Ivabradine

*M Reed, G McKay, M Fisher**

Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality in diabetes. Although many drugs are proven to improve prognosis following myocardial infarction (MI), there is a shortage of evidence-based treatments for stable angina pectoris. Ivabradine is the first of a new class of anti-anginal drugs called selective I_f inhibitors. Ivabradine is currently licensed for use in patients with stable angina pectoris who have contraindications or are intolerant to treatment with β-blockers.

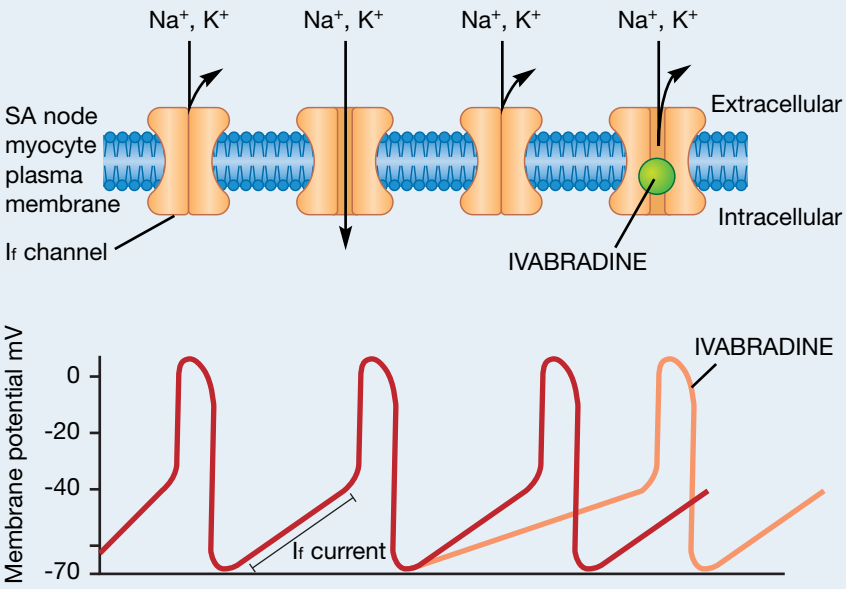
Pharmacology

Myocytes in the sinoatrial (SA) node undergo spontaneous depolarisation during diastole, allowing the SA node to act as the cardiac pacemaker. The I_f current is a trans-membrane current unique to SA node myocytes and is important in their intrinsic pacemaker activity. The I_f current is a mixed influx of sodium and potassium ions via cyclic-nucleotide-gated I_f channels, which are modulated by the autonomic nervous system. The I_f current is activated by hyperpolarisation and drives the membrane potential towards a threshold level for initiating a subsequent action potential (see Figure 1).

Ivabradine is a selective and specific I_f channel blocker. I_f channel blockade slows the progression towards depolarisation, reduces the rate of firing of the SA node pacemaker cells and slows heart rate. Ivabradine is effective at the SA node at concentrations lower than needed to affect other ionic currents so has no effect on myocardial contractility, AV conduction velocity, ventricular repolarisation or arterial BP. The effective half-life of ivabradine is 11 hours.

Patients with angina may benefit from heart rate reduction as this decreases myocardial oxygen requirement and lengthens diastole duration, promoting myocardial perfusion.

Figure 1. Ivabradine's effect on the I_f current and SA node action potential



NOTES. Normally, I_f channels open in response to hyperpolarisation, resulting in an influx of Na^+ and K^+ ions (the I_f current). This drives the membrane potential towards the threshold for initiating the next action potential. Ivabradine acts in a concentration dependent manner by entering the I_f channel pore from the intracellular side. This blocks the I_f channel so preventing the I_f current influx. The rate of progression of the I_f current towards threshold is slowed, so the subsequent action potential is delayed. The next heart beat is delayed and heart rate is reduced.

Trials of safety and efficacy

In a double-blind, placebo-controlled trial of 360 patients with chronic stable angina, participants received ivabradine 2.5mg, 5mg or 10mg twice daily or placebo for two weeks, then open-label ivabradine for two to three months, before a one-week radomised withdrawal to ivabradine or placebo.[1] In the initial two-week period, exercise duration until the development of 1mm ST-segment depression increased significantly in the ivabradine 5 and 10mg groups compared to placebo ($p<0.005$), and time to limiting symptomatic angina increased in the 10mg ivabradine group ($p<0.05$). Deterioration in all exercise tolerance test parameters occurred in patients who received placebo during randomised withdrawal but not in those receiving ivabradine.

