A short review of the I-f Channel Antagonist, Ivabradine

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Abstract

Ivabradine is a selective sinus node inhibitor which decreases resting heart rate. It is licensed for the treatment of chronic stable angina in patients with normal sinus rhythm, who have a contraindication or intolerance for beta blockers.

In five clinical efficacy studies, ivabradine has been directly compared with placebo, atenolol and amlodipine. They have shown ivabradine, given in doses of 5mg to 10mg twice daily is more effective than placebo in increasing time to angina onset and non-inferior to atenolol 50mg to 100mg daily and amlodipine 10mg daily in increasing total exercise duration in patients with chronic stable angina.

INTRODUCTION

Ivabradine (INN) (pronounced /I'vaebr□din/) is a novel medication used for the symptomatic management of stable angina pectoris. It is marketed under the trade name Procoralan (Servier), and was also known as S-16257 during its development. Ivabradine acts by reducing the heart rate in a mechanism different from beta blockers and calcium channel blockers, two commonly prescribed antianginal drugs. It is classified as a cardiotonic agent. Ivabradine provides all the benefits of pure heart rate reduction: Effective heart rate reduction of 10 to 14 bpm 66% reduction in anginal attacks and significant improvement in patients' effort capacity Free from effects on vasoconstriction and myocardial contractility.

MODE OF ACTION

Ivabradine acts on the I_f (f is for “funny”, so called because it had unusual properties compared with other current systems known at the time of its discovery) ion current, which is highly expressed in the sinoatrial node. I_f is a mixed Na^+–K^+ inward current activated by hyperpolarization and modulated by the autonomic nervous system. It is one of the most important ionic currents for regulating pacemaker activity in the sinoatrial (SA) node. Ivabradine selectively inhibits the pacemaker I_f current in a dose-dependent manner. Blocking this channel reduces cardiac pacemaker activity, slowing the heart rate and allowing more time for blood to flow to the myocardium.

USES

It is indicated for the symptomatic treatment of stable angina pectoris in patients with normal sinus rhythm, who have a contraindication to or intolerance to beta blockers. It has been shown to be non-inferior to the beta-blocker atenolol for this indication [3] and amlodipine. Apart from angina, it is also being used off-label in the treatment of inappropriate sinus tachycardia.

DOSAGE

A dose of 5 mg twice daily is recommended initially; after 1 month, it is recommended to increase to 7.5 mg twice daily to get the optimal efficacy linked to heart rate reduction. Given limited experience in the elderly, the manufacturer recommends a starting dose of 2.5 mg.

ADVERSE EFFECTS

14.5% of all patients taking ivabradine experience luminous phenomena (by patients described as sensations of enhanced brightness in a fully maintained visual field). This is probably due to blockage of I_h ion channels in the retina which are very similar to cardiac I_f. 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 (unusually slow heart rate) occurs at 2% and 5% for doses of 7.5 and 10 mg respectively (compared to 4.3% in atenonol). 2.6-4.8% reported headaches. Other common adverse drug reactions (1–10% of patients) include first-degree AV block, ventricular extrasystoles, dizziness and/or blurred vision.

CONTRAINDICATIONS

Ivabradine is contraindicated in sick sinus syndrome, and cannot be used concominantly with inhibitors of CYP3A4 such as azole antifungals (such as ketoconazole), macrolide antibiotics, nefazodone and the anti-HIV drugs nelfinavir and ritonavir.

CLINICAL TRIALS

The INITIATIVE study, a double blind non-inferiority study, randomised 939 angina patients to either ivabradine 7.5mg or 10mg twice daily or atenolol 100mg once daily. The primary outcome measure was change in total exercise duration (TED) from baseline at 4 months and the pre defined equivalence limit was35 seconds (i.e. change in TED from baseline with atenolol should be 35 seconds or less than change with ivabradine to demonstrate non-inferiority). Total exercise duration increased by+86.8s and +91.7s for ivabradine 7.5mg and 10mg groups respectively compared with +78.8s for the atenolol100mg treatment group. The secondary efficacy criterion: time to angina onset and time to limiting angina, were reduced in all treatment groups.The change from baseline in the number of angina attacks experienced per week was -2.2 ± 4.3 and -2.3 ± 4.2 in the 7.5mg and 10mg ivabradine groups and -2.7 ± 12.3 for the atenolol 100mg group statistical significance was not stated. There was no difference in the efficacy results between 7.5mg and 10mg ivabradine doses, however there was a higher incidence of visual adverse effects in the 10mg group.Limited information is available regarding the other studies as they have not been published in full to date.In CL3-023 1,195 angina patients were randomised to receive either ivabradine 7.5mg twice daily or 10mg twice daily or amlodipine 10mg once daily for 3 months. The primary efficacy endpoint of total exercise duration at trough of drug activity was increased in all treatment groups, +27.6s, +21.7s and 31.2s for the ivabradine 7.5mg, 10mg and amlodipine groups respectively. Time to angina onset, limiting angina and 1mm ST segment depression were all similarly reduced. The number of angina attacks and nitrate consumption were decreased across all treatment groups. The predefined confidence limit for non-inferiority was -30 seconds. The European Medicines Agency considered this and the margin used in the INITIATIVE study as too permissive. In CL3-018, 728 stable angina patients received either placebo or ivabradine 5mg twice daily or 7.5mg twice daily on top of amlodipine 10mg once daily for 3 months. The study showed no significant antianginal and anti-ischaemic effect with ivabradine 5mg or 7.5mg compared to placebo immediately prior to next dose. At peak of drug activity, ivabradine was clinically superior to placebo for time to angina onset and total exercise duration. In CL3-021, 386 patients with a three month history of angina received either ivabradine 5mg twice daily or 7.5mg twice daily. The objective of the study was to assess the long term safety and efficacy. After 12 months the number of angina attacks per week had reduced by -1.9±0.48 and -1.2±0.4 from baseline with ivabradine 5mg and 7.5mg respectively. Statistical significance was not stated.The studies to date were not designed to assess accurately the effect of ivabradine on angina attack frequency or the effect on cardiovascular morbidity and mortality. There is also very little efficacy data available with the 5mg twice daily dose as the clinical studies concentrated on assessing the 7.5mg and 10mg doses. Only one small study with no control group has shown statistical significance in the reduction of the number of angina attacks from baseline with ivabradine 5mg and 7.5mg doses.It is a small, open label study and its results are not robust enough to provide adequate evidence of efficacy. There have been no comparative studies with rate limiting calcium channel blockers such as diltiazem or verapamil which would have provided a more useful assessment of ivabradine efficacy and place in therapy. The BEAUTIFUL study (MorBidity-mortality evaluation of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) is currently underway. It aims to demonstrate the superiority of ivabradine over placebo in the reduction of cardiovascular mortality and hospital admissions for acute myocardial infarction and/or new onset or worsening heart failure in approximately 9650 patients and is due to report in 2008.

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Wikipedia and www.servier.com

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