

Bogotá D.C., 14 de julio de 2010.

Señores
DIRECCIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
Ministerio de Comercio, Industria y Turismo
E. S.

6.1. CONH_2 (10.0 g, 0.078 mol) $\text{H}_2\text{NCH}_2\text{CH}_2\text{NCH}_2\text{CH}_2\text{NH}_2$ (0.078 mol)

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No. 06-127373-00009-0000

No. 06-127373-00009-0000
 Date: 2006/04/15 21:55 Day: 2006/04/15 21:55
 IP: 2. PATENT S. Ver: 1. BLOC: 10000
 A: 10000. B: 10000. C: 10000. D: 10000

Expediente No.:	06 127 373
Asunto:	Contestación de requerimiento de fondo de la Patente de Invención: "Nueva Asociación de un Inhibidor de la corriente sinusal If y de un inhibidor cálcico y las composiciones farmacéuticas que lo contienen".
Solicitante:	LES LABORATOIRES SERVIER

JULIO CÉSAR RAMÍREZ PIÑA, abogado en ejercicio, identificado con la cédula de ciudadanía número 79'779.990 de Bogotá, portador de la tarjeta profesional número 113.206 del C. S. de la J., domiciliado en esta ciudad en la carrera 11 No. 86 – 32 (oficina 101) de Bogotá, D.C., en mi condición de apoderado de la sociedad **LES LABORATOIRES SERVIER**, tal y como consta en el poder que obra en el expediente radicado el pasado 22 de octubre de 2009, por medio del presente escrito doy respuesta al requerimiento de fondo que obra en el Oficio 005010 notificado mediante fijación en lista del 15 de abril de 2010, en el siguiente sentido:

I. CONTESTACIÓN AL REQUERIMIENTO DE FONDO

1. Al punto 4.1. Descripción (artículo 28 D. 486)

Teniendo en cuenta que en el requerimiento se manifiesta que el término "asociación" es confuso, se ha eliminado el término "asociación" y se solicita que se interprete como "Composición". La modificación está sustentada en la descripción de la presente solicitud, en las páginas 4, renglones 1-3 y no debería ampliar el asunto excediendo el contenido de la solicitud presentada.

El Título de la Patente se ha modificado por el siguiente: Nueva COMPOSICIÓN de un Inhibidor de la corriente sinusal If y de un inhibidor cálcico y las composiciones farmacéuticas que lo contienen.

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2. Al punto 4.2. Reivindicaciones (artículo 30 D. 486)

Las reivindicaciones se modifican respecto de la petición original en el siguiente sentido:

1. Se modifican las reivindicaciones números 1, 3, 4, 5, 6, 7, 8, 9, 10, 11.
2. Se eliminan reivindicaciones números 2 y 12.

En virtud de lo cual ruego que se conceda el privilegio de la patente bajo la siguiente redacción:

REIVINDICACIONES

1. Composición farmacéutica comprendida en un inhibidor selectivo y específico de la corriente sinusal If, y de un inhibidor de la Ivabradina, o 3-{3-[[[(7S)-3,4-dimetoxibencilo[4.2.0]octa-1,3,5-trien-7-yl]metil](metil)amino]propil}-7,8-dimetoxi-1,3,4,5-tetrahidro-2H-3-benzazepin-2-ona, o uno de sus hidratos, forma cristalinas o sales de adición de un ácido farmacéuticamente aceptable y un inhibidor cálcico.
2. Composición farmacéutica de acuerdo con la reivindicación 1, en la que el inhibidor selectivo y específico de la corriente sinusal If es el hidrocloruro de Ivabradina o 3-{3-[[[(7S)-3,4-dimetoxibencilo[4.2.0]octa-1,3,5-trien-7-yl]metil](metil)amino]propil}-7,8-dimetoxi-1,3,4,5-tetrahidro-2H-3-benzazepin-2-ona-hydrochloride, o uno de sus hidratos o formas cristalinas.
3. Composición farmacéutica de acuerdo con la reivindicación 1, en la que el inhibidor cálcico pertenece a la clase de las dihidropiridinas.
4. Composición farmacéutica de acuerdo con la reivindicación 1, en la que el inhibidor cálcico es el amlodipino o uno de sus hidratos, formas cristalinas o sales de adición de un ácido farmacéuticamente aceptable.
5. Composición farmacéutica de acuerdo con la reivindicación 1, en la que el inhibidor cálcico es el besilato de amlodipino, o uno de sus hidratos o formas cristalinas.
6. Composición farmacéutica de acuerdo con la reivindicación 1, que contiene la Ivabradina o uno de sus hidratos, formas cristalinas o sales de adición de un ácido farmacéuticamente aceptable, y el amlodipino o uno de sus hidratos, formas cristalinas o sales de adición de un ácido farmacéuticamente aceptable.
7. Composición farmacéutica de acuerdo con la reivindicación 1, que contiene hidrocloruro de Ivabradina, o uno de sus hidratos o formas cristalinas, y besilato de amlodipino, o uno de sus hidratos o formas cristalinas.

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8. Composiciones farmacéuticas que contienen como principio activo un inhibidor selectivo y específico de la corriente sinusal If en asociación con un inhibidor de Ivabradina, o 3-{3-[[[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]metil](metil)amino]propyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one, o uno de sus hidratos o formas cristalinas, solos o en combinación con uno o varios ácidos farmacéuticamente aceptables y un inhibidor de calcio, de acuerdo con las reivindicaciones 1 a 7, solos o en combinación con uno o varios excipientes farmacéuticamente aceptables.
9. Las composiciones farmacéuticas de acuerdo con la reivindicación 8, que contienen como principio activo hidrocloruro de ivabradina o uno de sus hidratos o formas cristalinas en asociación con besilato de amlodipino, o uno de sus hidratos o formas cristalinas, solos o en combinación con uno o varios excipientes farmacéuticamente aceptables.
10. Las composiciones farmacéuticas de acuerdo con las reivindicaciones 1 a 9, usadas para la fabricación de un medicamento para el tratamiento de la angina de pecho.

5. Al punto 5. Reivindicaciones relativas a un uso o aun uso distinto (artículos 14 y 21 D. 486)

Mi mandante desiste y renuncia a la reivindicación número 12.

II. MOTIVOS Y DERECHO

El examinador sostiene que las expresiones "un inhibidor selectivo y específico de la corriente sinusal If" y "un inhibidor de calcio" no son concisas y solamente mencionan actividades terapéuticas. Mi mandante considera que las expresiones "un inhibidor selectivo y específico de la corriente sinusal If" y "un inhibidor de calcio" están claramente definidas para el hombre capacitado en la técnica. Efectivamente, es un hecho bien conocido que "inhibidor de calcio" se relaciona con una clase de medicamentos de la clase dihidropiridina de bloqueadores de los canales de calcio y de la clase no dihidropiridina de bloqueadores de los canales de calcio y que bloquean la conducción de calcio de los canales de calcio, lo cual conlleva a la reducción de la contracción muscular.

Adjunto encontrará literatura general relacionada con inhibidores de los canales de Calcio.

Además la expresión "un inhibidor selectivo y específico de la corriente sinusal If" se refiere a un inhibidor de la corriente iónica del marcapasos cardíaco que está altamente expresada en el nódulo sinusal y en el nódulo atrioventricular. La ivabradina es el inhibidor de (la corriente) If más selectivo y específico; Por tanto, mi mandante ha reemplazado la expresión un inhibidor selectivo y específico de la corriente sinusal If por "ivabradina" a fin de acceder al requerimiento de fondo.

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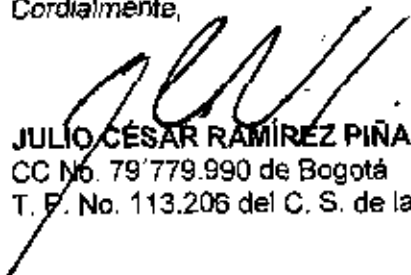
III. ANEXOS

Se adjunta literatura general relacionada con inhibidores de los canales de Calcio.

IV. NOTIFICACIONES

El suscrito recibirá notificaciones en la Carrera 11 No. 86 - 32 (Oficina 101) de la ciudad de Bogotá, D.C., o en el casillero asignado al suscrito por su Despacho.

Cordialmente,



JULIO CÉSAR RAMÍREZ PIÑA
CC No. 79'779.990 de Bogotá
T. E. No. 113.206 del C. S. de la J.

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Calcium channel blocker

From Wikipedia, the free encyclopedia

Calcium channel blockers (CCBs) are a class of drugs and natural substances that disrupt the calcium (Ca^{2+}) conduction of calcium channels.^[1]

It has effects on many excitable cells of the body, such as cardiac muscle, i.e. heart, smooth muscles of blood vessels, or neurons. Drugs used to target neurons are used as antiepileptics and are not covered in this article.

The main clinical usage of calcium channel blockers is to decrease blood pressure. It is for this action that they are used in individuals with hypertension.

Contents

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- 2 Mechanism of action
- 3 Classes of calcium channel blockers
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 - 3.2.1 Phenylalkylamine
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 - 3.2.3 Nonselective
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Explanation

Most calcium channel blockers decrease the force of contraction of the myocardium (muscle of the heart). This is known as the negative inotropic effect of calcium channel blockers. It is because of the negative inotropic effects of most calcium channel blockers that they are avoided (or used with caution) in individuals with cardiomyopathy.

Many calcium channel blockers also slow down the conduction of electrical activity within the heart, by blocking the calcium channel during the plateau phase of the action potential of the heart (see: cardiac action potential). This results in a negative chronotropic effect resulting in a lowering of the heart rate and the potential for heart block. The negative chronotropic effects of calcium channel blockers make them a commonly used class of agents in individuals with atrial fibrillation or flutter in whom control of the heart rate is an issue. Negative chronotropy can be beneficial in that elevated heart rate can result in significantly higher 'cardiac work', which can result in anginal symptoms: lower heart rates represent lower cardiac oxygen requirements.

Pharmacologic Beta blockade is superior to Calcium channel blockade regarding chronotropic properties of the myocardium. Titration of a Beta Blocker to a desired heart rate is decidedly easier than titration of a non dihydropyridine CCB.

Mechanism of action

Calcium channel blockers work by blocking voltage-gated calcium channels (VGCCs) in cardiac

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muscle and blood vessels. This decreases intracellular calcium leading to a reduction in muscle contraction. In the heart, a decrease in calcium available for each beat results in a decrease in cardiac contractility. In blood vessels, a decrease in calcium results in less contraction of the vascular smooth muscle and therefore an increase in arterial diameter (CCB's do not work on venous smooth muscle), a phenomenon called vasodilation. Vasodilation decreases total peripheral resistance, while a decrease in cardiac contractility decreases cardiac output. Since blood pressure is determined by cardiac output and peripheral resistance, blood pressure drops.

With a relatively low blood pressure, the afterload on the heart decreases; this decreases the amount of oxygen required by the heart. This can help ameliorate symptoms of ischemic heart disease such as angina pectoris.

Unlike β -blockers, calcium channel blockers do not decrease the responsiveness of the heart to input from the sympathetic nervous system. Since moment-to-moment blood pressure regulation is carried out by the sympathetic nervous system (via the baroreceptor reflex), calcium channel blockers allow blood pressure to be maintained more effectively than do β -blockers.

However, because calcium channel blockers result in a decrease in blood pressure, the baroreceptor reflex often initiates a reflexive increase in sympathetic activity leading to increased heart rate and contractility. A β -blocker may be combined with a dihydropyridine calcium channel blocker to minimize these effects.

