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Referencia: Radicación No. 06019926
PATENTE DE INVENCION
Complemento de información

JULIO CÉSAR RAMÍREZ PIÑA, identificado con la cédula de ciudadanía n° 79'779.990 de Bogotá, portador de la tarjeta profesional de abogado n° 113.206 del C. S. de la J., en calidad de apoderado de la sociedad **LES LABORATOIRES SERVIER**, tal y como consta en la sustitución de poder radicada en su Despacho el pasado 22 de octubre, por medio del presente escrito me dirijo a Usted para aportar en 7 folios en inglés el extracto de la traducción de la publicación denominada "Ivabradine hydrochloride antianginal HCN (LF current) blocker" 2003, Drugs of the future, Barcelona, ES, páginas 652 – 658, solicitadas por su Despacho a mi mandante mediante el oficio 9565, notificado el 20 de agosto de 2009.

Los documentos serán traducidos al español y se aportarán a la brevedad.

Recibo notificaciones en la carrera 11 No. 86 – 32, Oficina 101, de esta ciudad, o en el casillero asignado al suscrito por esa entidad.

De Usted,


JULIO CÉSAR RAMÍREZ PIÑA
CC n° 79'779.990 de Bogotá
tp n° 113206 del C. S. de la J.

Se anexan 7 folios.

Ivabradine Hydrochloride

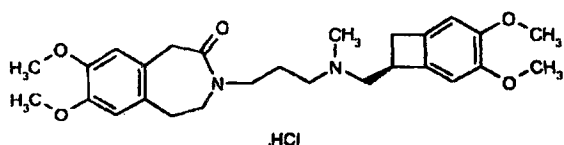
Prop INNM

Antianginal
HCN (I₁ Current) Blocker

S-16257-2

Procoralan®

(+)-3-[3-[N-[4,5-Dimethoxybenzocyclobutan-1(S)-ylmethyl]-N-methylamino]propyl]-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepin-2-one hydrochloride



C₂₇H₃₈N₂O₅·HCl

Mol wt: 505.0513

CAS: 148849-67-6

CAS: 148870-80-8 (as racemate)

CAS: 155974-00-8 (as free base)

EN: 210860

Abstract

Treatment for angina includes reducing heart rate with agents such as β -adrenergic blockers and calcium channel blockers. However, these agents also exert other unwanted activities such as negative inotropic and hypotensive effects which could have serious consequences. Thus, the search for novel heart rate-reducing compounds without unwanted inotropic effects was initiated. A new class of specific bradycardic agents act specifically on the SA node by directly interacting with the pacemaking cell of the SA node and the hyperpolarization-activated I_h, the primary pacemaking current of the SA node. Ivabradine is one such bradycardic agent to emerge that has been shown to specifically and selectively interact with f-channels of pacemaker cells to block I_h and consequently reduce the speed of diastolic depolarization and decrease heart rate. Due to its potent preclinical action, ivabradine was selected for further development as a treatment for stable angina and underlying myocardial ischemia as well as supraventricular arrhythmias.

Synthesis

Reduction of 4,5-dimethoxybenzocyclobutane-1-carbonitrile (I) with BH₃ in THF gives 4,5-dimethoxybenzocyclobutan-1-ylmethylamine (II), which is treated with ethyl chloroformate (III) and triethylamine in dichloromethane to yield carbamate (IV). Reduction of carbamate (IV) by means of LiAlH₄ in THF provides racemic N-(4,5-dimethoxybenzocyclobutan-1-yl)-N-methylamine (V), which is submitted to optical resolution with camphorsulfonic acid (CSA) to afford the desired (S)-enantiomer (VI). Reaction of the known 3-(3-chloropropyl)-7,8-dimethoxy-2,3-dihydro-1H-3-benzazepin-2-one (VII) with NaI in acetone yields the corresponding 3-iodopropyl derivative (VIII), which is condensed with the chiral amine (VI) by means of K₂CO₃ in acetone to afford adduct (IX). Finally, this compound is hydrogenated with H₂ over Pd(OH)₂ in AcOH (1). Scheme 1.

