Exciting developments in stable angina–the rise of the f-channels

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Abstract

Heart rate reduction is the cornerstone of the treatment of angina. To date, β-blockers have been the best drugs with which to achieve this. Heart rate is set by the pacemaker cells in the sinus node. Specific cardiac ion channels, f-channels, have been identified that control the rate at which these pacemaker cells initiate cardiac contraction. A selective and specific f-channel (f) current inhibitor, ivabradine, has now been developed that reduces heart rate to a degree similar to that achieved with β-blockers, but without their side effects. Ivabradine is now available for clinical use and promises to be a major and exciting treatment for individuals with angina.

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Keywords: Angina, β-blockers, heart rate, cardiac ion channels, f-channels, I_f current, ivabradine

Introduction

Angina pectoris affects around 2 million people in the UK [1], with a recent study revealing a sharp increase in the rate of admission to hospital for angina and other chest pain, in spite of a reduction in heart attacks in recent years [2]. Patients need long-term drug treatment and suffer markedly reduced quality of life and functional capacity. Moreover, patients with angina have a threefold risk of developing unstable angina and myocardial infarction and, therefore, often require emergency admission to hospital [3,4]. It is not surprising that a recent estimation of the direct cost of angina to the health service was £669 million (1.3% of total UK National Health Service expenditure), with hospital bed occupancy and procedures accounting for 32% and 35% of this total, respectively [5]. Angina is a common and costly problem.

According to the National Service Framework for Coronary Heart Disease, patients with suspected angina should be referred to a Rapid Access Chest Pain Clinic and assessed within a maximum of 2 weeks [6]. The National Service Framework for Coronary Heart Disease states that individuals with angina or suspected angina should be offered investigation and treatment to relieve their pain and reduce the risk of coronary events.

Guidelines produced jointly by the British Cardiac Society and the Royal College of Physicians [7] recommend that the management of angina has two main objectives: to reduce or abolish symptoms and to improve prognosis.

Medical management remains the first line of treatment. Antiplatelet therapy, statins, and angiotensin-converting enzyme inhibitors address the underlying disease, improve outcome, and should be prescribed for all patients who can tolerate them, but they do not affect existing symptoms.

Three classes of drug have traditionally been used to treat the symptoms of angina: β-blockers, calcium channel blockers, and nitrates. β-Blockers are probably the best drugs, usually used first line, and are recommended by all national and international guidelines. Although a lack of trials to evaluate mortality means that there is no evidence that β-blockers reduce this outcome in patients with angina, β-blockers do reduce mortality in patients after myocardial infarction [7,8].

There have been a number of comparisons between different classes of antianginal agents in terms of symptom reduction, but there is little evidence that one is superior to another. In practice, the choice of a particular agent depends on patient acceptability; individual patients differ markedly in their experience of side effects and co-morbidity.

β-Blockers are fundamental drugs for angina, but the side effects are well known, including bronchospasm, peripheral vasoconstriction of the extremities, exacerbation of Raynaud's phenomenon, leg fatigue, and worsening of peripheral vascular disease. Calcium antagonists are a common alternative, but ankle edema, hypotension, flushing, and headache are familiar unwanted effects. Nitrates are the oldest drugs for angina, but syncope, facial flushing, and headaches limit their use in some patients.

In this context, the availability of a new clinical entity for the treatment of stable angina is a welcome development. Indeed, a new drug for angina is a landmark in cardiovascular medicine; a new class of antianginal drugs appears on average every 20 years (*Table I*).

Heart rate and angina

Angina pectoris results from ischemia, an imbalance between myocardial oxygen supply and demand.

Heart rate reduction, the cornerstone of treatment of angina, reduces oxygen demand and increases supply by prolonging diastole, during which coronary blood flow occurs. The findings of a recent study suggested that resting heart rate should rank in cardiovascular risk factor charts, alongside hypertension, blood lipid concentrations, and blood glucose concentrations, because it was a predictor of overall and cardiovascular mortality, independent of known risk factors such as hypertension, smoking, and diabetes [9]. Indeed, resting heart rate proved to be an independent risk factor for total and cardiovascular mortality after adjustment had been made for left ventricular ejection fraction and use of β-blockers. Studying patients from the Coronary Artery Surgery Study registry (median 14.7 years), the investigators found that patients with a resting heart rate of at least 83 beats/min at baseline had a significantly greater risk for total mortality ($P < 0.0001$) and cardiovascular mortality ($P < 0.0001$). Compared with patients with a heart rate no more than 62 beats/min, the hazard ratio for time to first admission to hospital for cardiovascular causes was 1.14 ($P < 0.001$) [9].

