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COMPOSITION OF MATTER CONTAINING PROCAINE ADENYLATE

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The invention relates to compounds having therapeutic properties and prepared by reacting procaine with the individual nucleotide known as adenylic acid, as well as with the related adenosine diphosphoric acid and triphosphoric acid, and products containing such compounds.

It is the general object of the present invention to provide therapeutic preparations consisting of or containing procaine compounds of adenylic acid of the type more specifically described herein below and by whose use certain undesirable effects accompanying the use of free adenylic acid are avoided, while at the same time the therapeutic activity of such compounds can be taken advantage of.

More specifically, it is an object of the invention to provide therapeutic preparations based upon procaine compounds of adenylic acid which are characterized by highly desirable properties as explained more fully hereinafter.

It is a still further object of the invention to provide therapeutic preparations based upon more or less neutral compounds of adenylic acid which are practically non-irritating on injection.

Other objects and advantages of the invention will appear as the following more detailed description of the same proceeds.

Adenylic nucleotide therapy is particularly effective in the stabilization of the circulation, both in the high and low blood pressure conditions. In the case of high blood presure there is usually a vasoconstriction with elevation of diastolic pressure. Adenylic acid has the effect of lowering the diastolic pressure by counteracting the vasoconstriction through vasodilatation. In the case of low blood pressure the adenylic acid, through its improvement of muscular metabolism, increases the muscular tone of the heart and improves the blood pressure level.

It is known that on the injection of certain known adenylic compounds like adenylic acid itself and sodium adenylate, there occurs a peripheral vascular dilatation accompanied by flushing of the skin and sudden drop in blood pressure which subsequently rises so that the pulse pressure is increased. However, the immediate vascular reaction is in some cases sufficient to cause syncopy and accompanying dilatation of the coronary artery, while increase of the flow of blood to the heart muscles gives the patient who has a labile vasomotor mechanism a sense of tightness in the chest which may be distressing, despite the fact that the patient is in no real danger. With rising blood pressure this feeling disappears. This undesirable reaction has militated against a wider use of the adenylic nucleotide.

Adenylate nucleotide therapy is particularly effective in stabilizing, paradoxically enough, both high and low blood pressure. High blood pressure occurs by reason (among other reasons) of a constriction of the blood vessels, both internal and peripheral. Both systolic and diastolic pressures are usually increased, the latter primarily due to peripheral vasoconstriction. Adenylic acid, as well as its related nucleotides, ADP and ATP, having a strong vasodilating effect ipso facto counter vasoconstriction—hence reduce blood pressure. In fact, it is well known that the injection of adenylic nucleotides and related nucleotides frequently reduces blood pressure so

quickly and suddenly that a patient often faints from the sudden vasodilation—hence the reduction of blood pressure—that adenylic acid affords. One of the reasons for the instant invention is specifically to "slow-down" the sudden vasodilation by adenylic acid which causes patients to faint from the sudden reduction.

Paradoxically, adenylic acid also increases a chronically low blood pressure, which is usually accompanied by (or perhaps a cause of) lassitude, low energy and weakness. But adenylic acid increases blood pressure only in individuals who have a low blood pressure; in that fashion, adenylic acid can be considered a true normotensive agent. Its function in increasing low blood pressure is not, obviously, vasodilation, nor the expected vasoconstriction. It does not have a vasoconstricting effect in low blood pressure, for were it to be so, the patient to whom it is administered would have—which he does not—an immediate toning effect; this is quite unlike the immediate relief of high-blood pressure due to immediate vasodilation. Since the low blood pressure patient does not have an immediate relief from his low blood pressure, it cannot be that vasoconstriction has occurred as the operating mechanism. However, the effect of adenylic acid is due to its stimulation of metobolism, through supplying a metabolite which is a necessary component of the enzyme cycles of which adenylic acid is a part. This, in fact, means every change and conversion in the tissues, for every living cell trades in energy—and adenylates are well known as the coin of exchange in the realm of cells, organs and tissues, for adenylates, in their conversions and interconversions, are energy donors, energy vehicles, energy-carrying agents.

It is to harness that energy, by controlling its output—spreading a given amount over a longer period—inhibiting the sudden spurt leading to fainting and other untoward effects from vasodilation—and by putting into the tissues an "energy depot" or deposit in the form of procaine adenylate, that is the main object of this application. The repository effect of procaine adenylate delays the liberation of adenylic acid, releasing said adenylic acid at a slower rate, and over a longer time.

