Ranolazine in the management of chronic stable angina

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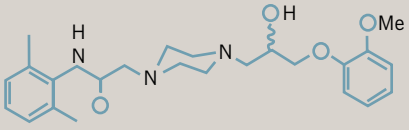
Ranolazine is a novel antianginal drug that does not have a clinically significant effect on haemodynamic parameters such as heart rate and blood pressure. It has been available as Ranexa® (ranolazine prolonged-release tablets) in the US since 2006 and it received approval from the European Medicines Agency (EMA) for use in the EU in 2008. The approved indication is as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta blockers and/or calcium antagonists).

Ranolazine has been evaluated in three trials in patients with stable angina (MARISA, CARISA and ERICA) and one large trial of patients with non-ST elevation acute coronary syndromes (MERLIN-TIMI 36). It has shown an improvement in exercise performance and a decrease in angina attacks. Ranolazine has similar efficacy in younger and elderly patients. Observational experience with ranolazine from a large UK centre is described.

Introduction

Coronary heart disease (CHD) remains the major cause of death throughout European and other developed countries. While death rates have been consistently falling, rates in the UK remain relatively high compared to some Western European countries. The commonest clinical presentation of CHD is angina pectoris. Angina incidence rates generally increase with age and are highest in the 65–74 years age group in both men and women. The prevalence of angina is estimated to be 5% in men and 4% in women in the UK, giving a total of nearly 2.1 million (>1.2 million <75 years of age) with the condition.[1] It is therefore a common disease, which carries a prognosis similar to patients who have had a myocardial infarction (MI) or who have been revascularised.[2] Many patients experience anginal attacks despite revascularisation and pharmacological antianginal treatments. In the Clinical Outcomes Utilization Revascularization and Aggressive Drug Evaluation (COURAGE) trial,[3] for example, over 25% of patients experienced angina up to five years post-percutaneous coronary intervention (PCI) with optimal medical treatment (OMT). Such findings suggest that we need better strategies to improve both symptoms and prognosis in patients with chronic stable angina.

Figure 1. The molecular structure of ranolazine



Ranolazine profile

This review looks at ranolazine, an antianginal which does not have a clinically significant effect on heart rate or blood pressure. Ranolazine is a piperazine derivative. Its molecular structure is shown in **figure 1**. It was approved by the US Food and Drug Administration in January 2006 as add-on therapy for the treatment of chronic angina and received a first-line indication in November 2008. The maximum approved dose in the US is 1,000 mg twice daily.

In Europe, it was registered as Ranexa® (ranolazine prolonged-release tablets) in July 2008. Its approved indication is as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta blockers and/or calcium antagonists). The recommended initial dose in adults is 375 mg twice daily. After two to four weeks, the dose should be titrated to 500 mg twice daily. According to the patient's response, it can be further titrated to the recommended maximum dose of 750 mg twice daily.

The mechanism of action is not fully elucidated but it is thought to be via selective inhibition of the late inward sodium current (I_{Na}) in cardiac muscle cells.[4,5]

This reduces intracellular sodium accumulation and calcium overload, and consequently improves myocardial relaxation and decreases left ventricular diastolic stiffness.[6,7]

Haemodynamic effects are minimal (decreases in mean heart rate <2 bpm and in mean systolic blood pressure <3 mmHg) in patients treated with ranolazine alone or in combination with other antianginal agents in controlled studies.[8] Dose- and plasma concentration-dependent increases in the QTc interval (about 6 ms at 1,000 mg twice daily), reductions in T wave amplitude and notched T waves have been observed in patients treated with ranolazine. These effects are thought to relate to inhibition of the fast-rectifying potassium current. In the Metabolic Efficiency With Ranolazine for less Ischemia in Non-ST-Elevation Acute Coronary Syndromes (MERLIN-TIMI 36) study,[9] there was a significantly lower incidence of arrhythmias among patients treated with ranolazine (74%) compared to placebo (83%), including ventricular tachycardias (5% *vs.* 8%). There has been no evidence of higher risk 'torsade de pointes' in clinical trials.

