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(54) Title: USE OF IKACH BLOCKERS FOR THE TREATMENT OF CARDIAC DISEASES

(57) Abstract: The present disclosure relates to methods of treating and/or preventing cardiac diseases in human patients by administration of an effective amount of one or more acetylcholine-activated potassium current (IKACh) blockers.

USE OF IKACH BLOCKERS FOR THE TREATMENT OF CARDIAC DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119(e) to U.S. Provisional Application Number 61/771,702, filed on March 1, 2013, which is hereby incorporated in its entirety.

FIELD

[0002] The present disclosure relates to methods of treating and/or preventing cardiac diseases in human patients by administration of an effective amount of one or more acetylcholine-activated potassium current (IKACh) blockers.

BACKGROUND

[0003] A healthy heart beats via regular, coordinated electrical impulses. The sinus node (also commonly called the sinoatrial node or sinuatrial node) is the impulse-generating (pacemaker) tissue and thus the generator of normal sinus rhythm. Electrical discharge from the sinus node stimulates adjacent cells, leading to stimulation of the atrioventricular (AV) node and then successive regions of the heart, in an orderly sequence.

[0004] Heart rhythm disturbances can result from abnormalities of impulse formation, impulse conduction, or both and can lead to serious complications such as angina and heart failure. Heart rhythm disturbances are also associated with serious cardiac diseases, such as sick sinus syndrome (SSS), sinus node dysfunction (SND), cardiac conduction disease (CCD), sinus bradycardia and AV block.

SUMMARY

[0005] It is contemplated that inhibition of the IKACh can treat disorders characterized by abnormal conduction and/or dysfunction of the sinus node. Accordingly, in one aspect, the disclosure provides a method for treating or preventing sick sinus syndrome, sinus node dysfunction, sinus bradycardia, cardiac conduction disease or atrioventricular block in a human patient in need thereof. The method comprises administering an effective amount of an IKACh blocker to the patient.

[0006] In one embodiment, provided is a method for treating or preventing sick sinus syndrome in a human patient in need thereof, comprising administering an effective amount of an IKACh blocker to the patient.

[0007] In another embodiment, provided is a method for treating or preventing sinus node dysfunction in a human patient in need thereof, comprising administering an effective amount of an IKACh blocker to the patient.

[0008] In yet another embodiment, provided is a method for treating or preventing sinus bradycardia in a human patient in need thereof, comprising administering an effective amount of a IKACh blocker to the patient.

[0009] In still another embodiment, provided is a method for treating or preventing cardiac conduction disease in a human patient in need thereof, comprising administering an effective amount of an IKACh blocker to the patient.

[0010] In still another embodiment, provided is a method for treating or preventing atrioventricular block in a human patient in need thereof, comprising administering an effective amount of an IKACh blocker to the patient.

[0011] In one embodiment, provided is a method of preventing the prolongation of the S-H interval in a human patient, comprising administering to the patient an effective amount of an IKACh blocker.

[0012] In another embodiment, provided is a method of shortening the S-H interval in a human patient, comprising administering to the patient an effective amount of an IKACh blocker.

[0013] In one embodiment, provided is a method of increasing the rate of firing of the sinoatrial node of the heart in a human patient, comprising administering to the patient an effective amount of an IKACh blocker.

[0014] In one embodiment, provided is a method of increasing conduction through the atrioventricular node of the heart in a human patient, comprising administering to the patient an effective amount of an IKACh blocker.

[0015] In one embodiment, the IKACh blocker is one or more compounds disclosed in US 8,361,998; US 8,323,911, US 8,258,138; US 8,022,076; US 7,456,187; WO 2003/000675; WO 2003/063797; WO 2005/121149; WO 2004/111057; WO 2007/066127; WO 2010/023445; WO 2010/023446; WO 2010/023448; WO 2007/109211, WO 2005/037780; US 2007/082037; US 2008/188509; WO 2005/041967; US 2009/203686; WO

2006/108837; WO 2009/079624; WO 2009/079630; WO 2010/023448; WO 2010/0139953; or WO 2010/0139967, all of which are hereby incorporated by reference.

