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DIHYDROQUINIDINE POLYGALACTURONATE AND DIHYDROQUINIDINE GALACTURONATE COMPOSITIONS

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ABSTRACT OF THE DISCLOSURE

Pharmaceutical compositions containing dihydroquinidine polygalacturonate and dihydroquinidine galacturonate are described together with the method for treating cardiac arrhythmias therewith.

This application is a division of application Ser. No. 535,736, filed Mar. 21, 1966, now abandoned, which was a continuation-in-part of application Ser. No. 373,827, filed June 9, 1964, and now abandoned. Application Ser. No. 761,819, filed Sept. 23, 1968, now Pat. No. 3,479,359, is a continuation-in-part of application Ser. No. 535,736.

This invention relates to new therapeutically important derivatives of the alkaloid dihydroquinidine which are formed by the interaction of a glycose component and the alkaloidal radical. In particular, this invention is concerned with dihydroquinidine polygalacturonate and dihydroquinidine galacturonate, the methods for their preparation, pharmaceutical compositions containing these compounds and the method of reversing a cardiac arrhythmia by administration of the new dihydroquinidine glycose compounds and compositions containing said compounds.

Disorders in the rhythm of the heart are among the very common problems encountered in medical practice. It has been estimated that about 25 percent of the average cardiac population presents the problems of disordered heart rhythm. The number of these cases does not, however, satisfactorily reflect the importance of a drug which is effective in controlling this disturbance since, among another sizeable group, the abnormal rhythms take on the aspect of other serious heart disease and among these, depending on the kind of disorder of the heart rhythm, the type of patient, and the condition of the heart are included the following symptoms: cardiac neurosis, panic, palpitation, cough, attacks of syncope, cardiac pain, pulmonary edema, congestive failure, emboli, shock and death. In many instances, however, the patient with the abnormal rhythm has a condition which is of no great consequence to him, effecting neither his ability to carry on nor his longevity. In many patients, the arrythmias produce no overt symptoms and the disorder of the rhythm may first be discovered as an incident during an examination for some other purpose.

While cinchona bark contains more than twenty alkaloids, quinidine is the most important member of this group indicated for the treatment of disorders of the heart and the largest part of the clinical literature on the cardiac action of the cinchona alkaloids relates entirely to quinidine. Disorders of the cardiac rhythm constitute the only therapeutic indication for the use of quinidine in disturbances of the heart. It has no primary place in the treatment of cardiac pain or failure. While under some conditions quidine acts to prevent or abolish cardiac pain or failure, such results are due neither to the direct dilatation of the coronary arteries nor to the direct action of the force of contraction of the cardiac muscles, and quinidine remains the drug of choice in the treatment of the abnormal rhythms of the heart.

Some of the inherent limitations to the use of quinidine inclinical cardiology and the experimental approaches to correct these are described in U.S. Pat. 2,878,252. Clinical literature recognizes still another probem associated with the use of quinidine to correct the abnormal heart rhythm and that is, that it is effective only in approximately 75 percent of the cardiac arrhythmias. While a portion of these patients who are not benefited by the administration of the older quinidine compound may be benefited by the administration of the newer quinidine compound derivatives, there remains a significant group for whom quinidine exerts no therapeutic affect on their cardiac arrhythmias. This group of patients are often treated with other potent agents such as digitalis, adrenergic drugs and procaine amide, but usually without significant effect and the arrhythmia continues to persist for the remainder of their lives, causing varying degrees of limitation and distress.

Among the alkaloids isolated from the cinchona plant is the hydrogenated form of quinidine. This compound is known as dihydroquinidine and may be distinguished from quinidine in its chemical, physical, pharmacologic and therapeutic properties. Irrespective of the structural relationship between quinidine and dihydroquinidine, there is a marked contrast in behavior of the hydrogenated and the compounds. Apart from the well known generic differences between the hydrogenated and unhydrogenated compounds, these separate entities have their own level of chemical reactivity and toxicologic reactivity, and the chemical behavior of one member of the cinchona alkaloid group may not be imputed to another member of the same group. Thus, it is known that the presence of an unsaturated or unhydrogenated linkage in an organic compound will interfere with physiologic enzyme reactions and also that the hydrogen unsaturation of an organic compound may convert an essentially benign substance into a noxious irritant, as for example, compare the properties of alkyl alcohol and its saturated analog, propyl alcohol. The United States Pat. No. 2,230,631, notes in column 1 (lines 36 through 52), that dihydroquinidine nicotinate is a crystalline solid melting at 209° C. and is "slightly soluble in water." The very next paragraph (colume 1, lines 52–68) of the same reference, describes the preparation and properties of quinidine nicotinate as a "non-crystalline substance, without a melting point" and which is easily soluble in water. Here we find that a physical and chemical change in the state of matter and its properties results from the simple chemical reaction of a salt formation when nicotinic acid is reacted with the separate reagents, quinidine and hydroquinidine. Whereas the hydrogenated dihydroquinidine produces a crystalline, slightly water-soluble reaction-product; the dehydrogenated quinidine results in a non-crystalline glassy material, which is "easily soluble in water."