Pharmacokinetics

The mean bioavailability after oral administration of ranolazine varies from roughly 35 to 50%, and peak plasma concentrations are reached two to six hours after administration. Steady state is usually achieved within three days of twice-daily dosing. Trough concentrations occur about 12 hours after administration. Approximately 62% of ranolazine is bound to plasma proteins. It is eliminated primarily by metabolism (less than 5% is excreted unchanged). The terminal half-life at steady state after oral administration of ranolazine is about seven hours. Ranolazine undergoes rapid and extensive metabolism. In liver, ranolazine is metabolised principally by CYP3A4, but also by CYP2D6.

Clinical trials and drug efficacy

The development programme began with ranolazine immediate-release; later clinical trials used the sustained-release formulation. Some trials used doses of ranolazine which are outside the recommended doses but they have been included in this review for the sake of completeness. The Summary of Product Characteristics (SPC)[10] should be consulted for more comprehensive prescribing information.

The principal dose-response study was the Monotherapy Assessment of Ranolazine In Stable Angina (MARISA) trial,[11] which randomised 191 patients. The main clinical study was the Combination Assessment of Ranolazine In Stable Angina (CARISA) trial,[12] which included 823 patients; ranolazine 750 mg twice daily or 1,000 mg twice daily were added to atenolol, amlodipine or diltiazem. In a supportive study, the Efficacy of Ranolazine In Chronic Angina (ERICA) trial,[13] 565 patients were randomised to receive ranolazine 1,000 mg twice daily or placebo in addition to amlodipine 10 mg daily for six weeks. Finally, in the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes (MERLIN)-TIMI 36 trial, a total of 6,560 patients were randomised to receive ranolazine (initially intravenously [IV] and then 1,000 mg twice daily orally) or matching placebo within 48 hours of ischaemic symptoms. They were followed for a median of 348 days.

MARISA

The main dose-response study for ranolazine is the MARISA trial.[11] The objectives of the trial were to assess the tolerability of three doses of ranolazine sustained-release compared to placebo and their effects on treadmill exercise performance.

Patients were at least 21 years old, with documented coronary artery disease and a history of at least three months of angina on effort. During the qualifying phase, prophylactic antianginal treatment was stopped and two modified Bruce exercise tolerance tests (ETTs) were conducted. Patients were randomised into the double-blind phase if they developed exercise-limiting angina and >1 mm ST segment depression during the ETTs.

The study was a double-blind, randomised, placebo-controlled, four-period crossover study. It enrolled 191 patients with stable angina: they received ranolazine SR at doses of 500 mg, 1,000 mg and 1,500 mg or placebo twice daily for one week. At the end of each treatment period, ETTs were performed four and 12 hours after dosing (these times approximate peak and trough plasma ranolazine concentrations). The primary efficacy end point was total exercise duration at trough. Other efficacy end points included time to onset of angina, time to 1 mm ST segment depression at trough, and the same ETT end points at peak.

Compared to placebo, treatment with ranolazine significantly improved total exercise duration: the mean difference at trough was 23.8 seconds for 500 mg twice daily, 33.7 seconds for 1,000 mg twice daily and 45.9 seconds for 1,500 mg twice daily, showing a clear dose-response pattern. The corresponding differences at peak were 29.3, 50.1 and 55.5 seconds, respectively.

Time to onset of angina, similarly, was longer with ranolazine than with placebo. At trough, the differences were 27.0, 45.9 and 59.6 seconds for ranolazine 500 mg, 1,000 mg and 1,500 mg twice daily, respectively. The time to 1 mm ST segment depression also improved against placebo, with trough value differences of 27.6, 44.5 and 64.6 seconds, respectively, for the three increasing doses of ranolazine. No clinically significant changes in rest or exercise heart rate or blood pressure were observed with ranolazine. In this study, exercise duration was longest in the 1,500 mg group; however, there was a disproportional increase in side effects and the 1,500 mg dose was not studied further.

A recent analysis from MARISA using exercise testing in 191 patients[14] suggests that the progressive magnitude of ischaemia reduction on ranolazine was proportionally more substantial than minor reductions in heart rate or rate pressure product (RPP), suggesting ranolazine's benefits may be due to an improvement in regional coronary blood flow in areas of myocardial ischaemia.

