ISOPRENAraline: A TOOL FOR INDUCING MYOCARDIAL INFARCTION IN EXPERIMENTAL ANIMALS

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ABSTRACT

Cardiovascular Diseases (CVDs) remain the principal cause of death in both developed and developing countries, accounting for roughly 20% of all worldwide deaths per year. Due to changing lifestyles in developing countries, such as India and particularly urban areas, Myocardial infarction is making an increasingly important contribution to mortality statistics. Myocardial infarction is defined as an acute condition of necrosis of the myocardium that occurs as a result of imbalance between coronary blood supply and myocardial demand. Isoprenaline/Isoproterenol (ISO) is a synthetic catecholamine and beta adrenergic agonist, which causes severe stress in the myocardium, resulting in an infarct like necrosis of the heart muscle in experimental animal. ISO-induced myocardial infarction serves as a well standardized model because the pathophysiological changes in heart muscle of experimental animal, similar to that observed in human myocardial infarction. The present studies cover the cardioprotective activity of various drugs against Isoprenaline induced Myocardial infarction in animal model.

Keywords: Cardiovascular diseases, Myocardial infarction, Isoprenaline, Experimental animal, necrosis.

INTRODUCTION

Isoprenaline (isoproterenol) is a sympathomimetic that acts almost exclusively on beta-adrenergic receptors. It is listed in the 2004 WHO Model List of Essential Medicines. It is used to increase the heart rate for the treatment of patients with severe bradycardia that is unresponsive to atropine; for the short-term emergency treatment of heart block; for ventricular arrhythmias secondary to atrioventricular nodal block [1], during electrophysiological study, to facilitate the induction of supraventricular and ventricular tachycardias [2-6]. Isoprenaline (Figure 1) is known to accelerate the sinus node and to enhance AV nodal conduction; the drug has no effect on His-Purkinje conduction time [7]. Paradoxical bradycardia is an unusual phenomenon. Pharmacological alternatives include atropine and for Torsades de Pointes magnesium sulfate. Cardiac pacing is an option for the treatment of patients with bradyarrhythmias or Torsades de Pointes [8,9].

![Figure 1: Structure of Isoprenaline](image-url)
PHARMACOLOGY

Pharmacodynamic

- **Cardiovascular system**: Isoproterenol produces powerful stimulation of the heart to increase its rate and force of contraction, causing increased cardiac output. It is as active as epinephrine in this action and, therefore, is useful in the treatment of atrioventricular block or cardiac arrest. Isoproterenol also dilates the arterioles of skeletal muscle (β2 effect), resulting in decreased peripheral resistance. Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressure. Isoproterenol is a more potent β2 stimulant compared to isoprenaline. Isoproterenol can be absorbed systemically by the sublingual mucosa but is more reliably absorbed when taken by inhalation (which is the recommended route). This action lasts about 1 hour and may be repeated by subsequent doses.

- **Pulmonary system**: A profound and rapid bronchodilation is produced by the drug (β2 action). Isoproterenol is as active as epinephrine and rapidly alleviates an acute attack of asthma when taken by inhalation (which is the recommended route). This action lasts about 1 hour and may be repeated by subsequent doses.

- **Other effects**: Other actions on β-receptors, such as increased blood sugar and increased lipolysis, can be demonstrated but are not clinically significant.

Pharmacokinetics

Isoproterenol can be absorbed systemically by the sublingual mucosa but is more reliably absorbed when given parenterally or as an inhaled aerosol. It is a marginal substrate for COMT and is stable to MAO action.

Adverse effects: The adverse effects of isoprenaline are similar to epinephrine.

- Cardiovascular: Angina, flushing, hyper-/hypotension, pallor, palpitation, paradoxical bradycardia (with tilt table testing), premature ventricular beats, Stokes-Adams attacks, tachyarrhythmia, ventricular arrhythmia.
- Central nervous system: Dizziness, headache, nervousness, restlessness, Stokes-Adams seizure.
- Endocrine & metabolic: Hypokalemia, serum glucose increased.
- Gastrointestinal: Nausea, vomiting.
- Neuromuscular & skeletal: Tremor, weakness.
- Ocular: Blurred vision.
- Respiratory: Dyspnea, pulmonary edema.

