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Ivabradine: Just another New Pharmacological Option for Heart Rate Control?

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Abstract

Ivabradine (IVB) is a heart rate lowering agent that acts via selective inhibition of the pacemaker funny current in sinoatrial nodal P cells, thus, reducing heart rate at rest and during exercise with minimal effect on myocardial contractility, blood pressure, and intracardiac conduction. IVB exerts no effect on external respiratory function parameters and it may also play a role in patients with concurrent chronic obstructive pulmonary disease. This property constitutes an important advantage over β-blockers.

IVB acts by reducing the heart rate in a mechanism different from β-blockers, calcium channel blockers or late sodium channel blockers, three commonly prescribed antianginal drugs. As clinical trials have shown, it is remarkably well-tolerated and offers an alternative for patients who cannot take β-blockers. The combination of IVB and atenolol at commonly used doses in patients with chronic stable angina produced additional efficacy with no untoward effect on safety or tolerability. Additionally, side effects are rare and largely limited to a luminous phenomenon or phosphenes. This sensation is thought to be due to a block of *Ih* in the retina, a current very similar to cardiac *If* channels. IVB is contraindicated in patients with sick sinus syndrome or sinus node dysfunction and in patients taking hepatic inhibitors of Cytochrome P450 family 3, subfamily A, polypeptide 4 (abbreviated CYP3A4), with exception of omeprazole or lansoprazole. This review briefly summarizes the main studies regarding this drug.

Keywords: Ivabradine; Heart rate; Pacemaker; Biologic

Introduction

Increased heart rate (HR) is a common profile of sympathetic hyperactivity and cardiovascular disorders [1-3]. Ivabradine (IVB) is a novel, specific, heart rate (HR)- lowering agent that acts by selectively inhibiting the pacemaker funny *If* current in a dose-dependent manner by slowing diastolic depolarization. *If* plays a prominent role in determining pacemaker activity within the central P cells of the sinoatrial node (SAN), and its inhibition unlike many rate-lowering agents. Therefore, it reduces HR in a dose dependent manner both at rest and during exercise with minimal effect on myocardial contractility, blood pressure, and intracardiac conduction [4].

The *If* channel was discovered in 1979 and manifests in pacemaker cells of the SAN, atrioventricular node (AVN), ventricular conduction pathways, and ventricular myocytes. Figure 1 shows a scheme of the *If* pacemaker current action during the P cell potential [4].

Clinical indications of IVB include symptomatic management of chronic stable angina with HR ≥ 60-70bpm, congestive heart failure (CHF), inappropriate sinus tachycardia (IST) and postural orthostatic tachycardia syndrome (POTS) [4].

IVB acts by reducing the HR in a mechanism different from β-blockers, calcium channel blockers or late sodium channel blockers, three commonly prescribed antianginal drugs. As clinical trials have shown, it is remarkably well-tolerated and offers an alternative for patients who cannot take β-blockade [5].

In this review we briefly described new and classical studies which investigated this potential drug and its relationship with the cardiac regulation.

Intrinsic mechanism of action

IVB acts on *If*, which is highly expressed in the SAN. *If* is a mixed Na^+–K^+ inward current activated by hyperpolarization and modulated by the autonomic nervous system. It is one of the most important ion channel currents for regulating pacemaker activity in the SAN. IVB selectively inhibits the pacemaker *If* in a dose-dependent manner. Blocking this channel reduces cardiac pacemaker activity, slowing HR and allowing longer dyastolic times. *If* channels contribute to the initial part of phase 4 of the action potential (AP) in a range from -60/-70 mV to -40 mV, determining the HR, which is mostly influenced by the P cells of the SAN [6].

