Treatment options for patients with angina have expanded in recent years. Ivabradine is one of the latest medicines to get to grips with

Ivabradine

By Mojgan Sani, DPharm, MRPharmS

M anagement of patients with coronary artery disease (CAD) has changed radically over the past few years with the introduction of new pharmacological therapies as well as options for percutaneous coronary intervention and surgical myocardial revascularisation.

Angina pectoris, the most common symptom of CAD, can have a major effect on patients' quality of life. Patients are at significant risk of suffering an acute coronary event and uncontrolled angina symptoms can force many patients into premature retirement.

“Gold standard” treatment Within the standard antianginal arsenal are medicines that prevent death or myocardial infarction (MI) with no direct anti-ischaemic effect, such as antiplatelet drugs, statins and angiotensin-converting enzyme inhibitors. Additionally there are therapies that help relieve ischaemia and symptoms — for example beta-blockers, calcium channel blockers, nitrates and nicorandil (potassium channel activator with a nitrate component). Ivabradine is one of the newer drugs developed for the treatment of angina. It has an exclusive heart-rate reduction activity.

Mechanism of action There are two major determinants of myocardial oxygen consumption: heart rate and myocardial contractility. Reduction of heart rate is an essential part of managing patients with CAD. Life expectancy has been shown to be inversely related to heart rate, both in the general population and in patients with angina. Ivabradine allows a simultaneous reduction in oxygen demand and an increase in oxygen supply as well as redistribution of regional myocardial blood flow. It is a selective and specific bradycardic medicine that inhibits the If (cardiac pacemaker or "funny") current, which is responsible for regulating the intrinsic pacemaker activity in the sinoatrial node. The heart rate is slowed accordingly.

Ivabradine decreases myocardial oxygen consumption and, by improving diastolic perfusion time, enhances oxygen supply. It has no effect on myocardial contractility or atrioventricular conduction.

Administration Ivabradine is licensed for the symptomatic treatment of chronic stable angina pectoris in patients who are in sinus rhythm and have a contraindication to or an intolerance of beta-blockers.

The usual starting dose of ivabradine is 5mg twice a day (or 2.5mg twice a day for patients aged over 75 years). The dose can be increased to 7.5mg twice a day if needed to control symptoms. If a patient's heart rate drops below 50 beats/min at rest, the dose should be reduced. Additionally, patients should be monitored for symptoms relating to bradycardia, such as dizziness, fatigue and hypotension.

No dose adjustment is required for patients with mild hepatic impairment, caution should be exercised when ivabradine is used for patients with moderate hepatic impairment and the drug is contraindicated for patients with severe hepatic insufficiency.

Oral ivabradine is rapidly and almost completely absorbed but its absolute bioavailability is 40% because of first-pass metabolism. Tablets should be taken with meals because food delays absorption by one hour and increases plasma exposure by 20–30%. Ivabradine is 70% plasma protein bound and it is extensively metabolised by the liver and the gut by oxidation through cytochrome P450. The metabolites are excreted in the faeces and urine. Only 40% of the drug is excreted unchanged in the urine.

VERDICT

Ivabradine is a novel and useful addition to the anti-ischaemic medicines available for the management of patients with angina pectoris, but its use should only be considered when patients’ symptoms are not controlled on optimised “gold standard” anti-ischaemic therapy.

Ivabradine use should be restricted to patients who are intolerant of beta-blockers, or whose baseline heart rate is above 70 beats/min and who could benefit from the drug's heart-rate-lowering effects. Further large clinical trials are needed to assess long-term efficacy and safety of ivabradine in the management of patients with coronary artery disease.

Mojgan Sani is head of clinical pharmacy at Royal Berkshire NHS Foundation Trust. E: mojgan.sani@nhs.net
Adverse effects

Visual disturbances Around 16% of patients taking ivabradine have shown visual side effects described as transient enhanced brightness in a limited area of the visual field — ie, luminous phenomena (phosphenes). Only 1% of patients experiencing this side effect had to withdraw from treatment in clinical trials. Blurred vision can also occur in 1–10% of patients. The possible occurrence of such luminous phenomena should be taken into account when driving or using machines in situations where sudden variations in light intensity may occur, especially when driving at night.1

Cardiac effects Cardiac side effects include bradycardia, shown in 3% of patients particularly during the first three months of treatment. Other adverse effects can include first-degree atrioventricular block and ventricular extrasystoles.

Other effects Headache, nausea, diarrhoea, constipation, dizziness and muscle aches are among the other adverse effects reported, but these are less common.

Clinical efficacy

Small-scale initial trials A double-blind randomised controlled trial evaluated the effectiveness of ivabradine (2.5mg, 5mg or 10mg twice a day) versus placebo for two weeks in 360 patients with chronic stable angina. Other antianginal drugs were stopped. The trial showed that ivabradine increased significantly the time to reach a 1mm ST depression during exercise tolerance test, compared with placebo (P<0.005 for the 5mg and 10mg doses).6

A second randomised clinical trial compared the effects of ivabradine (5–10mg twice a day) and atenolol (50–100mg daily) in 939 patients with stable angina. The trial investigated the effects of the two agents on exercise capacity in a non-inferiority design. The primary efficacy measure was change in total exercise duration during exercise tolerance test. Ivabradine was found to be non-inferior to atenolol (P<0.001).4

BEAUTIUL trial A large study looking at morbidity and mortality of patients taking ivabradine has been published recently.7 The trial — called BEAUTIUL — recruited around 11,000 patients with coronary artery disease and left-ventricular ejection fraction less than 40%, who were randomised to ivabradine (5–7.5mg twice a day) or placebo. Participants were also prescribed conventional therapies such as beta-blockers (87%), renin-angiotensin system drugs (eg, ACE inhibitors; 89%), lipid-lowering medicines (76%) and antimicrobics (94%).

