Comparative effect of Anacetrapib, Rivaroxaban and Alogliptin on cardiovascular dysfunction in cholesterol fed and Fludrocortisone treated rats

Thesis to fulfill MD degree in Clinical Pharmacology

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Summary

The objective of this study was to investigate and compare the potential protective effects of anacetrapib, rivaroxaban, and alogliptin in a model of hypercholesterolemia and hypertension induced by cholesterol and fludrocortisone. In this research, 48 adult male albino rats were examined, with 24 of them being orally administered cholesterol, fludrocortisone, and 1% NaCl for 21 days.

The rats were divided into eight groups as follows:

- Group 1: Rats received 1 mL of distilled water orally for 21 days.
- Group 2: Rats were given anacetrapib (5 mg/kg, as per Ku¨hnast et al., 2015) orally for 21 days.
- Group 3:Rats received Rivaroxaban (10 mg/kg) (Al-Harbi1 et al.,2020) orally 21 days.
- Group 4:Rats received Alogliptin (20 mg / kg) (Kabel et al.,2018) orally for 21 days.
- Group 5:Rats received high cholesterol diet and fludrocortisone (100 microgram/kg) orally (Bamberg et al., 2019) orally for 21 days .
- Group 6:Rats received anacetapib (5 mg/kg) + high cholesterol diet and Fludrocortisone (100 microgram/kg) orally for 21 days.
- Group 7 :Rats received Rivaroxaban (10 mg /kg) ,high cholesterol diet and Fludrocortisone (100 microgram/kg)orally for 21 days.
- Group 8 :Rats received Alogliptin (20 mg/kg) ,high cholesterol diet and Fludrocortione (100 microgram/kg) orally for 21 days.

After the 21-day period, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were assessed in all experimental groups. Subsequently, blood samples

were obtained from the fasting rats via retro-orbital veins, and the serum was separated for the evaluation of various parameters, including serum CETP, sodium (Na+), and lipid levels (triglycerides, total cholesterol, high-density lipoprotein, and low-density lipoprotein), as well as conducting ECG and contractility measurements.

Following the blood collection, the rats were humanely euthanized through cervical dislocation, and their hearts were removed for the measurement of cardiac contractility. Each heart was then divided into two portions: one portion was preserved in 10% formalin for subsequent histopathological examination, and the other part was stored in a deep freezer at -60^{o}C for the quantification of PAR1 using ELISA kits.

The findings indicated a significant increase in serum CETP and Na+ levels in rats with hypercholesterolemia and hypertension induced by cholesterol and fludrocortisone (HC/HTN). However, when treated with anacetrapib, rivaroxaban, or alogliptin, the serum CETP and Na+ levels were notably lower compared to the untreated HC/HTN group.

Regarding the lipid profile, the serum levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein (LDL) were substantially elevated in the HC/HTN groups, while the serum level of high-density lipoprotein (HDL) was significantly reduced. However, in groups receiving anacetrapib, rivaroxaban, or alogliptin, the levels of TG, TC, and LDL were lower, and the level of HDL was higher than in the untreated HC/HTN group.

The levels of cardiac PAR1 were notably elevated as a result of cholesterol feeding, and these levels exhibited a reduction with the administration of the three

drugs when compared to the untreated group with hypercholesterolemia and fludrocortisone-induced hypertension.

Systolic and diastolic blood pressures were significantly increased with cholesterol fed and fludrocortisone hypertensive rats and were significantly decreased with anacetrapib, rivaroxaban and alogliptin.

The histopathological analysis of cardiac tissues unveiled unusual degenerative alterations in the groups subjected to a cholesterol-rich diet. These changes encompassed congestion, inflammatory cell infiltration, and fibrosis. However, these pathological changes were mitigated with the administration of anacetrapib, rivaroxaban, and alogliptin.

Our study further identified a notable positive correlation between PAR1 and mean arterial blood pressure (MBP). Additionally, there was a significant positive correlation between CETP and MBP. Conversely, we observed non-significant negative correlations between serum CETP levels and the PR interval. Furthermore, there were non-significant negative correlations between the cardiac levels of PAR1 and the PR interval.

A significant negative correlation was found between serum CETP and serum HDL levels. Furthermore, a highly significant negative correlation was observed between cardiac PAR1 levels and serum HDL levels. On the other hand, there was a significant positive correlation between serum CETP and serum LDL levels. Likewise, a significant positive correlation was noted between cardiac PAR1 levels and serum LDL levels.