving constriction and for penetrating the innermost passages (alveoli) of the lungs, and for providing increased absorption area.

One of the objects of the invention is to produce a pneumo-dilating composition having an action which is prompt, effective and long-lasting. Another object is to produce therapeutic agents which may be effectively administered in the form of aerosols in the respiratory system. Other objects will be apparent as the details or embodiments of the invention are set forth hereinafter.

In accordance with the present invention there are provided therapeutic agents suitable for administration in the form of aerosols comprising preparations containing a lobeline salt, e. g., lobelia alkaloid, and a procaine salt or a cocaine salt, and containing also as desired, one or more additional agents, such added agents including antiseptics, anti-secretive agents, surface tension lowering agents, agents modifying the tonus of smooth muscles, etc.

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In order to facilitate a clear understanding of the invention, the following non-limitative illustrative examples are given. The pneumo-dilating efficiency of the compositions is tested by volumetric pneumography, in accordance with published procedures, and the following data are typical of results obtained with the compositions of the invention. All parts, amounts and percentages herein are by weight unless otherwise specified.

TABLE I

Ex-ample No.	Aerosol of	Volume of Aerosol Inhaled (in Liters)	Dilation Range (Maximum Increase in Lung Volume, in cc.)	Duration of Dilation (in Minutes)
A.....	10% aqueous solution of (10%) Tincture of Lobelia.	10	300 to 500....	2 to 4.
20 B.....	2% aqueous solution of Procaine Hydrochloride.	10	250 to 500....	2 to 4.
1.....	aqueous solution containing 5% of (10%) Tincture of Lobelia and 1% of Procaine Hydrochloride.	10	500 to 1000....	4 to 10.

The synergistic effect of the lobelia-procaine composition of Example 1 is apparent. With only one-half as much of the lobelia salt, as in comparative Example A, together with only one-half as much as the procaine salt, as in comparative Example B, the Example 1 effect is of the order of double the additive effect, or more, both as to dilation range and also as to the duration of the dilation, each of which varies in view of the variations in the average lung volume change of each of the human subjects used.

The tincture of lobelia may be an alcoholic extract containing 10% of lobelia constituents in the form of their naturally occurring alkaloids, the principal one of which is lobeline.

This Example 1 composition is particularly useful for the relief of various kinds of pneumo-constrictions, such as those caused by allergies, irritants, dusts, and the like, as mentioned hereinabove; and this composition may be diluted e. g., with distilled water with satisfactory results, even down to a five-fold dilution.

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Another illustrative composition of the invention suitable for inhalation as an aerosol is:

Example 2

	Per cent
Lobeline sulfate-----	0.5
Procaine hydrochloride-----	1.0
Water -----	98.5
Total -----	100.0

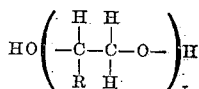
This composition also shows the synergistic effect, and may be used like the composition of Example 1.

The synergistic effect is characteristic of lobeline salt compositions containing either a procaine salt or a cocaine salt, or both, even in relatively small amounts. For maximum therapeutic effect, however, the preferred compositions contain per part of lobeline salt (lobeline part), 1 to 5 parts of procaine salt (procaine part) or 1 to 2.5 parts of cocaine salt (cocaine part).

Although compositions in the form of solutions are preferred, in view of their great lung penetrating power when administered as very fine aerosols and also in view of the facility with which dosage is controlled, the compositions, in substantially the above-mentioned proportions, may be in dry or solid form. In such case they would preferably be suitably diluted with an inert material in a sterilized and fine powdered form, to pass into the innermost respiratory regions. The slight constriction known to normally appear after inhalation of powders is easily overcome by the dilating agent.

