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Selective Inhibition of Cardiac Pacemaker (I_f) Current: the Role of Ivabradine in the Treatment of Angina

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ABSTRACT

Heart rate reduction plays a pivotal role in the management of myocardial ischemia and chronic stable angina. Rate-slowing drugs, such as beta-blockers are considered the cornerstone of antianginal therapy. However, the broad use of beta-blockers is limited by their side-effects. Ivabradine is the representative of a new class of agents that exclusively reduce heart rate through inhibition of the sinoatrial pacemaker (I_f) current. Ivabradine reduces cardiac heart rate in doses that do not affect other ionic currents, resulting in a decrease in cardiac oxygen consumption and in an increase in diastolic period. Ivabradine has no negative inotropic or lusitropic effects, and does not change any major electrophysiological parameter. Large randomized trials have provided evidence for its efficacy in stable angina and have demonstrated anti-ischemic properties similar to atenolol and amlodipine. Moreover, ivabradine provides an attractive alternative to conventional therapy, whenever use of beta-blockers or calcium-channel blockers is contraindicated. Treatment of sinus tachyarrhythmias is another area where the use of ivabradine seems promising. Ongoing trials with ivabradine will determine its effect on mortality and morbidity in patients with coronary artery disease and left ventricular dysfunction.

HEART RATE REDUCTION IN THE THERAPY OF ANGINA

Heart rate has been identified as an independent prognostic risk factor for mortality from cardiovascular diseases. Large-scale epidemiological studies, such as the Framingham Heart Study, showed that high resting heart rate correlates with increased all-cause and cardiovascular mortality [1]. Several mechanisms can explain this phenomenon. Accelerated heart rate is involved in the progression of atherosclerosis through mechanical and metabolic processes. Increased wall stress, resulting from tachycardia, may induce endothelial injury and easier penetration of lipids into the vessel wall, a mechanism which could also explain the higher incidence of atherosclerotic plaque disruption and new acute coronary events in patients with high resting heart rate [2,3]. Elevated heart rate usually reflects activation of the sympathetic nervous system with its attendant deleterious metabolic effects resulting in accelerated atherogenesis.

Heart rate reduction plays a pivotal role in the management of myocardial ischemia

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and chronic stable angina. It is well documented that myocardial ischemia can result from a mismatch between myocardial oxygen demand and supply. Heart rate is a major determinant of oxygen consumption and metabolic demand. Moreover, higher heart rate may induce or exacerbate ischemia and symptoms of angina, because it shortens the duration of diastole and subsequently decreases the perfusion of epicardial coronary arteries. This observation explains why rate-slowing drugs, such as beta-blockers, followed by calcium channel antagonists, are considered to be the cornerstone of antianginal therapy. The broad use of beta-blockers is limited by their side effects: fatigue, lethargy, insomnia, negative inotropic and lusitropic effect, depression and erectile dysfunction in men. In addition, beta-blockers are contraindicated in decompensated heart failure, chronic obstructive lung disease, peripheral vascular disease, severe atrioventricular conduction defects and finally, Prinzmetal angina related to coronary artery spasm. In this latter category of patients, with angiographically normal coronary arteries, beta-blockers might even exacerbate symptoms of angina due to unopposed α -receptor activation.

Angina is very common, despite the use of a combination of anti-anginal agents, restricting the quality of life of patients suffering from it. Revascularization has certainly improved outcomes, but symptoms of angina continue to be experienced by up to 60% of patients, as shown in the RITA2 trial [4]. New agents are needed to improve therapy of angina. Ivabradine is the representative of a novel class of agents that exclusively reduce heart rate through inhibition of the sinoatrial I_f current.

THE ROLE OF CARDIAC PACEMAKER (I_f) CURRENT

The sinoatrial node is the normal pacemaker of the heart, because action potentials begin earlier in this area than other regions, including the atrioventricular node, the bundle of His and the Purkinje fibers. The pacemaker cells are hyperpolarized at rest. At the next point, a slow diastolic depolarization begins, which turns the membrane voltage to the threshold level for a new action potential. The rate of depolarization actually reflects the heart rate [5]. The I_f current determines the slope of the depolarization curve towards the threshold level, which is -40 mV in humans. In this manner, time interval between action potentials, which in turn is expressed in the heart rhythm, is regulated by this inward Na^+/K^+ current known as the I_f current of the sinoatrial node.