Ionic calcium is antagonized by magnesium ions in the nervous system. Because of this, dietary supplements of magnesium oxide and other magnesium preparations may increase or enhance the effects of calcium channel blockade.^[2]

Classes of calcium channel blockers

Dihydropyridine

Dihydropyridine calcium channel blockers are often used to reduce systemic vascular resistance and arterial pressure, but are not used to treat angina (with the exception of amlodipine, nifedipine, and nifedipine, which carry an indication to treat chronic stable angina as well as vasospastic angina) because the vasodilation and hypotension can lead to reflex tachycardia. Dihydropyridine calcium channel blockers can worsen proteinuria in patients with nephropathy.^[3] This CCB class is easily identified by the suffix "-dipine".

- Amlodipine (Norvasc)
- Aranidipine (Sapresta)
- Azelnidipine (Calblock)
- Barnidipine (HypoCa)
- Benidipine (Coniel)
- Cilnidipine (Atelec, Cinalong, Siscard)
- Clevidipine (Cleviprex)
- Efonidipine (Landel)
- Felodipine (Plendil)
- Lacidipine (Motens, Lacipil)
- Lercanidipine (Zanidip)
- Manidipine (Calslot, Madipine)
- Nicardipine (Cardene, Carden SR)
- Nifedipine (Procardia, Adalat)
- Nilvadipine (Nivadil)
- Nimodipine (Nimotop)
- Nisoldipine (Baymycard, Sular, Syscor)
- Nitrendipine (Cardif, Nitrepin, Baylotensin)

- **Pranidipine** (Acalas)

Side effects of these synthetic drugs may include but are not limited to:

- Dizziness, headache, redness in the face
- Fluid buildup in the legs
- Rapid heart rate.
- Slow heart rate.
- Constipation
- Gingival overgrowth

Non-Dihydropyridine

Phenylalkylamine

Phenylalkylamine calcium channel blockers are relatively selective for myocardium, reduce myocardial oxygen demand and reverse coronary vasospasm, and are often used to treat angina. They have minimal vasodilatory effects compared with dihydropyridines and therefore cause less reflex tachycardia, making it appealing for treatment of angina, where tachycardia can be the most significant contributor to the heart's need for oxygen. Therefore, as vasodilation is minimal with the phenylalkylamines, the major mechanism of action is causing negative inotropy. Phenylalkylamines are thought to access calcium channels from the intracellular side, although the evidence is somewhat mixed [4].

- Verapamil (Calan, Isoptin)
- Gallopamil (Procorum, D600)

Benzothiazepine

Benzothiazepine calcium channel blockers are an intermediate class between phenylalkylamine and dihydropyridines in their selectivity for vascular calcium channels. By having both cardiac depressant and vasodilator actions, benzothiazepines are able to reduce arterial pressure without producing the same degree of reflex cardiac stimulation caused by dihydropyridines.

- Diltiazem (Cardizem)

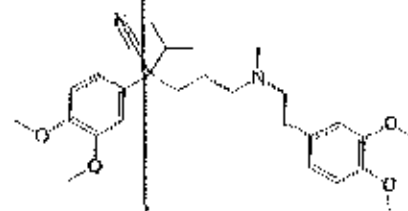
Nonselective

While most of the agents listed above are relatively selective, there are additional agents that are considered nonselective. These include mibefradil, bepridil and fluspirilene. [5]

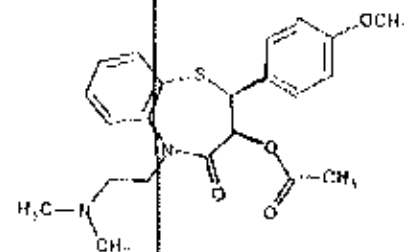
Another example is fendiline. [6]

Other drugs with similar uses

Other classes of pharmaceutical agents that have overlapping effects as calcium channel blockers include ACE inhibitors, beta-blockers, and nitrates.



Skeletal formula of verapamil



Structural formula of diltiazem

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+53
+53

Toxicity

Mild CCB toxicity is treated with supportive care. Non-dihydropyridine CCB may produce profound toxicity and early decontamination, especially for slow release agents, is essential. Treatment involves intravenous calcium, atropine, fluids, insulin and inotropes. Insulin is required because at high doses CCB block the effect of insulin. If unsuccessful ventricular pacing should be used.^[7]

See also

- Voltage-dependent calcium channel

References

- ¹ ^ *calcium channel blocker* at Dorland's Medical Dictionary
- ² ^ L. Iseri LT & French JH. "Magnesium: nature's physiologic calcium blocker." *Am Heart J*, 108, 188-193, 1984.
- ³ ^ Remuzzi G, Scheppati A, Ruggenenti P: Nephropathy in patients with type 2 diabetes. *N Engl J Med* 2002;346:1145.
- ⁴ ^ Hockerman et al. *Annu Rev Pharmacol Toxicol*. 1997;37:361-96
- ⁵ ^ Bezprozvanny I, Tsien RW (September 1995). "Voltage-dependent blockade of diverse types of voltage-gated Ca2+ channels expressed in *Xenopus* oocytes by the Ca2+ channel antagonist mibefradil (Ro 40-5967)". *Mol. Pharmacol* 48 (3): 540-9. PMID 7565636. <http://molpharm.aspetjournals.org/cgi/pmidlookup?view=long&pmid=7565636>.
- ⁶ ^ Scultéty S, Tamáskovits E (1991). "Effect of Ca2+ antagonists on isolated rabbit detrusor muscle". *Acta Physiol Hung* 77 (3-4): 269-78. PMID 1755331.
- ⁷ ^ Calcium Channel Blockers. *Medicine* 2007;35:599-602

External links

- MeSH *Calcium+Channel+Blockers*
- Official Adalat (Nifedipine) site, Bayer
- Video - Calcium Channel Blockers

Retrieved from "http://en.wikipedia.org/wiki/Calcium_channel_blocker"

Categories: Calcium channel blockers

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EP 1 362 590 A1

EUROPEAN PATENT APPLICATION

(51) Int Cl.7: **A61K 31/55, A61P 9/04**

(22) Date of filing: 25.07.2002

(71) Applicant: Boehringer Ingelheim Pharma GmbH
& Co.KG
55218 Ingelheim am Rhein (DE)

(72) Inventor: The designation of the inventor has not yet been filed

(57) The present invention provides the use in a pharmaceutical composition of a specific cyclic amine derivative, or its pharmaceutically acceptable salts, for the treatment or prevention of heart failure of any aetiology.

EP 1 362 590 A1

Description

FIELD OF THE INVENTION

[0001] The present invention relates to the novel use of a cyclic amine derivative, namely cilobradine, or the pharmaceutically acceptable salts thereof, for the treatment or prevention of heart failure of any aetiology.

BACKGROUND OF THE INVENTION

[0002] Heart failure is a major world-wide public health problem and is the only cardiac disorder that is increasing in incidence. In the United States alone, 5 million patients suffer from heart failure, with a new diagnosis made in 0.5 million patients per year. Despite advances in therapy, over the last decade, the annual number of hospitalisations has increased from 550 000 to 900 000 as a primary diagnosis, and from 1.7 to 2.6 million as a primary or secondary diagnosis (J. Am. Pharm. Assoc., vol. 41(5), pp. 672-681, 2001). Unless treated, heart failure may lead to death. Hence, new approaches are warranted to treat or prevent heart failure.

[0003] Although the terminology heart failure seems to be the most accepted terminology for describing this cardiac disorder, various further equivalent terminologies can be found in the scientific, patent or medical literature as, for example, cardiac failure, insufficient cardiac output, cardiac insufficiency, cardiac collapse and cardiac syncope.

[0004] Furthermore, though heart failure is invariably a chronic cardiac disorder, often with an insidious onset, heart failure may be present acutely or be punctuated by episodes of acute deterioration, so called "decompensated" heart failure. To describe these conditions also related to heart failure, further terminologies will commonly be found in the scientific, patent or medical literature such as, for example, chronic heart failure, acute heart failure, heart decompensation, cardiac decompensation and cardiac decompensation.

[0005] Lastly, as will be explained in the foregoing, as heart failure can be caused by a dysfunctioning of the heart reflected by various clinical presentations and sometimes subjected to further complications, further terminologies related to heart failure will also commonly be found in the scientific, patent or medical literature such as, for example, myocardial failure, myocardial insufficiency, heart muscle insufficiency, cardiac muscle insufficiency, heart muscle weakness, cardiac muscle weakness, systolic or left ventricular heart failure, diastolic heart failure, left or right sided heart failure, biventricular heart failure and congestive heart failure.

[0006] Hence, a distinction can be made between the systolic or diastolic origin of the dysfunctioning. Commonly, heart failure is a consequence of a progressive deterioration of myocardial contractile function, named systolic or left ventricular dysfunction. However, diastolic dysfunction is becoming increasingly recognised as

an important cause of heart failure too. This occurs when the heart chambers are unable to expand sufficiently during diastole (period of heart relaxation in which the chambers fill with blood) and hence blood volume in the ventricles is inadequate. Whether systolic and/or diastolic dysfunction is the basis of heart failure, cardiac output is diminished. When additionally there is "damming" back of blood in the venous system, congestion may ensue in the lungs (pulmonary oedema) and/or in the abdomen or peripheries (peripheral oedema). When both occur, the terminology congestive heart failure is often used.

[0007] In other respects, the distinction between left and right sided heart failure can be applied to reflect the clinical presentation (i.e. pulmonary oedema indicative of left sided heart failure, whereas the principal symptom of right sided heart failure is fluid retention in the peripheries) or to denote the underlying cause. Right sided heart failure is most commonly a consequence of left sided heart failure, although diseases of the lung (such as chronic obstructive pulmonary disease), the right ventricle (e.g. right ventricular infarction) or the vasculature (primary or secondary pulmonary hypertension, the latter due to conditions such as pulmonary embolism for example), may result in predominate right sided heart failure.

[0008] According to the International Classification of Functioning, Disability and Health, lastly published by the World Health Organization on 15 November 2001 (ISBN 91 4 1545429) and accepted by 191 countries during the 54th World Health Assembly (Resolution WHA 54.21), heart failure occurs when the heart function of pumping the blood in adequate or required amounts and pressure throughout the body is impaired.

[0009] As cardiac output is normally 5 litres/minute, although this can increase five fold with heavy exercise, in essence, heart failure occurs when the heart is unable to meet this demand.

[0010] As heart failure manifests itself in a variety of ways, at the time of this patent application, the treatment or prevention of heart failure comprises a combination of typical medications. These medications are based upon the principles of promoting fluid excretion to lessen oedema and volume overload (e.g. a various types of diuretics), vasodilatory drugs to reduce preload (i.e. atrial pressures) and/or afterload (i.e. pressure against which the heart has to beat), and inotropic drugs to increase contractility.

[0011] Vasodilatory drugs available at this time include Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin II Receptor blockers (ARBs) and nitrate venodilators. Inotropic drugs are usually administered only in acute situations. Although cardiac glycosides such as digoxin are sometimes prescribed for their inotropic properties, their use is more common in heart failure patients when atrial arrhythmias co-exist.

[0012] Recently, beta-blockers, which were once thought to be contra-indicated in heart failure per se due

use of cilobradine, or its pharmaceutically acceptable salts, for the treatment or prevention of heart failure of any aetiology.

[0035] The present invention is also a method for the treatment or prevention of heart failure of any aetiology, by administration to a patient in need thereof of a pharmaceutical composition comprising cilobradine, or its pharmaceutically acceptable salts, together with a pharmaceutically suitable carrier.

DESCRIPTION OF PREFERRED EMBODIMENTS

[0036] In accordance with one embodiment, the present invention provides for a novel use of the cyclic amine derivative (+)-3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-(S)-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one, named cilobradine, or its pharmaceutically acceptable salts.

