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METHOD OF TREATING CARDIAC ARRHYTHMIA WITH 1-(2-DIETHYLAMINOETHYL)-5-ETHYL-5-PHENYLBARBITURIC ACID

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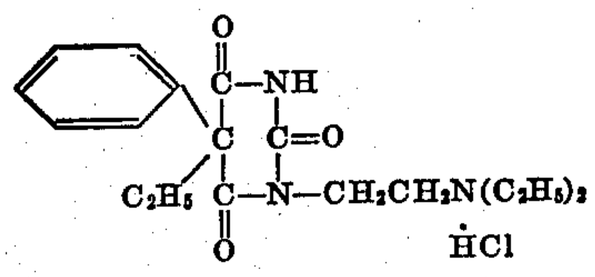
This invention relates to a new article of manufacture and to methods of compounding and using the same. More particularly, the invention relates to the compound 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid in dosage unit form suitable for use as an antiarrhythmia composition. The compound, 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride, has the following structural formula:



It is a white, crystalline, hydrochloride salt which is soluin water to a concentration of at least 2%. Solutions of this salt are stable at room temperature and begin to decompose only when subjected to prolonged boiling. The diethylaminoethyl side chain in the 1-position provides the possibility for forming acid salts through the basic nitrogen atom in said side chain.

Arrhythmia is a clinical term given to irregular rhythms of the heart. Atrial fibrillation is by far the most common of the cardiac arrhythmic conditions. Atria is an anatomical term applied to the upper two chambers of the heart. The atria normally show a pattern of orderly contractions which follow regular impulses arising from the sinus node in the cardiac tissue. Following each contraction, a necessary period of time must occur before the cardiac tissue can be re-excited. This period is known as the refractory period. Atrial fibrillation ultimately results when certain alterations come about in the normal pattern of excitability, conduction, refractoriness, or frequency of excitation.

One theory of fibrillation holds that it is the result of perpetuating a circular excitation of cardiac tissue. Another theory holds that fibrillation results from an ectopic focus of excitation. The fibrillation can be considered as paroxysmal when it arises after an acute infection, strenuous physical exertion, or inordinate use of alcohol, tobacco, anesthetics, epinephrine and other type of agents. The condition also appears without a traceable cause. Chronic fibrillation is the most common type, and may occur in thyrotoxicosis, mitral stenosis, and in certain other fundamental disturbances of cardiac function.

Antifibrillatory drugs are given to change the speed of conduction and period of refractoriness or alter the excitability of cardiac tissue and thereby obtain a normal excitation and contraction pattern. Quinidine is a known drug for treating this condition, however, a great deal of dissatisfaction is expressed by many practitioners because such therapy is marked by many failures. It is a potentially dangerous drug with a history of many deaths. Since it is a cinchona alkaloid, the possibility of incurring the syndrome known as "cinchonism" always confronts the physician.

It is the object of this invention to provide dosage unit forms of a compound having marked antifibrillatory properties.

A further object is to prepare said dosage forms in

solid and liquid carriers suitably for injectable and oral administration.

It has now been found that the compound 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid is an effective and non-toxic antifibrillatory agent, that is, it is effective in restoring normal patterns of cardiac contractions. The effective clinical dosage for adults ranges from about 20 mg. per day upwardly when injected directly into the circulatory body fluids of the patient. In children, the dosage ranges are correspondingly lower according to age and weight of the child. The drug may be administered orally in the form of tablets, capsules, powder or in a flavored, liquid form. It may also be presented in a suppository form for rectal administration by combining the drug with appropriate waxes.

A preferred form of oral administration is 10 mg. scored tablets which will provide the minimum dose for children and will provide, in multiples, amounts up to the maximum dose. In one of the preferred forms, the active ingredient 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid may be incorporated into tablets by utilizing accepted ingredients and steps in the prepaartion thereof. In particular, solid diluents and tableting adjuvants such as cornstarch, acacia, lactose, talc, stearic acid, magnesium stearate, gums and the like may be used. Any of the tableting materials used in the pharmaceutical art may be employed where there is no incompatability with the active material. Alternatively, the active material with or without its adjuvant materials may be placed in a soft or hard gelatin capsule and administered in capsule form.

In another embodiment of the invention, a solution dose form is made. The solubility of the active compound, while limited, is still sufficient to prepare a dosage level suitable for therapeutic administration. A solution dosage form can contain from about 2 mg./cc. to 5 mg./cc. of active ingredient (10 to 25/mg. per teaspoon). A liquid pharmaceutical dosage form of greater concentration may also be prepared by compounding the active material with suspending agents such as acacia or carboxymethylcellulose along with the usual flavoring materials. Such a liquid preparation is particularly suitable for children and infirm persons who have difficulty swallowing a tablet or capsule.