Introduction

Angina pectoris is characterized by recurring pain or discomfort in the chest and is usually triggered by physical exertion. It occurs due to an imbalance between myocardial perfusion and myocardial metabolic demands so that the oxygen requirement of the heart exceeds the supply available in perfusing blood. Angina can be a symptom of coronary artery disease, where blood vessels leading to the heart become narrowed or blocked due to atherosclerosis and therefore are unable to provide the heart with enough blood. There are several forms of angina: stable, unstable, Prinzmetal's (or variant) and microvascular (or Syndrome X) angina. The two most common forms are stable angina, which emerges gradually and in a regular pattern and results from predictable causes, and unstable angina (also known as

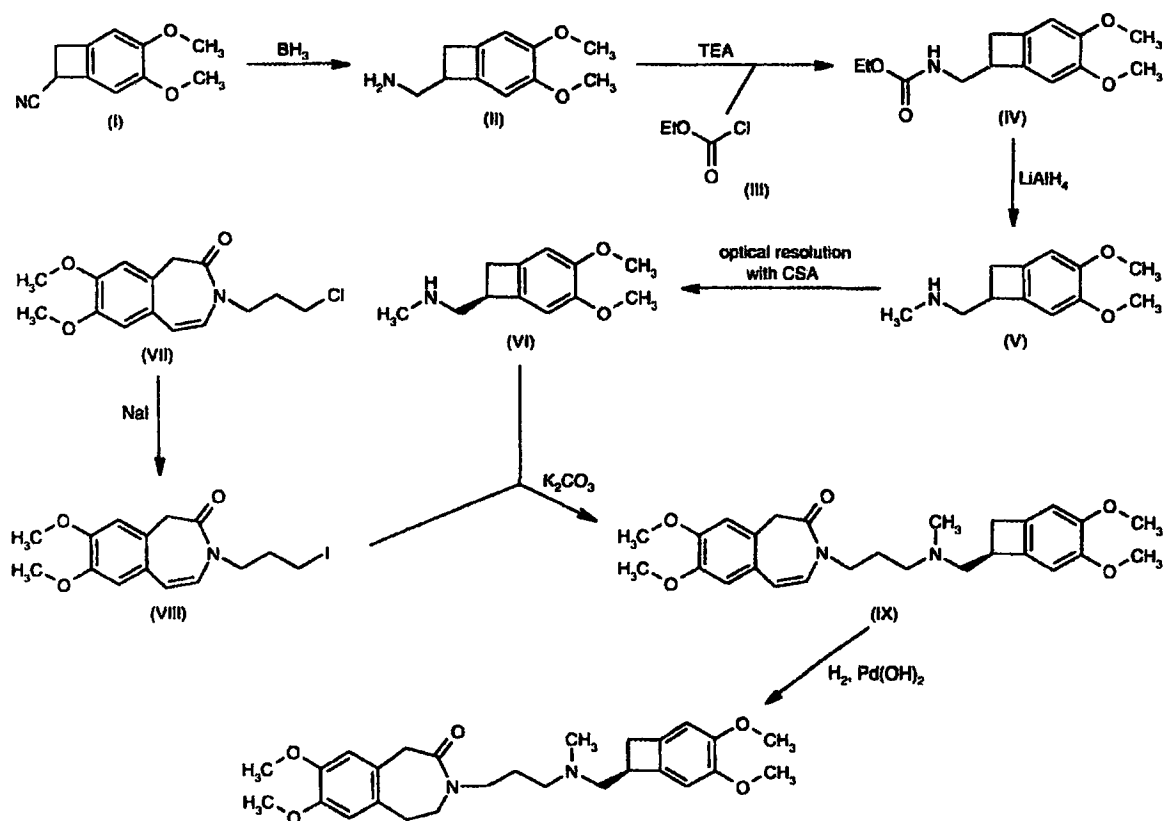
L.A. Sorbera, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

LB141B18 DST: 28.11.2003
PU32643ENG0
IVABRADINE CHLORHYDRATE
METABOLITE



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Scheme 1: Synthesis of Ivabradine



acute coronary syndrome), which can emerge as a sudden severe episode or in frequent bouts. According to the American Heart Association, more than 6 million individuals (approximately 2 million men and 4 million women) in the U.S. suffer from angina pectoris with about 400,000 new cases of stable angina and 150,000 cases of unstable angina reported each year. It is estimated that by the year 2030, the number of individuals at risk for ischemia and chronic angina will increase by 50% (2).