Table 1: Trade Names of Marketed Isoprenaline

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Brand Name</th>
<th>Manufacturers</th>
<th>Type</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Autohaler</td>
<td>Cipla Limited</td>
<td>Inhaler</td>
<td>400mcg/1mdi</td>
</tr>
<tr>
<td>2</td>
<td>Isolin</td>
<td>Samarth Pharma Pvt. Ltd</td>
<td>Injection</td>
<td>2mg/1ml</td>
</tr>
<tr>
<td>3</td>
<td>Isoprin</td>
<td>Unichem Laboratories Ltd.</td>
<td>Injection</td>
<td>2mg/2ml</td>
</tr>
<tr>
<td>4</td>
<td>Isosol</td>
<td>SG Pharma Pvt. Ltd.</td>
<td>Injection</td>
<td>2mg/3ml</td>
</tr>
<tr>
<td>5</td>
<td>Isuprin</td>
<td>Lemery</td>
<td>Injection</td>
<td>2mg</td>
</tr>
<tr>
<td>6</td>
<td>Neo – Epine</td>
<td>Glaxo Smithkline Pharmaceuticals Ltd.</td>
<td>Tablet</td>
<td>20mg</td>
</tr>
</tbody>
</table>
MECHANISMS OF ISOPRENALINE INDUCED MYOCARDIAL INFARCTION

Myocardial infarction induced by ISO has been reported to show many metabolic and morphologic aberrations in the heart tissue of the experimental animals similar to those observed in human myocardial infarction [14]. ISO induced necrosis is maximal in the subendocardial region of the left ventrical and in the interventricular septum. Continuous infusion of ISO in rats elicits typical cardiac gene expression similar to that observed in cardiac hypertrophy caused by pressure overload. Amidst several mechanisms proposed to explain the isoproterenol-induced myocardial harm, one might say: an unbalance between oxygen supply to and demand from cardiomyocytes inwardly, which is related to myocardial hyperfunction due to increase both in chronotropism and inotropism as well as to hypotension in the coronary bed [15]. Secondly, it is also claimed that there is an elevation of Ca++ overcharge inside the cell [16]. In addition, that ion is related to the activation of the adenylate cyclase enzyme and the depletion of ATP levels on the course of the events [17]. Eventually, there is an oxidative stress augmentation because of several metabolic products originated from isoproterenol, not to mention free radicals genesis [18]. A schematic diagram is shown to explain the mechanism of action of Isoprenaline (Figure 2).

![Mechanism of Isoprenaline induced myocardial infarction](image)

**Figure 2: Mechanism of Isoprenaline induced myocardial infarction**

**DOSE OF ISOPRENALINE TO INDUCED MYOCARDIAL INJURY**

Based on the available literature the ISO-induced effects on heart could be divided into 3 groups depending on the dose and duration of ISO administration:

- Low doses of isoproterenol (0.3–6 mg/kg body weight) administered acutely or repeatedly during 1–3 weeks
- Medium doses of isoproterenol (10–85 mg/kg body weight) applied in a single dose
- High doses of isoproterenol (150–300 mg/kg body weight) applied in a single dose or in two consecutive doses.

**Low-dose ISO models**

Very low doses of ISO 0.3 mg/kg applied for 7 days did not affect the blood pressure in rats [19]. However, it was shown that low doses of ISO (0.3 to 6 mg/kg) induce cardiac hypertrophy accompanied by fibrosis and necrosis of the tissue [20-29].
Medium-dose ISO models

Two days lasting administration of increased ISO dose (40 mg/kg body weight) led to a significant but temporary reduction in systolic and diastolic blood pressure, however, prolonged administration of ISO did not affect blood pressure [30-31]. The medium doses of ISO (10-85 mg/kg) induced structural changes of mitochondria that are characterized by swelling, by decreased amount of cristae and increased presence of the homogenized matrix in mitochondrial population [32-34].