The pacemaker current in the sinoatrial node, a slowly activated inward current, termed “funny” (I_f current) due to its atypical properties, was discovered in 1979 by Brown et al [6]. There are three other ionic currents in the sinoatrial node cells that are all together responsible for spontaneous diastolic depolarization: the outward potassium current (I_k), the long-

lasting calcium (I_{cal}) and the transient calcium current (I_{cat}). The I_f current is slowly activated during the hyperpolarization state. In the heart, I_f generates spontaneous activity and mediates autonomic neurotransmitter control of the heart rate. The “funny” (f) channels are hyperpolarization-activated, cyclonucleotide-gated (HCN) ion channels, whose cloning was accomplished in the late 1990s. HCN channels are found in the heart, retina and brain. The HCN1, HCN2 and HCN4 isoforms are expressed in the heart. The HCN4 isoform is mostly found in the sinoatrial node. These channels are active only in the sinoatrial node under normal circumstances, hence their relevance to regular pacemaker activity, but they might be active in other regions of the heart, such as the atrioventricular node and the Purkinje fibres, in pathological conditions like heart failure and hypertrophic cardiomyopathy [7]. There are indications that mutations of HCN4 may be linked to sinus node dysfunction [8].

The finding that I_f controls the heart rate has had a great impact on our understanding of the physiologic mechanisms underlying cardiac function, but it has also directed us to possible ways to influence heart rate and hence cardiac function by pharmacological agents or other means. Indeed, agents that selectively block the f channels, such as ivabradine, act as “pure” heart rate-reducing drugs and offer a potential for therapeutic intervention in diseases where heart rate reduction is of benefit, such as angina and heart failure. On a different note, molecular biology and recombinant DNA techniques may allow us to produce biological pacemakers by restoring pacing function in defective pacing cells or transforming regular cardiac cells into pacing cells, by transfection of HCN channels, thus replacing electronic devices in the future!

IVABRADINE, A SPECIFIC AND SELECTIVE I_f INHIBITOR

The molecule of ivabradine binds specifically to the HCN4 channel on the intracellular side of the sinoatrial cell membrane and inhibits the f current upon depolarization, which is when the channel is open. Ivabradine is then released by the channel during the closing phase of hyperpolarization [9]. Inhibition of the f current results in a decrease in the slope of diastolic depolarization curve, which in turn increases the time interval between effective action potentials leading to a reduction of heart rate [10]. The inhibition of the f channel is current-dependent, meaning that the higher the heart rate the more effective is ivabradine. Ivabradine is a selective I_f current inhibitor in concentrations used for clinical practice, whereas other currents become affected in higher doses. It has no effect on T-type Ca^{2+} channels, whereas the L-type Ca^{2+} channels are slightly inhibited in doses 60 times greater than the therapeutic dose in animal experiments [11]. This is why ivabradine affects heart rate without reducing myocardial

contractility. No significant effect on Na⁺ or K⁺ currents has been demonstrated with these experimental models.

Other selective I_f inhibitors have been proposed for use in practice. Alinidine is a selective agent that induces bradycardia, but showed a negative inotropic action in an animal experimental model [12]. Zatebradine is a compound with both selective and specific f channel inhibition properties that entered late-phase clinical testing. Although heart rate reduction was achieved both at rest and during exercise, the drug was abandoned because of severe ocular side-effects. The explanation for this is probably the fact that zatebradine exhibits its therapeutic effects in doses which substantially inhibit the HCN channels in the retina [13,14]. Ivabradine, first reported more than a decade ago, exhibits a unique specificity for the I_f current with a more favorable profile of adverse reactions than zatebradine [15]. Ivabradine has been used in the treatment of stable angina, an area where it displays anti-anginal and antischemic effects equivalent to the effects of atenolol and amlodipine.