Table I. The classes of antianginal drugs, and the dates of their introduction for clinical use

Drug	Date of introduction
Glyceryl trinitrate	1900
β-Blockers	1964
Calcium channel blockers	1975
K^+ channel activators	1998
f-Channel inhibitors	2005

What are sinus node f-channels?

The heart has many safety mechanisms. One of these is the sinus node pacemaker. Myocardial cells (cardiac myocytes) do not beat, or contract, spontaneously; an electrical depolarization is required to initiate the ionic currents that enable myocyte contraction. This depolarization spreads from the sinus node via cardiac conducting tissue in a controlled wave to enable coordinated cardiac contraction (*Figure I*) [10].

The sinus node pacemaker cells have unique properties of their ion channels that permit the control of the slow diastolic depolarization – which is what really gives the pacemaker its clock type function and allows it to beat regularly. Sympathetic nervous system activity, catecholamines, and many other stimuli can increase the rate of depolarization of these pacemaker cells; conversely, parasympathetic activity or β-blockade can slow them.

One of these specific ion channels is the f-channel. This channel determines the slope of the diastolic depolarization, which controls the frequency of action potentials and, therefore, heart rate (*Figure 2*) [11,12].

Ivabradine

Ivabradine (Procoralan) is the first of an exciting new class of drugs that has the ability of slowing the depolarization slope, reducing heart rate to a degree similar to that achieved at rest with β-blockers (*Figure 3*). It is the first selective and specific cardiac sinus node ion channel inhibitor, acting at the f-channel (I_f). It reduces heart rate while maintaining myocardial contractility and atrioventricular conduction [11], and is indicated in the treatment of chronic stable angina pectoris with normal sinus rhythm, where there is contraindication (eg, asthma, chronic obstructive pulmonary disease [COPD], or peripheral vascular disease) or intolerance to β-blockers [13].

Pure heart rate reduction

Ivabradine provides pure heart rate reduction. Through its selective action, the drug has no interactions with other cardiac ion currents in the sinus node cell [14] and thus, unlike β-blockers, no potential undesirable effects on myocardial contractility

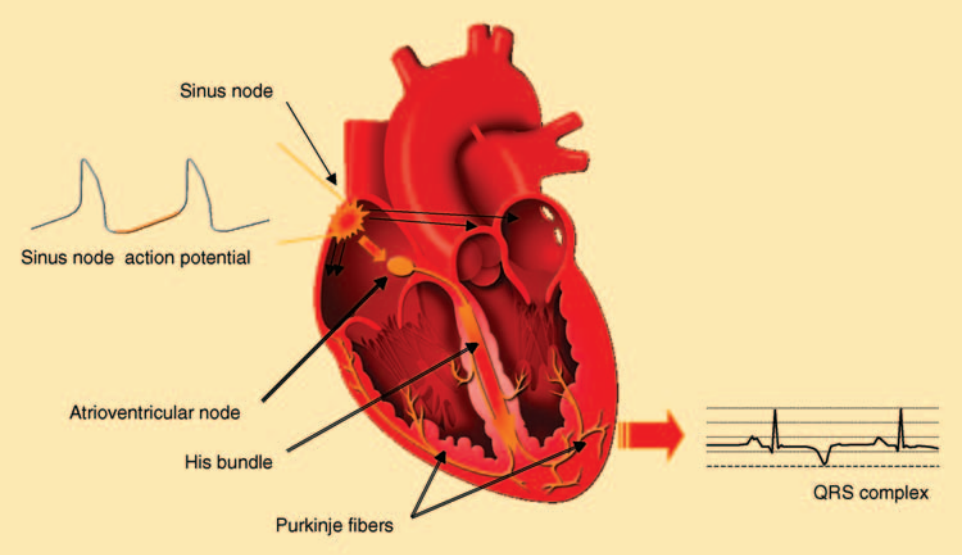

Figure 1. Sinus node: primary ''pacemaker'' of the heart. (From Goldberger [10], with permission.)

and cardiac electrophysiology [11]. In addition, it is not associated with the β-blocker side effects of fatigue, impaired libido, nightmares, mood disorders, and cold extremities.

The recommended starting dose is 5 mg twice daily, with a step-up to 7.5 mg twice daily after a 3–4 weeks of treatment, as required.