The molecular determinants of the *If* channel, belong to a family of channels activated at hyperpolarized potentials known as HCN channels. These channels are comprised of heteromultimers of 4 isoforms (HCN1, HCN2, HCN3, HCN4), with HCN2 (chromosome 19p13.3) and HCN4 being the most prevalent in the heart (Hyperpolarization-activated Cyclic Nucleotide-gated channels family

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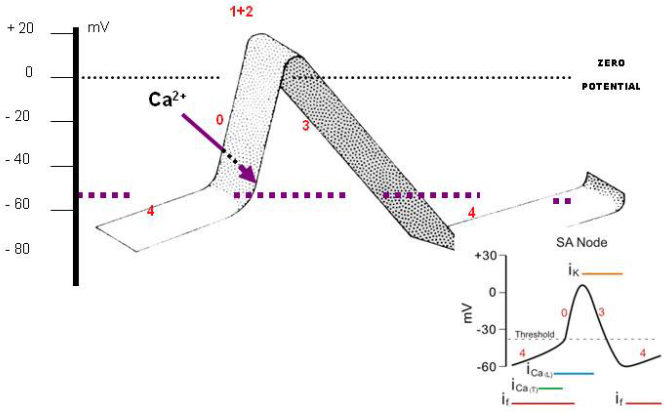

Figure1: Scheme of the moment that the If pacemaker current acts during P cell potential (Phase 4). SAN cells characteristics. Typical profile of APs of slow fibers, which are found in the SAN, AVN and mitro-tricuspid rings. It is characterized by having lower amplitude, absence of identifiable phase 1 and 2, and phase 4 with significant slope (automatism, rhythmycity or phase 4 diastolic despolarization). In the minor left inferior figure is represented the moment of action of If, ICa-T, and ICa-Lon phase 4.

(HCN). Based on the sequence of HCN channels, these are classified as members of a superfamily of voltage-gated K+ (Kv) and CNG channels [7,8].

Mutations in HCN4 (chromosome 15q24-125.3) and CNBD (S672R) isoforms are associated with familial inherited bradycardia, as they cause a similar effect to parasympathetic stimulation, reducing *If* channel activity [5].

Phase 4 depolarization maintained by *If* is a target for autonomic nervous system regulation. Adrenergic agonists such as catecholamines, activate adenylate cyclase, increasing local cAMP concentrations and thus increasing cAMP binding to the *If* channel. Conversely, vagal influences and cholinergic neurotransmitters reduce local cAMP concentrations by inhibiting adenylate cyclase, thereby decreasing cAMP binding to the *If* channel. *If* channels bound to cAMP are more likely to open, increasing the rate of slow diastolic depolarization, whereas unbound channels are more likely to remain closed, lowering the HR [9].

If is also present in the AV node and His-Purkinje system, and can influence physiologic and pathophysiologic automaticity in these cells as well. The SAN pacemaker is the dominant pacemaker in the heart and via overdrive suppression it inhibits the firing of these subsidiary pacemakers [6].

Given the complexity of the cellular processes involved in control of HR, an exact quantification of the extent to which If and other mechanisms contribute to pace-making remains controversial; nonetheless, a wealth of information collected since the current was first described more than 30 years ago, clearly contributed to identify If as a major player in both generation of spontaneous activity and HR control [9].

Given the prominent role in pace-making, f-channels are valuable targets for drugs designed to pharmacologically control HR. Molecules able to bind and to block If-channels can be used as pharmacological options for HR reduction with little or no adverse cardiovascular side effects. Indeed, the selective f-channel inhibitor IVB is today commercially available as an option for the treatment of CSA heart failure and inappropriate sinus tachycardia [4].

Dose and administration route

Initial oral doses of 2.5 mg twice a day are commonly used. A maximum of 7.5 mg daily is also acceptable. However, in several randomized controlled trials IVB was administered 5-10 mg twice daily [8].

Clinical applications

The IVB is a drugs used in several cardiovascular disorders, we describe below the some of the cases in which this pharmacological treatment is indicated.

Chronic stable angina (CSA): There are several agents that are considered vascular protective such as aspirin, angiotensin converting enzyme inhibitors and statins. Conventional anti ischemic therapy includes: β-blockers, calcium-channel blockers long-and short-acting nitrates, and potassium-channel activators. These drugs are often effective; either as monotherapy or in combination, but side effects and contraindications may limit their use. Particularly in elderly patients, the use of β-blockers is limited by poor compliance related to contraindications and comorbidities. In recent years, several other drugs with novel anti ischemic mechanisms have become available including ranolazine, nicorandil and IVB. Reduction of HR with IVB does not improve cardiac outcomes in all patients with CSA and left ventricle (LV) systolic dysfunction, but could be used to reduce the incidence of coronary artery disease (CAD) outcomes in a subgroup of patients who have HR ≥ 70 bpm [10].