[0016] In one embodiment, the IKACh blocker is selected from the group consisting of bretylium, ibutilide, dofetilide, azimilide, clofilium, E-4031, nifekalant, tedisamil, sematilide, fampridine, NCT-801, XEN-D0701, XEN-D0702, NIP-141, NIP-142, NIP-151, acacetin and tertiapin.

BRIEF DESCRIPTION OF THE FIGURES

[0017] **Figure 1** shows the tertiapin-caused concentration-dependent shortening of adenosine-induced prolongation of the S-H interval.

DETAILED DESCRIPTION

1. DEFINITIONS

[0018] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0019] It is to be noted that as used herein and in the claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutically acceptable carrier" in a composition includes two or more pharmaceutically acceptable carriers, and so forth.

[0020] "Comprising" is intended to mean that the compositions and methods include the recited elements, but do not exclude others. "Consisting essentially of" when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination for the intended use. Thus, a composition consisting essentially of the elements as defined herein would not exclude trace contaminants from the isolation and purification method and pharmaceutically acceptable carriers, such as phosphate buffered saline, preservatives, and the like. "Consisting of" shall mean excluding more than trace elements of other ingredients and substantial method steps for administering the compositions of this invention. Embodiments defined by each of these transition terms are within the scope of this invention.

[0021] The term "blocker" refers to an inhibitor, a modulator, etc.

[0022] As used herein, an "IKACh blocker" is a compound which inhibits the IKACh channel (acetylcholine-activated potassium channel). Acetylcholine-activated

potassium channels are found in cardiac muscle (specifically, the sinoatrial node and atria). Inhibition of IKACh, which is a G protein-gated ion channel, is expected to maintain sinus rhythm in patients who have experienced episodes of atrial fibrillation (AF). Although selectivity is not required, it is contemplated that compounds especially useful for the methods disclosed herein show enhanced activity as an IKACh blocker compared to other potassium channels. In some embodiments, the IKACh blocker is selective for the cardiac IKACh channel.

[0023] As stated above, compounds known to be potassium channel blockers are described in e.g., US 8,361,998; US 8,323,911, US 8,258,138; US 8,022,076; US 7,456,187; WO 2003/000675; WO 2003/063797; WO 2005/121149; WO 2004/111057; WO 2007/066127; WO 2010/023445; WO 2010/023446; WO 2010/023448; WO 2007/109211, WO 2005/037780; US 2007/082037; US 2008/188509; WO 2005/041967; US 2009/203686; WO 2006/108837; WO 2009/079624; WO 2009/079630; WO 2010/023448; WO 2010/0139953; or WO 2010/0139967, all of which are hereby incorporated by reference. A compound's ability to inhibit the acetylcholine-activated potassium channel may be tested according to Example 1 or methods known in the art (see, e.g., US 8,323,911). In addition to the compounds being taught in the references just described, methods of making the compounds, dosage forms, dosage amounts, and the like are also described and this information is also incorporated by reference. In one embodiment, the IKACh blocker is selected from the group consisting of bretylium, ibutilide, dofetilide, azimilide, clofilium, E-4031, nifekalant, tedisamil, sematilide, fampridine, NCT-801, XEN-D0701, XEN-D0702, NIP-141, NIP-142, NIP-151, acacetin and tertiapin.

[0024] The term "effective amount" refers to that amount of a compound that is sufficient to effect treatment, as defined below, when administered to a mammal in need of such treatment. The effective amount will vary depending upon the specific activity of the therapeutic agent being used, the severity of the patient's disease state, and the age, physical condition, existence of other disease states, and nutritional status of the patient. Additionally, other medication the patient may be receiving will affect the determination of the effective amount of the therapeutic agent to administer.

