Patented Sept. 22, 1936 2,055,064

UNITED STATES PATENT OFFICE

2,055,064

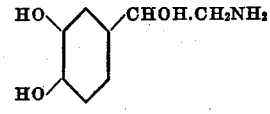
ANESTHETIC COMBINATIONS CONTAINING, BESIDES A LOCAL ANESTHETIC AGENT, A VASOCONSTRICTING AGENT

Max Bockmühl, Frankfort-on-the-Main, Otto Schaumann, Wiesbaden, and Gustav Ehrhart and Leonhard Stein, Frankfort-on-the-Main, Germany, assignors to Winthrop Chemical Company, Inc., New York, N. Y., a corporation of New York

No Drawing. Application March 16, 1934, Serial No. 715,995. In Germany October 11, 1933

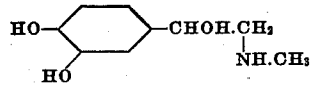
6 Claims. (Cl. 167—52)

Our invention relates to improvements in anesthetic combinations containing, besides a local anesthetic agent, a vasoconstricting agent, and methods of preparing the same. More particularly it relates to such combinations containing, besides a local anesthetic agent, a definite vasoconstricting agent, the 3.4-dihydroxy-phenyl-α-ethanol-amine of the following formula:



whereby the disadvantages of the local anesthetic combinations of this type, which have hitherto been known and employed, are obviated.

It is known to employ local anesthetic combinations containing, besides a local anesthetic agent, a vasoconstricting agent, the functions of the latter being to localize and prolong the anesthesia. The vasoconstricting agent, almost universally employed for this purpose, is epinephrin, i. e. 3.4-dihydroxy-phenyl-ethanol-methylamine of the following formula:



For example a commonly used anesthetic combination of this type contains a local anesthetic agent such as the monohydrochloride of para-amino-benzoyl-diethyl-amino-ethanol which is generally known as "Novacain" or "Procaine" and the vasoconstricting agent epinephrin.

There are, however, several disadvantages connected with the known anesthetic combinations containing the vasoconstricting agent, epinephrin. For example, it has been known for a long time that epinephrin is not ideal for this purpose on account of the toxic by-effects which follow its use. Thus, in his "Textbook of Exodontia" second edition, The C. V. Mosby Company, 1931, on page 92, Dr. Leo Winter states:

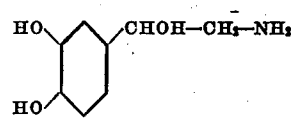
"Uncomfortable and even alarming systemic reactions may occur at times following the subcutaneous administration of slightly excessive doses of epinephrin. The patient experiences a feeling of general distress and anxiety, becomes pale and suffers from a sensation of precordial discomfort and pain, and shivers more or less violently. He may be conscious of an increase in the rate and in the force of the heart action, which may also become decidedly irregular, and rarely he may suffer a more or less typical anginal attack. Occasionally the rise in blood pressure may be pronounced. Vertigo, nausea and vomiting, paresthesia, and heart-burn are other symptoms which occasionally occur. As a rule, these exaggerated and more or less alarming symptoms last only a very few minutes and have no serious results. However, such pronounced effects on the blood pressure and heart action may well prove harmful in cases of hypertension, arteriosclerosis, apoplexy, aneurysm, or feeble dilated heart."

In an article entitled "Is epinephrin dangerous in regional local anesthesia," Dr. La Rossa and Dr. Riccio (Paris Medical, vol. 15, 1936, page 341) state that if epinephrin is to be used, cases with cardio-vascular derangements and hyperthyroidism must be excluded, and that the patient should preferably be studied for tolerance to epinephrin by injection of small quantities of it.

Furthermore, Dr. Meeker and Dr. Frazer (J. Pharmacol. & Exper. Therap., vol. 22, 1923, p. 390) state:

"By means of its vasoconstricting power, epinephrin (adrenalin) retards absorption of the anesthetic drug as well as intensifies its anesthetic power, and in that regard is a factor of safety. Certain persons, however, aside from those with hyperthyroidism, are hypersensitive to its action: in them its use should be discarded. Toxic manifestations due to the absorption of epinephrin (adrenalin) may be marked palpitation, a sense oppression in the head and chest, tremor, pallor, nausea, and a sensation of fear and anxiety. No doubt the incidence of reactions to local anesthetics would be greatly reduced were it possible to dispense entirely with epinephrin (adrenalin)."

We have discovered that the 3.4-dihydroxy-phenyl-α-ethanol-amine of the following formula:



can be successfully employed as substitutes for epinephrin with local anesthetic agents to localize and prolong anesthesia and much to our surprise we have found that such combinations do not produce the above described toxic manifestations which follow the use of local anesthetic combinations with epinephrin and are tolerated without by-effects in patients with hyperthyroidism or heart disease and in those cases with arteriosclerosis and high blood pressure. Furthermore, we have discovered that local anesthetic combinations with the above mentioned vaso-

constricting agent do not produce the collapse-like symptoms which follow the use of epinephrin in susceptible patients. The intensity and duration of anesthesia produced by local anesthetic combinations with the above mentioned vasoconstricting agent, are just as satisfactory as those produced by local anesthetic combinations with epinephrin.

By means of clinical experiments we have determined that the intensity and duration of anesthesia produced by the injection of an aqueous 2 per cent "Novocain" solution containing, 3.4-dihydroxy-phenyl-α-ethanol-amine 1:10,000 are approximately the same as those produced by the injection of an aqueous "Novocain" solution with epinephrin 1:50,000.

