Ranolazine: an Antiischemic Drug with a Novel Mechanism of Action

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Key Words: Angina pectoris—Carbohydrate oxidation—Heart—Ischemia—Pyruvate dehydrogenase—Ranolazine—Reperfusion

INTRODUCTION

It has been generally accepted that the primary mechanism of action of antianginal drugs is the improvement of the myocardial oxygen balance between supply and demand in the ischemic heart, by either an increase in coronary flow or a decrease in cardiac mechanical function, or both. Therefore, nitrates, \( \beta \)-adrenoceptor antagonists, and Ca\(^{2+} \) channel blockers, which are thought to improve the myocardial oxygen balance through changes in hemodynamic parameters, have been widely used to treat patients with ischemic heart disease.

Ranolazine (RS-43285) is a piperazine derivative developed by Syntex Laboratories (Edinburgh, UK). In 1987, Allely et al. (3) found that ranolazine attenuated metabolic derangements of the myocardium that were induced by the occlusion of the coronary artery in dogs. Subsequently, the antiischemic action of ranolazine has been demonstrated in both \textit{in vivo} (2) and \textit{in vitro} (14,23,24,45) animal studies. Clinical findings suggest that ranolazine is an orally active agent that is useful for therapy of angina pectoris (16,33,54,59). Interestingly, the antiischemic (14,23,24,45) or antianginal action (16,33,53,59) of ranolazine can be produced without any detectable alterations in hemodynamics, and therefore the pharmacological property of ranolazine differs from that of nitrates, \( \beta \)-adrenoceptor antagonists, and Ca\(^{2+} \) channel blockers. Recent studies have demonstrated that the cardioprotective action of ranolazine is associated with the modulation of the myocardial metabolism (15,45,46). Ranolazine may, therefore, belong to a new group of antiischemic drugs. In the present review, we outline the pharmacological profile of ranolazine and discuss the mechanism of the antiischemic (or antianginal) action of the drug. A preceding review has been published by McCormack et al. (46).
CHEMISTRY

Ranolazine, (±)-N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazine acetamide (Fig. 1A), has a molecular weight of 427.54, and its molecular formula is C_{24}H_{33}N_{3}O_{4}. It is a white or slightly yellow crystalline powder with a melting point of about 120°C, and is stable for at least 5 y at 25°C. The free base of ranolazine is soluble in dichloromethane, sparingly soluble in methanol, slightly soluble in ethanol or acetonitrile, and practically insoluble in water (35). As the free base of ranolazine is insoluble in water, ranolazine hydrochloride, which is soluble in water, has been used in animal and clinical studies.

IN VIVO AND IN VITRO ANIMAL STUDIES

Antiischemic Action of Ranolazine

Table 1 summarizes the protective effect of ranolazine against myocardial derangements induced by ischemia (hypoxia) or ischemia-reperfusion (hypoxia-reoxygenation) in animal models. An in vivo study has revealed that ranolazine prevents the release of the enzymes (creatine kinase and lactate dehydrogenase) from the myocardium during reperfusion following occlusion of the coronary artery in baboons (2). Similar cardioprotective effects of ranolazine have been demonstrated in the following in vitro studies. Ranolazine attenuates the ischemia and reperfusion-induced changes such as decrease in contractile force, decrease in the tissue level of adenosine triphosphate (ATP), release of creatine kinase from the myocardium, increase in the tissue level of Ca^{2+}, and morphological alterations of the cells, in the isolated perfused rabbit heart (23). Furthermore, ranolazine reduces the incidence of ventricular fibrillation induced by hypoxia followed by reoxygenation in the presence of pinacidil, an ATP-dependent K+ channel opener, in the isolated perfused rabbit heart (24). These observations suggest that ranolazine is effective in attenuating myocardial derangements during post-ischemic reperfusion or post-hypoxic reoxygenation. According to a recent study using isolated working rat heart, ranolazine improves recovery of cardiac function during post-ischemic reperfusion if given before, but not after, ischemia (45). The cardioprotective action of ranolazine, therefore, may be produced during the period of ischemia rather than during reperfusion. Ranolazine attenuates both the release of enzymes and the decrease in the tissue levels of high-energy phosphates induced by low-flow ischemia (without reperfusion) in the isolated perfused guinea pig heart (14), and also attenuates the increase in the coronary venous levels of lactate and K+ induced by the combination of transient ischemia and pacing (without reperfusion) in open-chest dogs (3). Thus, both in vivo and in vitro studies have revealed that ranolazine protects the heart from derangements induced by ischemia (hypoxia) or ischemia-reperfusion (hypoxia-reoxygenation). Note that ranolazine exerts its cardioprotective action without producing a direct effect on hemodynamics (14,23,24,45). In several in vitro studies, the antiischemic action of ranolazine is observed at 10–20 μM (14,23,24,45). Ranolazine produces its cardioprotective action during hypoxia (24) or mild to moderate ischemia, such as low-flow (14), transient (3), or brief (within 30 min) ischemia (2,23,45), as shown in Table 1. It fails, however, to reduce infarct size or the release of enzymes from the myocardium during 18 h reperfusion following the occlusion of the coronary artery for 90 min in dogs (11). These observations indicate that ranolazine
FIG. 1. Chemical structure of ranolazine, (+)-N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)-propyl]-1-piperazine acetamide, and its major metabolites in plasma over the 0–12 h period following administration of the sustained release form of ranolazine (1,000 mg, b.i.d.). The plasma concentrations of these metabolites were greater than 10% of the parent compound concentration. (A) ranolazine. (B) desmethyl metabolite (4-[3-(2-hydroxyphenoxy)-2-hydroxypropyl]-N-(2,6-dimethylphenyl)-1-piperazine acetamide). (C) O-dearylated metabolite (4-(2,3-dihydroxypropyl)-N-(2,6-dimethylphenyl)-1-piperazine acetamide). (D) N-dealkylated metabolite (N-(2,6-dimethylphenyl)-1-piperazine acetamide).
**TABLE 1. Reports showing the protective effect of ranolazine against ischemia-reperfusion damage of the heart in animal models**