[0025] The term "treatment" or "treating" means any administration of a IKACh blocker as disclosed herein to a mammal, particularly a human, for the purposes including: 1) preventing or protecting against the disease or condition, that is, causing the clinical symptoms not to develop; 2) inhibiting the disease or condition, that is, arresting or

suppressing the development of clinical symptoms; and/or 3) relieving the disease or condition, that is, causing the regression of clinical symptoms. In some embodiments, the term "treatment" or "treating" refers to relieving the disease or condition, that is, causing the regression of clinical symptoms.

[0026] As used herein, the term "preventing" refers to the prophylactic treatment of a patient in need thereof. The prophylactic treatment can be accomplished by providing an appropriate dose of a therapeutic agent to a subject at risk of suffering from an ailment, thereby substantially averting onset of the ailment.

[0027] It will be understood by those skilled in the art that in human medicine, it is not always possible to distinguish between "preventing" and "suppressing" since the ultimate inductive event or events may be unknown, latent, or the patient is not ascertained until well after the occurrence of the event or events. Therefore, as used herein the term "prophylaxis" is intended as an element of "treatment" to encompass both "preventing" and "suppressing" as defined herein. The term "protection," as used herein, is meant to include "prophylaxis."

[0028] The term "susceptible" refers to a patient who has had at least one occurrence of the indicated condition or is genetically or otherwise predisposed to having an occurrence of the indicated condition.

[0029] The term "patient" typically refers to a "mammal" which includes, without limitation, human, monkeys, rabbits, guinea-pigs, rats, mice, domestic animals, such as dogs and cats, farm animals, such as cows, horses, or pigs, and laboratory animals. In a preferred embodiment, the term patient refers to a human in need of treatment as defined herein.

[0030] "Administering" or "administration" refers to the delivery of one or more therapeutic agents to a patient. In one embodiment, the administration is coadministration such that two or more therapeutic agents are delivered together at one time. In certain embodiments, two or more therapeutic agents can be co-formulated into a single dosage form or "combined dosage unit" or "fixed dose combination", or formulated separately and subsequently combined into a combined dosage unit, typically for intravenous administration or oral administration.

[0031] "Intravenous administration" is the administration of substances directly into a vein, or "intravenously". Compared with other routes of administration, the

intravenous (IV) route is the fastest way to deliver fluids and medications throughout the body. An infusion pump can allow precise control over the flow rate and total amount delivered, but in cases where a change in the flow rate would not have serious consequences, or if pumps are not available, the drip is often left to flow simply by placing the bag above the level of the patient and using the clamp to regulate the rate. Alternatively, a rapid infuser can be used if the patient requires a high flow rate and the IV access device is of a large enough diameter to accommodate it. This is either an inflatable cuff placed around the fluid bag to force the fluid into the patient or a similar electrical device that may also heat the fluid being infused. When a patient requires medications only at certain times, intermittent infusion is used, which does not require additional fluid. It can use the same techniques as an intravenous drip (pump or gravity drip), but after the complete dose of medication has been given, the tubing is disconnected from the IV access device. Some medications are also given by IV push or bolus, meaning that a syringe is connected to the IV access device and the medication is injected directly (slowly, if it might irritate the vein or cause a too-rapid effect). Once a medicine has been injected into the fluid stream of the IV tubing there must be some means of ensuring that it gets from the tubing to the patient. Usually this is accomplished by allowing the fluid stream to flow normally and thereby carry the medicine into the bloodstream; however, a second fluid injection is sometimes used, a "flush", following the injection to push the medicine into the bloodstream more quickly.

[0032] "Oral administration" is a route of administration where a substance is taken through the mouth, and includes buccal, sublabial and sublingual administration, as well as enteral administration and that through the respiratory tract, unless made through e.g. tubing so the medication is not in direct contact with any of the oral mucosa. Typical form for the oral administration of therapeutic agents includes the use of tablets or capsules.

[0033] A "sustained release formulation" is a formulation which is designed to slowly release a therapeutic agent in the body over an extended period of time, whereas an "immediate release formulation" is an formulation which is designed to quickly release a therapeutic agent in the body over a shortened period of time. In some cases the immediate release formulation may be coated such that the therapeutic agent is only released once it reached the desired target in the body (e.g. the stomach).