CARISA

The main clinical study of ranolazine in severe chronic angina is the CARISA trial.[12] It was a randomised, three group, double-blind and placebo-controlled trial that enrolled 823 patients from 118 participating outpatient departments to receive placebo or one of two doses of ranolazine.

All patients had confirmed coronary artery disease and a history of at least three months of exertional angina. They were stratified

according to the antianginal therapy that they were taking at enrolment (atenolol 50 mg, diltiazem 180 mg or amlodipine 5 mg daily). At the screening visit, patients had to have reproducible angina, ischaemic ST segment depression of at least 1 mm and limited exercise capacity on treadmill testing (three to nine minutes on a modified Bruce protocol). Eligible patients entered a single-blind qualifying phase during which they had two ETTs, conducted a week apart and each preceded by a 12-lead ECG. Subsequent exercise tests were performed at trough drug levels two, six and 12 weeks after randomisation. At two and 12 weeks after randomisation, a peak ETT was also performed four hours after dosing. The primary efficacy parameter was change from baseline in exercise treadmill time at trough. Angina frequency and nitroglycerin (NTG) consumption were also recorded.

The mean age was 64 years: fewer than 10% were aged 75 or older. About 23% were female. More than 60% were hypertensive and 58% had had a previous MI. Some 23% had diabetes. Patients were experiencing an average of 4.5 angina attacks per week; angina frequency and NTG consumption were similar across all groups. The patients were randomised to receive ranolazine 750 mg twice daily (n=279), 1,000 mg twice daily (n=275) or placebo (n=269) as add-on treatment to atenolol 50 mg once daily, amlodipine 5 mg once daily or diltiazem 180 mg once daily.

At baseline, all three treatment arms had an exercise duration of approximately seven minutes. Each individual ranolazine dose increased treadmill exercise duration at both trough (p=0.03) and peak (p<0.02). This effect was sustained throughout the 12 weeks of the study for both ranolazine doses, and similar results were observed for times to angina and ECG ischaemia.

At baseline, patients had approximately 4.5 angina attacks per week. Ranolazine reduced this number to 2.5 for the 750 mg twice-daily dose (p=0.006) and to 2.1 for the 1,000 mg twice-daily dose (p<0.001). It also reduced NTG consumption.

There was some concern about the robustness of these findings since baseline treatment was not maximised for all patients. A post hoc analysis of patients considered maximally dosed as a result of depressed heart rate, blood pressure and/or prolonged PR interval (n=249), showed similar results to those for the study population as a whole.[18]

ERICA

The ERICA trial studied ranolazine sustained-release in patients with stable angina who were also receiving conventional antianginal agents (here, the maximum recommended dose of amlodipine).[13]

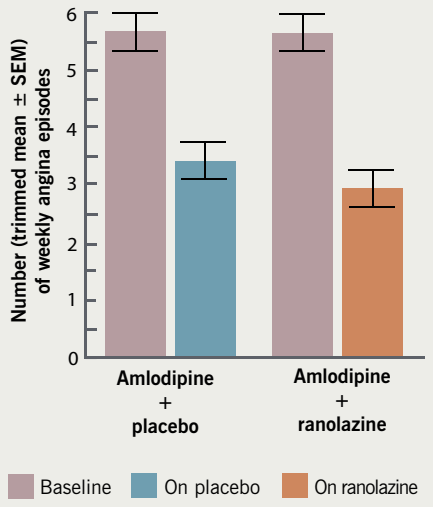
For inclusion, patients were to be aged 18 years or over, with a documented history of coronary artery disease, chronic stable angina for three months or longer, and three or more angina episodes a week during the qualification period despite treatment with amlodipine 10 mg daily. Long-acting nitrates and sublingual NTG, as required, were permitted during the study period but other antianginal agents were not allowed.

Following a two-week qualifying phase, patients were randomised to receive ranolazine or placebo. During the initial one-week phase, patients received either ranolazine 500 mg twice daily or placebo; during the subsequent full-dose treatment phase, patients received either ranolazine 1,000 mg twice daily or placebo. Amlodipine 10 mg daily was continued throughout. Patients were evaluated at two weeks and six weeks after initiation of the full-dose phase to assess efficacy and the occurrence of adverse events.

