

Drug & Innovation Updates

Ranolazine: A new class of anti-ischemic medication

Andrew Maslow, MD
Rhode Island Hospital
Brown University Medical School
Providence, RI

Prevention and treatment of myocardial ischemia involves multiple therapeutic avenues directed at improving coronary blood flow and reducing myocardial oxygen demand (MVO_2). The latter includes reductions of cardiac preload, afterload, contractility, and rate, while maintaining adequate forward flow and pressure. More recently, attention has been directed toward improving the efficiency of the heart muscle itself, especially during times of increased MVO_2 , and/or relative reductions in oxygen supply.¹⁻³ Specifically, these medications (ranolazine, perhexiline, trimezidine, etomoxir) alter substrate utilization for the generation of high-energy phosphates (ATP) in the mitochondria.

Mitochondria, which account for almost 50% of the heart muscle cell volume, generate ATP from the oxidation of stored sugars and fat. While the latter is a more efficient storage of substrate, the former provides greater production of ATP per mole of oxygen used. Therefore, any treatment that increases glucose oxidation should improve the efficiency of the heart muscle to make energy, especially during conditions of reduced oxygen delivery.¹⁻³ While at rest (low MVO_2), energy production is mainly due to oxidation of fatty acids. However, during moderate to heavy exercise, a normal increase in glucose oxidation occurs. For patients with reduced oxygen supply, a greater use of glucose utilization over fatty acids may improve muscle efficiency and, therefore, pump function. Ranolazine is a relatively new anti-anginal medication which inhibits fatty acid oxidation and subsequently results in increased oxidation of glucose.¹⁻³ In addition, it has minimal beta 1 and 2 adrenergic receptor blockade and mild anti-arrhythmic properties.^{4,5} These benefits occur without affecting cardiac loading conditions or the rate-pressure product.⁴ Improvement in cardiac efficiency without affecting hemodynamics has potential clinical benefits, especially for the perioperative patient, for which significant hemodynamic changes usually occur as a result of anesthetic medications, perioperative blood loss, and fluid shifts.

During clinical trials, the oral administration of ranolazine increased exercise capacity in patients with chronic heart failure and/or a history

myocardial ischemia. This is either due to superior anti-ischemic properties and/or the minimal effect on systemic hemodynamics.⁶⁻⁷ Similar benefits were seen in patients with hypertrophied hearts.⁸ Ranolazine may also possess antiarrhythmic effects similar to those of amiodarone.⁵ In rat hearts subject to ischemia and then reperfusion, the administration of ranolazine reduced fatty acid oxidation, increased glucose oxidation, increased the amount of ATP formed, and reduced the accumulation of fatty acid intermediates, lactate, and tissue acidosis.^{3,9-11}

During intravenous therapy in a dog model of heart failure (coronary microembolization), increases in left ventricular ejection fraction (27-36%), left ventricular dp/dt (1712- 1900 mmHg/sec), and stroke volume (20-26 cc/beat) were observed.¹² There were no changes in heart rate nor systemic blood pressure.¹² In normal dogs, there was no clinical effect.¹² When compared to dobutamine, both medications improve cardiac function while only dobutamine is associated with an increase in MVO_2 .¹³ In another ischemia model, a bolus of ranolazine, followed by an infusion, reduced the size of the myocardial infarct by 33% and troponin leak, when compared to saline.¹⁰

Reported adverse effects after prolonged oral administration occur in up to 29% of patients.⁷ These include asthma-like symptoms (12.3%), dyspepsia (4.5%), nausea (3.9%), constipation (3.6%), palpitations (2.6%), and dizziness (1.3%).⁷ Ranolazine's effects on gluconeogenesis, glycolysis, and increases in fatty acid stores may, in theory, alter insulin resistance (this has not yet been investigated). Others have reported an increased incidence of tissue dysplasia and colonic tumors in mice, perhaps cautioning administration of ranolazine in patients with a history of colonic polyps, previous colon cancer, or current malignant cancer (potential for drug-related increase in tumor burden).¹⁴

Although ranolazine has been used clinically in oral form in non-surgical patients with histories of chronic angina and/or congestive heart failure, its intravenous administration and short-term benefits may find its way to the surgical patient. The shift from fatty acid oxidation to glucose oxidation and improved oxygen utilization without affecting the rate-pressure-product may help improve hemodynamic stability while providing protection against perioperative ischemia. In addition, administration prior to cardiopulmonary bypass may attenuate "post-pump" dysfunction by improving substrate utilization and by reducing fatty acid intermediates and tissue acidosis.⁹ These potential perioperative benefits have yet to be studied.

References are on www.scahq.org