Pharmacologically quinidine may be distinguished from dihydroquinidine than of dihydroquinidine were required to prevent electrically induced auricular fibrillation, while the dose of dihydroquinidine required to abolish the after-affects to faradic stimulation was higher than that of quinidine. The toxicity of dihydroquinidine in mice is about 18 percent greater than the pure quinidine. Dihydroquinidine, (Chem. Abstracts, 48 9543b, 1954), is reported to reduce muscle potassium and accelerate liver and myocardial potassium loss during therapeutic use. This effect is in contradistinction to the properties of quinidine, which has been reported to augment muscle potassium (Proc. Soc. Exper. Med. & Biol., 92: 629,

1956) (Am. J. Physiol. 199; 151, 1960). While some investigators have shown that dihydroquinidine and pure quinidine were similar in the qualitative nature of their therapeutic action, on a weight for weight basis, dihydroquinidine appears to be clinically more potent. While the early references to a therapeutic equivalence of dihydroquinidine and quinidine appeared approximately 40 years ago, in the interim, more definitive experimental techniques have been developed and as a result of the broadening of the knowledge in this specialized field therapeutics, many limitations to the older experimental procedures have been established. Thus, some investigators, as for example Van Dongen, (Arch. Internat. De Pharmacodyn et de Therap., 63: 90–94, 1939) who originally proposed that dihydroquinidine is a more potent substance than quinidine, later abandoned this concept after continued research, (Arch. Internat. Pharmacodyna. et de Therap., 91: 399–403, 1952), De Boer also assumed, in 1936 (Proc. Acad. Sci., Amsterdam, 39: 266–271, 1936) that dihydroquinidine was a better anti-fibrillatory agent than is quinidine but on the basis of subsequent studies (Arch. Internat. de Pharmacodyn et de Therap., 51: 246–254, 1939) he reversed his position and concluded that quinidine is perhaps the more suitable therapeutic agent. A study of the literature establishes that many of the earlier workers later reversed their earlier position regarding the relative potencies of quinidine and dihydroquinidine and in view of the many inconsistent findings in the scientific literature, the therapeutic properties determined for one compound may not be imputed to the other compound.

It was found that dihydroquinidine polygalacturonate and dihydroquinidine galacturonate are especially useful to correct arrhythmias in those patients who are refractory to the conventional forms of quinidine and who would otherwise remain cardiac invalids, with serious threat to their life.

A comparative clinical study of quinidine polygalacturonate, quinidine hydrochloride and dihydroquinidine polygalacturonate was conducted in a series of 21 patients presenting cardiac arrhythmias. Each of the patients received a complete physical examination which included electrocardiographic analysis of the patient's cardiac status prior to the start of the study. The method of study utilized was as follows: The patients were prescribed one of the test compounds, to wit: quinidine polyquinidine hydrochloride and the cardiodynamic effects observed. A cross-over procedure was then utilized, with the patients receiving another test compound for clinical comparison of the cardiodynamic effects. In this manner, the specific antiarrhytmic properties of the respective test compounds were compared within the same patient. Thus, 7 patients were first treated with quinidine hydrochloride and then with dihydroquinidine polygalacturonate and 11 patients were treated first with quinidine polygalacturonate and then with dihydroquindine polygalacturonate. The results of this study are presented in Table I, following. The conclusions of the investigator, based upon the results of his study of the effects of quinidine hydrochloride, quinidine polygalacturonate and dihydroquinidine polygalacturonate in the series of patients described in Table I, are as follows:

(a) The total therapeutically successful dosage administration for dihydroquinidine polygalacturonate is lower than that amount required for quinidine hydrochloride and quinidine polygalacturonate. The control of the arrhythmia could generally be achieved on lower daily dosage of dihydroquinidine polygalaceuronate than with either quinidine hydrochloride or quinidine polygalacturonate. Dihydroquinidine polygalacturonate exerts more protracted and pronounced cardiodynamic effects than quinidine polygalacturonate.

(b) Dihydroquinidine polygalacturonate did not cause any side reactions such as nausea or diarrhea, which were observed after administration of quinidine polygalacturonate and quinidine hydrochloride. This absence of gastrointestinal irritation is important, since dihydroquinidine polygalacturonate was administered after the onset of side reactions with quinidine polygalacturonate or quinidine hydrochloride, in the same patient.

(c) The superior properties of dihydroquinidine polygalacturonate as compared with quinidine hydrochloride and quinidine polygalacturonate, could not have been anticipated from a knowledge of the literature and the known behavior of these compounds.