Efficacy of ivabradine

The antianginal and anti-ischemic efficacy of ivabradine have been extensively documented in a large, clinical program including four randomized, controlled, double-blind, parallel group, international, multicenter trials. It is the largest antianginal drug testing program, involving almost 5000 patients. The key findings from this program were the following.

- *Ivabradine provides anti-ischemic and antianginal efficacy with absence of rebound or tolerance*. In a placebo-controlled trial of 360 patients with a history of stable angina of at least 3 months' duration, patients received either placebo 2.5 mg twice daily or ivabradine 5 mg twice daily during a 2-week period. The primary efficacy criteria were

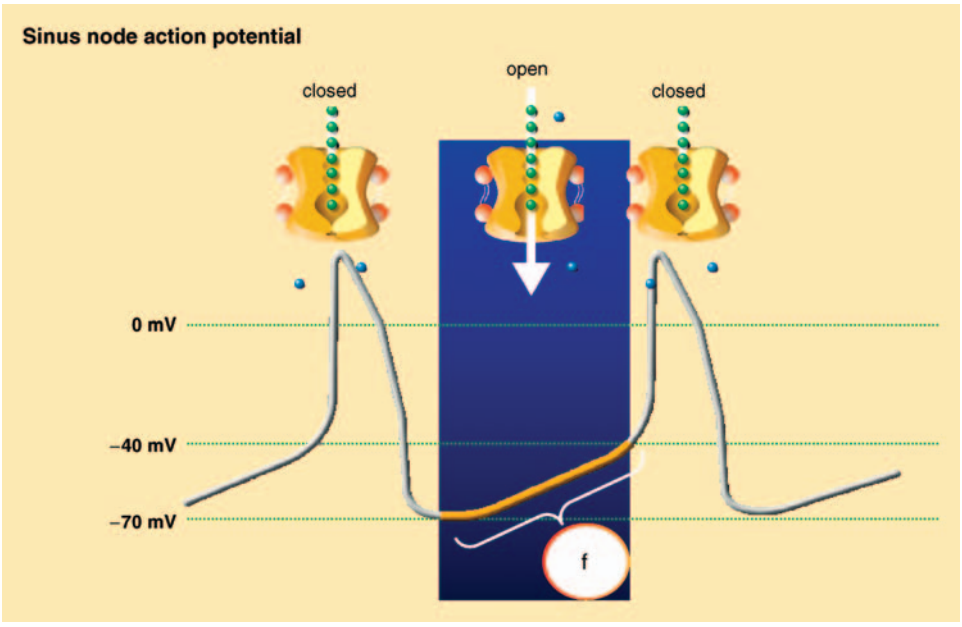

Figure 2. f-channels: a key determinant of heart rate regulation. The f-channels determine the slope of the diastolic depolarization, which controls the frequency of action potentials and, therefore, heart rate. (Adapted from Difrancesco et al [11] and Thollon et al [12], with permission.)

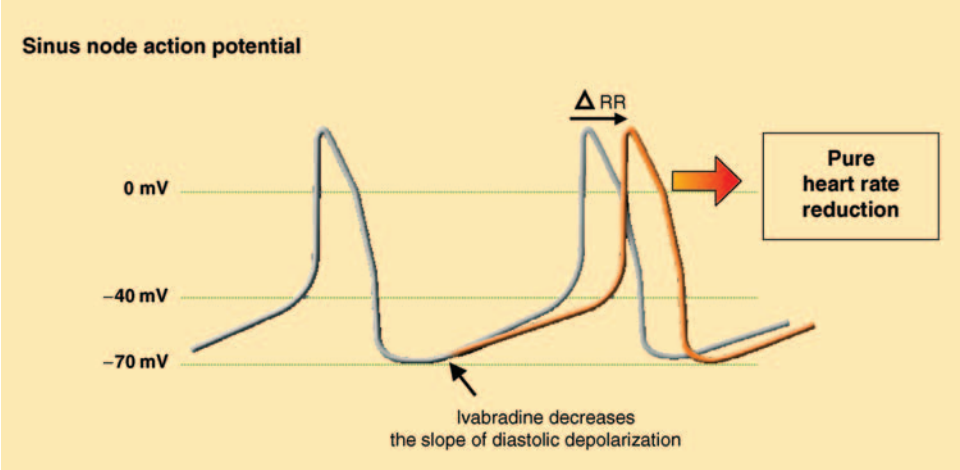

Figure 3. Selective inhibition of the I_f current reduces heart rate. Δ RR, reduction in heart rate. (From Thollon et al [12], with permission.)

changes in time to ST-segment depression and time to limiting angina during bicycle exercise. The 5 -mg twice daily dose was superior to placebo in the prevention of angina and ischemia. Ivabradine produced dose-dependent improvements in exercise tolerance and time to development of ischemia during exercise. Angina attacks and consumption of short-acting nitrate were reduced. Patients then received open-label ivabradine for 3 months, followed by a double-blind, randomized withdrawal to placebo [15].

