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METHOD OF OBTAINING PREANESTHETIC SEDATION AND DRYING WITH 1-(2-DIETHYLAMINOETHYL)-5-ETHYL - 5 - PHENYLBARBITURIC ACID

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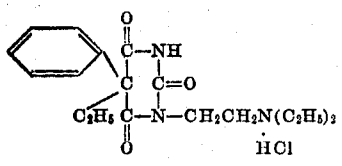
This invention relates to a new article of manufacture and to methods of compounding and using the same. More particularly, the invention relates to the compound, 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid, in dosage unit form suitable for use as a preanesthetic composition. The compound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



It is a white, crystalline, hydrochloride salt which is soluble in 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.

Among the desirable actions of a preanesthetic medicament are the counteracting of respiratory irregularities, cardiac irregularities and excessive flow of mucous and saliva. In general, such medication makes anesthesia more safe and comfortable for the patient and more efficient for the surgeon. Further usfulness resides in raising the patient's threshold of reflex exitability to allow the use of inhalant anesthetics such as ethylene and nitrous oxide.

Most preanesthetic medications comprise a mixture of a narcotic such as morphine, meperidine, methadone or a barbiturate with an anti-sialogogue such as atrophine and scopolamine, that is, an agent which inhibits secretions of the respiratory tract and the salivary glands. The use of such mixtures, however, is accompanied by objectionable features such as diffuse pharmacological effects on the entire organism and the other disadvantages associated with narcotic usage.

It is the object of this invention to provide in dosage unit forms a single compound possessing all the properties desirable in preanesthetic medications.

A further object is to prepare said dosage forms in solid and liquid carriers suitable for oral, suppository and injectable administration.

It has now been found that the compound, 1-(2-diethyaminoethyl)-5-ethyl-5-phenylbarbituric acid possesses properties which makes it highly desirable as a preanesthetic medicament. The compound causes inhibition of respiratory tract secretions and salivary gland secretion. It exhibits a further action in counteracting cardiac arrhythmia, that is, it maintains normal cardiac rhythm. This latter condition is often disrupted in the subsequent state of general anesthesia. Furthermore, it is expected that it will reduce reflex excitability and apprehension.

The effective clinical dose for adults ranges from about 10 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. This drug may be administered by hypodermic syringe in the form of a sterile water solution of said compound prepared to the desired concentration. The compound can be made available in said fresh solution form or in powder form present in capsules or vials and other carriers which allow easy conversion to the solution form. The drug may be also administered orally in the form of tablets, capsules, powder or in a flavored, liquid form. A suppository form for rectal administration can also be prepared 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 preparation 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 incompatibility 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 meant to restrict the dosage forms to the ingredients and proportions named therein.

EXAMPLE I

A solution of 1-(2-diethylaminoethyl)-5-ethyl-5-phenyl-barbituric acid hydrochloride is prepared by adding 20 mg. of said 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid 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 then 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 in running water. The prepared ampoules contain a 2% solution of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid which is suitable for introduction into the body by injection.

EXAMPLE II

The compound, 1-(2-diethylaminoethyl)-5-ethyl-5-phenyl-barbituric 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 corn-

starch and 5.98 lbs. of distilled water. This 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 lb.), 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-phenyl-barbituric 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 is prepared by combining the following ingredients:

1-(2-diethylaminoethyl)-5-phenylbarbituric acid hydrochloride	grams	50
Sodium carboxymethylcellulose, medium viscosity	grams	8.0
Sucrose	do	100
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., 1000.0 cc.

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 in solution dose form

A pharmaceutical solution of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid 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, Ilco, q.s., 1000.0 cc.

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

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-phenyl-barbituric 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 of obtaining preanesthetic sedation and drying conditions which comprises administering to a human, prior to inducing general anesthesia, at least about 10 mg. of a water-soluble salt of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid.

2. The method of obtaining preanesthetic sedation and drying conditions which comprises administering to a human, prior to inducing general anesthesia, 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 of obtaining preanesthetic sedation and drying conditions which comprises administering to a human, prior to inducing general anesthesia, about 100–150 mg. of a water-soluble salt of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid.

4. The method of obtaining preanesthetic sedation and drying conditions which comprises administering to a human, prior to inducing general anesthesia, at least about 10 mg. of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride.

5. The method of obtaining preanesthetic sedation and drying conditions which comprises administering to a human, prior to inducing general anesthesia, about 100–150 mg. of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride.

6. The method of obtaining preanesthetic sedation and drying conditions which comprises administering to a human, prior to inducing general anesthesia, at least about 100–150 mg. of 1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid hydrochloride and a non-toxic pharmaceutical carrier.

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