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Isoprenaline: A tool for inducing myocardial infarction in experimental animal

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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 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].

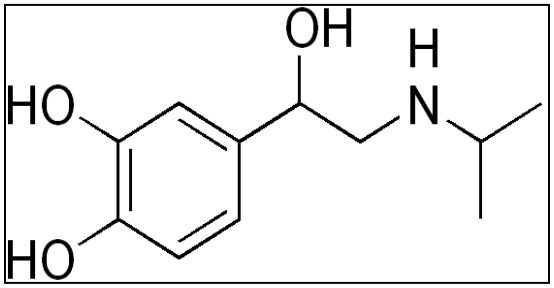

Figure 1: Structure of Isoprenaline

Pharmacodynemic

- **Cardiovascular**

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Isoproterenol produces powerful stimulation of the heart to increase its rate andforce 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 [10].

- **Pulmonary**

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 [10].

- **Other effects**

Other actions on β- receptors, such as increased blood sugar and increased lipolysis, can be demonstrated but are not clinically significant [10].

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 [10].

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, ventrical 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 [11].

Indications

- Mild or transient episodes of heart block that do not require electric shock or pacemaker therapy
- Serious episodes of heart block and Adams-Stokes attacks (except when caused by ventricular tachycardia or fibrillation)
- Cardiac arrest until electric shock or pacemaker therapy is available.
- Bronchospasm during anesthesia
- Adjunct to fluid and electrolyte replacement therapy and other drugs and procedures in the treatment of hypovolemic or septic shock.
- Low cardiac output states (eg, decompensated heart failure, cardiogenic shock) [11].

Product

Isoprenaline is available as an injection containing *isoprenaline hydrochloride* 20mcg/mL (1 - 3ml) [12].

Dosage

- The Formulary recommends isoprenaline for the treatment of adults with *bradyarrhythmias,* for which it is administered by intravenous infusion at a dose of 1-4mcg/minute
- For the treatment of adults with *other cardiac disorders* administered by slow intravenous injection at a dose of 20 – 60 mcg adjusted according to ventricular rate

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- For adults with *heart block* (acute Stokes-Adams attack) administered by intravenous infusion at a dose of 4-8 mcg/minute [12].

Trade Names:

India: Isoprin , Isolin, Autohaler, Neo –Epinine, Isosol , Isuprin

International : Isoprenalina Cloridrato, Aldo Asam, Asthpul, Isomenyl, Isopal P, Isoprenalina Cloridrato Galenica, Isoprenalina Cloridrato Monico, Isoprenalina Cloridrato Salf, Isoprenaline Haiderun Pharm, Isoprenalinhydrochlorid-Braun, Isoproterenol Clorhidrato, Isoproterenol, Isuprel, Proternol L, Saventrine, Aleudrina, Frenal Compositum , Isoprenalin SAD, Stmerin D [13].

MECHANISMS OF ISO 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].

ISOPRENALINE 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**

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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].