[0037] For the preparation of cilobradine or the pharmaceutically acceptable salts of cilobradine, reference is made to EP 0 224 794 and its US counterpart US Patent 5,175,157, which describes the chemical synthesis of these compounds.

[0038] In accordance with a further embodiment of the present invention, amongst the pharmaceutically acceptable salts of cilobradine described in EP 0 224 794 and its US counterpart US Patent 5,175,157, the hydrochloride and hydrobromide salts of cilobradine are preferred.

[0039] More particularly, the present invention is directed to the use of cilobradine, or its pharmaceutically acceptable salts, for the preparation of a pharmaceutical composition for the treatment or prevention of heart failure of any aetiology.

[0040] In accordance with a further embodiment, the present invention is directed to the use of cilobradine, or its pharmaceutically acceptable salts, for the preparation of a pharmaceutical composition for the prevention of heart failure of any aetiology.

[0041] In accordance with a further embodiment of the present invention, the treatment or prevention of heart failure may be assessed by the ability of the compound or pharmaceutical composition in accordance with the present invention to reduce the mortality and morbidity associated with heart failure of any aetiology.

[0042] In accordance with a further embodiment of the present invention, the treatment or prevention of heart failure also comprises the treatment or prevention of cardiac insufficiency, cardiac failure, heart insufficiency, myocardial failure, myocardial insufficiency, heart muscle insufficiency, cardiac muscle insufficiency, insufficient cardiac output, heart muscle weakness, cardiac muscle weakness, cardiac collapse, cardiac syncope, chronic heart failure, acute heart failure, heart decompensation, cardiac decompensation, cardiac decompensation, diastolic heart failure, right sided heart failure, systolic heart failure, left ventricular heart failure, left sided heart failure, biventricular heart failure and congestive

heart failure.

[0043] In accordance with a further embodiment of the present invention, heart failure of any aetiology means heart failure diagnosed as a consequence or complication of any other condition, disease or disorder such as, for example, systolic dysfunction, diastolic dysfunction, ischaemic heart diseases, including myocardial infarction, right ventricular infarction and chronic ischaemia, coronary heart diseases, hypertension, primary pulmonary hypertension, secondary pulmonary hypertension, pulmonary embolism, pulmonary arterial stenosis, chronic obstructive pulmonary disease, restrictive cardiomyopathies, dilated cardiomyopathies due to infectious, toxic, metabolic, familial or unknown reasons, myocarditis, congenital anomalies, tachycardias and ventricular hypertrophy secondary to genetic or valvular disorders such as tricuspid valve insufficiency, mitral and/or aortic valve disorders, heart infarcts, thyroid diseases and anaemia.

[0044] In accordance with a further embodiment, for the treatment or prevention of heart failure, a combination of cilobradine, or its pharmaceutically acceptable salts, with other substances such as, for example, diuretics, cardiac glycosides, ACE (Angiotensin Converting Enzyme) inhibitors, ARBs (Angiotensin Receptor Blockers), vasodilators, beta blockers and inotropes, present in the same pharmaceutical composition, or given as separate therapies (so-called adjunctive therapy), is also within the scope of the present invention.

[0045] In accordance with a further embodiment of the present invention, the pharmaceutical composition for use in accordance with the present invention, comprising cilobradine or its pharmaceutically acceptable salts, alone or in combination with other heart failure therapies including ACE inhibitors, ARBs, diuretics or cardiac glycosides, may be administered to patients in any medically acceptable manner.

[0046] In accordance with a further embodiment of the present invention, the pharmaceutical composition for use in accordance with the present invention, comprising cilobradine or its pharmaceutically acceptable salts, may be formulated as liquid formulation or lyophilised powder for oral or parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally an aqueous solution. Such formulation is especially suitable for oral administration, but may also be used for parenteral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone or hydroxycellulose to the composition.

[0047] In accordance with a further embodiment of the present invention, the liquid formulation may be administered directly per orally or filled into a soft capsule.

[0048] Alternatively, the ingredients may be encapsulated, tableted or prepared in a syrup for oral administration. Pharmaceutically acceptable solid or liquid car-

over zatebradine to produce a pharmacological effect with less side-effect, and thus its superiority for the treatment of heart failure.

Claims

1. Use of clobradine or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment or prevention of heart failure.
2. Use in accordance with claim 1, wherein the pharmaceutical composition is for the prevention of heart failure.
3. Use in accordance with claim 1 or 2, wherein the galenical formulation of the pharmaceutical composition is a tablet, a drinking solution, a capsule, a suppository or an injectable formulation.
4. Use in accordance with any one of claims 1 to 3, wherein the galenical formulation of the pharmaceutical composition is a tablet.
5. Use in accordance with any one of claims 1 to 3, wherein the galenical formulation of the pharmaceutical composition is a drinking solution.
6. Use in accordance with any one of claims 1 to 5, wherein the pharmaceutical composition is administered following a single or multiple stage daily application scheme.
7. Use in accordance with claim 5, wherein the administered dose of clobradine or its pharmaceutically acceptable salt is comprised between 0.01 and 20 mg/kg body weight.
8. Use in accordance with claim 5, wherein the administered dose of clobradine or its pharmaceutically acceptable salt is comprised between 0.05 and 5 mg/kg body weight.
9. Use in accordance with claim 5, wherein the administered dose of clobradine or its pharmaceutically acceptable salt is comprised between 0.1 and 2.5 mg/kg body weight.
10. Use in accordance with claim 5, wherein the administered dose of clobradine or its pharmaceutically acceptable salt is comprised between 0.1 and 1 mg/kg body weight.
11. Use in accordance with claim 5, wherein the administered dose of clobradine or its pharmaceutically acceptable salt is comprised between 0.1 and 0.75 mg/kg body weight.

12. Use in accordance with any one of claims 1 to 11, wherein the treatment or prevention of heart failure is performed in combination with other therapeutic agents for the treatment or prevention of heart failure, such as diuretics, cardiac glycosides, ACE inhibitors, ARBs, vasodilators, beta blockers or inotropes.

13. A method for the treatment or prevention of heart failure, which comprises the administration to a patient in need thereof of a pharmaceutical composition comprising clobradine or a pharmaceutically acceptable salt thereof, together with a pharmaceutically suitable carrier.

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REVIEW

Current and Future Treatment Strategies for Refractory Angina

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Patients with refractory angina are not candidates for revascularization and have both class III or IV angina and objective evidence of ischemia despite optimal medical therapy. An estimated 300,000 to 900,000 patients in the United States have refractory angina, and 25,000 to 75,000 new cases are diagnosed each year. This review focuses on treatment strategies for refractory angina and includes the mechanism of action and clinical trial data for each strategy. The pharmacological agents that have been used are ranolazine, ivabradine, nicorandil, L-arginine, testosterone, and estrogen; currently, only L-arginine, testosterone, and estrogen are approved by the Food and Drug Administration. Results with the noninvasive treatments of enhanced external counterpulsation and transcutaneous electrical nerve stimulation are provided. Invasive treatment strategies including spinal cord stimulation, transmyocardial revascularization, percutaneous myocardial revascularization, and gene therapy are also reviewed.

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EECP = enhanced external counterpulsation; FGF = fibroblast growth factor; PMR = percutaneous myocardial revascularization; SCS = spinal cord stimulation; TENS = transcutaneous electrical nerve stimulation; TMR = transmyocardial revascularization; VEGF = vascular endothelial growth factor

Cardiovascular medicine has seen many advances in the treatment of coronary artery disease during the past 3 decades. A consequence of this success is the increasing number of patients with severe coronary artery disease who now survive. This could perhaps be thought of as a reversal of Darwinian principles: "unnatural selection and survival of the fittest." From an epidemiological and clinical perspective, an increasing number of patients with severe chronic coronary artery disease present with congestive heart failure, arrhythmias, and refractory angina.

Refractory angina is a term used to describe patients who despite optimal medical therapy have both angina and objective evidence of ischemia and are not considered candidates for revascularization. Mannheim et al¹ reported that approximately 5% to 15% of patients with angina meet the criteria for refractory angina. When these data are combined with results from the Third National Health and Nutrition Examination Survey, an estimated 300,000 to

900,000 patients in the United States have refractory angina, and 25,000 to 75,000 new cases will be diagnosed each year.² Therefore, refractory angina is a clinical problem of considerable magnitude. This review focuses on current and future therapeutic options for the management of refractory angina. Treatments can be organized into 3 groups: pharmacological therapies, noninvasive nonpharmacological therapies, and invasive therapies (Table 1). The mechanism of action and clinical trial data for each treatment option are provided.

PHARMACOLOGICAL THERAPIES

OPTIMAL STANDARD THERAPY

Angina is the result of myocardial ischemia that occurs when the supply of oxygen is unable to meet the demand. Treatment strategies focus on decreasing oxygen demand and/or increasing the supply. The standard treatment for symptomatic relief in patients with chronic stable angina should include β -blockers and/or non-dihydropyridine calcium channel blockers titrated to the lowest heart rate and blood pressure level tolerated. In addition, a long-acting nitrate should be given with use of an interrupted dose schedule to prevent nitrate tolerance. Aggressive risk factor modification with smoking cessation, cholesterol-modifying agents, and exercise training should be offered. Patients who have ongoing anginal symptoms despite receiving optimal standard therapy should be considered for the alternative treatment strategies described subsequently.

RANOLAZINE

Ranolazine is a partial inhibitor of fatty acid oxidation that has been shown to have antianginal effects.³ The actual mechanism by which it reduces anginal symptoms is not entirely known but is thought to be related to its metabolic effects that reduce oxygen demand.

The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) trial investigated the anti-ischemic effects of ranolazine and long-term survival of 191 patients with chronic severe angina.⁴ Treatment with ranolazine resulted in a 24- to 56-second improvement in exercise tolerance ($P < .001$) in patients who took 500 to 1500 mg of ranolazine twice daily. The Combination Assessment of Ranolazine in Stable Angina (CARISA) trial investigated the effects of ranolazine in combination with other anti-

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TABLE 1. Summary of Treatment Strategies for Refractory Angina*

Treatment	Improvement in time to onset of ST-segment depression	Improvement in total exercise time	Reduction in anginal class	Improvement in myocardial perfusion	FDA approved (AHA class indication)
Pharmacological					
Ranolazine	No	Yes	Yes	NA	No
Ivabradine	Yes	Yes	Yes	NA	No
Nicorandil	Yes	Yes	Yes	Yes	No
L-arginine	Yes	Yes	NA	NA	Yes
Testosterone	Yes	No	NA	NA	Yes
Estrogen	Yes	Yes	Yes	NA	Yes
Noninvasive					
EECP	Yes	Yes	Yes	Yes	Yes (Ib)
TENS	Yes	Yes	Yes	NA	Yes
Invasive					
SCS	Yes	Yes	Yes	Yes	Yes (Ib)
TMR	No	Yes	Yes	No	Yes (IIa)
PMR	No	No	No	No	No
Gene therapy	Yes	Yes	Yes	Yes	No

*AHA = American Heart Association; EECP = enhanced external counterpulsation; FDA = Food and Drug Administration; NA = not available; PMR = percutaneous myocardial revascularization; SCS = spinal cord stimulation; TENS = transcutaneous electrical nerve stimulation; TMR = transmyocardial revascularization.

anginal agents.⁵ In this phase 3 double-blind, placebo-controlled clinical trial, 823 patients with refractory angina who were receiving standard therapy with atenolol, diltiazem, or amlodipine were randomized to placebo, ranolazine at 750 mg twice daily, or ranolazine at 1000 mg twice daily. After 12 weeks, patients in both ranolazine arms had a 26% increase in total exercise time ($P=.03$) and a decrease in the number of anginal episodes per week. The time to onset of 1 mm of ST-segment depression during exercise testing did not change. The most common adverse reactions to ranolazine were constipation, dizziness, nausea, and asthenia, which occurred in 8% of patients. Patients in the treatment arms also had an increase in the QT interval, the clinical importance of which is unknown. Ranolazine is currently not approved by the Food and Drug Administration (FDA) because of issues regarding prolongation of the QT interval.