These unusual properties of the new glycose acid derivatives of dihydroquinidine are in contrast to the reported research findings with hydroquinidine per se, in that its pharmacologic effect is identical to that of quinidine alkaloid and also that dihydroquinidine possesses no clinical advantages over the conventional quinidine preparations. Furthermore, this unusual and desirable property of dihydroquinidine polygalacturonate and dihydroquinidine galacturonate is not due to any variations in the potency of the dihydroquinidine moiety, since this latter compound has been described as being only slightly more potent than quinidine by some investigators and of equal or lesser potency by others. Neither can the clinical differences between dihydroquinidine and quinidine be ascribed to a preferential solubility and absorption of the former drug, since the solubility and absorption of both these compounds have been found to be virtually the same.

Dihydroquinidine polygalacturonate exhibits new and unexpected properties were compared with quinidine polygalacturonate in that it exerts an effect which is more protracted as well as more pronounced than that of quinidine polygalacturonate. This finding is of particular clinical significance since it affords a means for correcting cardiac arrhythmias which are not amenable to treatment with either quinidine inorganic acid salts or quinidine polygalacturonate. The advantage to the physician of having available a drug which exhibits a more intensive effect in controlling heart rhythm cannot be minimized. Thus, the superiority of dihydroquinidine polygalacturonate over quinidine polygalacturonate opens a new avenue of therapy for the cardiologist in the management of the patient with cardiac arrhythmias. These unusual and desirable antiarrhythmic property of these new agents which occurs in those patients who have been found to be refractory to the conventional salts of quinidine, is a finding which cannot be predicted on the known behavior of dihydroquinidine.

Dihydroquinidine polygalacturonate and dihydroquinidine galacturonate may be prepared through the interaction between polygalacturonic acid or galacturonic acid and dihydroquinidine in an inert medium. The respective compounds also may be formed through the interaction of the alkali salts of the polygalacturonic acid or galacturonic acid with the acid salt of the dihydroquinidine, as for example, dihydroquinidine sulfate, or dihydroquinidine hydrochloride. When dihydroquinidine polygalacturonic acid is being prepared, it is first necessary to determine the neutralization equivalent of the acid in order that its combining power with the dihydroquinidine base be known. This neutralization equivalent will vary with the polymer chain length which may range in molecular weight of from 20,000 to 80,000. The polymer is composed of units of galacturonic acid and consequently the salt dihydroquinidine polygalacturonate consists of multiples of dihydroquinidine galacturonate which may range from 50 to 400 units or more. In the course of conducting this reaction, the separate components are dispersed, or dissolved, in equal portions of the inert solvent. Examples of the said inert solvents which may be used are water, alkanols of from 1 to 6 carbons, acetone and mixtures of these. A preferred inert medium is isopropyl alcohol. The alkaline component is added slowly to the acid component while the mixture is being stirred and gently heated (no greater than 50° C.). When all of the base moiety has been added, the stirring is continued until the pH of the reaction mix-