Chronic stable angina pectoris is extremely disabling, limiting everyday activities. A possible treatment solution is a reduction in heart rate which would increase diastolic filling time, thereby improving myocardial perfusion and myocardial oxygen demand. Heart rate reduction has been clinically accomplished by administration of β -adrenergic blockers and some calcium channel blockers. However, these agents also exert other unwanted activities such as negative inotropic and hypotensive effects which could have serious consequences in individuals with depressed left ventricular function (2-6).

The search has continued for agents that lower heart rate without the unwanted effects. One interesting target

is selective and specific modulation of the sinoatrial (SA) node which is responsible for generating pacemaker activity. Pacemaking is thought to involve 4 time-dependent currents: decay of the outward potassium current (I_K) activated during the preceding action potential, activation of the time-dependent inward current (I_T), activation of the T-type and activation of the L-type $I_{\text{Ca}^{2+}}$. I_f , a mixed Na^+/K^+ inward current activated by hyperpolarization, is considered the most important pacemaking modulator and, due to the important role it plays in the control of heart rate, I_f has been identified as an important pharmacological target. The I_f (i.e., funny) channels, a new family of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, are involved in the generation of spontaneous activity of pacemaker cells. Consequently, they mediate autonomic control of cardiac rate and are now considered an important pharmacological target for antianginal drugs. A new class of specific bradycardic agents have been described that act specifically on the SA node and its pacemaking currents and channels. These agents are associated with only limited inotropic effects and therefore have the potential to be used

clinically, where a reduction in the heart rate is required without alteration of other cardiovascular functions such as in the case of angina pectoris and other forms of myocardial ischemia (7-13).

Ivabradine (S-16257) is the (+)-enantiomer of the racemic compound S-15544 (S-16260 is the (-)-(*R*)-enantiomer) and it specifically and selectively interacts with I_f -channels on the intracellular side of the plasma membrane of pacemaker cells blocking I_f . The consequence is a reduction in the speed of diastolic depolarization and a decrease in heart rate; ivabradine has minimal effects on action potential duration. Ivabradine is an open channel, use-dependent blocker that inhibits when I_f is deactivated upon depolarization and relieved when I_f is activated upon hyperpolarization. Due to its potent pre-clinical negative chronotropic actions, ivabradine was selected for further development as a treatment for stable angina and underlying myocardial ischemia, as well as for supraventricular arrhythmias (10).

Pharmacological Actions

The potent and specific bradycardic effects of ivabradine have been demonstrated in several *in vitro* and *in vivo* preclinical models.

The stereospecific bradycardic effects of ivabradine and S-16260 were demonstrated in 2 studies using isolated rabbit guinea pig SA node tissue, right atria and ventricular papillary muscle and Purkinje fibers *in vitro* and anesthetized pigs *in vivo*. Results showed that ivabradine had an increased specificity with minimal direct effects on action potential (AP) repolarization. Both ivabradine and S-16260 (0.03, 0.1, 0.3 and 1 mg/kg i.v.) were equipotent *in vivo* in significantly reducing heart rate (-15.7 ± 3 and $-20.3 \pm 3.6\%$, respectively, at 0.1 mg/kg), although S-16260 (0.3 and 1 mg/kg) prolonged the QTc interval *in vivo* whereas ivabradine had no effect. Both enantiomers had negative chronotropic effects on spontaneously beating right atria ($plC_{50} = 5.07 \pm 0.19$ and 4.76 ± 0.18 for ivabradine and S-16260, respectively) and both (3 μ M) reduced AP firing rate in isolated spontaneously beating SA node preparations (-19.6 ± 2.5 and $-16.9 \pm 1.4\%$, respectively). However, ivabradine (3 μ M) only slightly increased AP duration in contrast to the (*R*)-enantiomer which exhibited a significantly more potent prolonging effect (APD₅₀ prolongation = 6.7 ± 2.2 vs. $19.2 \pm 22\%$). Similar concentration-dependent reductions in the maximum upstroke velocity (V_{max}) and amplitude of APs were observed for both enantiomers (at concentrations greater than 5 μ M) in guinea papillary muscle preparations paced at 1 Hz, with no alterations in resting membrane potential or AP duration observed (14-16).