The BEAUTIFUL trial [10] was a multicenter, randomized, double-blind, placebo-controlled study to evaluate the superiority of IVB over placebo in reducing cardiovascular events in patients with stable CAD and LV systolic dysfunction (ejection fraction < 39%). This trial has confirmed that elevated HR is a powerful negative prognostic predictor in patients with CAD and LV systolic dysfunction.

Particularly, subjects with a resting HR >70 bpm showed an increased risk of major adverse cardiovascular events. In these patients, HR reduction with IVB was associated with a reduction in major cardiac ischemic events, though not mortality. The study showed that IVB reduces the risk of cardiovascular death, hospitalization for myocardial infarction (MI), and reduction of HF around 24%. IVB significantly reduces the primary end point of cardiovascular death, hospitalization for MI, and new or worsening HF [10].

A subgroup analysis of the randomized, controlled BEAUTIFUL trial [10] studied the effect of IVB on cardiovascular outcomes in patients with stable CAD, LF systolic dysfunction and limiting angina. A total of 1507 patients were included. Among them, 734 patients were treated with IVB, while 773 received placebo. Nearly all patients were additionally receiving conventional treatment aimed at protecting against cardiovascular events, with approximately nine out of every 10 patients on β-blockers.

IVB reduced the risk of MI in angina patients, with a greater benefit in patients with HR >70 bpm. The benefit of IVB was even more striking in angina patients with higher resting HR (≥70 bpm). The primary end point of cardiovascular death, hospitalization for MI, and HF was reduced by 31%, the risk of hospitalization due to MI by 73%, and the need for coronary revascularization by 59%.These findings support the use of IVB as an antianginal agent with documented benefits in patients with angina [11].

Tardif et al. [12] evaluated the anti-anginal and anti-ischaemic efficacy of IVB in patients with CSA receiving β-blockers. The study was

a double-blinded trial. They studied 889 patients with CSA receiving atenolol 50 mg/day and were randomized to receive IVB 5 mg twice a day for 2 months, increased to 7.5 mg twice a day for a further 2 months, or placebo. Patients underwent treadmill exercise tests at the trough of drug activity, using the standard Bruce protocol for randomization and at 2 and 4 months. Total exercise duration at 4 months increased by 24.3 +/- 65.3 s in the IVB group, compared with 7.7 +/- 63.8 s in the placebo group. IVB was superior to placebo for all exercise test criteria at 2 months and 4 months. Only 1.1% of patients withdrew owing to sinus bradycardia in the IVB group. The authors concluded that the combination of IVB 7.5 mg twice a day and atenolol at commonly used dosage in clinical practice in patients with CSA produced additional efficacy with no collateral effect on safety or tolerability.

Ruzyllo et al. [13] compared the antianginal and anti-ischaemic effects of the IVB and amlodipine. Patients with a ≥3-month history of CSA were randomized to receive IVB 7.5mg (n = 400) or 10mg (n = 391) twice daily or amlodipine 10mg once daily (n = 404) for a 3-month, double-blind period. Bicycle exercise tolerance tests were performed at baseline and monthly intervals. The primary efficacy criteria were changes from baseline in total exercise duration after 3 months of treatment. The secondary efficacy criteria were changes in time to angina onset and time to 1mm ST-segment depression, rate-pressure product at trough drug activity, short-acting nitrate use and anginal attack rates. At 3 months, total exercise duration was improved by 27.6 and 31.2 s with IVB 7.5 and 10mg, respectively. Both IVB groups were comparable to amlodipine.

Similar results were observed for time to angina onset and time to 1mm STsegment depression. Heart rate significantly decreased by 11-13 bpm at rest and by 12-15 bpm at peak of exercise with IVB but not with amlodipine. Rate-pressure product decreased more with IVB than with amlodipine at rest and at peak exercise. Anginal attack rates and short-acting nitrate use decreased substantially in all treatment groups with no significant difference between them. Adverse events observed with IVB were visual symptoms (0.8%) and sinus bradycardia (0.4%); and with amlodipine were peripheral edema (1.5% withdrawals). The authors concluded that in patients with CSA, IVB has comparable efficacy to amlodipine in improving exercise tolerance, a superior effect on the reduction of rate-pressure product and similar safety profile [13].