TABLE I.—RESULTS OF CLINICAL STUDY

Patient	Age	Diagnosis	Drug administered	Dosage	Duration of therapy, days	Results	Side effects
1. L.R.	34	Massive ventricular extra-systoles; intermittent paroxysmal tachycardia; labile hypertension.	Q.Hcl [1]	1 tab., t.i.d.	3	Decrease of ventricular extra-systoles; from 15 per minute	Considerable diarrhea and nausea
				2 tabs., t.i.d.	6	to 5–8 per minute.	
			D.H.Q.P.G. [2]	1 tab., b.i.d.	8	Complete disappearance of extra-systoles	None.
2. I.S.	42	Ventricular extra-systoles	Q.Hcl	1 tab., t.i.d.	3	No effect	Diarrhea.
			D.H.Q.P.G.	1 tab., b.i.d.	7	Complete disappearance of extra-systoles	None.
3. E.D.	63	Coronary heart disease; massive supra-ventricular extra-systoles.	Q.Hcl	1 tab., t.i.d.	2	Decrease of supra-ventricular extra-systoles to 4–8 per	Do.
				1 tab., q.i.d.	2	minute.	
			D.H.Q.P.G.	1 tab., b.i.d.	4	Complete disappearance of supra-ventricular extra-systoles.	Do.
4. M.S.	57	Coronary heart disease; ventricular extra-systoles	Q.Hcl	1 tab., t.i.d.	4	No effect on extra-systoles.	Do.
			D.H.Q.P.G.	1 tab., t.i.d.	11	Complete disappearance of extra-systoles	Do.
5. H.W.	71	Coronary heart disease; supraventricular and ventricular extra-systoles.	Q.Hcl	1 tab., q.i.d.	6	Reduction of extra-systoles from average of 12 per minute to 4–7 per minute.	Do.
			D.H.Q.P.G.	1 tab., b.i.d.	8	Reduction of extra-systoles to 1–3 per minute	Do.
6. H.D.	65	Coronary heart disease; ventricular extra-systoles	Q.Hcl	1 tab., q.i.d.	3	Reduction of extrasystoles from 10–15 per minute, to 6–8	Nausea.
			D.H.Q.P.G.	1 tab., b.i.d.	2	per minute no effect.	None.
7. S.B.	51	Coronary heart disease; to some extent in form of salvos	Q.Hcl	1 tab., t.i.d.	3	Reduction of extra-systoles to 1–3 per minute (occasional). Slight decline of ventricular extra-systoles, no effect on salvo type rhythm interference.	Do.
			D.H.Q.P.G.	2 tabs., t.i.d.	3		
				1 tab., b.i.d.	3	Reduction of extra-systoles, salvo-type extra-systoles still sporadic.	Do.
				1 tab.	4	Reduction in extra-systoles; occasional 1–4 per minute; no salvo extra-systoles detectable.	Do.
8. St.A.	69	Coronary heart disease; supraventricular and ventricular extra-systoles.	Q.P.G. [3]	1 tab., d.i.d.	4	Reduction in extra-systoles from 10–14 per minute to 3–6 per minute.	Do.
			D.H.Q.P.G.	1 tab., b.i.d.	4	Complete disappearance of extra-systoles	Do.
9. K.W.	34	Post-operative mitral stenosis ventricular extra-systoles	Q.P.G	1 tab., q.i.d.	3	Reduction of bigeminal rhythm to 3 per minute	Do.
			D.H.Q.P.G	1 tab., t.i.d.	13	Complete disappearance of extra-systoles	Do.
10. M.D.	56	Ventricular extra-systoles post-myocardial infraction. Ventricular heart disease.	Q.P.G	1 tab., t.i.d.	4	Reduction of extra-systoles from 21 to 6 per minute	Do.
			D.H.Q.P.G.	1 tab., b.i.d.	11	Complete disappearance of extra-systoles	Do.
11. J.F.	66	Coronary heart disease; auricular extra-systoles intermittent cerebral blood flow disturbance.	Q.P.G D.H.Q.P.G.	1 tab., b.i.d.	4	Reduction of previous irregularity, and to some extent salvo-type estra-systoles, to 6:1 extra-systoles.	Do.
						Complete disappearance of extra systoles	Do.
12. S.O.	71	Complete A–V block; Pacemaker implantation, consideration parasystoles; fully digitalized.	Q.P.G.	1 tab., q.i.d.	10	Reduction of para-systoles from 12 per minute to 4–7 per minute.	Occasional nausea and diarrhea
			D.H.Q.P.G	1 tab., b.i.d.	16	Reduction of para-systoles to 1–4 per minute	None.
13. S.T.	67	Complete A–V block; Pacemaker implantation; considerable parasystoles; completely digitalized.	Q.P.G.	1 tab., q.i.d.	4	Reduction of para-systoles from 15 per minute to 4 per minute.	Do.
			D.H.Q.P.G.	1 tab., b.i.d.	7	Reduction to 3–5 para-systoles per minute	Do.
14. W.S.	27	Post-operative mitral stenosis; unstable ventricular stroke sequence auricular arrhythmia.	Q.P.G.	1 tab., t.i.d.	2	No effect	Do.
			D.H.Q.P.G.	1 tab., q.i.d.	2	Normal sinus rhythm restored	Do.
15. S.V.	65	Total A–V block; Pacemaker implantation; para-extra-systoles; fully digitalized.	Q.P.G.	1 tab., t.i.d.	4	Reduction in para-systoles from 10 to 13 per minute to 2–4 per minute.	Do.
			D.H.Q.P.G.	1 tab., b.i.d.	17	Reduction in para-systoles to 1–5 per minute	Do.
16. K.O.	56	Total A–V block; para-systoles; fully digitalized	Q.P.G.	1 tab. 6× daily	9	Decrease from 15 para-systoles per minute to 4–5 per minute.	Do.
			D.H.Q.P.G.	1 tab., t.i.d.	7	Para-systoles decreased to 3–5 per minute	Do.
17. N.D.	24	Post-operative atrial septum defect; massive supra-ventricular and ventricular extra-systoles.	Q.P.G.	1 tab., t.i.d.	4	Decrease in polytopic extra-systoles from 17–20 per minute to 2–7 per minute.	Nausea.
			D.H.Q.P.G.	1 tab., b.i.d.	12	Continued occurrence of extra-systoles; after 4 days complete disappearance.	None.
18. R.N.	27	Unstable ventricular stroke sequence associated with mitral stenosis auricular arrhythmia strong extra-systoles fully digitalized.	Q.P.G.	1 tab., q.i.d.	6	Extra-systoles of 12–18 per minute reduced to 5 per minute.	Do.
			D.H.Q.P.G.	1 tab., t.i.d.	14	Slight extra-systoles 2–5 per minute	Do.
19. R.R.	74	Coronary heart disease; ventricular extra-systoles	Q.P.G.	1 tab., t.i.d.	2	Complete disappearance of extra-systoles	Do.
20. P.S.	47	Cardiac decompensation; ventricular extra-systoles	D.H.Q.P.G.	1 tab., b.i.d.	13	Complete disappearance of extra-systoles	Do.
21. T.H.	70	Relative coronary insufficiency; sclerotic aortic stenosis; coronary heart disease; ventricular extra-systoles.	D.H.Q.P.G.	1 tab., b.i.d.	7	Reduction of extra-systoles from 7–16 per minute to 1–6 per minute.	Do.