By means of animal experiments we have determined that the intravenous toxicity of 3.4-dihydroxy-phenyl-alpha-propanol-amine is about 7 to 10 times less than that of epinephrin. An aqueous 2 per cent "Novocain" solution with epinephrin 1:50,000 is definitely more toxic when injected intravenously into experimental animals than an aqueous 2 per cent "Novocain" solution with 3.4 - dihydroxy - phenyl - α - ethanol-amine 1:10,000.

Our new local anesthetic combinations with the vasoconstricting agent defined above are just as suitable for use by injection or local application to obtain local anesthesia as similar local anesthetic combinations prepared with epinephrin.

We have further discovered that aqueous solutions of our vasoconstricting agent are stable provided a water-soluble reducing agent is added to the solutions to prevent deterioration.

Our new anesthetic combinations can be marketed in any of the forms usual in the pharmaceutical practice, such as a powder, a tablet or a ready-to-use sterile solution in sealed glass ampules, cartridges or bottles without fear of decomposition. In addition sterile ready-to-use aqueous solutions, or tablets of the above defined vasoconstricting agent can be marketed so that the surgeon or dentist can prepare for his own use local anesthetic combinations with 3.4-dihydroxy-phenyl-α-ethanol-amine by simply adding the desired amount of the sterile ready-to-use aqueous solution or the desired number of the tablets to any specified amount of a solution of a local anesthetic agent.

As the anesthetic agent in our new local anesthetic combinations with our vasoconstricting agent we prefer to use the monohydrochloride of para-aminobenzoyl-diethyl-amino-ethanol. Other alkamine esters of aromatic acids which may be used as the anesthetic agent are, for example, para-amino-benzoyl-gamma-butylamino-propanol sulphate, para-amino-benzoyl-dimethyl-amino-methyl-butanol hydrochloride, para-butylamino-benzoyl-dimethyl-amino-ethanol hydrochloride, para-amino-benzoyl-2.2-dimethyl-3-diethyl-amino-1-propanol hydrochloride, alpha-butyl-oxy-cinchoninic acid gamma diethyl-ethylene-diamide hydrochlor and gamma-(2-methyl-piperidino)-propyl-benzoate hydrochloride.

As a reducing agent in our ready-to-use aqueous solutions of 3.4-dihydroxy-phenyl-alpha-ethanol-amine for use with local anesthetic agents or their solutions and aqueous solutions of our new anesthetic combinations containing, besides a local anesthetic agent, the vasoconstricting agent, inorganic water-soluble products may be employed. Preferably, we use the salts of the sulphurous and hyposulphurous acids or their derivatives, for example, sodium bisulphite, potassium bisulphite, sodium sulphite, formaldehyde bisulphite, sodium hydrosulphite, acetone bisulphite, and formaldehyde sulphoxylate. The quantity of reducing agent required is relatively small and depends on the reducing agent employed. In general it is advisable to incorporate 50 milligrams to 200 milligrams in each 100 cc. of solution.

In order to more fully illustrate our invention the following examples are given, but it is to be understood that we do not restrict our invention to the specific compounds and proportions recited therein.

1. 20 grams of the hydrochloride of para-amino-benzoyl-diethylamino-ethanol, 2 grams of sodium chloride, 4 grams of potassium sulphate and 0.05 gram of the hydrochloride of 3.4-dihydroxyphenyl-ethanolamine are dissolved in such a quantity of distilled water that the whole volume to 1000 cc.

If desired, 2 grams of acetone bisulphite may be added to the solution.

2. 1 gram of the hydrochloride of para-butyl-amino-benzoyl-dimethyl-amino-ethanol, 9 grams of sodium chloride and 0.025 gram of the hydrochloride of 3.4-dihydroxyphenyl-ethanolamine are dissolved in 1000 cc. of distilled water.

3. 10 grams of the hydrochloride of para-amino-benzoyl-dimethylamino-methyl-butanol, 6 grams of sodium chloride and 0.05 gram of the hydrochloride of 3.4-dihydroxyphenyl-ethanolamine are dissolved in distilled water that the whole volume amounts to 1000 cc.

We claim:

1. A composition of matter comprising a local anesthetic agent and 3.4-dihydroxy-phenyl-α-ethanolamine.

2. Aqueous solutions comprising a water-soluble salt of 3.4-dihydroxy-phenyl-α-ethanol-amine and a local anesthetic agent.

3. Aqueous solutions comprising the hydrochloride of 3.4-dihydroxy-phenyl-α-ethanol-amine and a local anesthetic agent.

4. A sterile and stable aqueous solution of 0.005% of the hydrochloride of 3.4-dihydroxy-phenyl-α-ethanol-amine and 2% of the monohydrochloride of para-aminobenzoyl-diethyl-amino-ethanol, 0.2% of sodium chloride, 0.4% of potassium sulphate and 0.2% of acetone bisulphite.

5. An aqueous solution of 0.0025% of the hydrochloride of 3.4-dihydroxy-phenyl-α-ethanol-amine, 0.1% of the hydrochloride of para-butyl-amino-benzoyl-dimethylamino-ethanol and 0.9% of sodium chloride.

6. An aqueous solution of 0.005% of the hydrochloride of 3.4-dihydroxy-phenyl-α-ethanol-amine, 1% of the hydrochloride of para-amino-benzoyl-dimethylamino-butanol and 0.6% of sodium chloride.

MAX BOCKMÜHL.
OTTO SCHAUMANN.
GUSTAV EHRHART.
LEONHARD STEIN.