IVABRADINE

Ivabradine is a selective and specific inhibitor of the L₁ ion channel, which is responsible for the primary sinoatrial node pacemaker current.⁶ Because of its ability to decrease heart rate and myocardial oxygen demand with no negative inotropic effects, ivabradine is a potential therapy for chronic stable angina.

Borer et al⁷ conducted a randomized, double-blind, placebo-controlled trial investigating the use of ivabradine in patients with stable angina. Patients underwent a washout period during which β -blockers and calcium channel blockers were discontinued. Patients were then randomized to placebo or ivabradine (2.5, 5.0, or 10.0 mg twice daily) for 2 weeks, followed by a 3-month open-label extension

phase with 10 mg of ivabradine twice a day. At the end of the blinded phase, patients who received 10 mg of ivabradine twice a day had a 12% increase in the time to onset of 1-mm ST-segment depression ($P<.005$) and a 9.5% increase in exercise tolerance compared with patients who received placebo ($P<.02$). Also, patients who received ivabradine had a reduction in heart rate of 20 beats/min at rest and with peak exercise at the end of the study. During the open-label phase of the study, ivabradine use resulted in a 77% decrease in the frequency of anginal events ($P<.001$). Visual disturbances occurred in 14.8% of the patients who received 10 mg of ivabradine twice a day.

Tardif⁸ compared ivabradine with atenolol in 932 patients with stable angina. Total exercise duration increased by 86.8 ± 129.0 seconds with ivabradine at 7.5 mg twice daily and by 91.7 ± 118.8 seconds with ivabradine at 10 mg twice daily compared with an increase of 78.8 ± 133.4 seconds with atenolol at 100 mg daily. Like ranolazine, ivabradine has not yet been approved by the FDA.

NICORANDIL

Nicorandil is a nicotinamide ester that has both nitrate-like and adenosine triphosphate-potassium channel activating properties.⁹ Its pharmacological effects include the ability to reduce both preload and afterload by vasodilation of the arterial and venous systems. In addition, nicorandil's adenosine triphosphate-potassium channel activation may offer cardioprotection via a "preconditioning" effect on the myocardium.

Several small randomized trials have shown that nicorandil given at doses of 10 or 20 mg twice a day prolongs the time to onset of ST-segment depression and exercise

duration during stress testing in patients with stable angina.^{10,11} Nicorandil has also been shown to improve myocardial perfusion at rest and with exercise.¹⁴ The preconditioning and possible cardioprotective effects of nicorandil were investigated in the Impact Of Nicorandil in Angina (IONA) trial that randomized 5126 patients with stable angina to either placebo or nicorandil at 20 mg twice a day.¹⁵ After 3 years, patients treated with nicorandil had a 17% relative risk reduction ($P=.014$) in the composite primary end point of deaths due to coronary heart disease, nonfatal myocardial infarction, and admission for cardiac chest pain. Compared with the placebo group, the nicorandil group had no significant change in systemic blood pressure. The main adverse reactions to treatment were headaches and gastrointestinal discomfort. Nicorandil is available for clinical use in Europe and Japan but is not currently approved by the FDA for use in the United States.

L-ARGININE

Several other pharmacological therapies for chronic angina have been investigated in small clinical trials. L-arginine has been proposed as a potential therapy that would increase coronary blood flow by improving endothelium-dependent vasodilation.¹⁶ A single-center, double-blind, placebo-controlled trial involving 22 patients with stable angina showed that treatment with oral L-arginine resulted in an increase in exercise duration and maximum workload during stress testing as well as a decrease in the time to onset of ST-segment depression.¹⁷

TESTOSTERONE AND ESTROGEN

Testosterone has been shown to result in coronary artery dilatation and increased blood flow in humans. The mechanism appears to be endothelium independent and may involve the ion channels in vascular smooth muscle cells.^{18,19} A randomized, double-blind, placebo-controlled trial involving 46 male patients with stable angina receiving medical therapy showed that treatment with transdermal testosterone improved the time to onset of ST-segment depression during exercise testing and improved quality of life.²⁰ Although none of the patients experienced adverse prostatic or hematologic effects, concern exists regarding long-term therapy with testosterone.

Estrogen has been investigated as an antianginal agent and has been shown to dilate coronary arteries and improve endothelial function.^{21,22} A randomized, double-blind, placebo-controlled trial involving 74 female patients with stable angina showed that estradiol and norethindrone therapy improved exercise duration and the time to onset of ST-segment depression.²³ The number of ischemic events decreased in the treatment group. However, these benefits must be weighed against the initial increase in cardiac

events caused by estrogen therapy for females with coronary artery disease.²⁴

NONINVASIVE THERAPIES

ENHANCED EXTERNAL COUNTERPULSATION

Enhanced external counterpulsation (EECP) is based on the concept of counterpulsation and consists of 3 pairs of pneumatic cuffs placed around the lower extremities at the calves, lower thighs, and upper thighs (Figure 1). An electrocardiographic trigger is used to sequentially inflate the cuffs, starting at the calves, during onset of diastole and simultaneously deflate all cuffs before onset of systole. A standard course of EECP therapy consists of 35 one-hour sessions during a 7-week period. The mechanism by which EECP improves anginal symptoms is poorly understood but may involve nonspecific placebo effects and various hemodynamic factors. Hemodynamically, EECP acts like intra-aortic balloon counterpulsation by augmenting diastolic blood flow in multiple vascular beds, including the coronary arteries, and by reducing cardiac afterload.²⁵ Endothelial function has been shown to improve after a course of EECP therapy.²⁶ In addition, EECP therapy has been associated with the release of growth factors, such as vascular endothelial growth factor (VEGF), that promote the formation of collaterals in the coronary circulation.²⁷ Finally, EECP therapy may result in a "training effect" by decreasing peripheral vascular resistance in the same manner as physical exercise.²⁸

Several controlled and uncontrolled trials have investigated the use of EECP therapy for patients with refractory angina; and results are summarized in Table 2.²⁸⁻³⁰ The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) trial conducted by Arora et al³¹ is a double-blind, sham-controlled study in which 139 patients with chronic stable angina were randomized to either active EECP therapy or sham treatment with subtherapeutic cuff inflations. After 35 sessions, patients in the active treatment arm had a 15% increase in the time to onset of 1-mm ST-segment depression ($P=.01$) and 25% fewer anginal symptoms per week ($P<.035$). These effects were not seen in the patients in the sham-controlled arm. An international registry of patients who underwent EECP therapy showed an improvement in anginal symptoms and quality of life.³²

Although one trial involving a sham-controlled arm supports the use of EECP therapy, further larger-scale sham-controlled studies regarding the effectiveness of EECP therapy and its mechanisms of action need to be conducted. Currently, EECP therapy is one of the most widely used and promising treatments of refractory angina. Enhanced external counterpulsation therapy is FDA approved and is recommended by the American Heart Association as a

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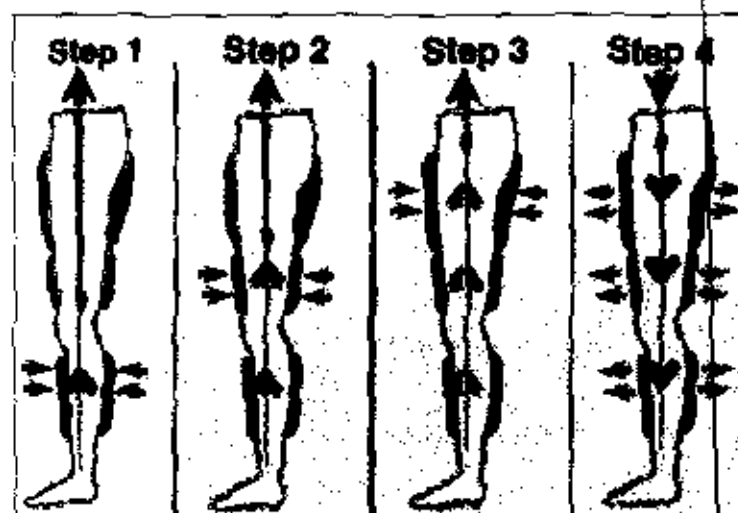


FIGURE 1. Enhanced external counterpulsation. Step 1, Inflation initiates retrograde pulse wave. Step 2, Inflation of cuffs on lower thigh, 50 milliseconds later. Step 3, Inflation of cuffs on upper thigh, 50 milliseconds later. Step 4, Simultaneous deflation of all 3 cuffs.

potential therapy for refractory angina. It has a class IIb indication (usefulness/efficacy is less well established).⁴⁹

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION

The concept of neurostimulation to regulate pain dates to the ancient use of acupuncture, and its use in modern medicine began in the 1970s. Currently, the 2 main methods of neurostimulation are transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation (SCS). TENS consists of a neurostimulator unit and 2 electrodes. One electrode is placed in the dermatome, the site of the highest intensity of pain, and the other is placed in the

contralateral dermatome. Stimulation of the larger non-pain-conducting nerves is believed to inhibit transmission through the smaller pain-conducting nerve fibers.

Several small clinical trials have investigated the efficacy of TENS in the treatment of refractory angina.⁴¹⁻⁴⁵ Mannheim et al⁴⁵ randomized 21 patients with class III or IV chronic angina to placebo or TENS therapy for 5 weeks. Patients in the active arm received 15 to 30 mA pulses at a frequency of 70 Hz for 1 hour 3 times a day with an additional 1 to 10 minutes of therapy as needed for breakthrough pain. After 5 weeks, patients treated with TENS had a 15% increase in exercise tolerance during stress testing ($P=.01$)

TABLE 2. Published Controlled and Uncontrolled Trials of Enhanced External Counterpulsation in Patients With Stable Angina*

Reference	No. of patients	Angina (% with ≥ 1 CCS class change)	Nitrate Use	Exercise tolerance (%)	Time to ST-segment depression	Cardiac perfusion (%)
Zheng et al ⁴⁶	200	Decrease (97)	NA	NA	NA	NA
Lawson et al ⁴⁷	18	Decrease (100)	Decrease	Increase (67)	NA	Increase (78)
Lawson et al ⁴⁸	27	NA	NA	Increase (81)	NA	Increase (78)
Lawson et al ⁴⁹	50	Decrease (100)	Decrease	NA	NA	Increase (80)
Lawson et al ⁵⁰	60	Decrease	NA	Increase	NA	Increase (75)
Arora et al ⁵¹	139	Decrease	Decrease	Increase	Increase	NA
Lawson et al ⁵²	33	Decrease (100)	Decrease	NA	NA	Increase (79)
Urano et al ⁵³	12	NA	NA	Increase	Increase	Increase
Miyashita et al ⁵⁴	11	NA	NA	Increase	Increase	Increase
Stys et al ⁵⁵	395	Decrease (88)	NA	NA	NA	NA
Barnes et al ⁵⁶	978	Decrease (81)	Decrease	NA	NA	NA
Stys et al ⁵⁷	175	Decrease (85)	NA	Increase	NA	Increase (83)

*CCS = Canadian Cardiovascular Society; NA = not available.

Adapted from *J Am Coll Cardiol*. 2003;41:1918-1925, with permission from the American College of Cardiology Foundation.