Results from experiments using whole isolated perfused rabbit hearts showed that ivabradine significantly reduced heart rate in a manner more potent than esmolol or nicorandil. Ivabradine did not compromise left ventricular (LV) function of flow (16).

An *in vitro* study using isolated guinea pig papillary muscle and rabbit SA node tissue and Purkinje fibers

examined the effects of ivabradine as compared to zatebradine (1, 3 and 10 μ M) on intracellular recording of APs. Results showed that both agents were equipotent in slowing spontaneous APs recorded from SA node tissue which occurred due to a reduction in the rate of diastolic depolarization (maximum = -23.8 ± 3.9 and $-27.9 \pm 26\%$, respectively, with 3 μ M). However, zatebradine had significantly more effect on AP duration at 50% of total repolarization (APD₅₀) as compared to ivabradine ($+29.1 \pm 3.7$ vs. $8.9 \pm 2.9\%$ at 3 μ M). Similarly, while ivabradine only slightly prolonged AP repolarization of papillary muscle preparations paced at 1 Hz and Purkinje fibers paced at 0.25 Hz, zatebradine had more marked elevating effects on the APD₅₀ ($+6.1 \pm 0.6$ vs. $+11.2 \pm 1.3\%$ at 1 μ M in papillary muscle; $+14.1 \pm 5$ vs. $149.4 \pm 51.2\%$ at 3 μ M in Purkinje fibers). Thus, ivabradine had a more specific bradycardic effect as compared to zatebradine since it caused a lesser increase in myocardial repolarization time (10).

The specific bradycardic action of ivabradine was confirmed to be via modulation of pacemaker current in several *in vitro* electrophysiological studies.

A study using whole-cell and inside-out macro-patch clamp recordings of isolated rabbit SA node cells showed that ivabradine markedly blocked I_f in an exponential use- and dose-dependent manner ($IC_{50} = 2.8 \mu$ M). Because similar blocking effects were observed in both whole-cell and inside-out macro-patch preparations, it was concluded that ivabradine interacts with I_f channels from the inside of the cell. Ivabradine (10 μ M) had no effect on T-type I_{Ca} and only slightly reduced L-type I_{Ca} and the delayed outward I_K . In contrast, zatebradine (3 μ M) reduced I_K by $20.3 \pm 2.5\%$. These results suggest that ivabradine has little potential to induce significant negative inotropic effects and, in contrast to zatebradine, would have less of a prolonging effect on repolarization time (17).

A study also using isolated rabbit SA node cells characterized the blocking effects of ivabradine on I_f . Ivabradine was shown to be an open channel blocker acting preferentially when channels deactivate upon depolarization. The ivabradine-mediated block was relieved by long hyperpolarizing steps. These characteristics are indicative of a use-dependent block and similar to those observed with zatebradine and ZD-7288. Further analysis of the ivabradine-induced block of I_f revealed that the block was dependent on the current driving force as opposed to voltage. Thus, ivabradine-induced block of I_f is coupled to ionic flow (18).

Further characterization of ivabradine blocking of the I_f -channel current was performed in an experiment using HEK293 cells expressing human heart HCN channels HCN2 and HCN4. Results indicated that ivabradine has a higher sensitivity for the HCN4 channel (IC_{50} at -140 mV = 3.6 ± 0.4 vs. $10.2 \pm 1.1 \mu$ M) and because it blocked the channel with a Hill coefficient near 1, the agent most probably binds to only one site on the HCN channel (19).