The INITIATIVE (international trial on the treatment of angina with ivabradine *vs* atenolol) study involved 939 patients with stable angina and documented CAD.[2] It compared the effects of ivabradine (5mg twice daily for four weeks, then 7.5 or 10mg twice daily for 12 weeks) to atenolol (50mg once daily, then 100mg once daily) on performance of treadmill exercise testing. Overall, ivabradine produced similar anti-anginal and anti-ischaemic

Michael Reed, MB ChB, Foundation Doctor
Gerry McKay, BSc(Hons), FRCP, Consultant Physician
Miles Fisher, MD, FRCP, Consultant Physician
Medical Directorate, Glasgow Royal Infirmary, Glasgow, UK
***Correspondence to:** Dr Miles Fisher, Wards 4 & 5, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK; e-mail: miles.fisher@ggc.scot.nhs.uk

effects to atenolol, with similar increases in total exercise duration and time until 1mm ST depression on treadmill testing, with non-inferiority of the ivabradine group *vs* atenolol. The number of angina attacks was reduced by two-thirds in both groups.

Another study randomised 1195 patients with stable angina pectoris to receive ivabradine 7.5mg twice daily, ivabradine 10mg twice daily or amlodipine 10mg once daily for a three-month, double-blind period.[3] Increase in total exercise duration with ivabradine was comparable to amlodipine as were the secondary outcomes of time to angina onset and time to 1mm ST-segment depression.

The BEAUTIFUL (morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and leFt-ventricULar dysfunction) study group recruited 10 917 patients with CAD and left ventricular dysfunction (left ventricular ejection fraction <40%) into a randomised, double-blind, placebo-controlled, parallel-group trial.[4] All patients received standard treatment for CAD, including β-blockers in 87% of subjects. Patients with recent MI, coronary revascularisation, stroke, TIA or severe heart failure were excluded. Patients were followed up for a median duration of 19 months and intention to treat analysis was used.

Ivabradine had no effect on the primary composite endpoint of cardiovascular death, or admission to hospital for MI, or new-onset or worsening heart failure. Similarly, in a pre-specified subgroup of patients with heart rate of 70 beats per minute or more, primary outcomes were unaffected with ivabradine *vs* placebo. However, in this subgroup, ivabradine was associated with a significant reduction in the coronary secondary outcomes, including hospital admissions for acute MI, admission for acute coronary syndrome and rates of coronary revascularisation.

No study to date has raised any major concerns over the safety of ivabradine. The most common adverse effect with ivabradine is bradycardia, which occurred in 13% of patients on ivabradine compared to just 2% in the controls in the BEAUTIFUL trial, most of whom were also on a β-blocker. Most subjects with bradycardia were asymptomatic. Ivabradine is contraindicated in patients with intrinsic sinoatrial node disease (e.g. sick sinus syndrome) and such patients were excluded from trials.

Several patients have reported visual symptoms with ivabradine, which is thought to be due to ivabradine acting at the retinal I_h channel, which is similar to the I_f channel. All reported visual disturbances have been transient, usually associated with abrupt changes in light intensity, with phosphenes (luminous phenomena described as increases in brightness in limited areas of the visual field) most common. There have been no reports of permanent ocular damage or visual disturbances.

Specific evidence for use in diabetes

In the BEAUTIFUL trial, 37% of patients had diabetes (37% in both study groups). Patients with diabetes aged 18 or above with documented CAD were included. This was in contrast to the minimum age of 55 for non-diabetic patients. The effect of ivabradine on the primary composite endpoint was similar whether the patients had diabetes or not.

Discussion

Each of the first-line agents for medical management of stable angina (nitrates, β-blockers and calcium channel blockers) can have additional undesirable effects. Furthermore, many patients have contraindications to standard management. Ivabradine has anti-anginal and anti-ischaemic effects in patients with stable angina and has been shown to be superior to placebo and non-inferior to atenolol and amlodipine; it received its initial licence for the symptomatic treatment of angina.

The BEAUTIFUL trial failed to demonstrate an improvement in survival or incidence of heart failure when ivabradine was added to standard medical therapy. However, in patients with resting heart rate >70, it was found to reduce hospital admission rates for acute MIs and coronary revascularisation,[4] and in this prespecified subgroup 42% of subjects had diabetes. This study may well form the basis for an application to extend the licence to other indications. Further studies may reveal a role for ivabradine in other cardiac diseases such as acute MI or heart failure.

Thirty-seven percent of participants in the overall study had diabetes, with a higher number of patients with diabetes in the subgroup. Diabetes is associated with an increase in resting heart rate related to autonomic neuropathy, and it could be hypothesised that people with diabetes might derive greater benefit from ivabradine treatment. Further studies of ivabradine in patients with diabetes are required.

Key points

- Coronary artery disease is a major cause of morbidity and mortality in diabetes. There is currently a shortage of evidence-based treatments for stable angina pectoris
- Ivabradine is an effective anti-anginal therapy for patients with stable angina, with few side effects
- The BEAUTIFUL trial demonstrated that some subgroups of patients might derive further benefit from ivabradine in reducing future coronary events, but further trials are needed

Conflict of interest statement

Dr Reed and Dr McKay have no conflict of interest. Dr Fisher has received lecture fees from and has advised on advisory panels for Servier.

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