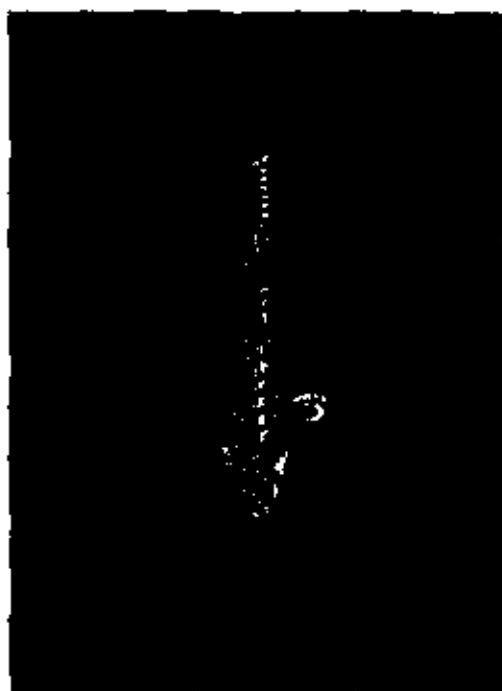


FIGURE 2. The spinal cord stimulator consists of an epidural lead, an extension wire, and a pulse generator. The lead is placed in the epidural space at the level of C7 through T1.

and a 17% decrease in anginal symptoms per week ($P=.05$). However, these modest improvements could have been due to a placebo effect since a sham-controlled arm was not included. During therapy, patients experienced skin irritation, breakdown at the electrode sites, and paresthesias.

INVASIVE THERAPIES

SPINAL CORD STIMULATION

Spinal cord stimulation (SCS) is similar to TENS in concept and consists of 3 components: an epidural lead, an extension wire, and a pulse generator (Figure 2). The epidural lead is placed in the epidural space at the level of C7 through T1, and the pacemaker-sized generator is surgically implanted in the left lower abdominal area. Patients receive 3 one-hour stimulations a day and can activate the device with a handheld magnet to treat episodes of breakthrough pain. It is believed that SCS blocks pain by stimulating the dorsal columns, which inhibits transmission through the pain-conducting spinothalamic tract.⁴⁵⁻⁴⁸ However, pain due to an acute coronary syndrome has not been shown to be blocked in clinical trials and will continue to cause typical symptoms despite stimulation.⁴⁹ Also, SCS has been shown to decrease sympathetic tone and improve myocardial blood flow.⁵²⁻⁵⁴

Several clinical trials have investigated the use of SCS for refractory angina.⁴⁵⁻⁴⁸ Hautvast et al⁴⁵ showed that 6 weeks of therapy with SCS in 25 patients with class III and IV chronic angina resulted in a 39% increase in the time to onset of ST-segment depression ($P<.05$) and a 19% increase in exercise capacity ($P<.05$) during treadmill testing. Also, SCS reduced the number of anginal attacks and use of nitroglycerin by 41% and 48% ($P<.05$), respectively.

In the Electrical Stimulation Versus Coronary Artery Bypass Surgery in Severe Angina Pectoris (ESBY) trial, 104 patients with chronic angina who were considered to have only symptomatic benefit from coronary artery bypass surgery were randomized to SCS or coronary artery bypass surgery.⁴⁸ Spinal cord stimulation was as effective as bypass surgery for improving anginal symptoms (4 vs 5 episodes per week, respectively) and was associated with less procedure-related mortality (2% vs 14%; $P<.05$) and stroke (4% vs 16%; $P<.05$).

Di Pede et al⁴⁹ recently published the results of a registry of patients who had undergone SCS. Treatment with SCS resulted in an improvement in the Canadian Cardiovascular Society angina class of 1 class or higher in 80% of patients and 2 classes or higher in 42% of patients. The main adverse reactions to SCS are the risk of epidural hematoma and infection, occurring in about 1% of patients. In addition, SCS may interfere with the function of pacemakers and implantable defibrillators.

Although results of the initial trials appear promising, these trials had a small number of patients, and none had a sham-controlled arm to prevent a placebo effect. The American Heart Association currently considers SCS a possible treatment of refractory angina. It has a class IIb indication (usefulness/efficacy is less well established).⁴⁰

TRANSMYOCARDIAL REVASCULARIZATION

The concept of myocardial revascularization began in 1956 when Goldman et al⁶⁰ proposed that the formation of artificial conduits in the subendocardium would improve oxygen delivery to myocytes. Initially, needles were used. In 1986, Okada et al⁶¹ became the first to use laser technology to generate myocardial channels. Currently, 2 types of lasers are used—carbon dioxide and holmium:YAG. The carbon dioxide system transmits the laser through a series of mirrors and lenses, whereas the holmium:YAG system uses an optical fiber. In transmyocardial revascularization (TMR), a left thoracotomy is performed, and the laser is transmitted directly into the myocardium. If a carbon dioxide laser is used, a single pulse is delivered to generate a channel. If a holmium:YAG system is used, several pulses are needed to form a single channel. With either system, a total of 25 to 40 conduits are formed.

TABLE 3. Summary of Trials of TMR in Patients With Refractory Angina

Reference	No. of patients	Laser	Percentage with decrease ≥ 2 CCS angina classes			Improvement in exercise time (s)			Survival, TMR vs control	Improvement in perfusion
			TMR	Control	P value	TMR	Control	P value		
Allen et al ⁶²	275	Holmium:YAG	76	32	<.001	+5	+3.9 MET	<.05	NS	No
Frazier et al ⁶³	192	Carbon dioxide	72	13	<.001	NA	NA		NS	Yes
Schofield et al ⁶⁴	188	Carbon dioxide	25	4	<.001	NA	NA		NS	No
Burkhardt et al ⁶⁵	182	Holmium:YAG	48	14	<.001	+65	-64	<.001	NS	No
Auberge et al ⁶⁶	100	Carbon dioxide	39	0	<.01	NS	NS		NS	NA
Jones et al ⁶⁷	86	Holmium:YAG	NA	NA		+119	-85	<.001	NA	No

*CCS = Canadian Cardiovascular Society; MET = metabolic equivalent; NA = not available; NS = not statistically significant; TMR = transmyocardial revascularization.

Adapted from *J Am Coll Cardiol*. 2003;41:173-178, with permission from the American College of Cardiology Foundation.

Several studies have investigated the use of TMR for refractory angina. In the largest trial, Allen et al⁶² randomized 275 patients with class IV refractory angina to TMR with a holmium:YAG laser plus continued medical therapy or medical therapy alone. At 12 months, the TMR group had a greater percentage of patients with a decrease of 2 or more angina classes (76% vs 32%; $P<.001$) and a greater amount of exertional tolerance on stress testing (5.0 vs 3.9 metabolic equivalents; $P<.05$). There was no improvement in mortality or perfusion. The second largest trial was conducted by Frazier et al⁶³ who randomized 192 patients with class III or IV refractory angina to TMR with a carbon dioxide laser plus medical therapy or medical therapy alone. At 12 months, the TMR group had a greater percentage of patients with a decrease of 2 or more angina classes (72% vs 13%; $P<.001$). Unlike patients in the study by Allen et al,⁶² TMR-treated patients did not have an improvement in exertional tolerance despite an improvement in perfusion. These 2 trials along with 4 other investigations of TMR are summarized in Table 3.⁶²⁻⁶⁷ In general, TMR has been shown to improve anginal symptoms and exertional tolerance but does not seem to improve mortality or myocardial perfusion.

Registry data from the Society of Thoracic Surgeons involving 3717 patients who underwent TMR showed an increase in the number of annual TMR procedures performed between 1998 and 2001 (59 in the first half of 1998 and 572 in the last half of 2001).⁶⁸ Interestingly, 67% of these procedures were for TMR plus bypass surgery, an off-label use for TMR. The perioperative mortality rate in the registry was 6.4%; this is higher than the rate from clinical studies of TMR, which ranges from 1.1% to 5.3%. The mortality rate was higher in older patients, diabetic patients, and patients with a recent acute coronary syndrome. Despite the trends reported in this registry, the use of TMR has decreased in recent years because of the availability of other treatments such as EECF.

The actual mechanism by which TMR improves anginal symptoms is unknown. It was originally believed to be due to improved myocardial perfusion through open channels.⁶⁹ However, subsequent studies have shown that the channels fill with necrotic debris and close shortly after the procedure.⁷⁰⁻⁷² Other proposed mechanisms have included angiogenesis through the release of growth factors and denervation of pain fibers by the laser.^{73,74} A placebo effect is certainly possible and is perhaps the most plausible theory given the lack of randomized trials with a sham-controlled arm. Although use of TMR for chronic angina has decreased, the American Heart Association considers it a class IIa indication (weight of evidence favors efficacy) for the treatment of chronic angina.⁶⁹

PERCUTANEOUS MYOCARDIAL REVASCLARIZATION

Percutaneous myocardial revascularization (PMR) is based on the same concept as TMR except that it is performed percutaneously. A guiding catheter is placed into the left ventricle via a femoral approach, and a holmium:YAG laser fiber is advanced through the catheter into the endocardium. Several pulses are then delivered to generate a channel. Clinical trials of PMR are summarized in Table 4.⁷⁵⁻⁷⁹ Unlike studies of TMR, several of these investigations used sham-controlled arms. In the Direct Myocardial Revascularization In Regeneration of Endomyocardial Channels Trial (DIRECT), Leon⁷⁶ randomized 298 patients with refractory angina to PMR or a sham procedure. He found no significant difference in anginal symptoms or exertional tolerance at follow-up. Stone et al⁷⁸ found similar results in their study of 141 patients with refractory angina who were randomized to PMR or a sham procedure. The only sham-controlled trial to show clinical benefit was the one by Salem et al⁷⁵ involving 82 patients. At follow-up, more patients in the PMR group had a decrease of 2 or more anginal classes than did the sham-controlled group (41% vs 13%; $P=.006$). Therefore, based on the results of the sham-controlled trials, PMR is not an effective therapy

TABLE 4. Summary of Trials of PMR for Refractory Angina*

Reference	No. of patients	Percentage with decrease ≥ 2 CCS angina classes			Improvement in exercise time (s)		
		PMR	Control	P value	PMR	Control	P value
Leon ³⁴	298	NS	NS		NS	NS	
Cesterle et al ³⁵	221	30	12	.002	+89	+13	.008
Stone et al ³⁶	141	NS	NS		NS	NS	
Salerni et al ³⁷	82	35	14	.04	NA	NA	

*CCS = Canadian Cardiovascular Society; NA = not available; NS = not statistically significant; PMR = percutaneous myocardial revascularization; †Sham-controlled trial.

Adapted from *J Am Coll Cardiol*. 2003;41:173-178, with permission from the American College of Cardiology Foundation.

for chronic angina. It is unknown why TMR is effective and PMR is not, but the placebo effect in the surgical TMR trials may be the reason. Percutaneous myocardial revascularization has not been approved by the FDA for the treatment of chronic refractory angina.

GENE THERAPY

The use of gene therapy to induce the formation of collaterals via angiogenesis was first pioneered by Isner et al.⁶³ The concept of gene therapy centers around 3 factors: the gene target to be delivered, the vector used to package the gene target, and the mode of delivery to the site of action. The 2 main gene factors currently being investigated are VEGF and basic fibroblast growth factor (FGF). These gene targets have been packaged in either a plasmid or an adenovirus for delivery to the target organ by surgical or percutaneous methods.