[0034] "AV conduction" or "atrioventricular conduction" is the forward conduction of the cardiac impulse from the atria to ventricles via the "atrioventricular node" or "AV node", represented in an electrocardiogram by the P-R interval. The AV node is a

part of electrical control system of the heart that electrically connects atrial and ventricular chambers and coordinates heart rate. The AV node is an area of specialized tissue between the atria and the ventricles of the heart, specifically in the posteroinferior region of the interatrial septum near the opening of the coronary sinus, which conducts the normal electrical impulse from the atria to the ventricles. AV conduction during normal cardiac rhythm occurs through two different pathways: the first has a slow conduction velocity but shorter refractory period, whereas the second has a faster conduction velocity but longer refractory period. "AV Block" or "atrioventricular block" involves the impairment of the conduction between the atria and ventricles of the heart.

[0035] "Atrial fibrillation" or "AF" occurs when the heart's two upper chambers (the right and left atria) quiver instead of beating and contracting rhythmically. Electrocardiographically, AF is characterized by a highly disorganized atrial electrical activity that often results in fast beating of the heart's two lower chambers (the right and left ventricles). Symptoms experienced by patients with AF include palpitation, fatigue, and dyspnea (shortness of breath).

[0036] There are three types of AF based on the presentation and duration of the arrhythmia: a) Paroxysmal AF: recurrent AF (>2 episodes) that starts and terminates spontaneously within 7 days (paroxysmal AF starts and stops spontaneously); b) Persistent AF: sustained AF that lasts longer than 7 days or requires termination by pharmacologic or electrical cardioversion (electrical shock); and c) Permanent AF: long standing AF (for >1 year duration) in which normal sinus rhythm cannot be maintained even after treatment, or when the patient and physician have decided to allow AF to continue without further efforts to restore sinus rhythm.

[0037] "Atrial flutter" is an abnormal heart rhythm that occurs in the atria of the heart. When it first occurs, it is usually associated with a fast heart rate or tachycardia (230–380 beats per minute (bpm)), and falls into the category of supra-ventricular tachycardias. While this rhythm occurs most often in individuals with cardiovascular disease (e.g. hypertension, coronary artery disease, and cardiomyopathy), it may occur spontaneously in people with otherwise normal hearts. It is typically not a stable rhythm, and frequently degenerates into atrial fibrillation (AF).

2. METHODS

[0038] Ion channels are proteins that span the lipid bilayer of the cell membrane and provide an aqueous pathway through which specific ions such as Na^+, K^+, Ca^{2+}, and Cl^- can pass. The movement of ions across the cell membrane creates a flow of current that generates excitation and signals in cardiac myocytes. Potassium channels represent the largest and most diverse sub-group of ion channels and they play a central role in regulating the membrane potential and controlling cellular excitability. The acetylcholine-regulated potassium channel current (IKACh) is an inward-rectifying potassium channel found in the sinus node and atria of cardiac muscle and contributes to the regulation of heart rate. The sinus node (also commonly called the sinoatrial node or sinuatrial node) is the impulse-generating (pacemaker) tissue located in the right atrium of the heart, and thus the generator of normal sinus rhythm. Activation of the IKACh allows for the flow of K^+ ions out of the cells of the sinus node, and hyperpolarization of the cells. In their hyperpolarized state, the cells cannot fire action potentials as quickly, which slows the heartbeat.

[0039] Provided herein are methods for treating or preventing sick sinus syndrome, sinus node dysfunction, sinus bradycardia, cardiac conduction disease and/or atrioventricular block, in a human patient in need thereof, comprising administering an effective amount of an IKACh blocker to the patient.

[0040] In one embodiment, the present disclosure is directed to a method for treating or preventing sinus node dysfunction (SND) in a human patient in need thereof, comprising administering an effective amount of an IKACh blocker to the patient. Sinus node dysfunction can also include sinus pause/arrest, chronotropic incompetence, and sinoatrial exit block. SND is frequently associated with conduction system disease in the heart and various supraventricular tachyarrhythmias, such as atrial fibrillation and atrial flutter. When associated with supraventricular tachyarrhythmias, SND is often termed tachy-brady syndrome.