[1] Q.Hcl=quinidine hydrochloride each tablet containing 200 mg. of quinidine hydrochloride.
[2] D.H.Q.P.G.=dihydroquinidine polygalacturonate each tablet containing 292.08 mg. of dihydroquinidine polygalacturonate.
[3] Q.P.G.=quinidine polygalacturonate each tablet containing 300 mg. of quinidine polygalacturonate.

ture is between pH 4 and pH 7. The solvent is then evaporated and the residue extracted with chloroform, dried and washed with water.

Dihydroquinidine polygalacturonate is obtained as a tannish to creamy white solid, with a characteristic melting point, which analyzes in good agreement with its theoretical values for carbon, hydrogen and nitrogen. The molecule is somewhat hygroscopic, containing two molecules of water of hydration. The ultraviolet spectrum obtained for this compound establishes the presence of the dihydroquinidine moiety and on treatment with aqueous alkali it is decomposed to yield a precipitate of the insoluble dihydroquinidine base while an aqueous acid solution precipitates the polygalacturonic acid moiety from a dispersion of the compound. Dihydroquinidine polygalacturonate is slightly soluble in water but insoluble in methanol, ethanol, chloroform and ether. The bitter taste of dihydroquinidine is modified by reacting it with polygalacturonic acid. The compound is stable for further pharmaceutical manufacturing.

Dihydroquinidine galacturonate is obtained through the interreaction of stoichiometric proportions of dihydroquinidine base and galacturonic acid in an inert medium, such as water, alkanols of from 1 to 6 carbons, or mixtures of these. The reaction is carried out in a suitable glass vessel to which is first added a solution of the galacturonic acid and with the aid of gentle heat and with stirring, small increments of dihydroquinidine base are added to this. When all of the dihydroquinidine base has been added, the solution is warmed to reflux temperature, allowed to cool to room temperature and set aside to crystalize in an ice-chest.

Dihydroquinidine galacturonate is a tan to white crystaline solid which melts at 134–136° C. It is soluble in water and alcohol and insoluble in ether and chloroform. Although the aqueous solution darkens on exposure to air and light, it is stable for pharmaceutical compounding purposes. It has the characteristic ultraviolet spectrum of dihydroquinidine and on treatment with alkali is decomposed so that the dihydroquinidine base precipitates.

When it is desired to utilize these new compounds in therapy, they may be administered in the form of tablets, capsules, powders granules or suppositories. Liquid dosage forms such as syrups, solutions, elixirs and tinctures may also be utilized. Irrespective of the dosage form selected, the concentration of active compound per unit dose ranges from 200 mg. to 200 mg. The new compounds may be administered from 1 to 5 times daily in order to achieve a conversion of the arrhythmia a normal sinus rhythm. Maintenance therapy will usually require from 200 to 400 mg. of the active compound administered once or twice daily.

In certain circumstances it may be desired to utilize parenteral therapy to achieve the antiarrhythmic effect.

A solution of dihydroquinidine galacturonate may be utilized for parenteral therapy and a dosage of from 200 mg. to 400 mg. is administered by intramuscular or intravenous injection. Although caution must be exercised when intravenous injection is utilized, the compound possesses sufficient freedom from local toxicity to be used satisfactorily by the intramuscular route. In practice it will be found desirable to dissolve the therapeutic dose requirement in a volume of from 2 to 4 cc., so that each 2 cc. of solution will contain 200 mg. of dihydroquinidine galacturonate. It should be noted that the same total dose requirements are necessary to reverse the cardiac arrhythmias when these drugs are administered by either the oral or the parenteral routes, so that the initial dosage required to reverse the arrhythmias, remains from 200 to 800 mg. of dihydroquinidine glacturonate, with the maintenance dosage of 200 to 400 mg. per day of the parenteral solution. Dihydroquinidine polygalacturonate exhibits an unexpected increased solubility in aqueous fluids. While it should be expected that the formation of a polymeric compound would render the resultant product insoluble in aqueous fluids, a contrary condition was found to be in excess of 5 percent and specifically, about 8.5 percent.

