Patented Jan. 28, 1947

2,414,918

UNITED STATES PATENT OFFICE

2,414,918

SOLUTIONS FOR THE IMPROVED NEBULIZATION THERAPY OF THE LUNGS AND BRONCHIOLES

Harold Alexander Abramson, New York, N. Y.

No Drawing. Application September 23, 1941, Serial No. 411,987

4 Claims. (Cl. 167—58)

1

This invention relates to therapeutic agents of the type which are useful for the treatment of the lungs and bronchioles by nebulization (mist or fog formation) in the inhalant therapy of asthma.

One of the objects of the invention is to obtain an improved therapeutic agent producing a more stable mist by nebulization so that it is more readily carried by the respiratory movements into the lungs where it may act upon the bronchioles and other tissues which are responsible for the asthmatic attack with a more effective therapeutic effect because the mist produced by nebulization is more stable.

Another object is to provide an improved inhalant suitable for nebulization which allows the patient to more readily estimate the dose when used in the inhalant therapy of asthma.

Another object is to produce a therapeutic agent which is effective as an antispasmodic in asthma, which is pleasant in effect, and of a character as to inhibit oxidations and the growth of microorganisms which would lead to deterioration.

In the broader aspects of my invention the new therapeutic agent comprises an aqueous solution of a polyhydroxyl alcohol base (e. g. glycerol; ethylene glycol; propylene glycol), and antispasmodic substance, sufficient preservative to inhibit the growth of microorganisms, as well as an antioxidant, like sodium bisulphite, to diminish the oxidation rate of the antispasmodic. The primary antispasmodic substances are epinephrine, amphetamine, ephedrine, neosynephrine or other substances having an antispasmodic effect on the lung or bronchiol tissue when used by nebulization to diminish the spasm of asthma. The antispasmodic substance, such as epinephrine, may be used in any form in which it is soluble in water, preferably in the form of salts like the phosphates or the chlorides, but the lactates or other equivalents may also be employed. It is preferably used in amounts to give a solution of about 1% of the alkaloid, but ½% or 2% may also be employed. In general, a satisfactory amount is the equivalent to 1% of the naturally occurring epinephrine base.

It will be shown that instead of glycerol, ethylene glycol, propylene glycol, and, other substances as well as solids under certain conditions may be employed to obtain enhanced nebulization.

It is well known to those versed in the art that to prevent bacterial growth in solutions of the type under discussion a preservative like chlorbutanol may be employed.

2

The discovery to be described had its origin in actual difficulties which I encountered in treating patients with asthma by means of the nebulization of solutions of epinephrine (adrenalin salts) containing 1% of epinephrine hydrochloride or 1% of epinephrine phosphate (adrenalin and epinephrine are used interchangeably) by the usual method. The usual method consists in the employment of a special device known as a nebulizer and a solution of 1% epinephrine salt which does not embody in its composition the improvements embodied in my invention. The patients complained that they did not know when the nebulizer functioned properly because they could not readily see the mist which disappeared too rapidly to be easily observed. Further, the dosage because of the rapid disappearance of the mist was uncertain. Psychologically, the technic was therefore disadvantageous and many patients discontinued the use of ordinary aqueous solutions of the material because they were uncertain that a mist was being formed that would have therapeutic value. The method which has subsequently been developed is generally applicable to the nebulization of dissolved substances, in general, as well as epinephrine.

Before discussing the method of producing nebulization it is important to distinguish clearly between an atomizer and a nebulizer. Aside from the difference in the construction of the two (which is readily observable in the usual commercial models) the effects of the two are quite different therapeutically. In the nebulization therapy of the lungs and bronchioles to which this invention specifically refers, the size of the nebulized droplets differs from the atomized droplets in that the nebulized droplets are smaller and therefore not as readily observed. The effects of each, also, in therapy of the lungs and bronchioles are quite different because the larger atomized droplets are not readily transported into the lungs. An atomizer may not replace a nebulizer for the following reason: when an atomizer is employed with a 1% solution of epinephrine or concentrations in that vicinity, it produces droplets which are so large that most of the absorption occurs from the mouth, nose, or throat. Indeed, some may be swallowed leading to unpleasant results because of the local application. The present invention does not deal with the local application of material of this type but specifically refers to the nebulization therapy of the lungs and bronchioles where the material is carried by convection into the lungs with the inspired air. The problem, therefore, in the

