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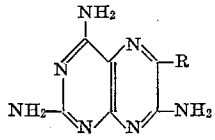
TRIAMINO ARYLPTERIDINES AS AN ANTIFIBRILLATORY AGENT

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ABSTRACT OF THE DISCLOSURE

This invention relates to triamino aryl pteridines and particularly to the use of 2,4,7-triamino-6-o-tolyl-pteridine and 2,4,7-triamino-triamino-6-phenyl-pteridine having the formula of:



wherein R is selected from the group consisting of o-tolyl and phenyl, as antifibrillatory, antiarrhythmic agents. It has been discovered that the aryl pteridines of this invention are devoid of vagolytic, local anesthetic, beta-blocking, ganglion blocking, and neuromuscular blocking actions when used as antifibrillatory and antiarrhythmic drugs.

BACKGROUND OF THE INVENTION

Field of the invention

The invention includes the use of certain triamino aryl pteridines as antifibrillatory and antiarrhythmic agents which are effective without interfering with the shortening and tension development of myocardial fibres.

Description of the prior art

The medicinal compositions of this invention are pharmacodynamically inert, and known to have diuretic and antihypertensive activities as described in U.S. Pat. No. 3,081,230, patented Mar. 12, 1963, by J. Weinstock et al.

The compounds are also noted to have a remarkable antimalarial activity and this use is the subject of a copending patent application, Ser. No. 467,134, filed June 25, 1965, by T. Osdene et al., now abandoned.

Toxicity limits, methods of synthesis, and pharmaceutical forms for medicinal application of the compounds of this invention are well known to those skilled in the art as witnessed by the discussion of the said patent and application.

The compounds consist of a highly resonant pteridine moiety connected in the sixth position of the ring structure to, in one case, an ortho tolyl group, and in the other a phenyl group. Unlike quinidine the compounds are devoid of a quinuclidine nucleus.

The compounds are soluble and stable in proylene glycol, glycerine, and acetone ketal of glycerine. Upon solution they develop a strong fluorescence which should facilitate retrieval in body fluids.

Di Palma in Pharmacology in Medicine, 624 (111 ed. 1966), includes all known antiarrhythmic agents under the heading of drugs that depress cardiac muscle. The implication being that the ability to restore rhythm is inevitable concomitant with multiple depression of cardiac parameters, and that, ultimately, suppression of abnormal rhythms and restoration of latency can be achieved only at the expense of myocardiac efficiency.

Accordingly, the ideal requirement for an antiarrhythmic agent is the ability to decrease irritability without a depressive effect on other myocardial properties.

Many compounds have antifibrillatory activity per se. Local anesthetics, barbiturates, phenylhydantoin (Dilantin), beta-blockers (propranolol), papavarine, potassium chloride, antihistaminics, and tranquilizers all show such activity. However, these compounds invariably depress other cardiac properties such as contractility and coronary flow.

An effective antiarrhythmic agent should be able to depress selectively only myocardial irritability. The prior art antiarrhythmic drugs, such as quinidine and procaine amide, fail to do this satisfactorily.

Therefore, as set out by Di Palma, the requirements for an ideal antiarrhythmic agent are:

(a) It should increase the refractory period without decreasing conduction velocity;

(b) It should depress excitability without depressing automaticity;

(c) It should be devoid of any depressant effects on other parameters of cardiac function.

SUMMARY OF THE INVENTION

This invention includes the use of 2,4,7-triamino-arylpteridines and more specifically 2,4,7-triamino-6-o-tolylpteridine and its phenyl congener as antifibrillatory and antiarrhythmic agents.

Accordingly, it is an object of this invention to provide relatively nontoxic, effective, antifibrillatory, antiarrhythmic agents.

It is another object to provide antifibrillatory, antiarrhythmic agents which are effective without depressing other parameters of cardiac functions.

These and other objects will become apparent with reference to the following discussion.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Toxicity has been evaluated by prior investigators. Even though both the o-tolyl and phenyl substituents are considered safe for use on man, several lab animal tests were conducted.

The pteridines were dissolved in Carbowax in concentrations of 10 mg./ml. and the solution was infused intravenously by mechanical syringe into six dogs under morphine chloralose anesthesia. The doses which caused hypotension and death were as follows:

2,4,7-triamino-6-phenyl-pteridine—119, 129, and 148 mg./kg. for three dogs; and

2,4,7-triamino-6-o-tolyl-pteridine—100, 160, and 181 mg./kg. for three dogs.