An earlier study using a mouse L cell line stably expressing human cloned K^+ channels hKv1.5 suggested

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that ivabradine (1-100 μ M) also time-, concentration- and voltage-dependently blocked this channel. The agent once again behaved as an open channel blocker (20).

The bradycardic efficacy and lack of negative inotropic action of ivabradine have been extensively demonstrated *in vivo* in rats and dogs.

The chronic cardiac and regional hemodynamic effects of single and repeated doses (1 mg/kg i.v. bolus or s.c. for 4 days) of ivabradine were examined in chronically instrumented rats. Intravenous injection of ivabradine resulted in an immediate, transient pressor effect. Later, significant reductions in heart rate, mean arterial blood pressure, cardiac index and total peripheral conductance and significant increases in stroke index and peak aortic flow were observed; the decreases in heart rate and cardiac index were not linearly related. Treatment with the agent was also associated within the first hour postinjection with reductions in renal, mesenteric and hindquarter blood flow and vascular conductances. No negative inotropic effects were observed. Similar effects were observed with 4-day s.c. administration except that the rates of onset of effects were slower; no desensitization or impairment of regional perfusion were observed with repeated s.c. dosing (21). Another study conducted in conscious rats reported that i.p. administration of ivabradine decreased heart rate by 29% while simultaneously increasing heart rate variability (22).

The bradycardic effects of ivabradine were also evident in rats with congestive heart failure (*i.e.*, chronic ligation), where long-term treatment (10 mg/kg/day p.o. for 3 months starting 7 days postligation) resulted in significant reductions in heart rate (299 $\pm$ 241 $\pm$ 8 vs. 385 $\pm$ 13 beats/min) and improvements in cardiac function (*i.e.*, LV end-diastolic pressure [LVEDP], stroke volume, cardiac output) which persisted even at 3 days after the end of treatment. After 3 months of treatment, LV collagen density was significantly reduced by 2.9 $\pm$ 0.1% and myocardial capillary density was significantly increased (103 $\pm$ 4 vs. 85 $\pm$ 6 capillaries/field) (23).

The bradycardic efficacy of ivabradine (0.1-1 mg/kg i.v. over 5 min) was demonstrated in chronically instrumented resting and exercising conscious dogs. Dose-dependent bradycardia was observed in resting dogs with significant effects noted at 0.5 (-16 $\pm$ 3%) and 1 (-23 $\pm$ 3%) mg/kg. Although both propranolol (1 mg/kg) and ivabradine (0.5 mg/kg) reduced resting heart rate and treadmill exercise-induced tachycardia in a similar manner, ivabradine did not increase mean coronary blood flow velocity or reduce coronary vascular resistance as was seen in propranolol-treated animals. Ivabradine had no effect on resting epicardial coronary artery diameter and attenuated its increase during exercise and did not affect cardiac output and stroke volume during exercise. In contrast, propranolol-treated dogs exhibited reduced epicardial artery diameter at rest and significantly constricted artery diameter, reduced cardiac output and stroke volume during exercise. No negative inotropic or vasoconstrictor effects were observed in animals treated with ivabradine (24).

Ivabradine was shown to exert bradycardic and anti-ischemic effects in a canine model which combines treadmill exercise and partial coronary stenosis. In this model, LV wall thickening in the ischemic zone was depressed in saline-treated animals during exercise followed by prolonged myocardial stunning. When ivabradine was administered before exercise, heart rate was significantly decreased at resting (-22 $\pm$ 7%) and during exercise (-33 $\pm$ 4%) and recovery (-21 $\pm$ 2%). During exercise, ivabradine-treated animals also showed improved LV wall thickening (14 $\pm$ 1 vs. 7 $\pm$ 1%) and subendocardial perfusion as compared to saline-treated controls. These anti-ischemic effects resulted in a marked reduction in intensity of myocardial stunning which were also observed when ivabradine was administered after exercise. Atrial pacing during exercise abolished the effects of ivabradine (25).