<table>
<thead>
<tr>
<th>Model</th>
<th>Species</th>
<th>Conditions</th>
<th>Effective dose (concentration) of ranolazine</th>
<th>Improved parameters</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td><em>In vitro</em></td>
<td>Guinea pig</td>
<td>Low-flow ischemia for 30 min (glucose)*</td>
<td>10 μM</td>
<td>Enzyme release Levels of HEP and lactate</td>
<td>14</td>
</tr>
<tr>
<td>(Langendorff)</td>
<td>Rabbit</td>
<td>Ischemia for 30 min followed by reperfusion for 60 min (glucose)*</td>
<td>10 and 20 μM</td>
<td>Cardiac function Enzyme release HEP level Ultrastructure</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td>Hypoxia for 12 min followed by reoxygenation for 40 min in the presence of pinacidil (glucose and pyruvate)*</td>
<td>10 and 20 μM</td>
<td>Tissue Ca<strong>2+</strong> content Arrhythmias</td>
<td>24</td>
</tr>
<tr>
<td><em>In vitro</em></td>
<td>Rat</td>
<td>Ischemia for 30 min followed by reperfusion for 60 min (glucose and palmitate)*</td>
<td>10 μM</td>
<td>Cardiac function</td>
<td>45</td>
</tr>
<tr>
<td>(Working heart)</td>
<td>Dog</td>
<td>Ischemia and pacing for 2 min</td>
<td>50 and 200 μg/kg (i.v.)</td>
<td>Levels of lactate and K⁺ in coronary venous blood</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Baboon</td>
<td>Ischemia for 30 min followed by reperfusion for 5.5 h</td>
<td>A bolus injection of 500 μg/kg followed by a continuous infusion of 50 μg/kg/min (i.v.)</td>
<td>Enzyme release</td>
<td>2</td>
</tr>
</tbody>
</table>

HEP, high-energy phosphates.
* Metabolic substrate contained in the perfusion solution.
protects the myocardium from damage induced by short-term ischemia-reperfusion, but does not protect it from damage induced by long-term ischemia-reperfusion. In contrast, some antiischemic drugs, such as nitrates (34), β-adrenoceptor antagonists (63), and Ca^{2+} channel blockers (31,63), have been shown to reduce the myocardial infarct size induced by reperfusion following long-term occlusion of the coronary artery in dogs. It is likely, therefore, that nitrates, β-adrenoceptor antagonists, and Ca^{2+} channel blockers are more effective than ranolazine in attenuating the myocardial damage induced by severe ischemia. One of the most characteristic properties of ranolazine is a protective action against myocardial damage induced by mild or moderate ischemia without causing alteration in hemodynamics.

