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Comparative effect of Febuxostat and Cilostazol on Isoproterenol induced cardiac dysfunction in rats

Thesis

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SUMMARY

Myocardial infarction is an acute condition of necrosis of the myocardium that occurs as a result of imbalance between coronary blood supply and myocardial demand. Oxidative stress resulting from increased production of free radicals is associated with decreased levels of antioxidants in the myocardium and plays a major role in cardiovascular diseases. It was proposed that Febuxostat, a selective inhibitor of xanthine oxidase, reduced myocardial oxidative stress and suppressed apoptosis. Cilostazol, a selective type-3 phosphodiesterase inhibitor that has been used to treat claudication had a growing evidence suggests that Cilostazol could be cardioprotective.

The aim of the present work was to investigate and compare the potential protective effect of pretreatment with Febuxostat vs. Cilostazol on Isoproterenol induced cardiotoxicity in rats.

In the present work, 36 male-albino rats were divided into 6 groups (6 rats each):

- **GROUP 1 (Control group)**
  Rats received 1ml distilled water orally and SC for 14 days.

- **GROUP 2 (Febuxostat group)**
  Rats received febuxostat 10 mg/kg orally for 14 days and 1 ml distilled water SC on the 13th and14th day.

- **GROUP 3 (Cilostazol group)**
  Rats received cilostazol 5.8 mg/kg orally for 14 days and 1 ml distilled water SC on the13th and 14th day.

- **GROUP 4 (Isoproterenol group)**

Rats received 1 ml distilled water orally for 14 days and Isoproterenol 100 mg/kg SC on the 13th and14th day.

- **GROUP 5 (Febuxostat + Isoproterenol)**

  Rats received febuxostat 10mg/kg orally for 14 days and Isoproterenol 100 mg/kg SC on the 13th and 14th day.

- **GROUP 6 (Cilostazol + isoproterenol)**

  Rats received cilostazol 5.8 mg/kg orally for 14 days and Isoproterenol 100mg/kg SCon the 13 th and 14 th day.

At the end of the 14 th day, ECG was performed ,blood samples were withdrawn for calculation of serum cardiac troponin I. Rats were sacrificed and hearts were excised and preserved for histopathological examination and calculation of TNF-α.

Results revealed that pretreatment of rats with Febuxostat led to significant increase in heart rate but significant decrease in QT,QTC intervals while Cilostazol treatment didn't lead to significant increase in heart rat or QT,QTc intervals when compared to Isoproterenol group.

Isoproterenol led to significant increase in TNF-α and cardiac troponin levels. Pretreatment with Febuxostat and Cilostazol in Isoproterenol group led to significant decrease in their levels. Cilostazol led to more significant reduction in TNF-α and insignificant reduction of cardiac troponin levels compared to Febuxostat.

Isoproterenol led to arrhythmia (extra-systoles) in 33% of rats, Febuxostat led to arrhythmia in 50% of rats,while Cilostazol didn't lead to any arrhythmias.

Histopathological examination of **control group** revealed regular myocardial architecture. Cardiomyocytes are short, branched and arranged in interlacing bundles with alternating light and dark bands. They have spindle shaped nuclei and abundant

eosinophilic cytoplasm. **Isoproterenol** led to loss of the normal myocardial architecture,inflammation, congested blood vesseles and edematous changes between the muscle fibers. Pretreatment with Febuxostat and Cilostazol led to significant improvement in the pathological changes caused by Isoproterenol .There was no significant difference between group V (Febuxostat+Isoproterenol) and VI (Cilostazol+Isoproterenol) regarding histopathological changes.

Febuxostat group (group II) and Cilostazol group (group III) showed the same histopathological picture of control group (group I).

In conclusion, pretreatment with Cilostazol is more cardioprotective than Febuxostat as it led to more reduction in TNF-α without increasing arrhythmias or affecting QT and QTC intervals as compared to Febuxostat.