The primary efficacy variable was the weekly average frequency of self-reported angina episodes during the six-week full-dose treatment phase. Secondary efficacy variables were average weekly NTG consumption during the six-week phase plus change from baseline of the five dimensions of the Seattle Angina Questionnaire (SAQ).

Some 565 patients were randomised; 98% of patients in each group completed the trial. **Figure 2** shows patients receiving ranolazine had a significantly lower weekly rate of angina episodes compared with patients receiving placebo (trimmed mean 2.88 *vs.* 3.31, respectively). The average weekly rate of NTG consumption was significantly lower in patients receiving ranolazine during the treatment phase (p=0.014) though baseline

Figure 2. The number of weekly angina attacks following treatment with amlodipine and ranolazine in the ERICA trial



Key: Adapted from Stone PH *et al.*[13]

NTG consumption did not differ between treatment groups.

The scores on the angina frequency dimension of the SAQ were significantly improved in patients receiving ranolazine (22.5 *vs.* 18.5) but the other SAQ dimensi ons were not significantly different between treatment groups. Subgroup analyses showed reductions of angina frequency and NTG use for those with a baseline frequency >4.5 per week, but only of angina frequency for those with fewer attacks at baseline.

Long-acting nitrates were used by 45% of the patients assessed. The treatment effect of ranolazine was consistent irrespective of gender, use of long-acting nitrates and age. Ranolazine had no clinically significant effects on heart rate or blood pressure.

Elderly patients

Age alone had no relevant effect on pharmacokinetic parameters. Pooled data from CARISA and ERICA[15] indicate that the efficacy of ranolazine is similar in older (70 years or more) and younger patients but that adverse effects are more common in the elderly. The incidence of serious adverse effects attributable to ranolazine did not differ significantly between age groups. Cautious up-titration is needed in the elderly, who may have an age-related decrease in renal function.

UK observational experience

Whilst randomised clinical trials of antianginal agents, such as those above for ranolazine, have established their efficacy as first- or second-line agents, in actual practice newer agents are often used in a serial and additive manner on top of existing established therapy. Furthermore, they may be introduced into a patient population that is challenging to manage either because they continue to experience anginal symptoms despite conventional therapy, or in whom there are (multiple) drug intolerances. With six classes of antianginal agents, the utility and impact of adding a new drug for angina on top of several others is not well defined. Previous experience has also suggested a limited incremental benefit beyond two antianginal drugs.

In order to look at this issue further with respect to ranolazine, we recently conducted a retrospective analysis of a consecutive series of 25 patients in whom ranolazine had been prescribed. We examined GP and hospital records covering a mean of 27 months per patient spanning the period both before and after initiation of ranolazine.

The patient characteristics are summarised in **table 1**. Most of these patients had advanced angina (Canadian Cardiac Society [CCS] Class III or IV) and more than half the patients had undergone at least one coronary revascularisation procedure. Prior to initiation of ranolazine, all of the patients had previously had coronary angiography undertaken to define the current extent of their coronary disease (including graft and/or stent patency) and the potential for further revascularisation. Importantly, many of the patients had undergone multiple coronary angiograms for recurrent chest pain and hospital admissions over the preceding years, suggesting a high burden of repeat angiographic investigations that did not result in revascularisation.

The mean number of other antianginal agents being taken by the patients prior to being prescribed ranolazine was 3.6 (range 2–5), with patients having tried an average of 4.2 (range 2–5) other antianginal agents (including those to which they were intolerant). Thus the data suggest that our use of ranolazine was often as a fourth-line agent in patients whose symptoms of chest pain were not controlled by multiple other antianginal drugs and in whom further revascularisation was not an option.

We sought to determine whether there was any subjective or objective evidence of antianginal benefit in this challenging patient group. Some 48% of patients reported a good symptomatic response following the initiation of ranolazine and a further 20% had at least some reduction in angina burden. A non-cardiac cause for the chest pain was subsequently diagnosed in half of the non-responders.