[0041] Sinus node dysfunction is referred to as sick sinus syndrome when it is accompanied by symptoms such as dizziness or syncope. Therefore, in one embodiment, the present disclosure is directed to a method for treating or preventing sick sinus syndrome in a human patient in need thereof, comprising administering an effective amount of an IKACh blocker to the patient. Also provided is a method of increasing the rate of firing of

the sinoatrial node of the heart in a human patient, comprising administering to the patient an effective amount of an IKACh blocker.

[0042] Dysfunction of the sinus node can also lead to various types of arrhythmias, although it is not the only mechanism by which an arrhythmia may arise as some may also arise when the sinus node is working properly. For example, it is believed that atrial fibrillation can occur when the regular impulses produced by the sinus node for a normal heartbeat are overwhelmed by rapid electrical discharges produced in the atria and adjacent parts of the pulmonary veins. Sources of these disturbances are either automatic foci, often localized at one of the pulmonary veins, or a small number of localized sources in the form of either reentrant electrical spiral waves (rotors) or repetitive focal beats; these localized sources may be found in the left atrium near the pulmonary veins or in a variety of other locations through both the left or right atrium.

[0043] However, dysfunction of the sinus node disrupts impulse generation at the earliest stage, and can be manifested as various forms of arrhythmia. The arrhythmias, which are typically diagnosed electrocardiographically, may be transient, and can include, for example, sinus bradycardia, atrial fibrillation, atrial flutter, sinus arrest, and atrial tachycardia–bradycardia syndrome (i.e., atrial tachycardia alternating with episodes of sinus bradycardia).

[0044] Sinus bradycardia is a heart rhythm that originates from the sinus node and is characterized by an abnormally low heart rate. In certain instances, sinus bradycardia is characterized by a heart rate of under 60 beats per minute. Accordingly, also disclosed herein are methods for treating or preventing sinus bradycardia in a human patient in need thereof, comprising administering an effective amount of an IKACh blocker to the patient.

[0045] Cardiac conduction disease (CCD), a potentially life-threatening disorder, is characterized by alteration of impulse propagation through the cardiac conduction system. In certain instances, cardiac conduction disease is characterized by a blockage at any level of the electrical conduction system of the heart. Provided herein is a method for treating or preventing cardiac conduction disease in a human patient in need thereof, comprising administering an effective amount of an IKACh blocker to the patient. Non-limiting examples of cardiac conduction diseases include, but are not limited to, blocks that occur within the sinus node; blocks that occur within the atrioventricular node (AV node

block); blocks that occur below the AV node (infra-Hisian blocks); blocks that occur within the left or right bundle branches; and blocks that occur within the fascicles of the left bundle branch (hemiblocks).

[0046] In one embodiment, provided is a method of preventing the prolongation of the stimulus-to-His bundle (S-H) interval in a human patient, comprising administering to the patient an effective amount of an IKACh blocker. In another embodiment, provided is method of shortening the S-H interval in a human patient, comprising administering to the patient an effective amount of an IKACh blocker.

[0047] One example of a cardiac conductive disease includes Lev's disease (or Lenegre-Lev syndrome). Electrocardiographically, Lev's disease is characterized by chronic conduction delay through the His-Purkinje system, resulting in partial or complete AV-block and right or left bundle branch block. Provided herein is a method for treating or preventing atrioventricular block in a human patient in need thereof, comprising administering an effective amount of an IKACh blocker to the patient. Also provided herein is a method of increasing conduction through the atrioventricular node of the heart in a human patient, comprising administering to the patient an effective amount of an IKACh blocker.

