**Trimetazidine : An innovative metabolic approach to ischemic heart disease**

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**Introduction**

Patients with stable angina require risk factor modification, education, and pharmacological treatment with beta-blocker, calcium channel blockers and nitrates, together with cardioprotection with aspirin, lipid-lowering drugs and ACE inhibitors. Despite this treatment, about one-third of patients do not become free of angina. Various combinations of haemodynamic agents did not demonstrate significantly superior efficacy on exercise test parameters. Therefore, there is a strong rationale for using new combined therapeutic approaches including metabolic drugs such as trimetazidine. But interventional treatment should be performed in higher risk cases those who have disabling angina despite pharmacological treatment.

**Antianginal cardioprotective metabolic modulators**

1. Inhibitors of fatty acid beta-oxidation  
   - Trimetazidine  
   - Ranolazine.
2. Inhibitors of carnitine palmitoyl transferase  
   - Peroxiline  
   - Etoxomir  
   - Oxfenicine.
3. Inhibitors of lipolysis  
   - Nicotinic acid & its derivatives

**Trimetazidine**

- Effective anti anginal agent.
- Cardiac Metabolism modulating drug.
- Without having direct hemodynamic effects.
- Cardioprotective.
- Favorable safety and excellent tolerability profile

**Mechanism of action**

Selectively inhibits mitochondrial long chain 3-Ketoacyl co-enzyme A thiolase, the last enzyme involved in beta-oxidation. Affects myocardial substrate utilization by inhibiting fatty acid oxidation and shifting ATP production with less O2 consumption from FFA to glucose oxidation.

**Figure 1: Mechanism of action of trimetazidine**

<table>
<thead>
<tr>
<th>TRIMETAZIDINE</th>
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<tbody>
<tr>
<td>Decrease Fatty acid oxidation</td>
<td>Increase glucose utilization</td>
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<td>Redirect fatty acids toward Membrane phospholipids</td>
<td>Increase glycolysis</td>
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<td>Increase cardiac efficiency</td>
<td>Increase pyruvate oxidation</td>
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<tr>
<td>Decrease angina Cell survival</td>
<td>ATP production with less O2 consumption</td>
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<tr>
<td>Decrease lactate</td>
<td>Decrease H+ accumulation</td>
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<tr>
<td>Decrease acidosis</td>
<td>Decrease calcium overload</td>
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<td>Decrease free radical induced injury</td>
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**Figure 2: Pharmacological effects of trimetazine**

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Effects of anti-anginal drugs on coronary blood flow, central hemodynamics, and myocardial contractility

Indications
- Angina pectoris
- Vertigo and tinnitus
- Visual disorders of circulatory origin.

Possible field of application
- Chronic ischemic contractile dysfunction
- Cytoprotective agent during myocardial revascularization procedures.

Trimetazidine and stable angina
The efficacy of trimetazidine as an antianginal drug has been assessed in randomized, placebo-controlled studies, both as solo treatment and in combination with beta-blockers and calcium channel blockers. Several studies have tested the efficacy of trimetazidine and have demonstrated this agent to be at least as effective as and better tolerated than haemodynamic agents. In stable angina it improves exercise tolerance, elevates the ischaemic threshold to an extent comparable with beta-blockers and calcium channel blockers. The combination of trimetazidine and a beta-blocker appears more effective than the combination of nitrates and a beta-blocker, and the addition of trimetazidine improves symptoms in patients resistant to diltiazem or metoprolol. It is ideal for combination therapy. Ideal target populations for trimetazidine are diabetic, not suitable for revascularization. It is beneficial for refractory symptoms in spite of maximal traditional therapy or following revascularization.

Trimetazidine and left ventricular ischemic dysfunction
Improves myocardial contractility and stroke volume
Improves peripheral perfusion
Decreases neurohumoral activation
Improves prognosis and decreases arrhythmogenic risk.

Trimetazidine should be considered as a valuable therapeutic adjunct to be used on top of other more traditional available agents, especially in patients with severe, chronic ischaemic dysfunction, particularly if this is not amenable to revascularization. The myocardial effects of trimetazidine have been assessed in three randomized, double-blind, placebo-controlled studies in patients with ischaemic cardiomyopathy, stable angina or hibernating myocardium showed improved LV function and improved contractile response to inotropic stimulation.

Trimetazidine in myocardial revascularization procedures
Myocardial injury during revascularization procedures is an important determinant of clinical outcome. Therefore, protection of the ischaemic myocardium during such procedures should be an important goal, both for cardiac surgeons and interventionists. In elective coronary angioplasty, primary coronary angioplasty and coronary surgery, patients who were pretreated with trimetazidine exhibited lesser release of markers of myocardial injury.

Conclusion
Clinical efficacy profile and favorable safety built a reputation as the ideal drug for chronic angina. Use of trimetazidine should not be restricted to angina, its indication might include left ventricular dysfunction due to severe ischemic cardiomyopathy to hibernating myocardium.

References
Review Article

2001; 3(Supplement 0):08-11.