When it is desired to utilize the subject compounds in therapy to correct cardiac arrhythmias then the respective dosage forms described above are administered for a series of 5 doses, at 2 to 3 hour intervals for 1 day. This course of therapy will convert the arrhythmia to a normal sinus rhythm in the majority of cases. However, in those patients wherein the arrhythmia still persists, a second and even a third course of therapy may be utilized. After the achievement of a normal sinus rhythm, maintenance dosage of from 200 mg. to 400 mg. administered once or twice daily, will generally be found satisfactory to maintain the normal sinus rhythm. Parenterally, the administration of dihydroquinidine galacturonate will cause a satisfactory maintenance effect when administered in a dosage range of 200 mg. to 400 mg. per day. When the pharmaceutical dosage forms of dihydroquinidine polygalacturonate are compared with those of quinidine polygalacturonate, unexpected advantages are observed. Dihydroquinidine polygalacturonate will be found to cause a more pronounced action which persists for a longer period than that of quinidine polygalacturonate as well as quinidine inorganic acid salts. There are no noxious side reactions such as nausea and diarrhea after the administration of the new compounds and they are excreted from the body at a rate which does not lead to accumulation. This favorable rate of excretion permits the administration of multiple dosages without additive effects and cumulative toxicity. The rapid onset of action and the uniform blood levels resulting after the administration of dihydroquinidine polygalacturonate permits a more desirable control of the cardiac arrhythmia than has hiterto been possible with derivatives of the cinchona plant. The active compounds are readily assimilated and absorption and the beneficial cardiotonic effects will be observed to take effect within 15 minutes after administration.

The following examples illustrate the scope of this invention.

EXAMPLE 1

The neutralization equivalent of a sample of polygalacturonic acid is determined by titration with one-tenth normal alkali.

In a round-bottom, three-neck flask fitted with a stirrer, a dropping funnel and a condenser, is placed 1 liter of 50 percent (vol./vol.) mixture of isopropyl alcohol and water. To this is added, with stirring, 100 gm. of polygalacturonic acid and when complete dispersion has been obtained, the stoichiometric equivalent of dihydroquinidine alkaloid dissolved in just sufficient isopropyl alcohol, is slowly added. The pH of the reaction mixture is determined periodically and the mixture is gently warmed (below 50° C.). After about 4 hours or when the pH has stabilized between the range of from pH 4 to pH 7, the stirring is stopped and the mixture cooled to 0° C., and filtered. The solvent is then evaporated under reduced pressure (10 mm./Hg) and the residue extracted with two volumes of hot chloroform and dried. The dried powder is then suspended in two volumes of 50 percent water methanol and filtered. The insoluble powder is dried and is dihydroquinidine polygalacturonate. The compound is tannish to white in color and melts (with decomposition) at 205–207° C. and possesses two molecules of water of hydration. The empirical formula for the compound is $C_{26}H_{36}N_2O_9 \cdot H_2O$, with a calculated molecular weight of 556.54. The compound is insoluble in chloroform, ether and methanol, and slightly soluble in water. It possesses a characteristic ultraviolet spectrum for dihydroquinidine and a characteristic infrared spectrum which is different from that of its components or a mixture of these. It analyzes in good agreement with its theoretical values of carbon, nitrogen and hydrogen.

Theory: Carbon: 56.1%; hydrogen: 7.2%; nitrogen: 5.0%
Found: Carbon: 55.87%; hydrogen: 7.09%; nitrogen: 4.66%

EXAMPLE 2

In place of the isopropyl alcohol described in Example 1, may be substituted, wholly or in part, a member of the class of alkanols having 1 through 4 carbon atoms, water and mixtures of these, the remainder of the steps being the same and the compound obtained is dihydroquinidine polygalacturonate, corresponding in every way to that described in Example 1 above.

EXAMPLE 3

A solution containing 200 grams of polygalacturonic acid in two liters of 60 percent mixture of methanol-water is prepared, with the aid of an exact neutralization equivalent of sodium hydroxide. The solution is stirred and to this is added a solution consisting of an exact equivalent of dihydroquinidine sulfate (based upon the neutralization equivalent determined for the polygalacturonic acid). The dihydroquinidine sulfate is dissolved in a just sufficient quantity of 60 percent mixture (vol./vol.) methanol-water. The mixture is warmed to 60° C. and after the pH of the solution has stabilized within the range of pH 4 to pH 6, an additional liter of methanol is added. The mixture is then cooled to 0° C. and filtered. The solvent is evaporated to dryness, the residue is washed with two 50 cc. portions of water and dried. The resulting product is dihydroquinidine polygalacturonate which melts at 205–207° C. and corresponds in every way to that obtained as a result of Example 1.

EXAMPLE 4

In place of dihydroquinidine sulfate used in Example 3 above, may be substituted in equimolar proportions dihydroquinidine chloride, dihydroquinidine bromide and dihydroquinidine nitrate.

In place of the sodium hydroxide used to neutralize the polygalacturonic acid in Example 3 above, may be substituted, in equimolar proportions, a metal hydroxide, carbonate and bicarbonate in which the molecular weight of the metal ion is less than 55, as for example, lithium, potassium, calcium, magnesium and aluminum.