**MECHANISM OF ANTIISCHEMIC ACTION**

As mentioned earlier, one of the characteristic pharmacological properties of ranolazine is its cardioprotective action against ischemic derangements without producing a direct effect on hemodynamics, such as cardiac function and blood pressure (14,23,24,45,46). Furthermore, there is no report on the coronary vasodilating effect of ranolazine. These findings lead to a view that the antiischemic action of ranolazine is probably not due to an improvement in the myocardial oxygen balance by either an increase in coronary flow or a decrease in cardiac mechanical function, or both. Therefore, the primary mechanism of the antiischemic action of ranolazine contrasts with that of nitrates, β-adrenoceptor antagonists, and Ca^{2+} channel blockers. According to binding studies, ranolazine has negligible affinity for adrenergic α_{1}, β_{1} and β_{2}, muscarinic M_{1} and M_{2} and adenosine A_{1} and A_{2} receptors (13). In addition, ranolazine has practically no effect on Ca^{2+} channels of the cardiac and smooth muscle cells (5,13).

**Action of Ranolazine on Pyruvate Dehydrogenase**

Pyruvate dehydrogenase (PDH), located in the inner mitochondrial membrane, is an enzyme complex that catalyzes the oxidation of glucose, lactate, or pyruvate to acetyl CoA, which enters the tricarboxylic acid cycle (51). The activity of PDH is inhibited by acetyl CoA, which is derived from the oxidation of fatty acids and pyruvate. When the blood levels of fatty acids are high (e.g., in a fasted state), there is an increase in fatty acid oxidation and hence acetyl CoA, leading to the inhibition of PDH activity. Therefore, the main source of energy in the myocardium is fatty acids rather than carbohydrates, under conditions such as fasting (51,61). In contrast, when the glucose blood level is high (e.g., in a fed state) the enzyme PDH is activated (51,61). Ranolazine activates PDH indirectly, and therefore accelerates carbohydrate oxidation, although it does not modify cardiac function (14,15,46).

The activity of PDH is controlled by PDH kinase and PDH phosphatase; PDH kinase phosphorylates the active form of PDH to its inactive form, and PDH phosphatase dephosphorylates the inactive form of PDH to its active form (Fig. 2) (51,61). Ranolazine has no direct action on PDH kinase or phosphatase (15). According to a study using isolated perfused heart, ranolazine increases the amount of active PDH only when a fatty acid (such as palmitate) is present in the perfusion solution, and the ranolazine-induced increase in the active form of PDH is accompanied by a decrease in acetyl CoA (15). Why does ranolazine decrease acetyl CoA in spite of an increase in the active form of PDH? Probably because ranolazine inhibits the β-oxydation of fatty acids (15). If the β-oxydation...
FIG. 2. A scheme showing myocardial metabolism of carbohydrates and fatty acids that produces adenosine triphosphate (ATP), and the regulation of pyruvate dehydrogenase (PDH), which oxidizes pyruvate to acetyl CoA, which enters the tricarboxylic acid (TCA) cycle. The activity of PDH is controlled by both PDH kinase, which phosphorylates an active form of PDH to its inactive form, and PDH phosphatase, which dephosphorylates an inactive form of PDH to its active form. In normal (aerobic) myocardium, acetyl CoA and NADH, which are derived from the oxidation of fatty acids and pyruvate, inhibit the activity of PDH by activating PDH kinase, and therefore fatty acids rather than carbohydrates are used for the production of ATP. When coronary flow decreases by 50–60% of the initial level (mild or moderate ischemia), the heart produces ATP via anaerobic glycolysis and the oxidation of fatty acids, using limited amounts of oxygen. Under the mild or moderate ischemic conditions in which fatty acid oxidation is still working, metabolites of fatty acid oxidation, such as acetyl CoA and NADH, could suppress the activity of PDH and hence decrease carbohydrate oxidation. Suppression of the PDH activity (i.e., suppression of carbohydrate oxidation) is a disadvantage for the ischemic myocardium, because the ratio of ATP production to uptake of oxygen (phosphorylation/oxidation ratio) during carbohydrate oxidation is higher than during fatty acid oxidation (51,61). Ranolazine stimulates carbohydrate oxidation through the activation of PDH, probably by inhibiting β-oxidation of fatty acids, and therefore it could improve efficiency of energy production in the ischemic heart (45,46). On the other hand, suppression of the PDH activity may increase the accumulation of glycolytic metabolites (lactate and H⁺) in the ischemic myocardium. There is a report that indicates that an increase in glycolytic metabolites is one of the most important causes of myocardial ischemic damage (49). Ranolazine may attenuate the accumulation of lactate and H⁺ in the myocardium during ischemia, through activation of PDH (45,46). G1P, glucose-1-phosphate; G6P, glucose-6-phosphate; F6P, fructose-6-phosphate; FFA, free fatty acids.
of fatty acids is inhibited, the amount of acetyl CoA would decrease and produce a secondary increase in the active form of PDH which accelerates carbohydrate oxidation. Therefore, the ranolazine-induced activation of PDH may be due to the inhibition of β-oxidation of fatty acids (15,46). Eventually, ranolazine switches myocardial substrate utilization from fatty acids to carbohydrates. Because the heart uses more fatty acids than carbohydrates as a source of energy under normal conditions, the metabolic effect of ranolazine can be manifested to a greater extent in the normal state. Nevertheless, the detailed mechanism of the inhibitory action of ranolazine on fatty acid oxidation remains obscure (15).