3. COMPOUNDS

[0048] Compounds to be used in the methods disclosed herein effectively block the acetylcholine-activated potassium channel. In some embodiments, the IKACh blocker is a compound which selectively inhibits or blocks the IKACh channel over other potassium channels. In one embodiment, the IKACh blocker is one or more compounds disclosed in US 8,361,998; US 8,323,911, US 8,258,138; US 8,022,076; US 7,456,187; WO 2003/000675; WO 2003/063797; WO 2005/121149; WO 2004/111057; WO 2007/066127; WO 2010/023445; WO 2010/023446; WO 2010/023448; WO 2007/109211, WO 2005/037780; US 2007/082037; US 2008/188509; WO 2005/041967; US 2009/203686; WO 2006/108837; WO 2009/079624; WO 2009/079630; WO 2010/023448; WO 2010/0139953; or WO 2010/0139967, all of which are hereby incorporated by reference. A compound's ability to inhibit the acetylcholine-activated potassium channel may be tested according to Example 1 or methods known in the art (see, e.g., US 8,323,911).

[0049] Specific IKACh blockers contemplated for use in the methods and pharmaceutical compositions disclosed herein, include for example, an IKACh blocker

selected from the group consisting of bretylium, ibutilide, dofetilide, azimilide, clofilium, E-4031, nifekalant, tedisamil, sematilide, fampridine, NCT-801, XEN-D0701, XEN-D0702, NIP-141, NIP-142, NIP-151, acacetin and tertiapin.

4. DOSING AND ADMINISTRATION

[0050] The IKACh blocker may be given to the patient in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, for example as described in those patents and patent applications incorporated by reference, including buccal, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, or via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer. In one embodiment, the IKACh blocker is administered intravenously. In another embodiment, the IKACh blocker is administered orally. The IKACh blocker may also be administered as a combined dosage unit, such as, for example, in a tablet. In some embodiments, the dosage is from about 1 to about 1000 mg, or about 1 to about 400 mg, or about 1 to about 200 mg, or about 1 to about 100 mg, or about 1 to about 50 mg, or about 1 to about 25 mg, or about 1 to about 10 mg, or about 1 to about 5 mg. A specific dose and/or dosing regimen can be determined by a clinician.

5. PHARMACEUTICAL FORMULATIONS

[0051] In one embodiment, the invention is directed to pharmaceutical formulations comprising an effective amount of an IKACh blocker, and a pharmaceutically acceptable carrier for use in a method disclosed herein. In certain embodiments, the formulations are formulated for either intravenous or oral administration.

[0052] Formulations contemplated by the present invention for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles. Aqueous solutions in saline are also conventionally used for injection, but less preferred in the context of the present invention. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various

antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

[0053] Sterile injectable solutions are prepared by incorporating the component in the required amount in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0054] In making a pharmaceutical compositions that include a potassium channel blocker, the active ingredient are usually diluted by an excipient or carrier and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, in can be a solid, semi-solid, or liquid material (as above), which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compounds, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[0055] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[0056] The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art. In one embodiment, the formulation is a sustained release formulation. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolution systems containing polymer-

coated reservoirs or drug-polymer matrix formulations. Examples of controlled release systems are given in U.S. Patent Nos. 3,845,770; 4,326,525; 4,902,514; and 5,616,345.

[0057] The compositions are preferably formulated in a unit dosage form. The term "unit dosage forms" or "combined dosage unit" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of the active materials calculated to produce the desired effect, in association with a suitable pharmaceutical excipient (e.g., a tablet, capsule, ampoule). The active agents of the invention are effective over a wide dosage range and are generally administered in an effective amount. It will be understood, however, that the amount of each active agent actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compounds administered and their relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0058] For preparing solid compositions such as tablets, the principal active ingredients are mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredients are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[0059] The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can comprise an inner dosage and an outer dosage element, the latter being in the form of an envelope over the former. The IKACh blocker and the co-administered agent(s) can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner element to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0060] Activity testing is conducted in the Examples below using methods described herein and those well known in the art.

EXAMPLES

[0061] The following examples are included to demonstrate preferred embodiments of the disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the disclosure, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

List of abbreviations and acronyms.