Several phase 1 clinical trials of gene therapy have been conducted in patients with refractory angina and have shown improvement in exercise tolerance, anginal symptoms, and myocardial perfusion.⁶¹⁻⁶⁶ Two trials have had a placebo-controlled arm. The Angiogenic Gene Therapy (AGENT) trial involved 79 patients with class II or III angina who were randomized to direct injection of adenovirus containing basic FGF or placebo.⁶¹ After 12 weeks, patients in the active treatment arm had a 30% increase in exercise duration on treadmill testing. Although 2 patients in the active treatment arm experienced transient elevations in liver enzyme levels, no major adverse reactions occurred. In the follow-up placebo-controlled, double-blind trial, AGENT-2, 52 patients with refractory angina were randomized to an intracoronary injection of 10^{10} adenoviral particles containing a gene encoding FGF (Ad5FGF-4) or placebo.⁶² At 8 weeks, the Ad5FGF-4 injection resulted in a significant reduction in the ischemic defect size, determined by adenosine single-photon emission computed tomography (4.2% absolute reduction; $P < .001$), and placebo-treated patients had no improvement ($P = .32$). However, the change in reversible perfusion defect

size between Ad5FGF-4 and placebo was not significant (4.2% vs 1.6%; $P = .14$). The Vascular Endothelial Growth Factor in Ischemia for Vascular Angiogenesis (VIVA) trial randomized 178 patients with refractory angina to placebo, low-dose VEGF, or high-dose VEGF.⁶⁶ After 120 days, patients receiving high-dose VEGF had a significant improvement in angina class and a trend toward improvement in exercise duration and frequency of anginal symptoms.

At this time, gene therapy appears to be a promising therapy for refractory angina, but it is still considered experimental. Limitations include vector-associated toxicities and immune response to vectors. Larger randomized trials are needed to determine long-term efficacy and safety. Direct injection of progenitor cells is a possible strategy to induce angiogenesis, and phase 1 and 2 clinical trials are currently under way.

CONCLUSION

Refractory angina is a difficult clinical condition that is growing in prevalence. Current treatment options for refractory angina can be classified into 3 groups: pharmacological, nonpharmacological noninvasive, and invasive. Although none of these therapies have been shown to improve mortality, some improve symptoms and quality of life. At this time, L-arginine, testosterone, estrogen, BECP, TENS, SCS, and TMR are the only treatments that are FDA approved. Currently, BECP is the most widely used therapy and is the only FDA-approved treatment for refractory angina that has been supported by sham-controlled data. Trials with SCS are currently in progress and will hopefully result in an increase in clinical use for refractory angina. Use of TMR has decreased because of its invasiveness, and results may be due to a placebo effect. The pharmacological agents ranolazine, ivabradine, and nicorandil appear effective, but additional phase 3 trials need to be conducted before they can receive FDA approval. Finally, gene therapy appears promising but is currently considered experimental.

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ACTUALIZACIÓN EN FÁRMACOS **ANTIARRÍTMICOS**

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DROGAS ANTIARRÍTMICAS

INTRODUCCIÓN

Los recientes progresos en los conocimientos, a nivel celular y molecular, en la electrofisiología de las células cardíacas normales y patológicas, permitieron conocer la estructura y la función de los canales iónicos, que son los responsables de la actividad eléctrica y el sitio de acción de las drogas antiarrítmicas.

El mecanismo de acción de una droga antiarrítmica está relacionado a sus efectos sobre la generación del impulso en los diferentes tipos de células cardíacas, determinado a su vez, por el funcionamiento y los rangos de apertura y cierre de los canales iónicos (1). Se analizan aspectos de la electrofisiología celular en relación con los efectos de las drogas antiarrítmicas.

Potencial de membrana y potencial de acción: el potencial de reposo de la membrana en las células marcapasos (nódulo sinusal) disminuye en forma gradual, a diferencia de las células miocárdicas (auriculares y ventriculares) que tienen un potencial de reposo estable entre -70 y -90 mV. El valor negativo del potencial de reposo refleja el efecto dominante de un eflujo estable de iones potasio transportados por una corriente (IK1) a través de un canal denominado "rectificador interno". Las células marcapasos (nódulo sinusal y Purkinje) carecen de una IK1 significativa y muestran un potencial marcapasos que las despolariza gradualmente hasta desencadenar el potencial de acción (figura 1).

El potencial de acción provoca cambios positivos en el potencial de membrana (despolarización) por la apertura de canales iónicos selectivos que permiten la entrada de iones de sodio y calcio. La velocidad de despolarización durante el ascenso del potencial de acción (fase 0) en las células miocárdicas o de Purkinje es más rápida que en las células automáticas del nódulo sinusal, debido a que predomina la corriente transportada por los canales de sodio, mientras que en las células marcapasos predomina la corriente vehiculizada por canales de calcio.

Después del pico del potencial de acción (overshoot), el potencial de membrana es restaurado a sus valores negativos a través de un proceso denominado repolarización. Los canales responsables de la despolarización se cierran y los canales de la repolarización (predominando los canales de potasio) se abren. La fase 1 o repolarización precoz, es rápida y fugaz. La fase 2, plateau, es más evidente en células miocárdicas o de Purkinje. La fase 3, repolarización tardía, completa la recuperación del potencial de membrana. Finalmente, la fase 4 o período post repolarización, es estable en las células de miocardio común y tiene despolarización diastólica espontánea en las células marcapasos.

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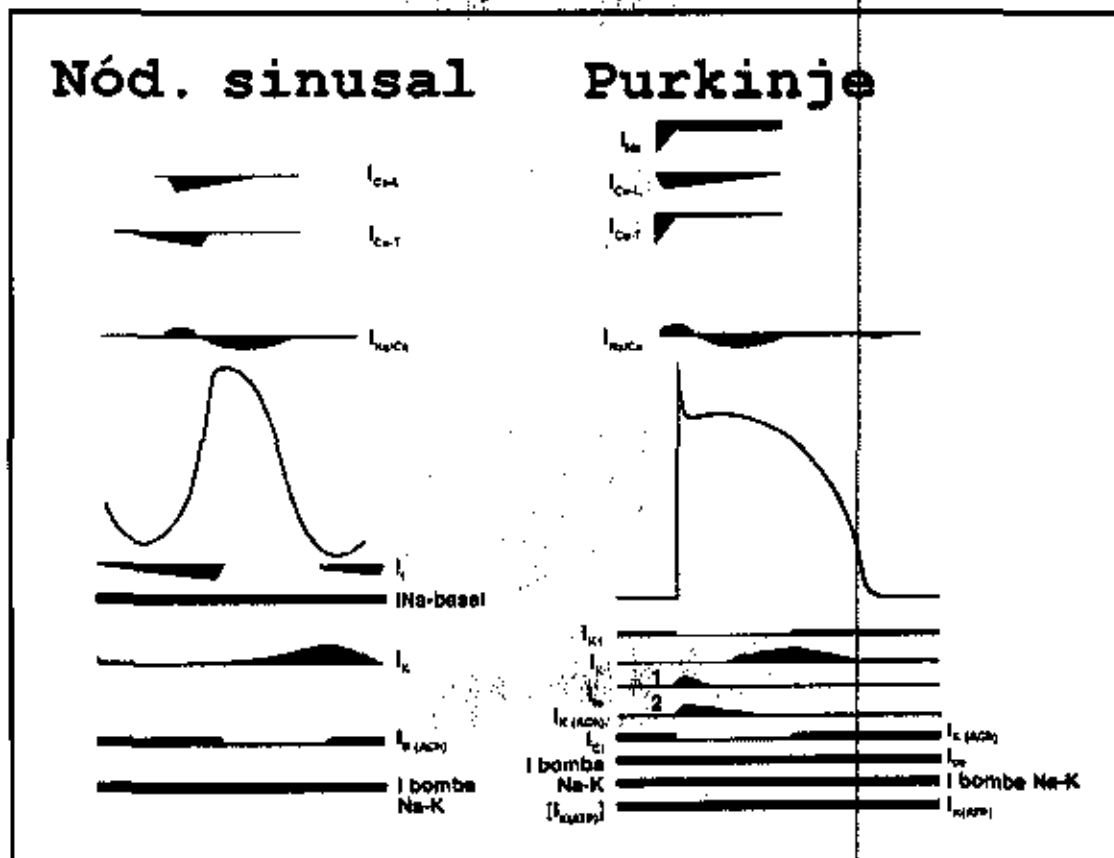


Figura 1: Se muestran las corrientes de entrada (despolarizantes) y las de salida (repolarizantes), en una célula automática del nódulo sinusal (izquierda) y en una fibra de Purkinje (derecha) con su automatismo deprimido.

Canales iónicos: la generación del potencial de acción depende de la acción combinada de diferentes canales iónicos unidos a la membrana celular. Simultáneamente, bombas proteicas con consumo de ATP intercambian Na/K y Ca para sostener los gradientes transmembrana. En forma simple, los canales iónicos pueden definirse como proteínas que contienen un sensor de voltaje acoplado a un poro a través del cual fluyen los iones. El poro incorpora un filtro selectivo que determina que ión pasa cuando el poro se abre.

La célula en reposo está cerca del potencial de equilibrio del potasio (cerca a -90 mV), el proceso de despolarización tiende a llevarla hacia el potencial de equilibrio del sodio y calcio y la repolarización la acerca, otra vez, al potencial de equilibrio del potasio.

Los canales responden a cambios del voltaje de la membrana y tienen compuertas en las que el voltaje regula la magnitud y el tiempo de su apertura. El canal iónico no permite el paso de corriente (iones) hasta que se aplica un estímulo despolarizante. En reposo, el canal se considera cerrado. Cuando se aplica un estímulo despolarizante, el cambio del potencial de membrana es detectado por el sensor y el canal se abre para permitir el flujo de corriente. El cambio de estado del canal de cerrado a abierto se denomina "activación". La probabilidad que un canal se mueva de cerrado a abierto depende de la magnitud del cambio de voltaje (la activación es voltaje dependiente) (2).

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Algunos canales solo muestran dependencia del voltaje para la activación, pero en otros un segundo proceso influye en el flujo de corriente. Si el estímulo despolarizante se mantiene, ocurre un segundo cambio en el canal, una parte de la proteína se mueve y ocluye el poro, de modo que aunque el canal está abierto conduce pobremente los iones. Este proceso voltaje y tiempo dependiente se denomina "inactivación". Las propiedades del canal: activación, inactivación, sensibilidad al voltaje y selectividad iónica se estudian experimentalmente con técnicas de clamping de voltaje (2).

Resumiendo: 1) Una variedad de canales iónicos generan las corrientes despolarizantes y repolarizantes responsables del potencial de acción., 2) los canales iónicos con diferentes funciones sobre los que actúan las drogas antiarrítmicas son la base para la clasificación del efecto de estas, 3) la dependencia del estado del canal con el voltaje, implica, al menos teóricamente, que la droga puede unirse a canales en reposo (cerrados), activados (abiertos) o inactivados.

Las drogas que se unen a canales abiertos o inactivados pueden ejercer efectos que varían con la frecuencia de estimulación o la frecuencia cardíaca y como tales muestran "dependencia del uso". Una droga ideal, bloqueante de un canal, debería tener dependencia del uso mostrando mayor acción inhibitoria a frecuencias más rápidas. Las drogas que se unen a canales cerrados pueden ejercer acciones "independientes del uso" o "inversión de la dependencia de uso", separándose de su unión durante la activación del canal mostrando mayor acción inhibitoria a frecuencias más lentas y menor a frecuencias rápidas.

Los canales iónicos como sitios de acción de las drogas antiarrítmicas:

En los canales comprometidos en la actividad automática (células del nódulo sinusal), la corriente de calcio tipo T (ICaT) y la corriente hiperpolarizante (If) aportan la despolarización que precede a la fase 0. Las drogas que disminuyen estas corrientes deberían disminuir la frecuencia cardíaca y tener un efecto cronotrópico negativo (3). El mibefradil es un bloqueante de la ICaT que relaja la vasculatura coronaria y disminuye la frecuencia cardíaca, es así, un agente bradicardizante potencial (4). Este compuesto fue retirado de la venta por detectarse interacciones clínicas peligrosas.