It has been found that certain procaine compounds of adenylic acid and related compounds conteract these disturbances by slowing the speed of utilization of the adenylic nucleotide, thereby diminishing the effect of the disturbing factors, and thus provide a less intense but longer-lasting adenylic effect. By combination with the procaine, the adenylic acid is made much more suitable for injection not only because of the decrease in acidity but generally also because of the mutual improvement in the solubility.

It has been discovered that procaine adenylate can be administered in repeated dosages of 100 to 200 milligrams. When so administered, it has been found to be extremely effective both in arthritis in which it presents substantially improved results as compared with iron adenylate, and in psoriasis.

Furthermore, it has been found that procaine adenylate gives a prolonged action of a unique and distinctive character which has not been observed with any other adenylic acid compounds which have been investigated. In the clinical use of procaine adenylate, a double period of activity has been repeatedly observed, following the injection of the procaine adenylate. The first period of activity occurs directly after the injection, with an initial peripheral vasodilatation, and this peripheral vasodilatation can be observed in the lowering of blood pressure and the feeling of well being which the patient secures. However, the lowering of the blood pressure is not precipitate, as in the case of the administration of other nucleotides. This feeling of well being wears off after a period of three or four hours and then again a second period of well

being occurs, so that a patient who receives his injection of procaine adenylate in the morning reports that toward noon the stimulation he had obtained following the injection appears to wear off, but that toward the late afternoon another period of recovery from fatigue and restoration of energy and well being occurs, so that, instead of the patient feeling tired in the evening he feels refreshed and able to accomplish work which previously he could not do. This double action, with two periods of activity, is unique and has not been observed with any other adenylic preparation.

This long-lasting effect or repository action of procaine adenylate is entirely unexpected. Procaine solutions, upon intramuscular injection, are readily absorbed and therefore do not remain long at the injection site. Accordingly, it has been customary to incorporate, in procaine solutions, vasoconstrictor drugs such as, for example, epinephrine, to retard absorption of the procaine. For dental use, procaine is almost always used with epinephrine. Adenylic acid also is avidly reacted upon in the body. Therefore, neither procaine nor adenylic acid would be expected to exhibit a repository action; and it is entirely unexpected that procaine adenylate and its related compounds, formed by the reaction of procaine with adenosine-3'-monophosphoric acid, exhibit this repository action which produces a long-lasting adenylic effect.

Procaine adenylate is readily obtained as a fine solid salt that can be readily sterilized in solution and that is stable in solution. Moreover, procaine adenylate is free from objectionable toxic effects and exhibits surprising unexpected prolonged action for two successive and separate periods of time.

In preparing procaine compounds for use in the therapeutic compositions of the present invention, the procaine can be treated with adenylic acid, in combining proportions in aqueous solution, preferably with the aid of heat. The procaine adenylate can be recovered by evaporation or by precipitation by a water-miscible organic liquid in which the adenylate is relatively insoluble, like lower aliphatic alcohols, acetone, etc. Where the procaine is employed in the form of its acid salt, a neutralizing agent like an alkali metal base can be added to bind the acid. Where the procaine hydrochloride is used, the chloride can be bound also by silver. The related compounds are similarly produced by treating procaine with adenosine diphosphoric acid or adenosine triphosphoric acid, respectively, in combining proportions.

The invention will be described in further detail by way of the following examples which are presented for purposes of illustration only and not as indicating the scope of the invention.

EXAMPLE 1

Preparation of Procaine Adenylate

To 0.1 gram of procaine suspended in 2 cc. of water 0.215 gram adenosine triphosphoric acid was added. The procaine base promptly dissolved giving a clear solution. 5 cc. of ethyl alcohol were then added and a precipitate promptly formed which upon evaporation yielded rosette-shaped crystals of procaine adenosine-5-phosphoric acid.

EXAMPLE 2

Alternative Preparation of Procaine Adenylate

Two grams of procaine base were suspended in 35 cc. of water. Upon the addition of 2.9 g. of adenylic acid, both went into solution. The clear solution was filtered from a very slight residue. The pH of the filtrate was 5.1. The filtrate was evaporated to a syrup which dissolved readily in 10 cc. methyl alcohol. 20 cc. of ethyl alcohol were now added and a permanent turbidity was obtained. On standing overnight, a white crystalline precipitate of procaine adenylate formed.

Instead of reacting one mole of adenylate with one mole of procaine, two moles of adenylate may be used; and instead of adenylic acid, adenosine-5-diphosphoric acid or adenosine-5-triphosphoric acid may be used.