Sterile, isotonic, liquid forms are prepared for injection into the body by placing the desired amount of active ingredient into sterile water, adjusting the osmotic tension to coincide with the osmotic tension of body fluids, sealing said solution in an ampoule and sterilizing said ampoule.

The following examples illustrate preferred embodiments of the dosage forms, but it should be understood that they are not means to restrict the dosage forms to the ingredients and proportions named therein.

EXAMPLE I

A solution of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride is prepared by adding 20 mg. of said 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride to each cc. of water. The solution is made isotonic to physiological fluids by adding sodium chloride and thereafter the solution is filtered. From this solution, a 10 cc. aliquot is placed in an ampoule, and the ampoule is sealed. The ampoules are sterilized in an autoclave at 121° C. at 10 lbs. pressure for 20 minutes. Immediately thereafter the ampoules are removed and cooled with running water. The prepared ampoules contain a 2% solution of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride which is suitable for introduction into the body by injection.

EXAMPLE II

1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride (1.33 lbs.) is mixed with 37.33 lbs. of

lactose and passed through a 30-mesh screen. A starch paste is prepared using 1.05 lbs. of cornstarch and 5.98 lbs. of distilled water. The prior mixture is massed with the starch paste and passed through a 4-mesh screen and then dried at 105° F. for 17 hours. The dried product is granulated and passed through a 16-screen. Stearic acid (0.446 lbs.), cornstarch (3.87 lbs.) and talc (2.036 lbs.) are passed through a No. 40 screen and blended well with the granulated 1-(2-diethylaminoethyl-5-ethyl-5-phenylbarbituric acid hydrochloride, lactose and cornstarch.

The blended material is compressed into scored tablets each containing 10 mg. of active material.

EXAMPLE III

A pharmaceutical suspension of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride is prepared by combining the following ingredients:

1-(2-diethylaminoethyl)-5-ethyl - 5 - phenylbarbituric acid hydrochloride	grams	50
Sodium carboxymethylcellulose, medium viscosity	grams	8.0
Sucrose	do	100.0
Aseptoform M	do	1.5
Aseptoform P	do	0.15
F. D. & C. green #1	do	0.05
Imitation cherry	cc	0.75
Water, deionized, q.s	cc	1000.0

The foregoing liquid preparation provides a concentration of active ingredient at a level of 50 mg./cc. of which about 20 mg./cc. is in solution and the remainder in suspension.

Aseptoform M and P are trade names for esters of p-hydroxybenzoic acid which prevent fermentation and mold formation.

EXAMPLE IV

1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride in solution dose form

A pharmaceutical solution of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride is prepared by combining the following ingredients:

1-(2-diethylaminoethyl)-5-ethyl - 5 - phenylbarbituric acid hydrochloride	grams	2.0
Sucrose	do	200.0
Glycerin	cc	150.0
Aseptoform M	grams	1.5
Aseptoform P	do	0.15
F. D. & C. orange #1	do	0.05
Imitation orange aroma	cc	0.02
Oil orange	cc	0.5
Water, deionized, q.s	cc	1000.0

The foregoing preparation provides a concentration of the active ingredient, 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride at a level of 2 mg./cc. or 10 mg./tsp.

EXAMPLE V

A pharmaceutical suppository of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid is prepared by

melting 300 grams of spermacetti, U. S. P. and 695 grams of theobroma oil, U. S. P. The mixture is cooled to 50° C. and then 5 grams of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid is added. The combined mixture is stirred to a state of uniformity and then delivered to individual molds and chilled. The molds yield suppositories weighing 2 grams which melt at 50° C. Each suppository contains 10 mg. of active material.

Others may practice the invention in any of the numerous ways which will be suggested by this disclosure to one skilled in the art. All such practice of the invention is considered to be a part hereof provided it falls within the scope of the appended claims.

I claim:

1. The method which comprises administering to a human host afflicted with cardiac arrhythmia a composition comprising at least about 10 mg. of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride.

2. The method which comprises administering to a human host afflicted with cardiac arrhythmia a composition comprising at least about 10 mg. of a water-soluble salt of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid and a non-toxic pharmaceutical carrier.

3. The method which comprises administering to a human host afflicted with cardiac arrhythmia a composition comprising at least about 20 mg. of a water-soluble salt of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid and a non-toxic pharmaceutical carrier.

4. The method which comprises administering to a human host afflicted with cardiac arrhythmia a composition comprising at least about 20 mg. of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride and a non-toxic pharmaceutical binding agent placed together in a tablet.

5. The method which comprises administering by injection to a human host afflicted with cardiac arrhythmia a sterile water solution containing at least 20 mg./cc. of a water-soluble salt of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid and an inert non-toxic material to provide osmotic tension.

6. The method which comprises administering to a human host afflicted with cardiac arrhythmia a composition comprising an aqueous pharmaceutical suspension containing non-toxic suspending agents and at least 20 mg./cc. of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride.

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