Ranolazine: novel add-on treatment for stable angina

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KEY POINTS

- ranolazine is licensed as add-on treatment for stable angina when first-line therapy is unsuccessful
- available as 375mg, 500mg and 750mg prolonged-release tablets, all £48,98 (60)
- its mechanism of action is unclear and the pharmacokinetics are variable
- care is needed during dose titration to minimise the risk of adverse effects
- clinically significant drug interactions may occur with verapamil and diltiazem
- compared with placebo, the highest licensed dose of ranolazine increases exercise time and time to onset of angina by approximately 20-30 seconds in patients with severe symptoms, regardless of other antianginal therapy
- it appears to be well tolerated at the licensed doses
- ranolazine increases the choice of treatments for patients with angina who have not responded to or are intolerant of first-line therapies

Ranolazine is a new antianginal drug with a novel mode of action. In our New products review, Steve Chaplin discusses the clinical data relating to its efficacy and safety, and Dr Connolly describes its place in angina management.

Current guidance on the management of stable angina recommends a beta-blocker as first-line therapy to relieve symptoms – or, if not tolerated, a rate-limiting calcium-channel blocker, long-acting nitrate or nicorandil (Ikorel) – with glyceryl trinitrate spray or sublingual tablets for immediate symptom relief and short-term prevention.[1] If monotherapy is ineffective, a (non-rate-limiting) calcium-channel blocker and a beta-blocker should be combined.

The evidence for treatment with a combination of three drugs for symptom relief is limited and referral to a cardiologist is recommended if dual therapy is ineffective.

Properties

Ranolazine (Ranexa) is licensed as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant of first-line antianginal therapies.

Its mechanism of action is uncertain. It inhibits the late sodium current in cardiac cells, reducing intracellular sodium accumulation and decreasing intracellular calcium overload; in ischaemia, this may improve myocardial relaxation and decrease left ventricular diastolic stiffness.[2,3]

After one week's administration in patients with severe angina, ranolazine increased exercise duration dose dependently with no clinically significant effect on heart rate or blood pressure.[4]

Ranolazine is formulated as a modified-release (m/r) tablet. The recommended dose is initially 375mg twice daily, increasing after two to four weeks to 500mg twice daily, and then to a maximum of 750mg twice daily if necessary. The pharmacokinetics of ranolazine are very variable.[5]

To minimise the risk of adverse effects, careful dose titration is required in older patients and in those with impaired liver or kidney function, low body weight or heart failure. There are clinically significant interactions with CYP3A4 inhibitors (diltiazem, erythromycin)

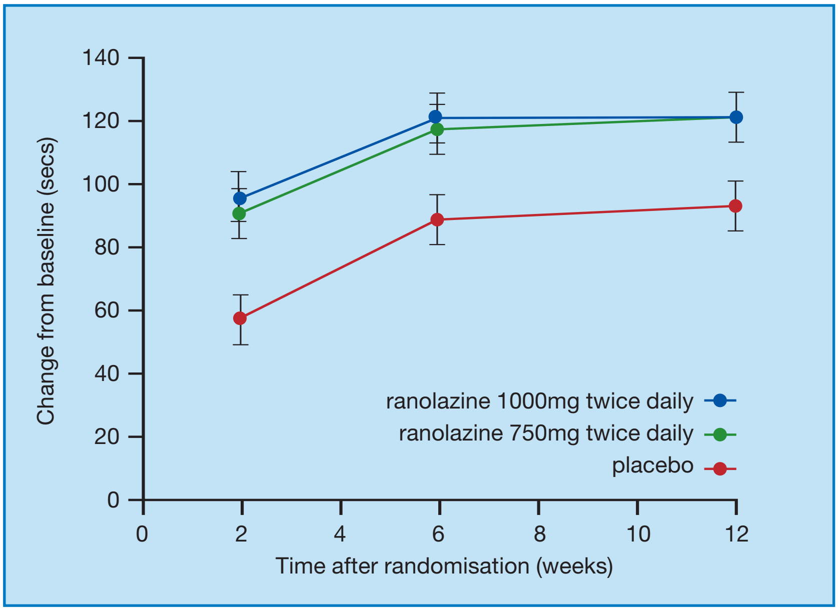

Figure 1. Change in exercise tolerance from baseline at trough ranolazine levels with 750mg and 1000mg twice daily and placebo; mean exercise duration increased by 115 seconds with ranolazine (both doses) and by 92 seconds with placebo[6]

and P-glycoprotein inhibitors (verapamil, ciclosporin).[2]