EXAMPLE 3

Therapeutically Useful Solution of Procaine Adenylate

135 gms. of sodium citrate dihydrate were dissolved in about 2 liters of pyrogen-free water. After the sodium citrate had dissolved, 148.7 gms. of 100% adenylic acid were added and dissolved. 102.2 gms. of procaine base were then added and dissolved over a 60 minute period. The solution was then filtered. After filtering, the filtrate was made up to a total volume of 4 liters by adding 95 cc. of benzyl alcohol and pyrogen-free water.

This solution was assayed for procaine and for adenylic acid. The volume of the solution was then adjusted and reassayed. Nitrogen gas was bubbled through the solution throughout the entire process. After the volume of the solution was adjusted in a satisfactory manner, the solution was ampuled.

A satisfactory way to package the material is in one cc. ampules each containing 50 mg. of procaine adenylate. This is equivalent to 30 mg. of adenylic acid (adenosine-3-monophosphate) and 20 mg. of procaine base, approximately. Ampules containing 100 mg. of procaine adenylate each or even 200 mg., are also useful.

EXAMPLE 4

Dry Powdered Procaine Adenylate

An alternative procedure for producing dry powdered procaine adenylate, differing from that described in Examples 1 and 2, has also been used successfully.

3.47 gms. of adenylic acid (adenosine-3-monophosphate) were slurried in 40 cc. of water and 2.36 gms. of procaine base were added and the mixture was agitated, whereupon a clear solution formed. The solution was then concentrated to a thick syrup by vacuum distillation, and then dried in a vacuum oven, to obtain a light yellow powder. The powder can be stored until needed.

The dried product is a white to light yellow crystalline material that melts in the range 73° C. to 77° C. It is extremely hygroscopic. Absorption maxima are 257 and 228 millimicrons in the ultraviolet region. The pH of a 0.01 molar aqueous solution is 5.0.

Procaine resembles quinidine in its cardiac actions in that it increases the effective refractory period, raises the threshold for stimulation, and prolongs conduction time. The therapeutic value of procaine as an antifibrillatory and antiarrhythmic agent is limited by its short duration of action as a result of the rapid enzymatic destruction of the drug.

The unexpected, unpredictable repository action of procaine adenylate makes it valuable as an antiarrhythmic and antifibrillatory agent. The benefits flowing from the unitary action of the procaine adenylate are highly desirable, and the repository action of the compound makes this a practical therapeutic measure.

Dosages as high as 1.0 gram at intervals of three to six hours can be used, for oral or intramuscular administration. However, somewhat lower dosages can be employed for intravenous administration. In many cases, 50 mg. of procaine adenylate, I.M. every three to six hours, suffice for the control of arrhythmias.

The following valuable effects of procaine adenylate administration for arrhythmia therapy have been observed: a tranquillizing effect; establishment of regular sinus rhythm; and decreased extra systoles. Procaine adenylate also has value in reducing the frequency and severity of anginal attacks.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modification, and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the prin-

ciples of the invention and including such departures from the present disclosure as come within known or customary practice in the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as fall within the scope of the invention or the limits of the appended claims.

This application constitutes a continuation-in-part of former copending applications Serial Numbers 27,355 and 364,943 of Simon L. Ruskin, which were filed on May 15, 1948, and June 29, 1953, respectively, and which have since been abandoned.

What is claimed is:

1. An oral repository composition in oral dosage unit form comprising a pharmaceutical carrier and an amount not greater than about 1 gram per dosage unit of a reaction product of procaine and an adenylic acid wherein the phosphoric acid residue that is present in the adenylic acid is esterified with the sugar portion thereof.

2. A parenteral repository composition in parenteral dosage unit form comprising a pharmaceutical carrier and an amount not greater than about 1 gram per dosage unit of procaine adenylate.

3. Process for the treatment of cardiac conditions, especially arrhythmias and fibrillation, that comprises, administering to the afflicted host at a unit dosage level of up to about one gram, a reaction product of procaine and an adenylic acid, wherein the phosphoric acid residue present in the adenylic acid is esterified with the sugar portion thereof.

4. Process for the treatment of cardiac conditions, especially arrhythmias and fibrillation, that comprises, administering procaine adenylate to the afflicted host at a unit dosage level of up to about one gram.

5. Process for securing the slow release of procaine and adenosine phosphoric acid values in therapeutic applications of the same that comprises, administering said values at a unit dosage level of up to about one gram in the form of a reaction product of procaine and an adenylic acid wherein the phosphoric acid residue present in the adenylic acid is esterified with the sugar portion thereof.

6. Process for securing the slow release of procaine and adenosine phosphoric acid values in therapeutic applications of the same that comprises, administering said values in the form of procaine adenylate at a unit dosage level of up to about one gram.

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