The effects of ivabradine were also compared to the β -blocker atenolol in 2 studies using treadmill exercised, instrumented dogs. Both agents (1 mg/kg i.v.) reduced heart rate by about 30% without altering LV mean ejection wall stress and reduced myocardial oxygen consumption (from 8.1 $\pm$ 0.6 ml/min to 6.7 $\pm$ 0.6 and 4.7 $\pm$ 0.4 ml/min with ivabradine and atenolol, respectively). Both agents also increased diastolic time, although ivabradine exhibited a more marked effect (from 123 $\pm$ 4 ms to 233 $\pm$ 11 vs. 195 $\pm$ 6 ms with atenolol). In contrast to ivabradine which had no effects, atenolol decreased LV dP/dt_{max} . Ivabradine had no significant effects on myocardial oxygen consumption or diastolic time under atrial pacing in contrast to atenolol, which significantly decreased these parameters (26). Further comparison of the two agents revealed that in order to induce similar reductions in heart rate at rest and during exercise, atenolol increased the extent of LV relaxation during rest and impeded the shortening of LV relaxation during exercise. Ivabradine exhibited no such negative lusitropic effects (27).

Pharmacokinetics

A selective HPLC method with fluorescence detection to determine ivabradine and its *N*-demethylated metabolite in human, rat and dogs plasma and in human urine, was described and validated. Calibration curves were linear at concentrations of 0.5-100 ng/ml in plasma and 2-500 ng/ml in urine; the limit of quantitation for plasma and urine was 0.5 and 2 ng/ml, respectively. The method was validated using plasma and urine samples from clinical and nonclinical trials in which subjects were administered single- and multiple-dose i.v. or p.o. ivabradine (28).

Another method to simultaneously determine ivabradine and 6 potentially active metabolites in human plasma has been described. The method is a rapid, selective LC method with tandem mass spectrometric detection. Linear responses were obtained for the agent and its metabolites from 0.1 or 0.1-20 ng/ml with the limit of quantitation ranging from 0.1-0.2 ng/ml. The method was validated using plasma samples from healthy volunteers participating in a clinical trial and administered a single

10-mg oral dose of ivabradine. Results showed that the AUC values for active *N*-demethylated metabolite (S-18982) and the unsaturated compound (S-33170) accounted for about 27% and 4.5%, respectively, of the unchanged compound; the O-demethylated metabolites were not detected (29).

Several studies have reported the development of simulation models to describe the pharmacokinetic-pharmacodynamic relationship of ivabradine and its metabolite S-18982.

In one such study, data of reductions in heart rate were pooled from 2 randomized, placebo-controlled studies involving a total of 78 healthy subjects administered ivabradine (10 or 20 mg p.o. b.i.d.). Modeling revealed that both ivabradine and S-18982 exerted bradycardic effects and a multiple ligand pharmacodynamic model was concluded to provide the best fit to the data (30). Another study pooled data from 66 healthy male volunteers participating in randomized, placebo-controlled trials and administered ivabradine (8, 10, 16, 20, 24, 28, 30 or 32 mg p.o. b.i.d. for 5-7 days) in order to create a simulation model to describe the concentration-time course of ivabradine and S-18982. The pharmacokinetics of ivabradine and S-18982 were best described using a 2-linked, 2-compartment i.v. bolus and first-order input with first-pass loss and first-order output model. This model was later simplified for both i.v. and p.o. dosing in another report (31, 32).

These pharmacokinetic and pharmacodynamic simulation models reported for ivabradine and S-18982 were used to design an optimal parsimonious population pharmacodynamics trial (33).