treatment of asthma consists of getting very small droplets in very large numbers deeply into the lungs so that the anti-spasmodic activity of the active drug (e. g. epinephrine) may be effective. With the use of the nebulizer, the air is drawn in with inspiration and the mist which is formed during successful nebulization is carried with the respiratory movements of the air into the lungs. This movement is essentially a convection process. When the bulb of an atomizer, however, is suitably compressed, the movement of the droplets of the spray produced by the atomizer is primarily due to the momentum imparted by the blast of air. In the case of the nebulizer, however, the spray should be mist-like or fog-like in character and it should be carried along with the air currents in the manner just described. In other words, the droplet size and the droplet permanence in nebulization should be produced to allow the air inspired to be carried along a sufficient distance and with a sufficient amount of material so that the mist-like or fog-like spray enters the bronchi and bronchioles where it attacks directly the pathological tissues producing the asthma. For this reason, it is important in treating the lungs in the asthmatic state with a 1% solution of epinephrine salt, or concentrations in that vicinity, to use a nebulizer which produces a fine, permanent, mist and to use solutions or modify them so that they lend themselves readily to the formation of mists.

With the droplets from ordinary aqueous solutions in use in the therapy of asthma formed by nebulization, evaporation is rapid and an insufficient number are formed to produce a mist sufficiently permanent to be readily inspired by the patient.

The problem involved, then, is to produce by nebulization a larger number of visible particles and to control the droplets during the period of treatment so that a more permanent mist results with enhanced therapeutic effect. Examination of the thermodynamic equation which deals with the evaporation of small droplets discloses that not alone is vapor pressure important in droplet formation and permanence but the radii of the droplets, the density of the material and the surface tension of the droplets are also involved. Because of the large number of variables it is, therefore, difficult if not impossible from a purely theoretical consideration of the theory of mist formation to decide just how all of the parameters could be controlled in the nebulization of epinephrine salts. An experimental examination of all the parameters separately may be made so that the control of droplet size, number, and stability could be achieved. After suitable experimentation it was decided to scrutinize most carefully the roles played by vapor pressure and nuclei formation as well as surface tension in improving the nebulization solutions for the therapy of the lungs and bronchioles.

Experiments considering the effects of substances which would be present in sufficient quantity to lower the vapor pressure of small droplets (which, as I have pointed out, distill rapidly and disappear) disclosed that substances like potassium chloride, sodium chloride, triacetin, monoacetin, ethylene glycol, propylene glycol, urea, sorbitol, dextrose and glycerol in sufficient concentrations increased the nebulization efficiency of solutions of antispasmodics and led to improved therapy in the treatment of asthma by the method of nebulization. It is evident that potassium chloride in the solid state can not be nebulized, nor can sodium chloride be nebulized in the solid state. Indeed, with the type of nebulizer employed, pure glycerol, itself, can not be readily nebulized. The viscosity in this case is another parameter which prevents nebulization in practise by the patient. However, on forming saturated solutions of potassium chloride and sodium chloride in water or on adding sufficient amounts of any of the substances mentioned in the foregoing to the epinephrine solution, a complete change occurs in the nature of the nebulization as compared with the solvent alone or with small quantities of these materials. Depending on the concentration, the addition of these substances markedly enhances the ease of nebulization. Mists are formed which have a more permanent character. These mists also contain a larger number of visible droplets. Since potassium chloride and sodium chloride do not lower the surface tension but raise the surface tension, it is evident that the surface tension factor need not be important and that other factors play a more dominant role.

Saturating water with potassium chloride at room temperature increased the nebulization with mist formation markedly improved. But only a slight increase in the efficiency of nebulization was observed when water was only ⅕ saturated with potassium chloride. It is not necessary, therefore, to have a liquid dissolved in the solution which is nebulized but a sufficient amount of solid non-toxic substances like potassium chloride, the sugars, urea, or salts may be employed with an antispasmodic to relieve the spasms in the asthmatic state. These substances act as nuclei for the formation of more permanent mists.