EXAMPLE 5

To a solution of one-tenth mol of galacturonic acid dissolved in 500 cc. of butyl alcohol is added exactly one-tenth mol of dihydroquinidine. The mixture is stirred and warmed to reflux temperature for 2 hours and the solvent evaporated to dryness under reduced pressure. The residue is extracted with chloroform and dried. The resulting product is dihydroquinidine galacturonate which melts at 134 to 136° C. and is a tan to white crystalline substance, soluble in water and methanol, ethanol, acetone and insoluble in chloroform and ether. The ultraviolet spectrum is characteristic for dihydroquinidine and the compound is decomposed by alkali to result in an insoluble precipitate of dihydroquinidine base.

EXAMPLE 6

In place of the butyl alcohol used in Example 5 above, may be substituted a member of the group of alkanols containing from 1 through 4 carbon atoms, water and mixtures of these. The remainder of the steps are the same and the resultant product is identical to that obtained as a result of Example 5.

EXAMPLE 7

To a solution of 1 mol of sodium galacturonate dissolved in 1 liter of ethanol is added one mol of dihydroquinidine chloride dissolved in 1 liter of ethanol, and 500 mg. of copper powder. The mixture is stirred and heated to about 60° C. A copious precipitate forms as the reaction progresses, and after 4 hours the stirring is stopped; the mixture filtered and the solvent evaporated to dryness. The residue is extracted with 25 cc. of chloroform, dried and dissolved in a just sufficient quantity of hot isopropyl alcohol. The solution is filtered, set aside to crystallize in an ice-chest. The crystals are collected on a filter, dried and melt at 134–136° C. and correspond to dihydroquinidine galacturonate.

EXAMPLE 8

In place of the sodium galacturonate used in Example 7 above, may be substituted in equimolar amounts a metal hydroxide, carbonate and bicarbonate in which the molecular weight of the metal ion is less than 55, as for example, lithium, potassium, calcium, magnesium and aluminum.

In place of the dihydroquinidine chloride used in Example 7 above, there may be substituted in equimolar quantities, dihydroquinidine sulfate, dihydroquinidine nitrate and dihydroquinidine bromide.

EXAMPLE 9

When it is desired to administer the new compounds in therapy, then they may be utilized in the form of tablets, capsules, powders, granules or suppositories. The quantity of active ingredient in the respective pharmaceutical dosage form ranges 200 mg. to 800 mg. per unit dose. For the preparation of the tablets, capsules, powders and granules, a basic granulation mixture is prepared by mixing the active compound with from 1 to 10 parts of a pharmaceutically acceptable diluent selected from the group consisting of lactose, sucrose, dextrose, starch, sorbitol, mannitol or mixtures of these. After thorough mixing, the whole is wetted with a 50 percent ethanol-water mixture and air-dried. In the preparation of tablets, suitable binders, such as gum acacia and gum tragacanth, are added at a concentration of 0.1 percent to 1 percent by weight, and a tablet lubricant, as for example, magnesium stearate, is added at a concentration of up to 0.5 percent by weight and the whole granulated with ethanol-water granulating solution, as described above. The granulation is then compressed into tablets of suitable size and shape, so as to contain from 200 mg. to 800 mg. of active ingredient per tablet.

In the preparation of capsules, the basic granulation or the active ingredient alone may be filled into a capsule of suitable size and shape. The dosage of active compound per capsule is from 200 mg. to 800 mg. of active compound.

In the preparation of powders and granules, the basic granulation described above is utilized. For the preparation of powders, the particle size of the granulation is reduced to a No. 60 standard mesh size or finer. For the preparation of granules the particle size is that obtained by passing the granulation mixture through a No. 8 standard mesh screen. Suitable flavoring and coloring matter may be added to the granules and powders, if desired. For both powders and granules the unit dose is 1 teaspoonful (5 grams) each unit dose containing from 200 mg. to 800 mg. of active compound.

For the preparation of suppositories the active compound may be mixed with a pharmaceutically suitable suppository base, as for example, cocoa butter, polyoxyethylene glycol, having an average molecular weight of from 1500 to 6000 and which are known in the trade as "Carbowaxes," spermacetti, glycerol-gelatin suppository base, or any other pharmaceutically suitable suppository vehicle. The active ingredient is dispersed in the suppository base by means of levigation. Either the cold extrusion process or the hot pour technique may be utilized for the manufacture of suppositories. Each suppository will contain from 200 mg. to 800 mg. of the active compound.

Should it be desired to utilize liquid dosage forms, then these may be prepared utilizing a pharmaceutically ac-

ceptable vehicle such as ethanol, glycerin, propylene glycol, sorbitol, water and mixtures of these. Suitable flavoring and sweetening agents may be added and syrup may also be used as a vehicle for the preparation of liquid dosage forms. The active ingredient is dispersed in the preferred liquid pharmaceutically acceptable vehicle, so that each 5 cc. (1 teaspoon) will contain from 200 mg. to 800 mg. of the active compound.