The pharmacokinetics and efficacy of single- or multiple-dose ivabradine (10 or 20 mg p.o. or 10 mg i.v. bolus) were examined in 18 healthy volunteers at rest and during bicycle exercise tests in a study including double-blind, open and control phases. Significant reductions in exercise heart rate were observed after single (11 ± 4 and $18 \pm 6\%$, respectively) and repeated (18 ± 4 and $27 \pm 6\%$, respectively) oral dosing with 10 and 20 mg and after the i.v. bolus ($19 \pm 4\%$). An indirect relationship was found between the bradycardic effect and plasma concentration of ivabradine and S-18982. $C_{\max}$ values for ivabradine and S-18982 were detected at 1-1.5 h after oral dosing; peak plasma S-18982 levels were seen 1 h following i.v. dosing. The metabolite/drug AUC ratios following single and repeated oral dosing were 32.3 ± 5 and $41.4 \pm 9\%$, respectively, with 10 mg and 32.5 ± 5.2 and $43.9 \pm 9.2\%$, respectively, with 20 mg; this ratio was $19.3 \pm 4.9\%$ after the i.v. bolus. The absolute bioavailability of ivabradine was 0.4 ± 0.14 and 0.53 ± 0.17 with 10 and 20 mg, respectively. The cytochrome P450 (CYP) 2D6 metabolic phenotype had no influence on the pharmacokinetics or efficacy of ivabradine (34).

Clinical Studies

The bradycardic effects and tolerability of ivabradine were demonstrated in several studies conducted in

healthy subjects and in patients with chronic stable angina.

A randomized double-blind, placebo-controlled trial involving 60 healthy male volunteers examined the effects of single increasing i.v. bolus doses (1, 2, 4, 8, 16 and 24 mg) of ivabradine on maximal exercise (ergocycle) parameters. Significant, dose-dependent and exclusive reductions in heart rate were observed. No unwanted effects were observed, suggesting that the agent had no negative inotropic action (35).

A randomized, placebo-controlled study in 12 male volunteers examined the electrophysiological effects (*i.e.*, surface ECG) of single-dose ivabradine (10, 20 and 30 mg i.v.). The agent was well tolerated and the space-temporal structures of P, QRS and T waves were unaffected by ivabradine. Bradycardic effects of the agents included significant, dose-related increases in the RR and QT intervals and a slight increase in QTc (Bazett correction) (36, 37).

Another randomized, double-blind, placebo-controlled, parallel-group study involving 60 healthy male volunteers examined the effects of repeated-dose ivabradine (8, 16, 20, 24, 28 and 32 mg b.i.d. for 6 days and once on day 7). Subjects treated with ivabradine had significantly lower mean heart rates over 24 h on day 6 as compared to placebo (50 vs. 75 beats/min). In addition, during exercise on days 1, 2 and 7 postdosing, the heart rate at maximum load was significantly higher in subjects treated with ivabradine as compared to placebo. All doses of the agent were well tolerated (38).

Clinical trial simulations were performed to determine the best protocol to use in a phase III trial in patients with angina pectoris. The simulations predicted the optimal size of treatment effect, dose and number of patients to be included in such trials. Simulations for 100 clinical trial including 200 patients were performed. These included oral dosing with 2.5, 5, 10, 20 and 40 mg q.d. or b.i.d. Efficacy for doses up to 10 mg q.d., 10 mg b.i.d., 20 mg q.d. and 40 mg q.d. ivabradine were seen in 25%, 48%, 55% and more than 80%, respectively, of the simulated trials, respectively. At least 1 adverse effect was experienced by 4% of the patients in both treated and untreated populations (39).

A clinical trial conducted in 360 patients with a 3-month or greater history of chronic stable angina and including a 2-week randomized, double-blind, placebo-controlled phase (2.5, 5 or 10 mg p.o. b.i.d.) followed by 2- to 3-month open label extensions (10 mg b.i.d.) and a 1-week randomized withdrawal to ivabradine (10 mg b.i.d.) or placebo, examined the safety and efficacy of ivabradine on relieving angina and underlying ischemia during exercise. Ivabradine was concluded to be safe and dose-dependent improvements in exercise tolerance and time to development of ischemia during exercise were observed in patients treated with the agent. The time to 1 mm ST-segment depression significantly increased in patients receiving the 5 and 10 mg doses and the time to limiting angina significantly increased in patients in the 10 mg b.i.d. dose group. All exercise tolerance test param-

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ters worsened in patients randomized to placebo in the withdrawal phase of the trial; no rebound phenomena were observed when ivabradine was withdrawn (40).

Ivabradine continues to undergo phase III development as a treatment for myocardial infarction and its cardiovascular repercussions (41).

Source

Servier Laboratoires (FR).

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