Ranolazine

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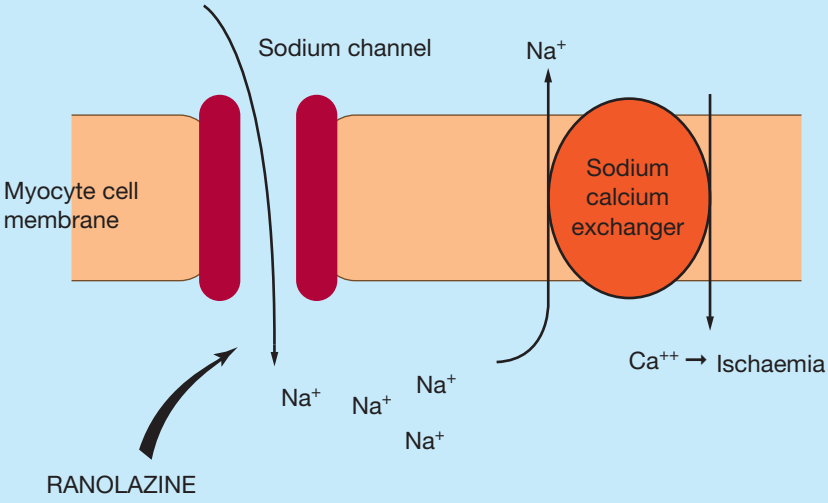
Introduction

Ranolazine is a novel anti-anginal drug first licensed for use in the USA in 2006. It has been shown to objectively improve exercise capacity and lengthens the time to symptom onset in patients with coronary heart disease. It achieves these effects without significantly influencing pulse rate or blood pressure. In patients with diabetes it has been noted to bring about a sustained reduction in HbA1c in a dose-dependent manner, with an enhanced effect seen in patients receiving exogenous insulin. Interestingly, ranolazine appears to reduce HbA1c even in patients who do not have diabetes, with heightened effects seen in those with impaired fasting glucose. The anti-anginal and blood glucose lowering effects appear to be independent, and the adverse event profile is similar in patients with or without diabetes.

Pharmacology

The mechanism by which ranolazine achieves its physiological effects is unclear. Ranolazine inhibits the slowly inactivating component of the cardiac sodium current and may therefore reduce cardiac myocyte dysfunction by avoiding intracellular sodium and calcium overload (Figure 1). It has been suggested that similar ion channel blockade is responsible for the observed pancreatic islet effects with it improving insulin sensitivity through increased pancreatic insulin secretion in response to glucose loads. This effect has been demonstrated *in vitro* and *in vivo* using rat models, but has not been demonstrated in humans. It has also been suggested that ranolazine's effects on glycaemic control are indirectly achieved by facilitating greater exercise capacity through its anti-anginal effects.

Figure 1. Mechanisms of action of ranolazine



NOTES. Defective sodium (Na^+) channel gating leads to calcium (Ca^{++}) overload and ischaemia. Ranolazine inhibits the slowly inactivating component of the cardiac sodium current and may therefore reduce cardiac myocyte dysfunction by avoiding intracellular sodium and calcium overload.

Trials of safety and efficacy

MARISA (Monotherapy Assessment of Ranolazine In Stable Angina) was the first double-blind, placebo-controlled randomised trial to establish the anti-anginal effects of ranolazine monotherapy.[1] The study had a four-period Latin Square crossover design, involving 191 patients with exercise-induced angina. Patients discontinued their usual anti-anginal medication and were randomised to receive ranolazine at doses of 500mg, 1000mg or 1500mg bd, or placebo, each for one week. Exercise tolerance tests were performed at the times of peak and trough serum ranolazine concentrations. In the 168 patients who completed all four periods of the trial, ranolazine was seen to significantly improve total exercise duration, the time to angina and the time to developing 1mm ST segment depression, in a dose-dependent manner.

CARISA (Combination Assessment of Ranolazine In Stable Angina) evaluated the efficacy of ranolazine as add-on therapy in severe coronary artery disease.[2] The trial recruited 823 patients who had exercise-induced angina, and were maintained on daily atenolol 50mg (354 patients, 43%), diltiazem 180mg (256 patients, 31%) or amlodipine 5mg (213 patients, 26%). They were randomised to additionally receive placebo, ranolazine 750mg twice-daily or ranolazine 1000mg twice-daily, over a 12-week period. Both ranolazine groups experienced significantly fewer angina episodes and used less nitroglycerine spray than the placebo group. The exercise capacity, measured on a treadmill, was increased for patients who received ranolazine compared with those receiving placebo (p=0.01).