High-dose ISO models

It was shown that high doses of ISO, within the 85-300 mg/kg range, induced diffuse myocardial necrosis and ultimately lead to progressive left ventricular dilatation and myocardial hypertrophy [35-39]. The high dose of ISO induced in rat heart similar myocardial damage as acute myocardial infarction. This finding suggested that high dose of ISO could be used as a model of heart failure induced by acute myocardial infarction [40]. Table 2 shows list of various drugs used for cardioprotection and dose of Isoprenaline required for inducing myocardial infarction.

### Table 2: Cardioprotective effect of various drugs against Isoprenaline induced Myocardial Infarction in animals

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drugs</th>
<th>Effective Dose of Drugs</th>
<th>Isoprenaline Dose to induce MI</th>
<th>Investigation Parameters</th>
<th>Ref. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Garcinia indica</em></td>
<td>250 mg/kg b.w., 500 mg/kg b.w.</td>
<td>25 mg/kg b.w.</td>
<td>AST, ALT, LDH, CPK, and CK-MB in serum</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>Atorvastatin and Quercetin</td>
<td>10 mg/kg and 50 mg/kg for 14 days</td>
<td>100 mg/kg; s.c. in last 2 days</td>
<td>CK-MB activity as well as cTn-I, CRP, TNF-α, and IL-10 levels, ECG, histopathology</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>Ritonavir</td>
<td>10 mg/kg/day i.p. twice daily for 2 days</td>
<td>150 mg/kg/day, i.p. for 2 consecutive days</td>
<td>Serum markers SGOT and CK, heart/body weight ratio, nitric oxide level, SOD, GSH, TBARS and catalase, histopathology</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td><em>Commiphora mukul</em></td>
<td>Three doses 100, 200 and 400 mg kg-1 p.o. for 30 days</td>
<td>85 mg kg-1; s.c. for 2 consecutive days</td>
<td>Myocardial antioxidants SOD, CAT, GSH, GSHPx, marker enzymes CK-MB, LDH, histopathology</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>Glycyrrhizic acid</td>
<td>Three doses 5, 10 and 20 mg/kg BW i.p. for 14 days</td>
<td>85 mg kg-1; s.c. for 2 consecutive days</td>
<td>SOD and GSH levels, LPO and IP levels, histopathology</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td><em>Curcuma longa</em></td>
<td>50, 100 and 200 mg/kg p.o. for 30 days</td>
<td>85 mg kg-1; s.c. for 2 consecutive days</td>
<td>Biochemical SOD, CAT, TBARS, GSHPx, CPK, hemodynamic MAP, LVEDP and histopathology</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td><em>Tylophora indica</em></td>
<td>100 mg/kg, 200 mg/kg for 30 days orally</td>
<td>150 mg kg-1; s.c. for 2 consecutive days</td>
<td>Enzymes LDH, CK-MB, antioxidants such as SOD and catalase, histopathology</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td>Abana</td>
<td>75 mg / 100 g</td>
<td>20 mg / 100 g subcutaneously twice at an interval of 24 hrs</td>
<td>Serum enzymes CPK, GOT, GPT and γ-GT</td>
<td>48</td>
</tr>
<tr>
<td>9</td>
<td>Magnesium chloride</td>
<td>40 mg/kg body weight i.v.</td>
<td>2 mg/kg body weight</td>
<td>Etermination of cardiac enzyme CK and histopathological changes</td>
<td>49</td>
</tr>
<tr>
<td>10</td>
<td>Garlic</td>
<td>250 and 500 mg kg-1 once daily for 3 weeks</td>
<td>100 mg kg-1; s.c. for 2 consecutive days</td>
<td>Etermination of cardiac enzyme CK and histopathological changes</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td><em>Urtica parviflora</em></td>
<td>350 mg/kg and 500 mg/kg, p.o for 15 days</td>
<td>200 mg kg-1; s.c. for 2 consecutive days</td>
<td>ALT, AST, ALP, LDL, TC, CAT, GSH, body weight</td>
<td>51</td>
</tr>
<tr>
<td>12</td>
<td>Syzygium</td>
<td>250 mg/kg and</td>
<td>20 mg/100 g s.c.</td>
<td>AST, ALT, CPK, LDH</td>
<td>52</td>
</tr>
<tr>
<td>13</td>
<td>Luteolin</td>
<td>cumini 500 mg/kg</td>
<td>0.3 mg/kg body weight for 30 days</td>
<td>85 mg kg⁻¹; s.c. for 2 consecutive days</td>