ACTION SCIENTIFICALLY EVALUATED

- Kumar *et al*., (2013) studied the effect of ethanolic extract of *Garcinia indica* for their cardioprotective effect on isoprenaline hydrochloride (25mg/kg. b.w.) induced cardio toxicity on wistar albino rats. The degree of cardio protection was measured by assessing biochemical parameters such as AST, ALT, LDH, CPK, and CK-MB in serum. The ethanolic extract at a dose of 250mg/kg b.w., 500mg/kg b.w. produced significant ($p<0.005$) protective activities in rats when compared to isoprenaline hydrochloride induced rats.Result of the study was found to be that *Garcinia indica* fruit extract exerts equipotent cardioprotective activity in the experimental model of isoprenaline hydrochloride induced myocardial necrosis in rats [41].
- Zaafan *et al*., (2013) investigate the effects of pretreatment with atorvastatin (10 mg/kg) and quercetin (50 mg/kg), as well as their combination on isoprenaline-induced MI in rats. Pretreatment with atorvastatin suppressed significantly the elevated levels of cTn-I, CRP, TNF-a, and IL-10 in serum coupled with reduction in cardiac lipid peroxides; however, it increased cardiac nitrite content. Quercetin decreased isoprenaline-induced changes in oxidative stress and inflammatory biomarkers with marked improvement in ECG and histopathologic alterations. Combination of quercetin with atorvastatin resulted in similar protective effects.The result was found to be that quercetin can be regarded as a promising cardio-protective natural agent in MI alone or combined with atorvastatin [42].
- Gupta *et al*., (2013) studied that administration of phlorizin, a SGLT1 inhibitor has been found to exhibit partial protection in Isoproterenol (150 mg/kg/day, i.p for 2 consecutive days) induced myocardial necrosis as observed by significant decrease in heart/body weight ratio and myocardial nitric oxide level; significant increase in myocardial SOD and catalase activities along with no histopathological alterations. On the other hand, administration of ritonavir, a nonspecific GLUT inhibitor has been found to exhibit complete protection as observed by normalisation of heart/ body weight ratio, serum markers, antioxidant enzymes activities and histopathological alterations. In vitro study with heart homogenate confirmed no antioxidant effect of ritonavir and phlorizin in the absence and presence of isoproterenol. The result was found to be that ritonavir, a nonspecific GLUT inhibitors showed complete protection in catecholamine induced myocardial necrosis [43].
- Ojha *et al*., (2011) evaluate the cardioprotective potential of *Commiphora mukul* against isoprenaline-induced myocardial necrosis in rats. *Commiphora mukul* was administered in three doses 100, 200 and 400 mg kg-1 p.o. for 30 days. On 29th and 30th day the animals were treated withisoprenaline (85 mg kg-1; s.c.) consecutively at an interval of 24 hr. Result was found to be that *Commiphora mukul* may be a potential preventive and therapeutic agent against the oxidative stress associated ischemic heart disease owing to antioxidant and antiperoxidative activity[44].
- Haleagrahara *et al*., (2011) studied the protective effects of Glycyrrhizic acid (GA) against isoproterenol-induced acute myocardial infarction in Sprague-Dawley rats. Glycyrrhizic acidwas administered in three doses 5, 10 and 20 mg/kg BWi.p. for 14 days and ISO was administered 85 mg/kg BW at two consecutive days. Treatment with GA significantly increased SOD and GSH levels and decreased myocardial LPO and IP levels. Histopathologically significantly reduced with GA treatment. Result was found to be that Gycyrrhizic

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acid treatment effective against isoproterenol-induced acute myocardial infarction in rats and GA acts as a powerful antioxidant and reduces the myocardial lipid hydroperoxide and 8-isoprostane level [45].

- Mohanty *et al*., (2009) investigate whether *Curcuma longa* (Cl), a natural herb, would attenuate the acute myocardial infarction in isoproterenol (ISP)-treated rat model via maintaining cardiac function and activities of endogenous antioxidant enzymes. Oral administration of Cl (50, 100 and 200 mg/kg, respectively) to animals for 30 days and ISP (85 mg/kg) on 29th and 30th day, s.c. *Curcuma longa* (100 & 200 mg/kg) pre-treatment for 30 days, resulted in significant mitigating effects on several myocardial injury induced biochemical {SOD ($p<0.05$), CAT($p<0.05$), GSHPx(0.05), TBARS ($p<0.05$), CPK ($p<0.05$)}, hemodynamic {MAP($p<0.05$),, LVEDP($p<0.05$)} and histopathological perturbations. Cl (100 mg/kg) was found to be the optimum cardioprotective dose. The results indicate that chronic Cl administration causes myocardial adaptation by augmenting endogenous antioxidants and protects rat hearts from decline in cardiac function and oxidative stress associated with ISP induced myocardial injury [46].
- Asdaq *et al*., (2009) studied the effect of hydroalcoholic extract of *Tylophora indica* (HETI) on experimentally-induced myocardial infarction (MI) in rats. Albino rats were treated with HETI at doses of 100 mg/kg, (HETI-100) or 200 mg/kg (HETI-200) and propranolol 10 mg/kg (PRO-10) for 30 days orally. MI was induced by subcutaneous administration of isoprenaline (IPL) 150 mg/kg for two consecutive days. The result was found to be that protection offered by HETI could be attributed to the presence of flavanoids which shows antioxidant effect by either inhibiting the release of oxygen free radicals (OFR) or enhancing the synthesis of endogenous antioxidants such as SOD and catalase in IPL-induced cardiotoxicity. These biochemical findings were further confirmed by histological investigations [47].
- Sasikumar *et al*.,(2000) studied the effect of Abana(75 mg / 100 g)) on myocardial infarction induced by isoprenaline(20 mg / 100 g subcutaneously twice at an interval of 24 hrs)) inAdult male albino rats of Wistar strain and found that Abana pretreatment offers significant protection to myocardium against the damage caused by isoproterenol induced lipid peroxidation[48].
- Sangeetha *et al*., (2011) studied cardio protective role of intravenous administration of magnesium chloride was evaluated in albino rats by injecting (i.v.) isoprenaline 2 mg/kg body weight of animal.Efficacy of cardioprotection by gold standard, Verapamil (5 microM) and Magnesium chlorideMgCl 2 (i.v) at 40 mg/kg body weight. The study clearly highlighted and confirmed the valuable role of magnesium chloride as cardio protective agent [49].
- Vibha *et al*., (2011) evaluate the cardioprotective effect of medicinal garlic (MG) against isoprenaline (ISO) induced myocardial damage in rats. Sprague dawley male rats were orally given MG 250 and 500 mg kg-1 once daily for 3 weeks and losartan (LTN, 30 mg kg-1) for one week orally in their respective groups. Myocardial damage was induced by subcutaneous administration of isoprenaline (100 mg kg-1) for two consecutive days. The results of the study demonstrate that both high dose of MG (500 mg kg-1) and low doses of MG (250 mg kg-1) dose dependently protect the myocardium against ISO damage in rat heart [50].
- Brodowicz *et al*.,(2013) evaluate the effect of ethanolic extract of *Urtica parviflora* Roxb. in isoproterenol (ISO) induced myocardial infarction (MI) in rats by administration of U. parvifloraRoxb. (350 mg/kg and 500 mg/kg, p.o) for 15 days in rats. MI was induced with a single dose of ISO (200 mg/kg, s.c.) on the 14 th and 15 thday.And it was found that U. parviflora (350 and 500 mg/kg p.o.) is effective in controlling serum LDL levels and reduced cardiac complication in experimentally induced MI in rats[51].
- Mastan *et al*.,(2005) scientifically evaluate the cardioprotective potential of methanolic extract of *Syzygium cumini* (250 mg/kg and 500 mg/kg)seeds, a medicinal herb, on isoproterenol (20 mg/100 g subcutaneously) induced myocardial infarction (MI) in rats.Study confirms the cardioprotective potential of methanolic extract of Syzygium cumini seeds against isoproterenol-induced biochemical alterations in rats[52].