In the 18 months prior to initiation of ranolazine, there had been a mean of 3.96 admissions/patient for angina. Notably, the monthly hospital admission rate dropped by 54.5%, following commencement of ranolazine. Furthermore, only one patient (non-responder) went on to have repeat angiography and revascularisation. These observations are more striking when recalling that these patients had advanced angina and were already taking multiple antianginal agents. These data support a potentially useful role of ranolazine in reducing both symptoms and hospital admissions in some patients with difficult to control angina.

MERLIN-TIMI 36 study

The MERLIN-TIMI 36 trial was designed to evaluate the efficacy and safety of ranolazine as an intervention to reduce cardiovascular death, MI or recurrent ischaemia in the short and long term in acute coronary syndrome (ACS) patients at moderate to high risk who were already receiving standard therapy.[9]

It was a phase III, double-blind, parallel group, placebo-controlled trial that randomised 6,560 patients within 48 hours of ischaemic symptoms. Patients were randomised either to ranolazine 200 mg IV over one hour, followed by an 80 mg/h IV infusion for 12–96 hours, or to matching placebo. Once the infusion was completed, ranolazine extended-release 1,000 mg twice daily or matching placebo was instigated; patients were followed up for a median of 348 days.

The primary efficacy end point was the first occurrence of cardiovascular death, MI or recurrent ischaemia. Other secondary end points included failure of therapy (cardiovascular death, MI, recurrent ischaemia, positive findings on Holter monitoring for ischaemia, hospitalisation for heart failure or an early positive ETT). Quality of life was assessed by the SAQ. Safety end points included death from any cause, time to first occurrence of death from any cause or any cardiovascular hospitalisation, symptomatic documented arrhythmia, and clinically significant arrhythmia detected on Holter monitoring.

Table 1. UK observational experience with ranolazine

Patient characteristics (n=25)	
Mean age (years; range)	67; 49–93
Male (%)	72
Female (%)	28
Canadian Cardiac Society angina class (%)	
–I	0
–II	17.4
–III	47.8
–IV	34.8
Previous revascularisation (%)	52
–Percutaneous coronary intervention (PCI)	20
–Coronary artery bypass graft (CABG)	16
–CABG and PCI	16
Antianginal therapy (%)	
–Beta blockers	64
–Oral/transdermal nitrates	96
–Nicorandil	88
–Calcium channel blockers	64
–Other (e.g. ivabradine)	20

At baseline, 96.1% were being treated with aspirin and 90.3% with heparin. Median time from symptom onset to randomisation was 24 hours. Study drug was given intravenously to 6,541 patients (99.7%) for a median of 23 hours, and follow-up with oral administration of study drug took place in 6,399 patients (97.5%).

The composite primary efficacy end point occurred in 696 patients (21.8%) in the ranolazine group compared with 753 patients (23.5%) in the placebo group (hazard ratio [HR] 0.92, p=0.11). Failure of therapy occurred in 1,173 patients (36.8%) in the ranolazine group compared with 1,233

patients (38.3%) in the placebo group (HR 0.94, p=0.16).

Although ranolazine had no effect on the rate of cardiovascular death or MI, recurrent ischaemia was significantly lower in the ranolazine group (**figure 3**).

Recurrent ischaemia was defined here as: recurrent ischaemia with ECG changes, leading to hospitalisation or prompting revascularisation; or worsening angina by at least one Canadian Cardiovascular Society (CCS) class requiring intensification of therapy.