When the compositions of the invention are used in the form of solutions, the particular dilution or concentration thereof is dependent upon the degree or intensity of medication desired. For general administration, an aqueous composition containing from 0.2 to 2% of procaine hydrochloride and from 0.1 to 0.5% lobeline sulfate produces satisfactory medication. A more concentrated solution which when dispersed as an aerosol will provide effective dilation with but a single inspiration of the aerosol contains about 0.2% lobeline hydrochloride and either 2% procaine hydrochloride or 1% cocaine sulfate. Less concentrated solutions than the above may be employed according to the sensitivity of the subject, but I have found that solutions containing less than about 0.1% lobeline alkaloid salt, e. g., sulfate and less than about 0.1% procaine or cocaine salt, e. g., hydrochloride, require a longer time to produce the requisite degree of dilation.

Solvents other than water may be used in such compositions. Replacement of some or all of the water in the above-mentioned solutions by a lower glycol compound, e. g., ethylene glycol, diethylene glycol, triethylene glycol or propylene glycol results in an increased therapeutic efficacy and prolongation of the duration of therapeutic effect. These materials may be represented by the formula



wherein x may be 1, 2 or 3; and R is H where x is 2 or 3, but R is H or —CH_3 where x is 1. It is preferred to employ the above glycols in aqueous solutions of concentrations of about 20 to about 80%, since these concentrations provide a substantial increase in the therapeutic activity of the dilating compositions but do not increase

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the viscosity of the solutions to such an extent that the production of aerosols therefrom is made difficult. Care should be taken to use only pure glycols since even relatively small amounts of the impurities as frequently are present in crude glycols are constrictive in effect and may even produce an asthmatic crisis.

The pneumo-dilating compositions of the invention may be used directly as pneumo-dilating agents to relieve various kinds of pneumo-constrictions, such as those caused by allergies, irritants, caustics, infections, dusts, powders, and the like. They may be used before or together with i. e., include other medicating agents, such as antiseptics for the respiratory system, for example, guaiacol, guaiacol salts, creosote, menthol, eucalyptol, penicillin, streptomycin, sulfa drugs, and the like; anti-secretive materials, such as an atropine salt; tonic agents for the blood vessels, such as a strychnine salt; or other agents, such as ethylene glycol, propylene glycol, diethylene glycol, triethylene glycol, and the like, or any other drug with systemic action.

The following (non-limitative) example and table illustrate a glycol-containing composition and the improved dilation effect obtained therewith.

TABLE II

Ex-ample No.	Aerosol of	Volume of Aerosol Inhaled (in Liters)	Dilation Range (Maximum Increase in Lung Volume, in cc.)	Duration of Dilation (in Minutes)
35	aqueous solution containing 5% of Tincture of Lobelia and 1% of Procaine Hydrochloride.	10	500 to 1000...	4 to 10.
C	pure Ethylene Glycol or pure Propylene Glycol.	10	200 to 700....	2 to 3.
40	aqueous solution containing 5% of Tincture of Lobelia and 1% of Procaine Hydrochloride plus 10% of Ethylene or Propylene Glycol.	10	500 to 1400...	5 to 10.

The lobelia-procaine-glycol composition of Example 3 shows an additional and improved effect as compared to the lobelia-procaine composition of Example 1 and the glycol of comparative Example C, even though the amount of glycol inhaled in the Example 3 test is comparable to only about 10% the amount inhaled in the Example C test.

This type of effect is also obtained if any of the other above-mentioned glycols are used in proportions in the range of 1 to 20 parts of the glycol per 20 parts of the lobelia-procaine solution.

The following specific composition illustrates a very effective pneumo-dilating and expectorant composition, which is useful for and has found good acceptance by medical practitioners for treatment of chronic asthma, chronic bronchitis, bronchiectasis, etc. by dispersion as an aerosol and inhalation:

Example 4

	Grams
Lobelia (10% tincture of)-----	10
Procaine hydrochloride-----	2
Guaiacol -----	0.25
Potassium sulfoguaiacolate-----	2
Ethylene glycol-----	10
Water -----	75.75
Total -----	100.00

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The following (non-limitative) examples and table illustrate other compositions and the improved dilation effect obtained therewith.