Despite reducing heart rate by an average of 6 beats/min more than placebo, treatment with ivabradine did not result in a significant reduction of the primary composite endpoint (cardiovascular death, admission to hospital for acute MI and admission to hospital for heart failure). However, for patients whose baseline heart rate was above 70 beats/min, ivabradine reduced the risk of hospital admission for fatal or non-fatal MI by 36% (P=0.001) and the risk of coronary revascularisation by 30% (P=0.016).7

Combination with beta-blocker A randomised double-blind controlled trial published recently evaluated the effect of combination therapy with atenolol 50mg daily and ivabradine 5–7.5mg twice a day versus atenolol alone.8 The combination therapy was shown to improve total exercise time (the primary outcome) and all exercise variables. The combination therapy was also well tolerated. The authors therefore suggested that in patients with angina pectoris who cannot tolerate full doses of beta-blockers the addition of ivabradine could be of value with careful monitoring of heart rate.

Further clinical evidence is needed in the future to support using lower, more tolerable doses of beta-blockers in combination with ivabradine to achieve the desired heart rate reduction. This strategy is outside the licensed indication of ivabradine and this combination therapy is not included in European Society of Cardiology guidelines at present.9

Place in therapy Ivabradine is a useful anti-ischaemic agent licensed for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm who have a contraindication or intolerance to beta-blockers. ESC guidelines on the management of patients with stable angina pectoris mention the use of sinus node inhibitors for patients intolerant of beta-blockers.4

Ivabradine may also be useful for patients whose baseline heart rate remains greater than 70 beats/min despite optimised gold standard anti-ischaemic therapy. It may also be a useful option for patients with asthma who cannot be prescribed a beta-blocker. Patients should be carefully

### How much antianginal medicines cost the NHS

<table>
<thead>
<tr>
<th>MEDICINE</th>
<th>DOSE</th>
<th>APPROXIMATE ANNUAL COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivabradine</td>
<td>5–7.5mg twice a day</td>
<td>£500</td>
</tr>
<tr>
<td>Atenolol</td>
<td>100mg once daily</td>
<td>£11</td>
</tr>
<tr>
<td>Diltiazem (modified release)</td>
<td>180–360mg once daily</td>
<td>£60 to £120</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>10–20mg twice a day</td>
<td>£100 to £190</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>5–10mg once daily</td>
<td>£15 to £17</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>40–120mg once daily</td>
<td>£14 to £30</td>
</tr>
</tbody>
</table>
Substances that interact with ivabradine

The following interactions are highlighted in the summary of product characteristics for ivabradine:5

**Enzyme inhibitors**
Concomitant use of potent enzyme inhibitors such as imidazole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin) and HIV protease inhibitors (nefalinavir, ritonavir) is contraindicated due to significant increase in mean ivabradine plasma exposure.

**Grapefruit juice**
Ivabradine exposure was increased two-fold following co-administration with grapefruit juice. Therefore, grapefruit juice consumption should be avoided by patients being treated with ivabradine.

**Enzyme inducers**
Enzyme inducers, for example rifampicin, barbiturates, phenytoin and *Hypericum perforatum* (St John’s wort) can decrease ivabradine exposure and activity. Use of St John’s wort should be restricted throughout ivabradine treatment.

**Heart-rate-reducing calcium channel blockers**
Combination of ivabradine with other heart-rate-reducing medicines such as diltiazem or verapamil results in an increase in ivabradine exposure and an additional heart rate reduction of 5 beats/min. Concomitant use of ivabradine with these drugs is not recommended.

References


Practice points

- Clinical pharmacists need to ensure “gold standard” anti-ischaemic therapy (p229) is optimised before considering patients for treatment with ivabradine.
- Ivabradine can be a useful addition to treatment for patients intolerant of beta-blockers or other heart-rate-reducing agents (such as diltiazem or verapamil) and those whose baseline heart rate remains above 70 beats/min.
- It is important for clinical pharmacists to monitor: patient treatment for potential interactions; optimisation of dosing (according to anginal pain, patient age, and renal and hepatic function); the extent of heart rate reduction; and side effects such as visual disturbances (and effect on driving and operating machinery if such side effects are experienced).

monitored for potential interactions (see Box above) and side effects.

Long-term safety and efficacy data will become available from further clinical trials, but at the present time gold standard therapy with anti-ischaemic and antiplatelet medicines remains the best option for patients with stable angina pectoris.

**SPOTLIGHT ON MEDICINES**

This *Clinical Pharmacist* series looks at prominent or recently launched medicines or classes of drugs. Pharmacists who have ideas for the series or wish to write about medicines are invited to contact the editor.

E: clinicalpharmacist@pharmj.org.uk
T: 020 7572 2425