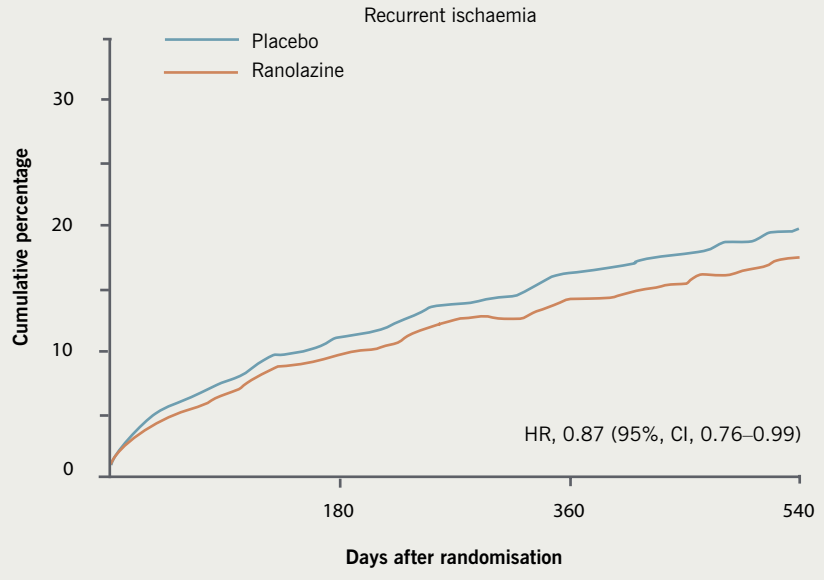
There was also a trend towards an early reduction in recurrent ischaemic complications (30-day cardiovascular death, MI, severe recurrent ischaemia, positive ischaemic changes on Holter monitoring) with ranolazine: this end point occurred in 23.1% of ranolazine patients and 25.1% of placebo patients, RR 0.92, p=0.055. Worsening angina by at least one CCS class was lower with ranolazine (4.2% *vs.* 5.9%, HR 0.77, p=0.02). An increase in antianginal therapy was less frequent in the ranolazine group (10.6% *vs.* 13.0%, HR 0.80, p=0.003). An improvement in angina frequency using the SAQ was recorded with ranolazine (p<0.001), particularly among patients who had a history of angina at study entry.

Effects on glycosylated haemoglobin

A post-hoc analysis of the CARISA trial examined the effect of ranolazine on glycosylated haemoglobin (HbA_{1c}) in patients with diabetes.[16] HbA_{1c} values were obtained from 160/189 (85%) of patients at baseline and from 140/189 (74%) of patients with diabetes at 12 weeks. Ranolazine 750 mg and 1,000 mg twice daily reduced HbA_{1c} compared with placebo by 0.48% (p=0.008) and 0.70% (p=0.0002), respectively. The reduction in HbA_{1c} was greater among those patients receiving insulin. After adjusting for baseline differences, the percentage of patients with HbA_{1c} <7% was significantly higher in the ranolazine 1,000 mg group (p=0.004). Levels of HbA_{1c} appeared to remain unchanged beyond 12 weeks of ranolazine treatment in the long-term, open-label extension study (for up to two years).

A reduction in HbA_{1c} was also observed in the MERLIN-TIMI 36 trial.[17] At four months, HbA_{1c} fell from 7.5% to 6.8% with ranolazine, and 59% of patients with diabetes had reached the target HbA_{1c} of <7%. Additionally, subjects without diabetes in the ranolazine group were 32% less likely to develop new hyperglycaemia, new increases in HbA_{1c} >6% and new fasting glucose >110 mg/dL (p=0.003).

Figure 3. Graph showing recurrent ischaemia in the MERLIN-TIMI 36 study



Adapted from: Morrow DA *et al.*[17]

Safety and tolerability

For full recommendations on the use of ranolazine, prescribers are advised to consult the SPC.[10] Ranolazine is generally well tolerated with undesirable effects generally being mild to moderate in severity and often developing within the first two weeks of treatment.[10]

The most common adverse events reported in patients receiving ranolazine in the phase 2/3 chronic angina programme were constipation, nausea and asthenia. The incidence of adverse events leading to study discontinuation was 6.3% for ranolazine-treated patients compared with 3.0% for placebo-treated patients.[18] In the dose-finding MARISA study, increasing the dose from 1,000 mg twice daily showed a disproportionate increase in the most frequent adverse events. Furthermore, early withdrawal from the study because of adverse events also occurred more frequently during dosing with 1,500 mg twice daily.[11] As a result, this higher dose was not studied further; within the therapeutic range, ranolazine is generally well tolerated.