EXAMPLE 10

In place of the dihydroquinidine polygalacturonate used in Example 9, may be substituted in equivalent amounts, dihydroquinidine galacturonate to prepare tablets, capsules, powders, granules and suppositories, as well as the liquid dosage forms.

When an aqueous injectable solution of dihydroquinidine galacturonate is desired, the solution is prepared so that the concentration of dihydroquinidine galacturonate is from 200 to 400 mg. per cc. of solution. Using an aseptic technique, the correct amount of dihydroquinidine galacturonate is dissolved in ¾ the total volume required of water-for-injection. Gentle heat may be utilized to achieve solution, but this is not necessary. When all of the dihydroquinidine has dissolved, the solution is filtered through a selas bacteriologic filter and additional water-for-injection added, so that the final volume contains from 200 to 400 mg. of dihydroquinidine galacturonate per 2 cc. of solution. The solution is then packaged in amber glass ampules and may be sterilized by autoclaving.

EXAMPLE 11

When it is desired to correct the cardiac arrhythmias, as for example, atrial fibrillation, atrial flutter, paroxysmal atrial fibrillation, paroxysmal atrial tachycardia, premature atrial contractions and premature ventricular contractions, either dihydroquinidine polygalacturonate or dihydroquinidine galacturonate may be administered in the form of capsules, tablets, powders, granules, suppositories and liquid dosage forms. Dihydroquinidine galacturonate may be injected intramuscularly or intravenously. Irrespective of the route of administration or the particular dosage form employed, the amounts of the therapeutic compound used will be the same for the respective dosage form selected. Thus, it will be found that 200 mg. to 400 mg. of either dihydroquinidine polygalacturonate or dihydroquinidine galacturonate administered every 2 to 3 hours for 5 doses, will revert the arrhythmia to a normal sinus rhythm in a preponderance of patients. A maintenance dosage of 200 to 400 mg., once or twice a day, of the respective active compound may then be instituted to sustain the therapeutic effects observed.

When there is no urgency in obtaining a reversion of the arrhythmia, the patient may be prescribed a dosage of from 200 to 400 mg. of the selected compound, three to four times daily, for a period of 3 to 4 days. If the desired response is not obtained with this dosage level, the total daily requirement is increased by 200 mg. of the selected compound, per day, for an additional two-day period, with subsequent increases of 200 mg. of the compound per day after similar intervals, until a normal sinus rhythm is achieved.

A maintenance regimen of from 200 to 400 mg. once or twice a day, of the selected compound, as for example, dihydroquinidine polygalacturonate, dihydroquinidine galacturonate, is then instituted to sustain the therapeutic results achieved. The utilization of this slower procedure for reversing the cardiac arrhythmia will be found to be successful in a preponderant number of patients who are refractory to other forms of antiarrhythmic therapy.

I claim:

1. A pharmaceutical composition in unit dosage form for treating cardiac arrhythmia comprising from 200 mg. to 800 mg. of a compound selected from the group consisting of dihydroquinidine polygalacturonate and dihydroquinidine galacturonate and a pharmaceutical carrier therefor.

2. A pharmaceutical composition as described in claim 1, said compound being dihydroquinidine polygalacturonate.

3. A pharmaceutical composition as described in claim 1, said compound being dihydroquinidine galacturonate.

4. The method of treating cardiac arrhythmia in a patient suffering therefrom which comprises administering to said patient an antiarrhythmic amount of a pharmaceutical composition as described in claim 1.

5. The method of claim 4, said pharmaceutical composition comprising from 200 mg. to 800 mg. of dihydroquinidine polygalacturonate and a pharmaceutical carrier therefor.

6. The method of claim 4, said pharmaceutical composition comprising from 200 to 800 mg. of dihydroquinidine galacturonate and a pharmaceutical carrier therefor.

7. The method of treating a cardiac arrhythmia in a patient suffering therefrom which comprises administering to said patient from 1 to 5 times daily a unit dosage form of a pharmaceutical composition as described in claim 1.

8. The method of claim 7, said pharmaceutical composition comprising from 200 to 800 mg. of dihydroquinidine polygalacturonate and a pharmaceutical carrier therefor.

9. The method of claim 7, said pharmaceutical composition comprising from 200 to 800 mg. of dihydroquinidine galacturonate and a pharmaceutical carrier therefor.

10. The method of treating cardiac arrhythmia in a patient suffering thererom which comprises administering to a said patient an antiarrhythmic amount of a compound selected from the group consisting of dihydroquinidine polygalacturonate and dihydroquinidine galacturonate.

11. The method of claim 10, said compound being dihydroquinidine polygalacturonate.

12. The method of claim 10, said compound being dihydroquinidine galacturonate.

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