In all instances after infusion of 50 mg/kg. there was an elevation of threshold to electrical stimulation of the atrial muscle. The antiarrhythmic properties of both compounds were accompanied by slight depression of the force of contraction as reflected by a strain gauge sutured on the surface of the left ventricle.

Further details of laboratory toxicity tests may be found in the report of Dubois et al., Report No. 1, Studies on the Toxicity and Biomedical Actions of Antimalarial Drugs, U.S. Army Medical Research and Development Command, Contract No. DA-49-193-MD-2745.

The following tests are exemplary of the effectiveness of the compounds of this invention.

Auricle-Vagus of the guinea pig

A spontaneously contracting guinea pig auricle and its vagal supply (cervical branch of the parasympathetic) was introduced into a constant temperature bath (150 ml.) containing a modified Krebs solution (pH 7.4) saturated at 33° with 94% oxygen and 6% carbon dioxide. The organ was connected semiisotonically to a differential

displacement transducer (Sanborn Lynearsyn Model 1595D5005—sensitivity of 1.9-volt/inch displacement, excitation at standard carrier frequency). This transducer was accurately calibrated and measures displacement, a function linearly related to the amplitude of contraction of the atrial muscle. The electrical activity (changes in potential across the muscle) was occasionally monitored by extracellular microelectrodes. All parameters, mechanical and bioelectrical, were recorded on a dual beam memory storage oscilloscope (Tektronix 564), or on a direct writing multichannel oscillograph.

After a suitable control period, the compound under study was introduced into the bath and allowed to remain in contact with the preparation for 10 minutes. The compound was subsequently removed, and a fresh solution allowed into the bath. Percent changes in rate and amplitude of contraction and changes in the threshold to electrical stimulation of the vagus nerve were recorded and plotted. Compounds were tested at least twice at each dose level. This preparation allows the prompt detection of negative isotropic and chronotropic effects on the myocardium and of the parasympatholitic and neurotoxic properties of the compounds.

Isolated perfused guinea pig heart

(Langendorff preparation.) As myocardial depression is one of the main parameters of toxicity, this test is directed toward the quantitative effects of the compounds on coronary blood flow. The isolated heart was perfused through the root of the aorta with modified Krebs solution (pH 7.4) saturated at 33° with 94% oxygen and 6% carbon dioxide. The perfusate escaping from the coronary sinus was collected by a funnel flowmeter which provided continuous measurement of the rate of flow through the coronary system before and after drug exposure. Amplitude and rate of contraction were also recorded. Changes induced by the drug in the fibrillation threshold induced by electrical stimuli to the ventricular muscle were also routinely determined.

The following table is a compilation of the results of the above tests.

2,4,8-triamino-6-phenyl-pteridine

A marked depression of myocardial contractility and heart rate was noted with the highest dose tested. This induced marked refractoriness of the ventricular myocardium to high frequency electrical stimuli.

Following the above tests, the compounds were further tested in the following manner.

Adult guinea pigs (300–350 grams body weight) of both sexes were sacrificed by cervical concussion. The heart was removed surgically and perfused through the root of the aorta with modified Krebs solution saturated at 34° C. with 94% oxygen and 6% carbon dioxide. The rate and amplitude of myocardial contraction were recorded along the ventricle vector by means of a linear displacement differential transformer (Sanford Model 595 DT–005) coupled to a multichannel direct writing oscillograph. Changes in electrical potential across the ventricle were recorded by means of atraumatic epicardial electrodes coupled to a Tektronix 564 memory oscilloscope.

Ouabain (3 micrograms/ml.) was administered in the previously described manner and induced a marked positive inotropic and chronotropic effect followed within 10 minutes by atrio-ventricular block, ventricular tachycardia and fibrillation. These abnormalities were followed by a progressive disorganization of contraction leading to complete disruption and mechanical deficit of the isolated heart. The electrocardiogram showed the characteristic abnormalities of digitalis intoxication.

In the same manner aconitine (3 micrograms/ml.) when administered as previously described induced ventricular tachycardias and the concomitant electrocardiographic aberrations.

