

CHAPTER (10)

ANTI-ISCHEMIC DRUGS ACTING PRIMARILY BY METABOLIC MANIPULATION

METABOLIC ANTIANGINAL DRUGS

- Myocardial Metabolism
- Drugs
 - Perhexiline
 - Trimetazidine
 - Ranolazine
 - Etomoxir
 - Nicorandil

- This group exerts its anti-ischemic effect through metabolic action and have little or no effect on coronary hemodynamics.
- They do not affect blood pressure, pulse rate or LV systolic function.
- They have considerable potential as adjunctive therapy for angina, particularly in patients refractory to standard therapy. They may be a primary therapeutic option in certain circumstances.
- These agents (trimetazidine, ranolazine, and perhexiline) have documented anti-ischemic effects. They are, in theory, useful in patients with angina secondary to hypertrophic cardiomyopathy, aortic stenosis, and cardiac syndrome X (microvascular disease) due to their anti-ischemic effects in the absence of vasodilatation.
- They may be of potential benefit in heart failure as some can improve myocardial function.

Myocardial Metabolism

- Sixty to ninety percent of the energy generated by the normal adult heart is from free fatty acids (long-chain free fatty acid, LCFA). LCFA entry into the mitochondria is facilitated by the enzyme carnitine-palmitoyl-transferase (CPT).
- Carbohydrate metabolism contributes only to about 10-40% of energy generated by the healthy human adult heart.
- Fatty acids require approximately 10-15% more oxygen to generate an equivalent amount of ATP when compared to glucose.
- Suppression of FFA uptake and/or oxidation stimulates an increase in myocardial glucose utilization.

Perhexiline

- It acts by shifting myocardial substrate utilization from fatty acids to carbohydrates through inhibition of CPT, resulting in increased glucose and lactate utilization.
- Perhexiline can cause hepatic toxicity and peripheral neuropathy, but this risk can be reduced by maintaining a low plasma concentration between 150 to 600 ng/mL.
- The mechanism for toxicity appears to be due to phospholipids accumulation, which is a direct consequence of CPT inhibition.
- The drug improves angina frequency and exercise capacity.
- It is used as adjunctive treatment for refractory angina in patients not suitable for, or awaiting, coronary intervention. It is given as a short-term therapy (less than 3 months).
- Serum level monitoring is necessary when perhexiline is administered.
- Dose: 100 mg twice daily with subsequent plasma guided dose titration.

Trimetazidine

- It exerts no significant negative inotropic or vasodilator properties.
- It reduces the rate of FFA oxidation, with a concomitant increase in glucose oxidation rates during ischemia, but the exact molecular mechanism of action is unclear. The metabolic effect of trimetazidine is mediated by inhibition of mitochondrial long-chain 3-ketoacyl Co A thiolase, a fundamental enzyme that operates in the FFA beta-oxidative chain. As a result, myocardial glucose oxidation is increased and substrate utilization is shifted from fatty acid to carbohydrate metabolism.
- It has a favorable side-effect profile.
- In clinical trials (meta-analysis) trimetazidine demonstrated a significant reduction in anginal frequency in patients with stable angina, but only a non-significant trend towards prolongation of the duration of treadmill exercise.
- It improves resting ventricular function in patients with CAD and various degrees of contractile impairment.
- It has no short or long term mortality benefit when infused intravenously immediately post-MI for 48 hours.
- Though the clinical efficacy of trimetazidine has been demonstrated, yet, there is uncertainty regarding its role, particularly its safety profile at higher doses in management of CAD. It remains a potential treatment for the future
- Dose: two forms
 - Short acting: 20 mg three times a day.
 - Slow release (MR): 35 mg twice a day.

Ranolazine

- It stimulates glucose oxidation and act as a partial fatty-acid-oxidation inhibitor. It inhibits fatty-acid oxidation during the periods of elevated plasma FFA levels associated with myocardial ischemia.
- It has a significant antianginal effects both as monotherapy and in combination with other antianginal agents.
- Two studies using high doses of ranolazine (up to 1500 mg twice daily) in patients with chronic stable angina either as monotherapy (MARISA study) or as background antianginal therapy (CARISA study) showed that ranolazine significantly increased duration of exercise, time to angina and fewer anginal episodes compared to placebo. There was minor prolongation of QT interval.
- Long term safety, particularly with relation to QT prolongation is not known.

Etomoxir

- It was initially introduced as a potential antidiabetic agent on the basis of its hypoglycemic effects.
- It is potent CPT inhibitor.
- It is an experimental drug.
- In experimental animals, it reduces oxygen consumption during ischemic recovery and prevented depression of myocardial function.
- Etomoxir administered 80 mg/day to patient with heart failure, improved LV ejection fraction and clinical status.

Nicorandil

- A vasodilator that opens ATP-sensitive potassium channels in blood vessels and heart muscle.
- Possibly its action is through enhancing ischemic preconditioning, a process whereby one episode of ischemia makes the heart more tolerant to subsequent episodes.
- It may have also anti-adrenergic actions by inhibition of norepinephrine release.
- It resulted in a 17% reduction in the relative risk of nonfatal MI or unplanned hospitalization for angina (IONA trial, 2001).
- Nicorandil can be a useful adjuvant to the treatment of patients with chronic angina.