Joannnides et al. [14] evaluated the effects of IVB and propranolol on cardiac and systemic haemodynamics at rest, during tilt, exercise, and during sympathetic stimulation. Acute administration of IVB decreased myocardial oxygen demand to the same extent as with propranolol but without evidence of depression on cardiac function.

In summary, the studies cited above demonstrated the benefic effects of IVB on CSA and cardiopulmonary function.

Chronic heart failure (CHF): A randomized, double-blind, placebo-controlled, parallel-group study investigated patients with symptomatic CHF and LV ejection fraction (LVEF) ≤35%, with HR≥ 70 bpm, admitted to hospital for CHF within the previous year, and on stable background treatment including a β-blocker if tolerated. Patients were randomly assigned by computer-generated allocation schedule to IVB titrated to a maximum of 7.5 mg twice daily or matching placebo. Patients and investigators were blinded to treatment allocation. The primary endpoint was the composite of cardiovascular death or hospital admission consequence of worsening CHF. The authors observed significant bradycardia as a consequence of improvement on CHF. They concluded that raised resting HR is a marker for both cardiovascular risk and cardiovascular events in CHF [15].

Böhm et al. [16] confirmed that high HR is a risk factor in CHF. Selective lowering of HRs with IVB improves cardiovascular outcomes. HR is an important target for treatment of CHF.

In a small trial [17], it was suggested that in patients with decompensate CHF on conventional therapy, the co-administration of levosimedan and IVB was more effective than the use of dopamine.

Chronic HR reduction therapy following myocardial infarction using either the pure HR reduction agent IVB or the β-blocker atenolol has been shown to preserve maximal coronary perfusion. It occurs via reduction of perivascular collagen and a decrease in renin-angiotensin system activation. In addition, IVB, but not atenolol, treatment attenuated the decline in EF and decreased LV wall stress. HR reduction by either IVB or atenolol facilitates a more favorable O_2 microenvironment via improved venous flow and decreased O_2 demand. Chronic HR reduction by these agents may serve to limit infarct expansion and wall thinning and may serve to reduce the potential for ventricular rupture [18].

Inappropriate sinus tachycardia (IST): Inappropriate sinus tachycardia (IST) is another indication to medical and, in refractory cases, radiofrequency ablation interventions [19,20]. The experience with IVB in patients with IST is scarce. Larger studies are needed to confirm the role of IVB for the treatment of this unusual condition [19].

When IST is associated with LV dysfunction and the conventional treatment is not well tolerated by the patient, IVB seems to improve EF and quality of life [21].

Giving these initial experiences, IVB appears as very promising drug for the treatment of IST [22].

Tachycardia-induced cardiomyopathy: Also known as tachycardiomyopathy, this condition is a weakening of the myocardium contraction due to prolonged periods of elevated HR. The rate and duration of the elevation in HR necessary to cause a cardiomyopathy is not well defined.

Recently, Bohora et al. [23] and Zwicker et al. [24] demonstrated the efficacy of IVB in cases of tachycardiomyopathy (one related to left atrial tachycardia and one after heart transplantation).

The primary treatment for a tachycardia-induced cardiomyopathy is to correct the underlying cause of tachycardia. Supportive agents such as beta blockers and ACE inhibitors / angiotensin receptor blockers are of benefit to prevent the remodeling of the left ventricle. All causes of sustained sinus tachycardia (hyperthyroidism, anemia, hypovolemia, etc) should be ruled put (and corrected if necessary) before considering IVB as part of the treatment [25].

Postural orthostatic tachycardia syndrome (POTS): The definition of POTS is an increase in HR when changing from a supine to upright position. An increase of more than 30 beats per minute or to a HR greater than 120 bpm within 12 minutes of head-up tilt defines POTS. This tachycardic response is sometimes accompanied by a decrease in blood pressure and a wide variety of symptoms associated with hypotension. The marked tachycardia during orthostasis was attributable to a small heart coupled with reduced blood volume. Lifestyle changes, particularly exercise training, drinking extra water and avoiding trigger situations such as standing still or getting hot, are necessary for all patients. Sometimes these recommendations improved or even cured this syndrome in most patients [26].