After the above control evaluations the compounds of this invention were used to pretreat the isolated heart, and in doses of 5–20 mg./l. the o-tolyl congener prevented the mechanical and electrical abnormalities induced by the subsequent induction of ouabain and was equally effective against subsequent aconitine induced abnormalities. The phenyl congener was found to share these

Chemical name and/or formula	Conc., mg./l.	Isolated perfused heart percent change from control value	Auricle-vagus preparation percent change from control value
2,4,7-triamino-o-tolylpteridine	(1) 10 (2) 50 (3) 100	Amplitude: (1) None. (2) 20% irreversible decrease in 20 min. (3) 35% irreversible decrease—20 min. Rate: (1) None. (2) 25% reversible decrease—20 min. (3) 50% delayed decrease—40 min. Coronary flow, ml./min.: (1) None. (2) No apparent effect. (3) 60% decrease—30 min. Ventricular fibrillation threshold: (1) and (2) Not tested. (3) 500%+ stable increase in ten minutes.	Amplitude: (1) and (2) None. (3) Slight decrease. Rate: (1) 20% irreversible decrease—20 min. (2) 25% irreversible decrease—20 min. (3) 10% decrease. Vagal threshold: (1) Not tested. (2) Complete block in 40 min. (3) Complete block in 30 min.
2,4,7-triamino-6-phenylpteridine	(1) 10 (2) 20 (3) 50 (4) 100	Amplitude: (1) 20% decrease—40 min. (2) 25% reversible decrease—10 min. (3) 95% reversible decrease—10 min. Rate: (1) None. (2) 20% reversible decrease—10 min. (3) 70% reversible decrease—10 min. Coronary flow, ml./min.: (1) 30% increase in 10 min. (2) 40% increase in 20 min. (3) 90% reversible decrease—10 min. Ventricular fibrillation threshold: (1) Not tested. (2) 300%+ increase in 10 min. (3) 400%+ increase—myocardial excitability reverts to normal upon removal of the compound.	Amplitude: (1) Initial 50% decrease in 5 min. followed by 30% increase—40 min. (2) 25% increase. (3) 80% increase—10 min. Rate: (1) 15% decrease in 5 min. (2) None. (3) 25% increase in 30 min. Vagal threshold: (1) 40% increase in 40 min. (2) None. (3) Reversible block in 30 min.

In summary the following effects were noted:

2,4,7-triamino-6-o-tolyl-pteridine

A moderate myocardial depression at the highest dose tested (100 mg./l.) was noted. This induced marked refractoriness of ventricular myocardium to high frequency electrical stimuli.

antifibrillogenic properties although it was somewhat less effective.

Both compounds were evaluated also in comparison with propranol (5 mg./l.). It was found that propranol will reverse the dysrhythmic actions of ouabain, though this action is accomplished by a far greater depression in rate and amplitude of contraction. Propranol failed to con-

trol ouabain induced arrhythmics similar to digitalis intoxication following reserpinization of the heart "in vitro."

These tests indicated that the mechanism of the action of the o-tolyl and phenyl substituents of the triamino aryl pteridines of this invention is substantially different from that of propranol.

2,4,7-triamino-o-tolyl-pteridine in an effective dose of 5 mg/kg. i.v. and 2,4,7-triamino-6-phenyl-pteridine in an equally effective dose of 8–10 mg./kg. i.v. were found to be devoid of vagolytic, local anesthetic, beta-blocking, ganglion blocking, and neuro-muscular blocking actions. The compounds in the above doses also were found to induce a four-fold increase of the LD_{50} dose of ouabain in dogs without accompanying dysrhythmic actions of its own.

These comparison tests show that the compounds of this invention meet the enumerated requirements for an ideal antiarrhythmic agent, and are vastly superior to any presently known.

The invention herein described was made in the course of or under a contract or subcontract thereunder (or grant) with the Department of the Army.

I claim:

1. The process for the therapeutic application of an antifibrillatory and antiarrhythmic agent which comprises intravenously administering to an animal requiring such treatment an effective amount of a compound having a molecular structure in which there is attached to a 2,4,7-triamino-pteridine nucleus, an aryl group at the 6-position selected from the group consisting of phenyl and ortho-tolyl.

2. The process of claim 1 wherein the aryl group is phenyl.

3. The process of claim 1 wherein the aryl group is ortho-tolyl.

References Cited

UNITED STATES PATENTS

3,081,230 3/1963 Weinstock et al. ------ 424—251

STANLEY J. FRIEDMAN, Primary Examiner