MERLIN-TIMI 36 was a large international study that established

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the safety and anti-anginal effects of ranolazine in 6560 patients presenting with acute non-ST elevation myocardial infarction.[3] Patients across 440 sites in 17 countries were randomised to receive placebo or ranolazine 1000mg twice-daily, with median follow up of almost one year. There was no difference between the ranolazine and placebo groups in the primary endpoint, a composite of cardiovascular death, myocardial infarction or recurrent ischaemia (HR 0.92, 95% confidence interval 0.83–1.02, p=0.11), nor was there any difference for any of these individual endpoints. A trend toward fewer recurrent ischaemic events was seen in the ranolazine group, though this failed to reach statistical significance (HR 0.92, 95% CI 0.84–1.0, p=0.055).

The most common adverse effects of ranolazine are nausea, constipation and dizziness, reported in both MARISA and CARISA trials. Despite the proposed mechanism of action of the drug, there was no increase in documented arrhythmias in any of the above trials, and in particular there was no significant prolongation of the QTc. None of the trials demonstrated increased mortality in patients taking ranolazine.

Specific evidence for use in diabetes

The MARISA trial was not specifically designed to evaluate the glucose lowering effect of ranolazine, but some 24% of the study group had diabetes mellitus at baseline, permitting useful subgroup analysis. There was no statistical difference in anti-anginal effect of ranolazine in patients with diabetes (p=0.77). A similar result was seen in CARISA, in which 23% of patients had diabetes at baseline. The treatment effect of ranolazine was observed in patients with or without diabetes, with no difference in the dose-dependent effects. Subgroup analysis of CARISA data has shown reductions in HbA1c in patients with diabetes taking ranolazine, with a dose-dependent effect. At each dose the reduction in HbA1c was greater in patients whose diabetes was treated with insulin.[4]

The largest evaluation of patients with diabetes using ranolazine comes from the MERLIN TIMI-36 trial, in which some 2220 patients (33.8% of the study population) had diabetes mellitus at baseline.[5] A proportion of patients (271, 6%) without known diabetes were found at baseline to incidentally have a fasting glucose compatible with the diagnosis of new diabetes. Serial HbA1c values were obtained in all study participants, regardless of their diabetes status. Reductions in the HbA1c were noted at four months in all patients taking ranolazine (0.3% ± 0.03%), regardless of a diagnosis of diabetes. In those who had diabetes, the mean HbA1c declined by 0.64% at four months, compared with a mean 0.22% reduction in the placebo group. Patients treated with ranolazine were also less likely to increase their HbA1c. The incidence of a ≥1% rise in HbA1c was 14.2% at one year in the ranolazine group, and 20.6% in the placebo group (p<0.001). In patients without diabetes, a small but statistically significant decline in HbA1c was seen in patients taking ranolazine at four months (-0.12% ± 0.03%, p<0.001), while a rise in HbA1c was observed in patients without diabetes taking placebo.

The 664 patients with normal baseline glucose parameters (fasting glucose <100mg/dl, HbA1c <6%) had significantly less chance of developing a new fasting glucose >110mg/dl or HbA1c >6% on ranolazine (HR 0.68, p=0.003), though the incidence of new diabetes was not reduced by ranolazine (10.8% *vs* 11.5% at one year, p=0.28).

Discussion

Ranolazine is a safe, effective anti-anginal therapy and has great potential for use in diabetes patients with chronic stable angina. Ranolazine appears to lower the HbA1c in diabetes patients and may also improve glucose tolerance in patients without diabetes, independent of its other effects. Other drugs with similar anti-anginal efficacy tend to increase HbA1c, but ranolazine lowers HbA1c, making it an attractive therapy for this patient group. Its anti-anginal and glucose lowering effects are independent of one another, and the drug has little haemodynamic effect. Ranolazine appears compatible with other anti-anginal drugs. It is well tolerated, and safety data to date show no increase in all-cause mortality nor in the incidence of arrhythmias.

Key points

- Ranolazine reduces angina episodes in patients with stable coronary artery disease including those patients with diabetes
- Adding ranolazine to standard anti-anginal therapy lowers the HbA1c in patients with or without diabetes, with greater effects seen in those treated with exogenous insulin
- The anti-anginal and glucose lowering effects appear independent of one another, and occur without significant haemodynamic effect

Conflict of interest statement

There are no conflicts of interest.

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