Los canales comprometidos en la despolarización, canales de sodio (INa) y de calcio tipo L (ICaL) son importantes sitios de acción de las drogas antiarrítmicas.

La ICaL es la corriente dominante en la despolarización de las células del nódulo sinusal y del nódulo AV. Esta dependencia de la conducción nodal de la corriente ICaL hace a las drogas bloqueadoras del canal de calcio, como el verapamilo y el diltiazem, útiles en el tratamiento de las taquicardias supraventriculares (5). En las taquicardias SV paroxísticas, cuando la conducción en el nódulo AV forma parte del circuito de reentrada, el bloqueo de la ICaL puede interrumpir la taquicardia y prevenir las recurrencias. Pueden ser efectivos también para disminuir la frecuencia en la fibrilación auricular (6).

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Los estudios experimentales y clínicos preliminares, mostraron que las propiedades electrofarmacológicas de la dronedarona y de la amiodarona son similares (250). La incidencia de TdEP provocadas por la droga son muy bajas.

Las propiedades de la dronedarona modificando los intervalos QT y QTc y la frecuencia cardíaca son importantes para el desempeño del fármaco como *antifibrilatorio, a nivel auricular y ventricular*. La dronedarona aumenta los intervalos QT y QTc en función de la dosis (1200 a 3200 mg/día). Un ensayo clínico que usó dronedarona a 800 mg/día (dosis que prolonga de manera poco significativa el QT y QTc) es superior al placebo para mantener el ritmo sinusal después de la reversión de la fibrilación auricular. Su eficacia clínica está siendo evaluada.

DROGAS ANTIARRÍTMICAS CLASE IV BLOQUEANTES del CANAL de CALCIO

Los efectos electrofisiológicos de los bloqueantes del canal de calcio usados para controlar las arritmias cardíacas se parece a los de los beta-bloqueantes, especialmente por sus acciones sobre el nodo AV. Estas acciones son responsables de la mayoría de los efectos de esta clase de drogas en el control de *las taquiarritmias supraventriculares* (251,252).

El grupo más numeroso de bloqueantes del canal de calcio, las dihidropiridinas, no modulan el nodo AV, ni ejercen efectos específicos sobre la refractariedad en las aurículas o los ventrículos. Tienen escaso o ningún efecto para terminar el aleteo y fibrilación auricular o en controlar las formas comunes de taquicardia ventricular.

Solo unos pocos de los antagonistas del calcio sintetizados y desarrollados, (verapamil y diltiazem) tienen efectos antiarrítmicos específicos y directos; las acciones antiarrítmicas fueron primero descritas para el verapamil.

Estas drogas son poderosos antiisquémicos y algunos de sus efectos antiarrítmicos pueden deberse a la corrección del desbalance entre aporte y demanda de oxígeno en *pacientes con enfermedad coronaria*. Sin embargo, a pesar de sus acciones antiisquémicas, su impacto sobre la mortalidad después del infarto agudo de miocardio es incierta y en algunos pacientes puede ser perjudicial (253).

Una mejor comprensión de los efectos electrofarmacológicos de los antagonistas del calcio siguieron al conocimiento de las corrientes depolarizantes de entrada en las membranas celulares de diferentes órganos y tejidos. Estas corrientes reguladas por el voltaje, ayudan a controlar importantes funciones fisiológicas, en la contracción de las fibras musculares y la secreción de hormonas.

Se identificaron seis clases de canales de calcio, pero solo dos se hallaron en el sistema cardiovascular, los canales de calcio tipo L y tipo T (254).

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Los canales calcio tipo L se encuentran en células de músculo esquelético, cardíaco y liso; están relacionados con la actividad electromecánica del músculo cardíaco y vascular normal.

Los canales tipo T no se encuentran en cantidad significativa en los miocitos ventriculares; sus concentraciones más altas en el corazón están en las células marcapasos y en las de Purkinje. No están sometidos a la estimulación beta adrenérgica. Así, el influjo de calcio por los canales tipo T es de poca importancia para la contractilidad miocárdica pero es crítico en la formación y conducción del impulso (255).

La importancia farmacológica del bloqueo del canal tipo T radica en la capacidad de influenciar las mismas funciones que los canales tipo L sin producir efectos inotrópicos negativos en los ventrículos.

El conocimiento de las propiedades del canal lento en el músculo cardíaco permite explicar los efectos electrofisiológicos y antiarrítmicos de los antagonistas del calcio. La inhibición selectiva de la actividad del canal lento aumenta la refractariedad dependiente del tiempo en las fibras de respuesta lenta en el corazón.

Arritmogénesis y Actividad del Canal Lento: Los estudios experimentales mostraron el rol del canal lento en la génesis del automatismo gatillado (256) en la forma de post potenciales precoces (PPP) y post potenciales tardíos (PPT). Los PPP pueden ser gatillados por el flujo transmembrana de calcio durante la repolarización cardíaca prolongada, especialmente por el uso de bloqueantes de los canales de potasio. En ciertas condiciones, pueden ser responsables de las TdeP (257). Algunos casos de TdeP clínicas se deben a un aumento de la corriente de calcio a través del canal lento.

Los datos experimentales sugieren que los PPT son mediadores de las arritmias inducidas por digital. Esta forma de automatismo gatillado puede deberse a intervenciones que elevan el nivel de calcio intracelular más allá de un valor crítico como puede ser una concentración extracelular de calcio alta, frecuencias de estimulación rápidas, digital y catecolaminas (258).

El rol del canal lento en la génesis de arritmias clínicas es muy importante en las taquicardias supraventriculares paroxísticas reentrantes, que utilizan los nodos AV y SA (259). La eficacia clínica de la adenosina y el ATP en las mismas condiciones apoya el rol fundamental de los receptores purinérgicos en la modulación de la conducción y refractariedad en el nodo AV (260).

Electrofarmacología del Canal Lento: La conducción del nodo AV normal es dependiente del canal lento y los antagonistas cálcicos bloquean la conducción en un modo dependiente de la concentración o de la dosis. Por otra parte, no tienen efectos significativos sobre los períodos refractarios de células auriculares, ventriculares o de His-Purkinje, ni sobre la velocidad de conducción.

Disminuyen la depolarización en la fase 4 en las células de los nodos SA y AV, con enlentecimiento de la velocidad de conducción en estas zonas. Los efectos

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,
Abogado
JULIO CÉSAR RAMÍREZ PIÑA
(Apoderado)

ASUNTO Radicación 06127373
 Trámite 002
 Evento 001
 Actuación 430
 Oficio 09810
 Folios 025

Patente de Invención ☒ Patente de Modelo de Utilidad ☐
Via Nacional ☒
Via PCT (fase nacional) ☐ Cap. I ☐ Cap. II ☐
No. Sol. Internacional No aplica
Fecha de Presentación Internacional No aplica

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

- 1.1. Descripción: (Folios: 27 a 34) como se radicó inicialmente.
1.2. Reivindicaciones: 1 a 12 (Folios: 35 y 36) como se radicó inicialmente. Modificadas: 1 a 10 (folios: 147 y 148).
1.3. Prioridad: 21/12/2005 FR 05.13008.

2. Análisis de la Prioridad:

La prioridad de la presente solicitud corresponde al objeto reivindicado.

3. Objeto de la Invención:

La presente solicitud se titula: "Nuevas composición de un inhibidor de la corriente sinusal If y de un inhibidor cálcico y las composiciones farmacéuticas que lo contienen" (Ver folio: 146).

El objeto de la presente solicitud se refiere a una nueva asociación de un inhibidor selectivo y específico de la corriente sinusal If, que es la ivabradina, así como sus hidratos, formas cristalinas y sales de adición de un ácido farmacéuticamente aceptable, y de un inhibidor cálcico y más particularmente un inhibidor cálcico de la clase de dihidropiridinas; éstos inhibidores cálcicos en la asociación según la presente solicitud son: amlodipino, nifedipino, felodipino y sus hidratos, formas cristalinas y sales de adición de un ácido o de una base farmacéuticamente aceptable y más particularmente el besilato o el maleato.

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Según la descripción, los inhibidores selectivos y específicos de la corriente sinusal If y más particularmente ivabradina, tienen propiedades cronotrópicas negativas (*reducción de la frecuencia cardíaca*), que hacen a estos compuestos útiles en el tratamiento o prevención de diferentes situaciones clínicas de *isquemia miocárdica tales como la angina de pecho, el infarto de miocardio y los trastornos del ritmo asociados*, así como las diferentes patologías que implican *trastornos del ritmo, especialmente supra-ventriculares y en la insuficiencia cardíaca*.

Los inhibidores cálcicos son moléculas que tienen como propiedad esencial bloquear la permeabilidad al calcio de ciertos canales de la membrana celular. Ellos impiden la *abertura de los poros de los canales dependientes del voltaje*. Se oponen así a la penetración del calcio en las fibras musculares lisas de los vasos. Disminuyen la *tasa de calcio libre intracelular, lo que tiene como consecuencia reducir el tono de los músculos lisos de los vasos periféricos y coronarios*.

Así, estos compuestos, particularmente los que pertenecen a la clase de las dihidropiridinas están *especialmente indicados en el tratamiento de la angina de pecho* porque disminuyen el retorno venoso aliviando así el trabajo del ventrículo izquierdo y disminuyen el consumo miocárdico de *oxígeno por una parte y por otra parte mejoran el flujo sanguíneo coronario gracias a su acción vasodilatadora al nivel de las arterias epicárdicas mayores*. Los *efectos indeseables de estos compuestos* son taquicardias, palpitaciones, cefaleas, edemas de los miembros inferiores dependientes de las dosis.

En el capítulo reivindicatorio se reclama lo siguiente:

Reivindicaciones 1 a 7 (folio: 147): Composición farmacéutica comprendida en un inhibidor selectivo y específico de la corriente sinusal If, y de un inhibidor de la ivabradina,... o uno de sus hidratos, formas cristalinas o sales de adición de un ácido farmacéuticamente aceptable y un inhibidor cálcico.

Reivindicaciones 8 y 9 (folio: 148): Composiciones farmacéuticas que contienen como principio activo un inhibidor selectivo y específico de la corriente sinusal If en asociación con un inhibidor de ivabradina,... o uno de sus hidratos o formas cristalinas, solos o en combinación con uno o varios ácidos farmacéuticamente aceptables y un inhibidor de calcio, de acuerdo con las reivindicaciones 1 a 7, solos o en combinación con uno o varios excipientes farmacéuticamente aceptables.

Reivindicación 10 (folio: 148): Las composiciones farmacéuticas de acuerdo con las reivindicaciones 1 a 9, usadas para la fabricación de un medicamento para el tratamiento de la angina de pecho.

El problema planteado en esta solicitud es la necesidad de nuevos tratamientos que permitan beneficiarse de los efectos positivos de los inhibidores cálcicos aumentando su margen de seguridad, especialmente cardiovascular.

La solución propuesta por la presente solicitud consiste en una asociación de un inhibidor selectivo y específico de la corriente sinusal If y de un inhibidor cálcico.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/55; A61P 9/06.

4. De la solicitud de Patente

4.1. Descripción (artículo 28 D. 486)

De acuerdo con lo revelado en la descripción, el título modificado de la presente solicitud debe mencionar los componentes específicos de la composición que se desea proteger. Además, se debe aclarar si se trata de una composición dentro de

otra composición y analizar si ello se encuentra sustentado dentro de la descripción, para lo cual requeriría una nueva modificación al título de la solicitud.

4.2. Reivindicaciones (artículo 30 D 486)

De acuerdo con lo revelado en el capítulo reivindicatorio modificado, continúa siendo poco conciso por cuanto se refiere a las actividades de los fármacos que estarían en la composición farmacéutica. Por otra parte, se debe aclarar el término "inhibidor de la Ivabradina".