Abbreviation	**Meaning**
AV	Atrioventricular
AF	Atrial Fibrillation
bpm	Beats Per Minute
°C	Degree Celsius
CCD	Cardiac Conduction Disease
g	Gram
mL	Milliliter
mm	Millimeter
EDTA	Ethylenediaminetetraacetic acid
mM	Millimolar
msec	Milliseconds
Hz	Hertz
IKACh	Acetylcholine-Activated Potassium Channel Current
IV	Intravenous
K-H	Krebs- Henseleit
μM	Micromolar
nM	Nanomolar
S.E.M.	Standard Error of the Mean
S-H	Stimulus-to-His Bundle
SND	Sinus Node Dysfunction
SSS	Sick Sinus Syndrome

Example 1

S-H interval measurement in Guinea-pig isolated heart model

[0062] Male Guinea-pig, weighing 350-450 g, were anesthetized with isoflurane and sacrificed by cervical dislocation. The hearts were quickly removed and rinsed in ice-cold Krebs-Henseleit solution. The aorta was cannulated for perfusion of the coronary arteries at a constant flow rate of 10 mL/mm with Krebs- Henseleit (K-H) solution that contains (in mM): 118 NaCl, 4.0 KCl, 1.2 KH_2PO_4, 2.5 $CaCl_2$, 0.5 $MgSO_4$, 2.0 pyruvate, 5.5 glucose, 0.57 Na_2EDTA, and 25 $NaHCO_3$. The K–H solution was warmed to 36.5 °C. To facilitate pacing of the heart and measurement of the His bundle electrogram, the sinoatrial nodal region (which included the vena cava) and part of the right atrium were excised. The hearts were electrically paced at a cycle length of 250 msec (4 Hz) by a bipolar electrode placed on the residual atrium. AV nodal conduction time was measured from His bundle electrograms during constant atrial pacing. The S-H interval was used as the index of AV nodal conduction time. Adenosine (7-12 μM, Figure 1) was superfused to cause ~50 msec prolongation of the S-H interval. Tertiapin (1-300 nM), a potent inhibitor of acetylcholine-dependent K^+ current was superfused in the continuous presence of adenosine.

[0063] Data are reported as means ± S.E.M. To compare values of measurements obtained from the same heart before and after a drug treatment, repeated measures one-way analysis of variance was used, and Student-Newman-Keuls test was applied to determine which pairs of group means were significantly different. Paired and nonpaired Student *t* tests were used to determine the significance of a difference between two means before (as control) and after drug treatment in same or different hearts, respectively. A significant difference between two group means was defined as $P < 0.05$.

[0064] The data shows that tertiapin, a selective IKACh blocker, caused a concentration-dependent shortening of adenosine-induced prolongation of the S-H interval (Figure 1). This data shows that modulating heart rhythm is achieved by blocking the IKACh in the sinus node and atria of cardiac muscle.

WE CLAIM:

1. A method for treating or preventing sick sinus syndrome, sinus node dysfunction, sinus bradycardia, cardiac conduction disease or atrioventricular block in a human patient in need thereof, comprising administering an effective amount of an acetylcholine-activated potassium channel current (IKACh) blocker to the patient.

2. The method of claim 1, wherein the IKACh blocker is selected from the group consisting of bretylium, ibutilide, dofetilide, azimilide, clofilium, E-4031, nifekalant, tedisamil, sematilide, fampridine, NCT-801, XEN-D0701, XEN-D0702, NIP-141, NIP-142, NIP-151, acacetin and tertiapin.

3. The method of claim 1, wherein the IKACh blocker is tertiapin.

4. The method of claim 1, wherein the IKACh blocker is administered intravenously.

5. The method of claim 1, wherein the IKACh blocker is administered orally.

6. A method for treating or preventing sick sinus syndrome in a human patient in need thereof, comprising administering an effective amount of an IKACh blocker to the patient.

7. A method for treating or preventing sinus node dysfunction in a human patient in need thereof, comprising administering an effective amount of an IKACh blocker to the patient.

8. A method for treating or preventing sinus bradycardia in a human patient in need thereof, comprising administering an effective amount of an IKACh blocker to the patient.