- *Efficacy at least equal to that of atenolol*. In the 4-month INITIATIVE study of 939 patients with documented coronary artery disease and stable angina, ivabradine 5 mg twice daily and atenolol 50 mg once a day were compared for 4 weeks and then increased to ivabradine 7.5 mg twice daily or atenolol 100 mg once a day. Results confirmed the antianginal and anti-ischemic efficacy of ivabradine and demonstrated efficacy and safety at least as great as those of atenolol [16].
- *Efficacy and safety equal to those of amlodipine*. In a 3-month study of 1195 patients, efficacy of ivabradine 7.5 mg twice daily was the same as amlodipine 10 mg once a day for total exercise duration, time to limiting angina, time to angina onset, and time to 1-mm ST-segment depression [17]. The tolerability of the two regimens was good and comparable during the study.

In this clinical program, ivabradine reduced the number of spontaneous angina attacks and consumption of short-acting nitrate by more than two-thirds.

Safety of ivabradine

Ivabradine has been associated with a good safety profile during its clinical development. Its long-term safety was assessed in a 1-year, randomized, double-blind trial, in which two parallel groups of 386 patients with a history of at least 3 months of chronic stable angina and documented coronary artery disease were assessed from a safety perspective while receiving two doses of ivabradine (5 mg twice daily and 7.5 mg twice daily) over a 12-month period [18]. Safety was assessed on reported adverse events in follow-up visits at 1, 3, 6, 9 and 12 months. Ivabradine was well tolerated, with fewer than 1% of withdrawals as a result of treatment. In the INITIATIVE study, the most common adverse events reported were mild visual effects associated with abrupt changes in light intensity, attributable to the pharmacological activity of the drug [16]: f-channels exist in cardiac pacemaker cells and an isoform of the channel is present in the retina; this retinal isoform is called the h-channel. A few patients reported a mild visual stimulus, not necessarily unpleasant and without effects on, eg, driving. These visual stimuli were often transient and were fully reversible if the drug was discontinued. Fewer than 1% of patients discontinued treatment, and stimuli resolved in 77.5% of patients during treatment and in all patients after discontinuation of treatment.

Rate-corrected or controlled studies have shown no QTc prolongation, and treatment with ivabradine has not been associated with an excess of ventricular tachycardias. However, the drug should not be given to patients with the long QT syndrome. In addition, ivabradine is not suitable for patients with atrial fibrillation, because it has no effect on the electrophysiology of the atrioventricular node. At present, ivabradine is also contraindicated in patients with class III or class IV heart failure, because of a lack of data in this population.

The concomitant use of ivabradine with strong inhibitors of CYP 3A4, such as ketoconazole, erythromycin, or with diltiazem or verapamil is contraindicated,

and may lead to a significant increase in plasma exposure to ivabradine, possibly resulting in excessive bradycardia.

Decrease in the efficacy of ivabradine

Beginning now in many cardiac centers across the UK and worldwide is the BEAUTIFUL study, a double-blind, randomized, placebo-controlled study of ivabradine in patients with coronary heart disease and left ventricular dysfunction. This landmark trial, which will include 10 000 patients, will define the long-term benefit of ivabradine with regard to the critical outcomes of myocardial infarction and mortality.

Place of ivabradine in clinical practice

Given the absence of cardiac effects other than pure heart rate decreasing, ivabradine could be considered for patients with stable angina in whom β-blockers are contraindicated or not tolerated (those with asthma, COPD, or peripheral arterial disease). In addition to the side effects of β-blockers (including depression, fatigue, and cold extremities), erectile dysfunction is a particularly important problem associated with their use in older men and, therefore, ivabradine may be a useful alternative. Ivabradine can be combined with other cardiovascular drugs such as antiplatelet agents, statins, and angiotensin converting enzyme inhibitors.

Conclusions

New drugs for angina are rare indeed. A drug as good as a β-blocker but with fewer side effects will, I believe, rapidly become a powerful ally in our scant resource of antianginal drugs. Ivabradine is now available and will be welcomed by patients and their physicians in the journey of care through coronary heart disease. ■

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