CLINICAL TRIALS OF IVABRADINE IN STABLE ANGINA

The first large randomized double-blinded trial of ivabradine as monotherapy involved 360 patients (Table 1) [16]. The aim of the trial was to prove whether ivabradine has anti-anginal properties, whether the effects persist during 3 months of continual use and finally if there is a rebound phenomenon of ischemia after abrupt cessation of the drug. Patients were randomized to placebo or to one of the doses of ivabradine (2.5, 5, or 10 mg twice daily) [16]. The variables used to as-

TABLE 1. Randomized Trials of Ivabradine in Stable Angina

| Study | Patients | Follow-up | Results |
|-------------------------|----------|-----------|--|
| Borer et al [16] | 360 | 3 months | dose-dependent improvement in exercise tolerance |
| INITIATIVE [17] | 939 | 4 months | decrease in anginal attacks by 2/3 with both ivabradine & atenolol (non-inferiority of ivabradine) |
| Ruzyllo et al [18] | 1195 | 3 months | ivabradine as effective and safe as amlodipine |
| Lopez-Bescos et al [19] | 386 | 12 months | ivabradine was safe and well-tolerated at doses of 5 and 7.5 mg bid |

sess drug efficacy were exercise tolerance during treadmill testing, ST segment variation and angina frequency in daily life. The drug reduced heart rate at rest and during exercise, with little change in blood pressure compared to placebo. Exercise-induced angina was less in the ivabradine arm and dose-dependent, as measured by time to 1mm ST segment depression. Angina attack rate requiring use of nitroglycerin was lower on ivabradine compared to placebo. Cessation of ivabradine does not lead to rebound effects, unlike short-acting beta-blockers, while no pharmacological tolerance is exhibited after prolonged use, a problem commonly seen with long-acting nitrates.

In the International Trial of the Antianginal effects of Ivabradine compared to atenolol (INITIATIVE), 939 patients with stable angina were randomized to receive ivabradine or atenolol [17]. Ivabradine, in doses of 7.5 and 10 mg bid, was not inferior to atenolol 100 mg once daily, in terms of their anti-anginal and anti-ischemic effects as demonstrated with an increase in total exercise duration and increase in time to 1 mm ST segment depression [17].

A large clinical trial compared ivabradine with the calcium -channel blocker amlodipine [18]. In this trial 1195 patients with stable angina were randomized to receive 7.5 to 10 mg ivabradine bid or 10 mg amlodipine once daily. Again ivabradine was proven to be as efficacious as amlodipine in preventing angina attacks [18].

The efficacy and safety of combination therapy with ivabradine has been demonstrated in a randomized, double-blind, multi-center trial conducted in 386 patients with stable angina already treated with nitrates or dihydropyridine calcium-channel blockers, who received ivabradine for 1 year in doses of 5 and 7.5 mg bid [19]. Ivabradine decreased heart rate in a dose-dependent manner and the reduction was constant over one year of follow-up. The number of angina attacks reported by patients was significantly lower after the addition of ivabradine to therapy [19].

A small double-blind study, comparing the effects of ivabradine and propranolol on systemic and cardiac hemodynamics at rest and during exercise, was conducted with nine healthy volunteers receiving ivabradine, or propranolol, or placebo [20]. This study demonstrated that, for a similar heart rate reduction at rest and during sympathetic activation, administration of ivabradine reduced myocardial oxygen demand at the same degree as propranolol, but without negative inotropic effect [20].

Ivabradine is generally well tolerated. The only side-effects mentioned in clinical trials were visual, including phosphenes, stroboscopic effect and non-typical blurred vision. Visual symptoms were dose-related, reversible with drug cessation and generally not bothersome enough to cause voluntary withdrawal of the drug. During the clinical development program of ivabradine for angina prevention, visual side-effects were reported in 2-15% of 5000 patients involved

and led to drug discontinuation in less than 1% [21]. Patients with sick sinus syndrome and atrial fibrillation cannot receive ivabradine, because the sinoatrial node is the sole target of the drug. Ivabradine does not affect the conduction system of the heart and does not alter electrocardiographic PR and corrected QT intervals.

In summary, ivabradine is the first selective I_f current inhibitor that has completed clinical development and assessment for stable angina. It reduces cardiac heart rate in doses that do not affect other ionic currents, resulting in a decrease in cardiac oxygen consumption and in an increase in diastolic period. Ivabradine has no negative inotropic or lusitropic effects, and does not change any major electrophysiological parameter. Its efficacy in stable angina has been shown in large randomized trials which have demonstrated its anti-ischemic properties, found to be similar to atenolol and amlodipine. Moreover, ivabradine provides an attractive alternative to conventional therapy, whenever use of beta-blockers or calcium-channel blockers is contraindicated. Treatment of sinus tachyarrhythmias is another era where the use of ivabradine seems promising [22]. Current trials, such as the BEAUTIFUL study, will answer to questions about the effect of this regimen on mortality and morbidity in patients with coronary artery disease and left ventricular dysfunction.

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