As is apparent from the foregoing discussion, activation of PDH is one of the primary mechanisms of the antiischemic action of ranolazine. In fact, ranolazine increases the amount of the active form of PDH in the low-flow (ischemic) heart at a concentration of 10 μM (14), which is the concentration capable of attenuating the ischemic derangements (14,23,24). By what mechanism then is the activation of PDH beneficial to ischemic myocardium?

When coronary flow decreases (or the heart becomes ischemic), the tissue level of ATP decreases and the myocardial metabolism shifts from aerobic to anaerobic (or the rate of glycolysis is accelerated to produce ATP anaerobically). Nevertheless, if the decrease in coronary flow is mild or moderate, the heart produces ATP not only via anaerobic glycolysis but also via oxidation of fatty acids, using a limited amount of oxygen. According to previous studies, ATP is produced primarily by oxidation of fatty acids even when coronary flow decreases by 50–60% of the initial level (mild or moderate ischemia) (45,61). Under the mild or moderate ischemic conditions in which fatty acid oxidation is still working, metabolites of fatty acid oxidation, such as acetyl CoA and NADH, and also metabolites of glycolysis, such as lactate and H⁺, accumulate in the myocardium. Because both acetyl CoA and NADH are physiological activators of PDH kinase, an increase in fatty acids oxidation suppresses the activity of PDH and hence carbohydrate oxidation (51,61). According to biochemical findings, the ratio of ATP production to the uptake of oxygen (phosphorylation/oxidation ratio; P/O ratio) during carbohydrate oxidation is higher than during fatty acid oxidation; the P/O ratios are about 2.6, 2.5, 2.5, and 2.3 when there is complete oxidation of glucose, lactate, pyruvate, or palmitate, respectively (51). Therefore, suppression of the PDH activity (i.e., suppression of carbohydrate oxidation) is a disadvantage for the ischemic myocardium in terms of efficiency of energy production. Ranolazine increases PDH activity and switches the substrate utilization from fatty acids to carbohydrates. It could, therefore, improve the efficiency of energy production in the ischemic heart (45,46).

Suppression of PDH activity would also increase the accumulation of glycolytic metabolites (lactate and H⁺) in the ischemic myocardium, because PDH catalyzes the oxidation of lactate or pyruvate to acetyl CoA. An increase in glycolytic metabolites has been demonstrated to be one of the most important causes of ischemic damage in the heart (49). In fact, an increase in intracellular H⁺ could lead to intracellular Ca²⁺ overload via the sarcolemmal Na⁺/H⁺ exchanger and Na⁺/Ca²⁺ exchanger, and hence to irreversible myocardial damage (7,41). Ranolazine may attenuate the increase in lactate and H⁺ during myocardial ischemia through PDH activation (45,46). The foregoing view is supported by findings that ranolazine decreases the ischemia-induced release of lactate from the myocardium in vivo (3) and in vitro (14). Thus, the cardioprotective action
of ranolazine may be derived from its ability to improve the efficiency of energy production and attenuate the accumulation of lactate and H⁺ in the mild or moderate ischemic heart.

If the degree of ischemia is severe, there is a marked reduction of oxygen supply to the myocardial cells that inhibits both fatty acid and carbohydrate oxidation (18,19). In such cases, the antiischemic action of ranolazine is expected to be diminished. In fact, ranolazine failed to exhibit cardioprotective action in an animal model subjected to severe ischemia (1,11).

Other Activators of PDH

Dichloroacetate (DCA) (9,10,44,47,55), carnitine palmitoyl transferase I (CPT I) inhibitors (17,30,39,57), MET-88 (3-(2,2,2-trimethylhydrazinium) propionate) (6,21,32) and trimetazidine (12,22,38,50) attenuate myocardial derangements (such as cardiac dysfunction and decrease in high-energy phosphates) induced by ischemia or ischemia-reperfusion in vivo and in vitro. Like ranolazine, these compounds could accelerate carbohydrate oxidation through the activation of PDH in the myocardium. Nevertheless, there are some differences in the mechanism of PDH activation and antiischemic action among ranolazine, DCA, CPT I inhibitors, MET-88, and trimetazidine as follows.