Clinical trials

The efficacy of ranolazine at licensed doses has been evaluated principally in two trials.[4,6] In a one-week dose-ranging study,[4] 191 patients with severe angina (48 per cent taking two antianginal drugs, 7 per cent taking three) discontinued their medication and were randomised to treatment with ranolazine 500mg, 1000mg or 1500mg twice daily. In those taking the lowest dose (the only one within the licensed range), mean exercise duration increased by 24-29 seconds (at trough and peak blood levels of ranolazine) compared with placebo. Mean time to onset of angina was increased by 27-36 seconds, and to onset of ischaemia (ST-segment depression) by 28-39 seconds.

In a 12-week trial, 823 patients with angina were stratified by treatment (atenolol 50mg per day, 43 per cent; m/r diltiazem 180mg per day, 27 per cent; or amlodipine 5mg per day, 32 per cent) and randomised to placebo or treatment with ranolazine 750mg or 1000mg per day.[6] Other antianginal medication (other than glyceryl trinitrate) was discontinued.

The primary end-point was change in exercise tolerance at trough levels of ranolazine. Mean exercise duration at baseline was approximately 416 seconds; this increased by 92 seconds with placebo and 115 seconds with ranolazine 750mg twice daily (p=0.03). There was no difference between the two doses of ranolazine (see Figure 1).

Both time to onset of angina (plus 30 seconds *vs* placebo) and ischaemia (plus 20 seconds *vs* placebo) were increased. The effect of ranolazine was similar regardless of concurrent antianginal therapy.

The mean frequency of angina attacks decreased from 4.5 per week to 3.3 with placebo and to 2.5 with ranolazine 750mg twice daily; this was associated with a corresponding reduction in use of glyceryl trinitrate.

Ranolazine has been evaluated at doses beyond the licensed range in two large trials.[7,8] However, due to the variation in pharmacokinetics of ranolazine, doses of 1000mg twice daily and above are associated with an unpredictable but increased risk of adverse effects.[5]

Adverse effects

There is a trend for adverse effects to become more common as ranolazine blood levels increase.[5] The frequency of adverse events associated with ranolazine 750mg twice daily in clinical trials was 16-31 per cent compared with 16-26 per cent with placebo.[4,6] Common adverse effects include dizziness, headache, constipation, vomiting, nausea and asthenia.[2] During treatment for up to 24 months, ranolazine 1000mg per day was not associated with increased cardiovascular events or decreased survival.[6,8]

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Place in therapy

Although the death rate from coronary heart disease is falling, the number of people surviving with stable coronary heart disease is still on the increase. Many of these patients have limiting angina despite revascularisation, and therefore the development of a new antianginal gives increased choice in the treatment armamentarium.

Ranolazine, a new drug with a novel mechanism of action, is licensed as add-on treatment for stable angina when first-line therapy is unsuccessful. Ranolazine appears to be well tolerated at the licensed doses and, compared with placebo, it can increase exercise time and time to onset of angina by approximately 20-30 seconds in patients with severe symptoms, regardless of other antianginal therapy.

In trials, ranolazine reduced both the frequency of angina attacks and the use of glyceryl trinitrate. Promisingly, according to the US Food and Drug Administration (FDA), ranolazine may also reduce the risk of ventricular arrhythmias, new-onset atrial fibrillation and bradycardia in patients with coronary disease and can lower glycosylated haemoglobin levels in diabetic patients.

During treatment for up to 24 months, ranolazine was not associated with significant changes in cardiovascular events such as myocardial infarction, or survival.

Careful dose titration is required in older patients and those with impaired liver or kidney function, low body weight or heart failure. There are clinically significant interactions with CYP3A4 inhibitors and P-glycoprotein inhibitors.

Ranolazine is generally well tolerated but adverse effects include dizziness, headache, constipation, nausea and vomiting.

This new agent holds great promise for those who still have angina despite traditional treatments or those intolerant of alternatives.

Dr Connelly is consultant cardiologist and honorary senior clinical lecturer at Sandwell and West Birmingham Hospitals NHS Trust