TABLE III

Ex-ample No.	Aerosol of	Volume of Aerosol Inhaled (in Liters)	Dilation Range (Maximum Increase in Lung Volume, in cc.)	Duration of Dilation (in Minutes)
D.....	aqueous solution containing 1% of Atropine Sulfate.	10	300 to 500....	2 to 4.
E.....	aqueous solution containing 0.2% of Strychnine Sulfate.	10	100 to 200....	1 to 2.
5.....	aqueous solution containing: 0.1% of Procaine Sulfate, 0.5% of (10%) Tincture of Lobelia.	10	400 to 600....	2 to 4.
6.....	aqueous solution containing: 0.2% of Atropine Sulfate, 0.2% of Strychnine Sulfate, 0.5% of (10%) Tincture of Lobelia, and 0.1% of Procaine Sulfate.	10	800 to 1300....	4 to 10.

The atropine - strychnine - lobelia - procaine composition of Example 6 shows an improved effect (synergism), even though the atropine material therein is present in only one-fifth the amount in the comparative Example D test.

The following example illustrates a particularly effective pneumo-dilating and anti-secretive composition, which has found good acceptance by medical practitioners, for the treatment of asthma accompanied by bronchorrhea, chronic bronchitis, bronchiectasis, and the like by dispersion in the form of an aerosol and inhalation:

Example 7

	Grams
Lobeline sulfate.....	0.1
Procaine hydrochloride.....	0.1
Atropine sulfate.....	0.2
Strychnine sulfate.....	0.2
Ethylene glycol.....	10.0
Water	89.4
Total	100.0

A composition suitable for the treatment of infectious asthma or respiratory infections is as follows:

Example 8

	Grams
Lobeline hydrochloride.....	0.2
Cocaine	0.5
"Aerosol OT" (dioctyl ester of sodium sulfosuccinate)	0.1
Potassium or calcium penicillin.....	5.0
Water	94.2
Total	100.0

In place of the alkaloid salts mentioned, other water-soluble salts may be used, using an equivalent effective concentration of the alkaloid. The free alkaloids may be compounded in the above-disclosed proportions, but it is preferred to administer the compositions in convenient soluble salt form. Of course, cocaine compositions are not to be used except with the usual precautions for cocaine. A soluble nicotine material, such as the sulfate, or the like, may be used in place of the lobeline material in certain instances, but, of course, the resulting compositions are not to be used except with the precautions usual for a nicotine material.

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In view of the foregoing disclosures, variations and modifications thereof will be apparent to those skilled in the art, and all such variations and modifications are contemplated broadly within the invention.

I claim:

1. A composition comprising as essential and primary ingredients, a lobeline salt and a salt selected from the group consisting of salts of procaine and of cocaine, said composition being adapted for dispersion in the form of an aerosol and inhalation to produce a pneumo-dilating effect.

2. The composition of claim 1 in the form of a solution containing at least 0.1% of each salt component.

3. A composition comprising as essential and primary ingredients, a lobeline salt, a procaine salt and a respiratory antiseptic material, said composition being adapted for dispersion in the form of an aerosol and inhalation to produce a pneumo-dilating effect.

4. A composition comprising as essential and primary ingredients, a lobeline salt, a procaine salt and a stimulating agent for the central nervous system, said composition being adapted for dispersion in the form of an aerosol and inhalation to produce a pneumo-dilating effect.

5. A composition comprising as essential and primary ingredients, a lobeline salt, a procaine salt and guaiacol said composition being adapted for dispersion in the form of an aerosol and inhalation to produce a pneumo-dilating effect.

6. A composition comprising as essential and primary ingredients, a lobeline salt, a procaine salt, an atropine salt and a strychnine salt, said composition being adapted for dispersion in the form of an aerosol and inhalation to produce a pneumo-dilating effect.

7. A composition comprising as essential and primary ingredients, a lobeline salt and a salt selected from the group consisting of salts of procaine and of cocaine, in a sterilized and fine powdered form.

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