DCA

DCA stimulates PDH and carbohydrate oxidation through direct inhibition of PDH kinase and reduces fatty acid oxidation through inhibition of fatty acid uptake by mitochondria (10,61). These effects of DCA on myocardial metabolism are believed to be involved in the mechanism of antiischemic action (10,47). According to a recent study, however, the attenuation of ischemia-reperfusion–induced cardiac dysfunction by DCA is not associated with either the activation of PDH or the inhibition of fatty acid oxidation (9). DCA fails to improve systolic function in ischemic pig heart, even when it stimulates the carbohydrate metabolism (44). Therefore, the detailed mechanism of the antiischemic action of DCA is not fully understood. In a clinical study, DCA was shown to increase left ventricular stroke volume in patients with coronary artery disease (65).

CPT I Inhibitors

CPT I converts acyl CoA to acylcarnitine, which can penetrate the mitochondrial inner membrane. Accordingly, inhibitors of CPT I, such as etomoxir (39), oxfenicine (30), POCA (2-[5-(4-chlorophenyl)-pentyl]oxirane-2-carboxylate) (17,57) and TDGA (2-tetradecyl-glycidic acid) (57) reduce fatty acid oxidation and produce a secondary activation of PDH, leading to acceleration of carbohydrate oxidation. Therefore, a shift in the substrate from fatty acids to carbohydrates in the myocardium may be one of the major mechanisms of the antiischemic action of CPT I inhibitors. It should be noted, however, that inhibition of CPT I reduces the ischemia-induced tissue accumulation of long-chain acylcarnitines, which leads to ischemic damage (18,19,60). Therefore, the effect of CPT I inhibitors in reducing the tissue accumulation of long-chain acylcarnitines may also contribute to its antiischemic action (17). A toxic effect of CPT I inhibitors is also reported; long-term inhibition of CPT I with oxfenicine (25) or TDGA (36) has been
shown to cause cardiac hypertrophy in animals, although long-term treatment with etomoxir improves the left-ventricular performance of the pressure-overloaded rat heart (64).

**MET-88**

MET-88 inhibits γ-butyrobetaine hydroxylase, which catalyzes the synthesis of carnitine from γ-butyrobetaine in the liver, and decreases both plasma and myocardial levels of carnitine, which is a necessary substance for the transport of fatty acids from cytosol into the inner mitochondrial space (58). Eventually, MET-88 inhibits fatty acid oxidation and stimulates carbohydrate oxidation in the myocardium (6). In addition, inhibition of carnitine synthesis with MET-88 may inhibit the tissue accumulation of long-chain acylcarnitines during myocardial ischemia (6). Because the site of action of MET-88 is in the liver and not in the myocardium (58), the compound is effective in attenuating the ischemic derangements of the myocardium only when it is given to the whole animal, whereas it is ineffective when it is given to the isolated heart. In fact, MET-88 attenuates both cardiac dysfunction and the decrease in high-energy phosphates induced by hypoxia or hypoxia-reoxygenation in the isolated perfused heart, when it is given to the whole animal before removal of the heart (6,21).

**Trimetazidine**

It has been demonstrated that trimetazidine, a piperazine derivative, produces an anti-ischemic or antianginal action without causing significant alteration in the hemodynamics in both animal (12,22,38,49) and clinical (20) studies. For example, trimetazidine reduces myocardial infarct size during reperfusion following coronary occlusion in rabbits (50), improves cardiac dysfunction induced by ischemia-reperfusion in isolated perfused rat hearts (12,38), and attenuates cellular damage induced by hypoxia-reoxygenation in rat cardiomyocytes (22). In clinical studies, acute or chronic administration of trimetazidine increases the time to onset of angina, exercise duration, and time to 1 mm of ST segment depression in angina patients (20). The compound was reported to have an antioxidant activity; however, this activity may not be the major mechanism of the antiischemic effect of trimetazidine (22). Recently, Lopaschuk (38) demonstrated that the antiischemic action of trimetazidine probably results from stimulating glucose oxidation in the myocardium. Like ranolazine, trimetazidine is likely to stimulate carbohydrate oxidation by inhibiting the β-oxidation of fatty acids and secondarily activating PDH (22,38,61).