9. A method for treating or preventing cardiac conduction disease in a human patient in need thereof comprising an effective amount of an IKACh blocker.

10. A method for treating or preventing atrioventricular block in a human patient in need thereof, comprising administering an effective amount of an IKACh blocker to the patient.

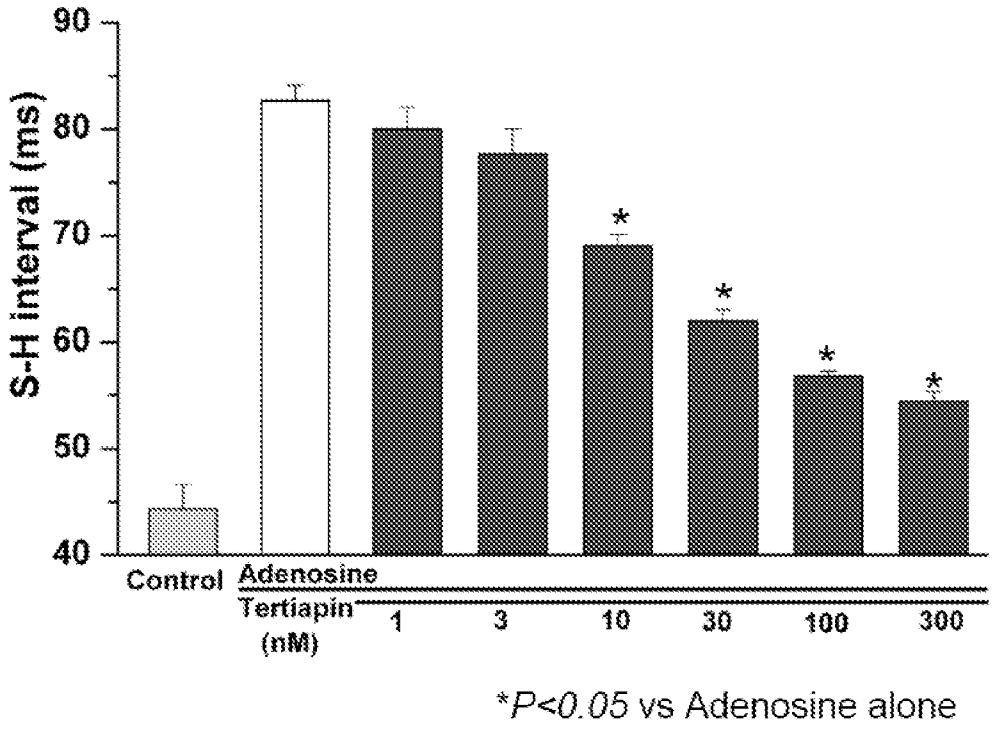
11. A method of preventing the prolongation of the S-H interval in a human patient, comprising administering to the patient an effective amount of an IKACh blocker.

12. A method of shortening the S-H interval in a human patient, comprising administering to the patient an effective amount of an IKACh blocker.

13. A method of increasing conduction through the atrioventricular node of the heart in a human patient, comprising administering to the patient an effective amount of an IKACh blocker.

14. A method of increasing the rate of firing of the sinoatrial node of the heart in a human patient, comprising administering to the patient an effective amount of an IKACh blocker.

Figure 1


S-H interval (ms)
90
80
70
60
50
40
Control
Adenosine
Tertiapin
(nM)
1
3
10
30
100
300
*
*
*
*
*P<0.05 vs Adenosine alone

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/019351

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/00 A61K31/14 A61K31/18 A61K31/416 A61K31/4409
A61K31/496 A61K31/4995 A61K31/513 A61P9/06 A61K38/17
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/167212 A2 (SIGNPATH PHARMA INC [US]; HELSON LAWRENCE [US]) 6 December 2012 (2012-12-06) the whole document in particular Summary of the Invention Examples Claims 1, 2, 6, 15, 17, 22, 26 ----- -/--	1,2,4-14

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 June 2014	30/06/2014

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International application No
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Information on patent family members

International application No
PCT/US2014/019351

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