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- Madhesh *et al*., (2013) evaluate the mitochondrial protection in acute and chronic periods after isoproterenol (ISO)-induced myocardial-infarction (MI) in male Wistar rats. Luteolin was supplemented by intra-gastric intubation at a daily dose of 0.3 mg/kg body weight for 30 days. In the acute MI model, luteolin had been administered once per day to rat groups during 30 days. On 29th and 30th days, the rats of the acute MI control groups were administered 85 mg/kg body weight, isoproterenol, intra-peritoneally at an interval of 24 h. In the chronic MI model luteolin was supplemented to the rat group during 30 days. On the 1st and 2nd days, the rats of the chronic MI control and luteolin treatment groups were administered ISO by the same way. The result was found to be that luteolin ameliorates mitochondrial damage in isoproterenol induced myocardial infarction by maintaining lipid peroxidation metabolism due to its free radical scavenging, mitochondrial lipids, antioxidants and mitochondrial enzymes. Histopathological observations were also in correlation with the biochemical parameters [53].
- Cha *et al*., (2010) studied whether metformin treatment prevents isoporterenol-induced cardiac hypertrophy in mice. Chronic subcutaneous infusion of isoproterenol (15 mg/kg/24 h) for 1 week using an osmotic minipump induced cardiac hypertrophy measured by the heart-to-body weight ratio and left ventricular posterior wall thickness. Cardiac hypertrophy was accompanied with increased interleukin-6 (IL-6), transforming growth factor (TGF)-β, atrial natriuretic peptide (ANP), collagen I and III, and matrix metallopeptidase 2 (MMP-2). Coinfusion of metformin (150 mg/kg/24 h) with isoproterenol partially inhibited cardiac hypertrophy that was followed by reduced IL-6, TGF-β, ANP, collagen I and III, and MMP-2. Chronic subcutaneous infusion of metformin did not increase AMP-activated protein kinase (AMPK) activity in heart, although acute intraperitoneal injection of metformin (10 mg/kg) increased AMPK activity. Isoproterenol increased nitrotyrosine levels and mRNA expression of antioxidant enzyme glutathione peroxidase and metformin treatment normalized these changes. These results suggest that metformin inhibits cardiac hypertrophy through attenuating oxidative stress [54].

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