**Action of Ranolazine on α-adrenoceptors**

The activity of sympathetic nerve increases markedly in response to myocardial ischemia (26). Within the first 30 min following myocardial ischemia, there is an excessive release of norepinephrine from sympathetic nerve endings (56) and a marked increase in the number of α₁-adrenoceptors in the sarcolemmal membrane (4,26). Stimulation of the α₁-adrenoceptors increases the cardiac contractile force and the resistance of the coronary arteries and systemic blood vessels, leading to an imbalance between the myocardial oxygen supply and demand, which is responsible for the exacerbation of ischemic damage (26). Accordingly, α-adrenoceptor antagonists are effective in attenuating ischemic damage (26,48). The increase in the number of α₁-adrenoceptors may be mediated by long-
chain acylcarnitines that accumulate in the tissue (because of the reduction in β-oxidation of fatty acids) during ischemia (4) or hypoxia (28). This view can be supported by findings that treatment of the heart cells with palmitoyl carnitine increases the number of α₁-adrenoceptors and that CPT I inhibitors attenuate the increase in the number of α₁-adrenoceptors in the ischemic myocardium (4, 28). Ranolazine has no affinity for α₁-adrenoceptors (13), nor does it inhibit CPT I (4). Nevertheless, ranolazine attenuates the increase in myocardial α₁-adrenoceptors induced by ischemia or by treatment with palmitoyl carnitine, although the exact mechanism of action remains unclear (4). The action of ranolazine to reduce the ischemia-induced increase in the number of myocardial α₁-adrenoceptors may contribute to its antiischemic action. According to a recent study, ranolazine attenuates the cardiac dysfunction and energy deficiency induced by palmitoyl carnitine in the isolated perfused heart (42).

**Action of Ranolazine on Reactive Oxygen Species**

There is ample evidence to show that reactive oxygen species, such as superoxide anion, hydroxyl radical, and hydrogen peroxide (H₂O₂), participate in ischemia-reperfusion damage in the heart (29, 37, 40). These reactive oxygen species are generated intra- and extra-cellularly in the myocardium and endothelium during ischemia and reperfusion, causing lipid peroxidation of the cell membrane, contractile dysfunction, and metabolic derangement of the heart (29, 37, 40). Therefore, agents that reduce the harmful effects of reactive oxygen may protect the heart against ischemia-reperfusion damage. In fact, antioxidants have been demonstrated to attenuate both lipid peroxidation and myocardial damage in the ischemia-reperfused heart (29, 37, 40). We (43) examined whether ranolazine attenuates myocardial derangements induced by exogenous H₂O₂ in isolated perfused rat hearts (Fig. 3), and demonstrated that H₂O₂ decreased the left ventricular developed pressure and the tissue level of ATP and that the H₂O₂-induced mechanical and metabolic alterations were significantly attenuated by ranolazine (10 or 20 μM). In contrast, DCA, another activator of PDH, was ineffective in attenuating the H₂O₂-induced mechanical and metabolic alterations (Fig. 3). Ranolazine, however, did not modify the H₂O₂-induced lipid peroxidation. These findings suggest that ranolazine protects the heart from H₂O₂-induced derangements and that the protective effect of ranolazine is not due to an antioxidant action or stimulation of PDH. Further studies are needed to determine the detailed mechanisms of the protective action of ranolazine on H₂O₂-induced derangements. Whatever the mechanism is, the action of ranolazine to reduce H₂O₂-induced derangements may contribute to its cardioprotective effect against ischemia-reperfusion damage (43).

**CLINICAL STUDIES**

**Antianginal Action of Ranolazine**

The results of clinical studies of ranolazine in patients with angina pectoris are summarized in Table 2. In a double-blind, crossover, and randomized study, Cocco et al. (16) examined the effect of a single oral administration of ranolazine (10, 60, 120, or 240 mg) on exercise tolerance in 104 patients who had chronic stable angina and still remained symptomatic despite treatment with a β-adrenoceptor antagonist or diltiazem. Their study...
FIG. 3. Effects of ranolazine (5, 10, and 20 μM) and DCA (1 mM) on the H₂O₂-induced changes in mechanical function (A) and the tissue levels of high-energy phosphates (B). The rat heart was perfused aerobically by the Langendorff’s technique at a constant flow and paced electrically. (A) changes in the left ventricular developed pressure (LVDP) in the vehicle (○), ranolazine (5 μM) (■), ranolazine (10 μM) (△), ranolazine (20 μM) (▲), and DCA (□) groups. Each value represents mean ± S.E.M. *P < 0.05 when compared with the value in the vehicle group.