Las reivindicaciones 8 y 9 (folio: 148) no son claras puesto que dice: "composiciones farmacéuticas que contienen como principio activo un inhibidor selectivo y específico de la corriente sinusal If en asociación con un inhibidor de Ivabradina": no se comprende a cuál inhibidor específico de la corriente sinusal If se refiere la reivindicación, ni qué se quiere decir con "inhibidor de Ivabradina". Tener en cuenta que el fármaco Ivabradina es un inhibidor de la corriente sinusal. Además, se dice que esta asociación o los fármacos en cuestión van solos o en combinación con uno o varios ácidos (no se especifica el número ni cuáles) o con uno o varios excipientes (tampoco se especifica el número ni cuáles) y no se especifica que los fármacos se encuentren en un mismo sistema de entrega (SENF). De la lectura de estas reivindicaciones se puede apreciar que se trata de dos o más formulaciones asociadas o combinadas para su posterior administración a un paciente. Favor aclarar.

5. Análisis de la(s) Oposición(es): (artículo 43 D. 486)

No se presentaron oposiciones al objeto reivindicado.

6. Determinación del Estado de la Técnica:

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 21-12-2005.

Teniendo en cuenta la fecha indicada, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se encontró como anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
D1	Artículo 1	Ivabradine in clinical practice: Benefits of If inhibition ¹	2005
D2	Artículo 2	Long term safety and antianginal efficacy of the If current inhibitor ivabradina ²	2004
D3	EP 1362590	Use of cilobradine or the pharmaceutically acceptable salts thereof for the treatment or prevention of heart failure	19 de noviembre de 2003
D4	Artículo 3	Current and future treatment strategies for refractory angina ³	Octubre de 2004
D5	Artículo 4	Actualización en fármacos antiarrítmicos ⁴	2004

1 TARDIF J-C: "Ivabradine in clinical practice: Benefits of If inhibition". European Heart Journal, Supplement, vol. 7, No. H, pp H29-H32. Refs: 26 ISSN: 1520-765X, Coden: EHJST, 2005.

2 López-Bascós L, Filipova S, Martí R, on behalf of the study investigators. Long-term safety and antianginal efficacy of the If current inhibitor ivabradine in patients with chronic stable angina. A one-year randomised, double-blind, multicentre trial (resumen). Eur Heart J, 2004;25:878.

3 YANG, E., BARNES G., GERSH B., CHANDRASEKARAN K., LERMAN A. "Current and future treatment strategies for refractory angina". Mayo Clin Proc. Oct 2004; 79(10): 12854-1292.

4 CACHARRÓN, J., ALDARIZ, A. "Actualización en fármacos antiarrítmicos". 2004.

7. Análisis de patentabilidad (artículo 14 D486)

7.1. Novedad (artículo 16 D486)

Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

La presente Solicitud de Patente Colombiana No. 06127373, se refiere a:

Composiciones farmacéuticas que contienen como principio activo un inhibidor selectivo y específico de la corriente sinusal If en asociación con un inhibidor de ivabradina, ... o uno de sus hidratos o formas cristalinas, solos o en combinación con uno o varios ácidos farmacéuticamente aceptables y un inhibidor de calcio, de acuerdo con las reivindicaciones 1 a 7, solos o en combinación con uno o varios excipientes farmacéuticamente aceptables.

La anterioridad: Artículo 1 (folios: 141 a 144), se relaciona con: composiciones de ivabradina y menciona además composiciones de amlodipina (es un bloqueador de calcio). Adicionalmente divulga la administración de estos fármacos solos o en combinación a pacientes con angina de pecho.

La anterioridad: Artículo 2 (folio: 145), trata sobre: un estudio realizado a pacientes con angina en donde se administran composiciones de ivabradina y de amlodipina solas o en combinación.

El elemento característico de las composiciones reivindicadas, ya era conocido en artículo 1 y artículo 2; por lo cual las composiciones de las reivindicaciones 8 y 9 no pueden considerarse nuevas.

7.2. Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica lo siguiente: Composición farmacéutica comprendida en un inhibidor selectivo y específico de la corriente sinusal If, y de un inhibidor de la ivabradina, ... o uno de sus hidratos, formas cristalinas o sales de adición de un ácido farmacéuticamente aceptable y un inhibidor cálcico.

El Artículo 1 (folios: 141 a 144) enseña un estudio clínico con ivabradina para el tratamiento de la angina en donde se comparan los efectos de éste fármaco con otro tipo de fármacos pertenecientes a las siguientes clases terapéuticas: β -bloqueadores y bloqueadores de calcio; además, menciona la terapia de combinación anti-anginal en donde se encontró evidencia importante que la terapia de combinación es más efectiva que la monoterapia (ver folio: 143). Allí se revela que la eficacia y seguridad de la terapia de combinación de ivabradina en 386 pacientes con angina estable tratados con nitratos o bloqueadores de calcio. Se concluyó que el número de ataques por angina se redujo significativamente por la adición de ivabradina.

El Artículo 2 (folio: 145) destaca el estudio de López-Bescós et al, con 386 pacientes con angina estable que recibían amlodipina o nitratos, a los que se añadió, a doble ciego, ivabradina o placebo. En un seguimiento de 12 meses se redujo la frecuencia cardíaca (FC) entre 10-12 lpm a dosis de 5 y 7,5 mg de ivabradina y se observó una disminución significativa de los episodios de angina respecto a la situación basal en los pacientes que recibían ivabradina.

La ivabradina, inhibidor selectivo de la corriente iónica de los canales If, prolonga el tiempo de despolarización espontánea diastólica de las células del nodo sinusal y consigue una reducción de la FC en reposo y en esfuerzo similar a la de los β -bloqueadores. En consecuencia, produce una franca mejoría de los síntomas de angina y de los parámetros de isquemia valorados en las pruebas de esfuerzo, en proporción similar a los antagonistas del calcio o los β -bloqueadores. También se ha

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demostrado beneficio adicional combinado con otros fármacos antianginosos. El nivel de eficacia y seguridad de ivabradina en cuanto a efectos adversos graves ha sido muy alto y similar al de placebo. Este documento revela que la ivabradina se ha utilizado en terapia combinada con otros antianginosos.

El documento EP 1362590 (folios: 154 a 157) se relaciona con el uso de cilobradina (un inhibidor de la corriente sinusal If) para el tratamiento de fallas cardíacas. Este compuesto se puede administrar solo o en combinación con otro tipo de medicamentos de las clases terapéuticas: inhibidores de la ECA, vasodilatadores, β -bloqueadores, inotrópicos, diuréticos o glicósidos cardiotónicos. Es sabido por una persona medianamente versada en la materia que las dihidropiridinas (por ejemplo amlodipina) tienen acción predominantemente vasodilatadora. Además, los inhibidores del calcio pueden actuar como inotrópicos negativos.

El artículo 3 (folios: 158 a 166) se refiere a varias estrategias de tratamiento para la angina refractaria. Entre las terapias farmacológicas se encuentran las que utilizan fármacos como la ranolazina (inhibidor de la oxidación de ácidos grasos), ivabradina (inhibidor de los canales iónico If), nicorandil (activa canales de potasio), L-arginina (vasodilatador endotelio-dependiente), testosterona y estrógeno (dilatador de arteria coronaria y agente antianginal, respectivamente).

En este artículo se divulga también el estudio realizado por Tardif (artículo 1) en donde se comparó ivabradina con atenolol y mostró mejores efectos. También menciona otro estudio realizado donde se comparó ivabradina con un placebo y mostró una reducción del 77% en la frecuencia de eventos de angina. De igual manera el estudio realizado con ranolazina revela combinaciones con otros antianginosos, como por ejemplo, amlodipina, mostrando mejores resultados a los de la monoterapia.

El artículo 4 (folios: 167 a 172) relaciona algunas generalidades sobre los fármacos antiarrítmicos y aspectos de la electrofisiología celular en relación con los efectos de los mismos. Enseña la importancia de los canales iónicos en la frecuencia cardíaca (iones Na, K, Ca) y los canales iónicos como sitios de acción de los fármacos antiarrítmicos, en donde los canales comprometidos en la actividad automática (células del nódulo sinusal), la corriente de calcio tipo T y la corriente hiperpolarizante (If) aportan la despolarización que precede a la fase 0 y que los fármacos que disminuyen estas corrientes deben disminuir la frecuencia cardíaca y tener un efecto cronotrópico negativo. Aquí se encontrarían fármacos como la ivabradina por ser inhibidor de la corriente If. Este documento también enseña los efectos electrofisiológicos de los bloqueadores del calcio (en esta categoría se encuentra amlodipina).

El problema técnico planteado en esta solicitud: la necesidad de nuevos tratamientos que permitan beneficiarse de los efectos positivos de los inhibidores cálcicos aumentando su margen de seguridad, especialmente cardiovascular, se había resuelto previamente mediante una asociación de un inhibidor selectivo y específico de la corriente sinusal If y de un inhibidor cálcico ya conocida. Por esta razón se considera que los componentes de las composiciones reivindicadas en la presente solicitud son evidentes para una persona medianamente versada en la materia.

La(s) reivindicación(es) 1 a 10 de esta solicitud no menciona(n) una característica que conceda un efecto inesperado o especial a las composiciones, que pueda considerarse como un aporte a la técnica, así que son obvias(as) para una persona versada en la materia.

Además, puesto que D1-D3-D5, D2-D3, D1-D4-D5 divulgaban previamente terapias de combinación de inhibidores de la corriente sinusal If y de un inhibidor de calcio (folios: 141 a 145, 154 a 172), una persona conocedora de la materia motivada por tales sugerencias lograría el objeto de esta solicitud composiciones de un inhibidor

selectivo y específico de la corriente sinusal If, y de un inhibidor de la Ivabradina, ... o uno de sus hidratos, formas cristalinas o sales de adición de un ácido farmacéuticamente aceptable y un inhibidor cálcico; de manera que para una persona medianamente versada en la materia sería obvio combinar estos documentos. Por lo cual puede no haber Nivel Inventivo.

8. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	Artículo 1	8 y 9	Novedad
		1 a 10	Nivel Inventivo
D2	Artículo 2	8 y 9	Novedad
		1 a 10	Nivel Inventivo
D3	EP 1362590	1 a 10	Nivel Inventivo
D4	Artículo 3	1 a 10	Nivel Inventivo
D5	Artículo 4	1 a 10	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 05 AGO 2010

CONCEPTO TÉCNICO No. 2683

EXAMINADOR TÉCNICO
Código No. 202005

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	06127373		20-12-2006
	FR 05.13008		21-12-2005

AMLODIPINE	IVABRADINE	DIDYDROPYRIDINE
COMPOSITION	ASSOCIATION	COMBINATION
CALCIUM BLOCKER	BRADYCARDIC	SINUS NODE

A61K 31/55	
A61P 9/06	

EP1800683	US 2007/0142356

EPOLINE	GOOGLE
ESPACENET	NCBI
USPTO	

EUROPEA	
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EP 1362590		
US 2004/013836		
ES 2303198		
ES 2266216		

TARDIF J-C: "Ivabradine in clinical practice: Benefits of If inhibition". European Heart Journal, Supplement, vol. 7, No. H, pp H29-H32. Refs: 28 ISSN: 1520-765X, Coden: EHJSFT, 2005. LOPEZ-BESCOS ET AL: "Long term safety and antilanginal efficacy of the If current inhibitor ivabradine". Eur Heart J. Vol. 25(supl), 2004, p. 138 RUZYLLO ET AL: "Antilanginal and antischemic effects of the If current inhibitor ivabradine". Eur. Heart J. Vol. 26(supl), 2004, p. 138		
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