Some 746 patients who completed the MARISA or CARISA trial participated in the Ranolazine Open Label Experience (ROLE).[19] Two years after initial dosing, 571 patients (76.7%) remained on therapy, and 72 patients (9.7%) discontinued ranolazine due to adverse events. Some 64 deaths occurred during a total of 2,102 patient years (3.0% annually). Such survival analyses suggest that symptomatic improvements attributable to ranolazine are not offset by increased mortality.[19]

In healthy volunteers and chronic angina patients, treatment with ranolazine was associated with small dose-related mean increases in QTc from baseline.[18] In the pivotal clinical studies, mean changes from baseline in QTcF (Fridericia's correction) after doses of 500 mg and 750 mg twice daily were 1.9 and 4.9 ms, respectively.[10] However, in the trial programme there has been no evidence of an increased risk of torsades de pointes.[18] No proarrhythmic effects were observed in 3,162 patients treated with ranolazine based on seven-day Holter monitoring in the MERLIN-TIMI 36 study. There was a significantly lower incidenced of arrhythmias in patients treated with ranolazine versus placebo, including ventricular tachycardia ≥ 8 beats.[10]

Ranolazine is contraindicated in patients with severe renal impairment (with creatinine clearance <30 ml/min). A 1.3- to 1.8-fold increase in ranolazine exposure is estimated to occur in these patients. It is contraindicated in patients with severe or moderate hepatic impairment. In moderate impairment, the ranolazine 'area under curve' (AUC) was increased 1.8-fold, and QT prolongation was more pronounced.[10] Contraindications with other drugs are discussed below.

Drug interactions

Inhibitors of CYP3A4 increase plasma concentrations of ranolazine and hence increase the potential for dose-related adverse events such as dizziness and nausea. The concomitant administration of ranolazine with potent CYP3A4 inhibitors (itraconazole, ketoconazole, voriconazol, posaconazol, HIV protease inhibitors, clarithromycin, telithromycin and nefazodone) should be avoided. Grapefruit juice is also a potent inhibitor of CYP3A4. Caution is recommended in combining ranolazine with moderately potent CYP3A4 inhibitors including diltiazem, erythromycin and fluconazole. Initiation of treatment with ranolazine should be avoided in those receiving CYP3A4 inducers e.g. rifampicin, phenytoin.

Simvastatin metabolism and clearance are highly dependent on CYP3A4. Ranolazine 1,000 mg twice daily increased plasma concentrations of simvastatin lactone, simvastatin acid, and the HMG-CoA reductase inhibitor activity by 1.4- to 1.6-fold. Co-administration of Class Ia (such as quinidine) or Class III (such as dofetilide and sotalol) antiarrhythmics other than amiodarone is contraindicated.

There is a theoretical risk that co-administration of ranolazine with other drugs known to prolong the QTc interval may cause an interaction that increases the risk of ventricular arrhythmias e.g. the antihistamines, terfenadine, astemizole and mizolastine; the antiarrhythmics, quinidine, disopyramide and procainamide; erythromycin; and the tricyclic antidepressants, imipramine, doxepin and amitriptyline.

Conclusions

Ranolazine is an antianginal with a non-haemodynamic mechanism of action. It is used as adjunctive therapy in patients with chronic stable angina whose angina is uncontrolled adequately with conventional treatment such as beta blockers and rate-limiting calcium antagonists. Randomised clinical trials show that the drug improves exercise performance, decreases angina and nitrate consumption, compared to placebo. Observational experience suggests that ranolazine response rates are encouraging in more therapeutically challenging patients after revascularisation and in the presence of multiple other antianginal medications. It is comparatively well tolerated with little effect on haemodynamics or cardiac conduction, apart from a modest increase in QT interval, which is not clinically compromising. Ranolazine has potential use in a number of other cardiovascular conditions[20] but presently it offers a useful alternative and adjunct to conventional antianginals in selected patients with chronic stable angina

Conflict of interest

KK has received fees for advisory services with A Menarini Pharma, UK SRL, manufacturers of ranolazine. He does not hold stock in the company. MJ: none declared.

Editors' note

Menarini has reviewed this article before publication for medical accuracy only. Full editorial control of this article resides with the authors and the journal.

Key messages

- Ranolazine is indicated at doses of up to 750 mg twice daily as an add-on treatment for angina pectoris patients with inadequately controlled symptoms or who are intolerant to first-line antianginals
- It does not depend on reductions in heart rate or blood pressure for its antianginal effects
- It is reasonably well tolerated, it increases exercise time duration, reduces angina attacks and nitrate consumption versus placebo

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