(B) shows the tissue levels of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), and creatine phosphate (CrP) at the end of perfusion in the normal (H₂O₂-untreated) (open column) and H₂O₂-treated (hatched column) hearts. Each value represents a mean ± S.E.M. *P < 0.05 when compared with the value in the corresponding normal group. †P < 0.05 when compared with the value in the vehicle group in the H₂O₂-treated heart.
<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Age (years)</th>
<th>Type of study</th>
<th>Doses and route for treatment</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>28–73 (median: 59)</td>
<td>Double-blind, crossover, randomized, placebo-controlled</td>
<td>10, 60, 120, and 240 mg (single dose)</td>
<td>Improvement in exercise duration and time to 1 mm ST segment depression at a dose of 240 mg</td>
<td>16</td>
</tr>
<tr>
<td>319</td>
<td>32–84</td>
<td>Double-blind, randomized, placebo-controlled</td>
<td>30, 60, and 120 mg (t.i.d.) for 4 w</td>
<td>No improvement in exercise duration, time to onset of angina and time to 1 mm ST segment depression</td>
<td>62</td>
</tr>
<tr>
<td>14</td>
<td>mean: 59.9</td>
<td>Single-blind, placebo-controlled</td>
<td>30 and 60 mg (t.i.d.) for 2 w</td>
<td>Improvement in exercise duration and time to onset of angina</td>
<td>33</td>
</tr>
<tr>
<td>158</td>
<td>n.a.</td>
<td>Double-blind, crossover, randomized</td>
<td>342 mg (t.i.d.) for 1 w</td>
<td>Improvement in exercise duration, time to onset of angina and time to 1 mm ST segment depression</td>
<td>54</td>
</tr>
<tr>
<td>312</td>
<td>n.a.</td>
<td>Double-blind, crossover, randomized, placebo-controlled</td>
<td>267 mg (t.i.d), 400 mg (b.i.d.) and 400 mg (t.i.d.) for 1 w</td>
<td>Improvement in time to onset of angina and time to 1 mm ST segment depression</td>
<td>59</td>
</tr>
<tr>
<td>15</td>
<td>mean: 58</td>
<td>n.a.</td>
<td>200 and 500 µg/kg (i.v.)</td>
<td>Improvement in diastolic function in the ischemic segments of the left ventricle</td>
<td>27</td>
</tr>
<tr>
<td>15</td>
<td>32–65</td>
<td>Open, non-randomized</td>
<td>140 µg/kg (bolus) followed by a continuous infusion of 1.2 µg/kg/min (i.v.) and 200 µg/kg (bolus) followed by a continuous infusion of 20 µg/kg/min (i.v.)</td>
<td>Decrease in cardiac uptake of free fatty acids</td>
<td>8</td>
</tr>
<tr>
<td>20</td>
<td>n.a.</td>
<td>placebo-controlled</td>
<td>50 and 250 µg/kg (i.v.)</td>
<td>Decrease in cardiac uptake of free fatty acids and increase in cardiac uptake of glucose</td>
<td>53</td>
</tr>
</tbody>
</table>

n.a., not available.
revealed that ranolazine at a dose of 240 mg improved the duration of exercise and time to 1 mm of ST segment depression, whereas lower doses of ranolazine (30, 60, and 120 mg) had no significant effects. Thadani et al. (62) reported that low doses of ranolazine (30, 60, and 120 mg) failed to produce the antianginal action, even when patients were treated orally with the drug t.i.d. for 4 w. In another double-blind, crossover, and randomized study, Rousseau et al. (54) reported that oral administration of ranolazine (342 mg, t.i.d.) for 1 w increased the time to onset of angina, exercise duration, and time to 1 mm of ST segment depression in patients with chronic stable angina, and that the effect of ranolazine in improving exercise duration was greater than that of atenolol (100 mg, once a day) for 1 w. Similar results with ranolazine, in terms of improvement of exercise parameters, were obtained by other investigators (33,59). Hayashida et al. (27) reported that intravenous infusion of ranolazine (200 and 500 µg/kg) improved the diastolic function of the noninfarcted myocardium under chronically ischemic conditions in patients who had transmural myocardial infarction in the past. Consistent with findings in animal studies, the antianginal property of ranolazine is observed without alteration in hemodynamics (16,33,53,59). Bagger et al. (8) and Pouleur et al. (53) have found that intravenous administration of ranolazine reduces cardiac uptake of fatty acids without hemodynamic alterations in patients with coronary artery disease. Thus, the pharmacological features of ranolazine differ from those of β-adrenoceptor antagonists and Ca^{2+} channel blockers, and, therefore, ranolazine might be a potential candidate for combinations with other antianginal drugs for the therapy of ischemic heart disease.

Adverse Effects of Ranolazine

Headache, dizziness, and asthenia were observed most frequently in angina patients who were treated acutely or chronically with ranolazine; however, the incidence of adverse reaction in the ranolazine-treated group was similar to that in the placebo-treated group (16,62). In many clinical studies, no serious adverse effects were reported during either acute or chronic treatment with ranolazine (16,33,46,59,62).

