Effect of Ivabradine and Lacosamide on Doxorubicin induced cardiotoxicity and hyperpolarization-activated cyclic nucleotide-gated channels (HCN-4) gene expression in rats

Thesis

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SUMMARY

Doxorubicin, is one of the most effective chemotherapeutic agents in a variety of cancer types; however, its use is seriously limited due to the risk of developing cardiotoxicity.

The aim of the present work was to investigatethe potential protective effect of ivabradine and lacosamide on doxorubicin induced cardiotoxicity and hyperpolarization activated cyclic nucleotide-gated channels (HCN-4) gene expression in rats.

In the present work, 24 male-albino rats were studied. Rats were divided into 4 groups 6 rats each:

The groups were as follows:

Group I:(Control group): rats received 1 ml distilled water intraperitoneally every other day for 14 days and 1 ml distilled water orally daily for 14 days.

Group II :(Doxorubicin group): rats received doxorubicin 2.5 mg/kg intraperitoneally every other day for 14 days and 1 ml distilled water orally daily for 14 days.

GroupIII:(Ivabradine + doxorubicin group): rats received doxorubicin 2.5mg|kg intraperitoneally every other day for 14 days and ivabradine 10 mg|kg orally daily for 14 days.

Group IV :(Lacosamide + doxorubicin group): rats received doxorubicin 2.5mg|kg intraperitoneally every other day for 14 daysand lacosamide 30 mg|kg orally daily for 14 days.

At the end of 14 days, ECG was traced to assess heart rate, QT interval, QTc interval and PR interval.

Rats were sacrificed by cervical dislocation and hearts were excised, then cannulated by Langendorff technique for cardiac contractility estimation. The hearts were thenwashed with ice-cold saline and preserved for histopathological examination, estimation of HCN-4 gene expression and for estimation of cardiac (catalase and superoxide dismutase).

Results revealed that heart rate was significantly decreased in doxorubicin rats but QT, QTc, and PR intervals were significantly increased. Ivabradine treatment significantly decreased heart rate but significantly increased QT and PR intervals. Lacosamide treatment significantly increased PR interval.

There was no significant change regarding cardiac contractility between doxorubicin and control groups. There was significant increase in percentage of cardiac contractility in ivabradine and lacosamide groups compared to doxorubicin group ($p<0.05$). There was also significant increase in percentage of cardiac contractility in ivabradine group compared to lacosamide group ($p<0.05$).

Cardiac HCN-4 gene expression was measured in by real time-PCR. It was noticed that the gene expression was increased significantly in doxorubicin rats. Treatment with ivabradine and lacosamide led to significant decrease in gene expression.

Catalase and superoxide dismutaseweredecreased significantly with doxorubicin but ivabradine and lacosamide treatment significantly increased the activities of the above mentioned enzymes.

Histopathological examination in the present study by light microscopy using hematoxylin and eosin revealed that doxorubicin led to loss of the normal myocardial architecture and edematous changes in the form of gapping, disorientation and vacuolations between the muscle fibers. Ivabradine and lacosamide treatment led to improvement in the pathological changes caused by doxorubicin.