Some patients also benefit from the addition of other treatments, such as fludrocortisone, β-blockers, midodrine (Proamatine), antidepressants, especially selective serotonin reuptake inhibitors and recently in IVB [27].

Further studies are necessary to confirm the effects of IVB on POTS.

Cardiogenic shock (CGS): Documented mortality from acute MI has significantly decreased from 30% in the early 1960s to currently 6-7%, following the introduction of intensive-care treatment, thrombolysis, effective antithrombotic therapy and coronary angioplasty. Nonetheless, the approximate mortality of 70-80% of patients with CGS following acute MI has hardly improved despite the introduction of modern treatment strategies. In this situation, oral IVB to control sinus tachycardia and further hypoperfusion may be advantageous and better tolerated than other drugs that can induce hypotension. In these cases treatment with IVB seemed to improve the prognosis [28].

Limitations to the use

Some side effects associated to the use of IVB are described below.

- Luminous phenomena or phosphenea [29]: Approximately 14.5% of all patients taking IVB experience luminous phenomena characterized by sensations of enhanced brightness in a fully maintained visual field. This is thought to be due to block of Ih in the retina, a current very similar to the cardiac If. These symptoms are mild, transient, fully reversible and non-severe. In clinical studies about 1% of all patients had to discontinue the drug because of these sensations, which occurred on average 40 days after commencement of the drug;
- Bradycardia: It is proportional to the resting HR, but extreme sinus bradycardia is uncommon. It occurs in 2% and 5% of patients taking doses of 7.5 and 10 mg, respectively (compared to 4.3% in atenolol) [30].

Other less frequent adverse events reported in the literature are:

- First-degree AV block;
- Premature ventricular contractions;
- Dizziness;
- Blurred vision;
- Headaches (2.6-4.8% of cases);
- Muscle cramps;
- Eosinophila;
- Hyperuricemia.

Formal contraindications for the use of IVB include:

- Sick Sinus Syndrome;
- Sinus Node Dysfunction [31];
- Familial inherited bradycardia: Mutant HCN4 channels have been found to be associated with inherited sinus bradycardia. Autosomal-dominant form of sinus node dysfunction caused by a missense mutation in the HCN4 ion channel pore carries a favorable prognosis without the need for pacemaker implantation during long-term follow-up [32];
- Administration with hepatic inhibitors of Cytochrome P450 family 3, subfamily A, polypeptide 4 (abbreviated CYP3A4): azole antifungals (such as ketoconazole), macrolide antibiotics, nefazodone and the anti-HIV drugs nelfinavir and ritonavir should be avoided.

Co-administration of either omeprazole or lansoprazole (CYP3A4 inhibitors) did not significantly affect the pharmacokinetics of a single dose of IVB. No pharmacodynamic interaction or safety concerns were evidenced [33].

The effects of the CYP3A4 inducer such as Hypericum perforatum, on the pharmacokinetics of a single oral dose of IVB were assessed. An open-label, 2-period, nonrandomized, phase-I, pharmacokinetic interaction design was used by Portolés et al. [34]. The authors observed a tendency toward shorter time to concentration in plasma and lower apparent half-life. Pharmacokinetic results are consistent with an induction of IVB metabolism by Hypericum perforatum.

QT behavior: Another important issue to be briefly discussed is the QT behavior. The QT interval is expectedly prolonged with the reduction of HR, however, after appropriate correction, no significant effect of IVB on ventricular repolarization duration was demonstrated. Consequently, IVB has no direct torsadogenic potential, although, for obvious reasons, this drug should not be administered with agents which have known rate-lowering and/or QT prolonging effects [31].

Concluding Remarks

Our review provides new evidence based on recent studies related to the beneficial effects of this drug on many cardiovascular diseases. This minireview does not allow us to accurately identify all the mechanisms involved in the pharmacologic effects of ivabradine on the cardiovascular system. Further studies investigating the molecular basis regarding the mechanism of this drug will contribute to new pharmacological therapies.

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