Plasma Levels of Ranolazine

The relationship between plasma levels and efficacy of ranolazine has been examined in patients with angina pectoris. According to Thadani et al. (62), the plasma level of ranolazine 1 h after oral administration of 30, 60, or 120 mg of ranolazine was 110, 256, or 597 ng/ml (−0.26, 0.60, or 1.40 µM) respectively, and 8 h after oral administration 21, 43, or 105 ng/ml (−0.05, 0.10, or 0.25 µM), respectively. At these plasma levels of ranolazine, however, there was no improvement in the exercise tolerance test. Smith et al. (59) demonstrated that in patients with angina pectoris who were orally treated with either 267 mg (t.i.d.), 400 mg (b.i.d.) or 400 mg (t.i.d.) of ranolazine for 1 w, there was improvement in the duration of exercise and time to 1 mm of ST segment depression at plasma levels of ranolazine between 1,350–2,130 ng/ml (−3.16 and 4.98 µM), whereas there was no improvement at plasma concentrations between 235–514 ng/ml (−0.55 and 1.20 µM). Cocco et al. (16) reported that in angina patients who were treated orally with single doses of ranolazine (10, 60, 120, and 240 mg), there was improvement in time to angina in 67% of the patients whose plasma levels of ranolazine were >500 ng/ml (−1.17
μM), and in only 40% of the patients whose plasma levels were <500 ng/ml. From these results, specifically with respect to the relationship between plasma levels of ranolazine and efficacy (time to 1 mm of ST segment depression or time to angina), the plasma concentration of ranolazine required for its antianginal action seems to be around 1,000 ng/ml (~2.34 μM).

**Metabolism of Ranolazine**

Penman et al. (52) analyzed the metabolites of ranolazine in plasma samples obtained from healthy male volunteers who were treated orally with either an instant release form of ranolazine (342 mg, single dose or t.i.d.), a sustained release form of ranolazine (1,000 mg, b.i.d.) or a combination of the instant release formulation of ranolazine (342 mg, t.i.d.) and diltiazem (60 mg), using liquid chromatography/mass spectrometry. The results of the analysis demonstrated that ranolazine was metabolized by hydroxylation in either the dimethylphenyl or methoxyphenyl moieties, by N-dealkylation at either of the piperazine nitrogen sites, by O-demethylation and O-dearylation at the methoxyphenoxy group, and by hydrolysis of the amide group, to a resultant carboxylic acid. In addition, ranolazine was found to be eliminated by direct conjugation with glucuronic acid, forming an uncharacterized adduct. These studies also indicated that the extent of metabolism was independent of the dose form, and that co-administration of diltiazem may suppress the metabolism of ranolazine. In one man, who was treated 12 h previously with the sustained release formulation of ranolazine (1,000 mg, b.i.d.), plasma levels of desmethyl metabolite (4-[3-(2-hydroxyphenoxy)-2-hydroxypropyl]-N-(2,6-dimethylphenyl)-1-piperazine acetamide), N-dealkylated metabolite (N-(2,6-dimethylphenyl)-1-piperazine acetamide) and O-dearylated metabolite (4-(2,3-dihydroxypropyl)-N-(2,6-dimethylphenyl)-1-piperazine acetamide) were higher than 10% of the ranolazine concentration (Fig. 1). It is still unknown whether these metabolites are pharmacologically active.

**SUMMARY**

Ranolazine exerts antiischemic and antianginal effects in animals and humans. In contrast to nitrates, β-adrenoceptor antagonists and Ca^{2+} channel blockers, ranolazine has a cardioprotective action without a direct effect on hemodynamics; this pharmacological property of ranolazine may be responsible for the clinical findings that indicate that the drug does not have any serious adverse effects. One of the mechanisms of cardioprotective action of ranolazine is the acceleration of carbohydrate oxidation, resulting from activation of PDH; the action of ranolazine on the myocardial metabolism is to improve the efficiency of energy production and to attenuate the ischemia-induced increase in lactate and H^+ in the myocardium. In addition, the effects of ranolazine in attenuating the increase in α1-adrenoceptors during myocardial ischemia and reducing the reactive oxygen-induced myocardial derangements may be responsible for its cardioprotective action. Thus, ranolazine is an antiischemic (or antianginal) drug that has a novel mechanism(s) of cardioprotective action.

**REFERENCES**


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Cardiovascular Drug Reviews, Vol. 17, No. 1, 1999