<td>Free radical scavenging, mitochondrial lipids, antioxidants and mitochondrial enzymes, histopathology</td>
</tr>
<tr>
<td>14</td>
<td>Caesalpinia crista</td>
<td>400 mg/kg body wt., administered orally for 30 days</td>
<td>85 mg kg⁻¹; s.c. for 2 consecutive days</td>
<td>Marker enzymes LDH, CK-MB, SGOT, SGPT, lipid peroxide, glutathione, Plasma TC, TG, HDL, VLDL, histopathology</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Cucumis trigonus</td>
<td>75 and 150 mg kg⁻¹l daily for a period of 14 days</td>
<td>200 mg kg⁻¹; s.c. for 2 consecutive days</td>
<td>Serum marker enzymes (ALT, AST, LDH and CPK), ECG, histopathology</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Tinospora cordifolia</td>
<td>350 mg/kg and 650 mg/kg body weight, orally for 28 days</td>
<td>85 mg kg⁻¹; s.c. for 2 consecutive days</td>
<td>Cardiac enzymes such as AST, ALT, CK-MB, LD, troponin-I, Physical parameters were gross examination of heart, heart weight/body weight ratio, histopathology examination</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Glutathione</td>
<td>200 mg/kg body wt) orally for 30 days</td>
<td>100mg/kg s.c. at an interval of 24 hrs on 31st and 32nd day</td>
<td>Marker enzymes (AST, ALT, LDH and CKMB), plasma and lipid peroxidation, and heart antioxidant enzymes (SOD, glutathione peroxides, catalase) and reduced glutathione</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Nigella sativa</td>
<td>150 mg/kg body weight intragastrically for a period of 15 days</td>
<td>85 mg/kg body weight</td>
<td>Enzymes (AST, ALT, LDH, CK), lipid profile (TG, cholesterol, free fatty acids, HDL, LDL, VLDL).</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Fenugreek</td>
<td>250 mg/kg body weight) intragastric intubation for 15 days</td>
<td>85 mg/kg body weight</td>
<td>Antioxidants (SOD, CAT, GPx and GSH), Histopathological studies</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Curcumin</td>
<td>100, 200, and 400 mg/kg orally for 15 days</td>
<td>85 mg/kg, s.c. on 13th and 14th day</td>
<td>Glutathione, SOD, CK-MB, LDH, TBRAS</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Folic acid and Vitamin B12</td>
<td>10 mg kg⁻¹, orally and 500 μg kg⁻¹, i.m. for 4 weeks</td>
<td>single injection of 300 mg kg⁻¹, s.c.</td>
<td>Electrocardiographic parameters, heart rate, ST segment, and blood pressure, CK and LDH levels, Histopathological studies</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Vitis vinifera (grapes seed)</td>
<td>100mg/kg</td>
<td>85 mg/kg</td>
<td>Maintained levels of marker enzymes (AST, ALT, and LDH &amp; CK) and antioxidants levels.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Punica granatum</td>
<td>100mg/kg</td>
<td>85mg/kg</td>
<td>Levels of marker enzymes (AST, ALT, and LDH &amp; CK) and antioxidants levels, Histopathology.</td>
<td></td>
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<td>-----------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Crocus sativus</td>
<td>20mg/kg</td>
<td>85mg/kg</td>
<td>Maintained levels of marker enzymes (AST, ALT, and LDH &amp; CK) and antioxidants levels.</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Sida cordifolia</td>
<td>100mg/kg</td>
<td>150mg/kg</td>
<td>Maintained levels of marker enzymes (AST, ALT, and LDH &amp; CK) and antioxidants levels.</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Metformin</td>
<td>150 mg/kg/24 h and 10 mg/kg for 1 week</td>
<td>Heart-to-body weight ratio, Histopathology</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CONCLUSION:**
This work highlights and summarizes the cardioprotective effects of Isoprenaline induced myocardial infarction. From above study we conclude that Isoprenaline acts as an effective tool for inducing myocardial infarction in experimental animal models.

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