It is important to note that I have discarded in the nebulization therapy of asthma (and which I shall subsequently show in actual use on patients) the notion that isotonic solutions or solutions nearly isotonic are needed. Preparations ordinarily used in the therapy of the nose contain isotonic salt solutions or isotonic sugar solutions or the solutions are nearly isotonic. However, these quantities are not sufficient to produce the high degree of nebulization required in the treatment of the lungs with substances like epinephrine salts.

In this invention it is recognized that a sufficiently high concentration of any one of these substances or of mixtures of these substances introduced can produce improved nebulization and mist formation without the addition of substances like alcohol specifically designed to lower the surface tension.

Evidently when a nebulizer produces a mist under the conditions described in the foregoing with sufficient amount of material added to produce increased nebulization, the materials being like the sugars, glycerol, etc., or their mixtures, the mist which is produced consists of water droplets which must be small enough to be breathed into the lungs and tiny bronchioles along with the air moving with the body of the air. The curvature of the droplets being very great, the vapor pressure of these droplets is probably decreased by the addition of substances which lower the vapor pressure and in this way produce a permanent mist which act as stable nuclei containing the active therapeutic agent.

Experiments on patients with asthma over a long period have shown that therapy with 1% epinephrine salt (or concentrations in that

vicinity) administered by nebulization is markedly improved by the addition of from 10% to 50% of glycerine by volume in the solution. There has been no irritation to the lungs or any damage to the patient. Psychologically, the patients have preferred this new mixture over a long period. Indeed, in one instance, a 50% solution of glycerine plus 1% epinephrine with the usual preservative and antioxidant has been used by an asthmatic patient for four months with no irritation of the throat or lungs. In addition, the sweet taste of the high concentration of glycerine has a soothing effect on the pharynx and makes this vehicle also more desirable. Substances other than glycerine, in addition to glycerine, may also be employed. These substances, mentioned previously, must be present in sufficient concentration to produce a permanent mist. Thus, mixtures of sugar and glycerine and sugar, or glycerine and urea, may also be conveniently used.

In actual practise 50% of glycerine has proved very serviceable and has been used extensively by many patients over long periods.

The best results are obtained by using more than 10% of glycerol or its homologs. There is no upper limit physiologically to the concentration of glycerol which may be used. The upper limit would depend on the ease with which the glycerine solution is forced through the particular nebulizer employed by the patient. Practically, there is no need to exceed 50% of glycerol.

The following two formulae are examples of solutions which have been used.

Epinephrine hydrochloride	grams	1
Glycerol	cubic centimeters	50
Sodium bisulphite	grams	0.1
Chloretone	do	0.4
Water to	cubic centimeters	100

Epinephrine phosphate (pH 4 to 5)	grams	1
Glycerol	cubic centimeters	10
Sodium bisulphite	grams	0.1
Chloretone	do	0.4
Water to	cubic centimeters	100

It is not intended that these formulae be taken as specific formulae to restrict the broader aspects of the invention which have been outlined in the main body of the patent. They are practical formulae embodying the principles enumerated.

I claim:

1. A therapeutic composition adapted for the nebulization therapy of asthma which comprises an aqueous solution of an epinephrine salt in a concentration of at least 0.5% by weight, in which solution is dissolved at least 10% by volume of a polyhydric alcohol so as to lower the vapor pressure of the therapeutic composition to a degree sufficient to stabilize the mist formed on nebulization of said therapeutic composition.

2. A therapeutic composition adapted for the nebulization therapy of asthma which comprises, an aqueous solution of an epinephrine salt in a concentration of at least 0.5% by weight, and glycerol in an amount of at least 10% by volume of the therapeutic composition, said glycerol serving to stabilize the mist formed on nebulization of said therapeutic composition.

3. A therapeutic composition adapted for the nebulization therapy of asthma which comprises the following ingredients in the stated amounts or proportions thereof:

Epinephrine hydrochloride	grams	1
Glycerol	cubic centimeters	50
Sodium bisulphite	grams	0.1
Chloretone	do	0.4
Water	cubic centimeters	50

4. A therapeutic composition adapted for the nebulization therapy of asthma which comprises the following ingredients in the stated amounts or proportions thereof:

Epinephrine phosphate (pH 4 to 5)	grams	1
Glycerol	cubic centimeters	10
Sodium bisulphite	grams	0.1
Chloretone	do	0.4
Water	cubic centimeters	90

HAROLD ALEXANDER ABRAMSON.