

---

# Some pharmacological studies of candesartan in experimental animals

**Sherif Ahmed El Sayed Shaloot**

Candesartan is a selective AT1 receptor antagonist. On the other hand, perindopril is an ACE inhibitor. The present work was carried out to screen the pharmacological effects of candesartan and perindopril on isoprenaline induced myocardial infarction and heart failure and STZ-induced diabetic nephropathy. Also, the effects of candesartan and perindopril on isolated rabbit's aortic strip and isolated rabbit's heart were evaluated. Myocardial infarction was experimentally induced by a single subcutaneous injection of isoprenaline (500mg/kg). The electrocardiograph tracing showed sinus tachycardia with injury currents in form of highly peaked T-wave, serum creatine phosphokinase (CPK-MB) and troponin-I levels increased in rats 4 hours after subcutaneous injection of isoprenaline. The mean percentage of infarction size percent was  $(47.71 \pm 2.4\%)$  and histopathological examination of cardiac sections of MI group revealed myocyte degeneration and necrosis and interstitial fibrosis. In the present work, it was observed that pre-treatment (10mg/kg/day for 7 days) and post-treatment (10mg/kg) with oral candesartan decreased significantly the T-wave voltage and levels of CPK-MB and troponin-I. However, it produced insignificant decrease in heart rate. On the other hand, pre-treatment (6mg/kg/day for 7 days) and post-treatment (6mg/kg) with oral perindopril decreased significantly the T-wave voltage and levels of CPK-MB and troponin-I. However, it produced insignificant decrease in heart rate. There was significant effect in the pretreated groups and no significant effect between candesartan and perindopril in the pretreated and post-treated groups. The degree of cardio-protective effect induced by candesartan and perindopril was evaluated by studying the changes in the severity of the cardiac necrosis evoked by isoprenaline in rats. It was found that candesartan and perindopril pretreatment minimized the infarction size with significant decrease in candesartan pre-treatment group. There was no significant effect of candesartan and perindopril post-treatment groups on the infarction size. Heart failure was experimentally induced in rats by a single subcutaneous injection of isoprenaline (150mg/kg). After 2 weeks, there was significant decrease in the systolic and diastolic blood pressure. Also, there was significant increase in the heart rate in comparison with control group. In the present work, it was observed that daily oral administration of candesartan (10mg/kg/day) and perindopril (6mg/kg/day) for 2 weeks produced significant reduction in the systolic and diastolic blood pressure when compared with control group. In comparison with HF group,

---

it produced insignificant reduction in SBP and DBP and significant decrease in HR. There was significant effect in perindopril treated group. Histopathological examination of cardiac sections of control group showed no detectable abnormality in cardiac smooth muscle cells. Sections of heart failure group revealed myocyte degeneration and necrosis and interstitial fibrosis. Candesartan and perindopril Summary and Conclusion 14 7 administration effectively decreased these changes with more significant effect in candesartan treated group. In the present study, diabetic nephropathy was experimentally induced in rats by single intraperitoneal injection of streptozotocin (70mg/kg). After one month, streptozotocin induced significant increase of fasting blood glucose, serum urea, serum creatinine and 24-hour collected urine albumin in rats and significant decrease of creatinine clearance level. Histopathological examination of renal tissues of diabetic nephropathy rats by light microscopy revealed diffuse glomerular sclerotic lesion. It was observed that daily oral administration of candesartan (10mg/kg/day) and perindopril (6mg/kg/day) for 4 weeks produced significant reduction in fasting blood glucose, serum urea, serum creatinine and 24-hour collected urine albumin in rats and significant increase of creatinine clearance level. There was insignificant difference between candesartan and perindopril treated groups except for 24-hour collected urine albumin, where perindopril was more significant than candesartan. Regarding histopathological examination of renal tissues, daily oral administration of candesartan and perindopril revealed mild degenerative changes and fibrosis compared to untreated rats. Perindopril was more effective in improvement of renal tissue than candesartan. Data obtained in the present study pointed out that candesartan in gradually increasing doses (2,4,8,16 and 32/ml bath) produce no effect on the isolated rabbit's aortic strip and basal myocardial contractility of Summary and Conclusion 14 8 isolated rabbit's heart. However, it antagonized angiotensin-II induced contractions in isolated rabbit's aortic strip and rabbit's heart. On the other hand, perindopril in gradually increasing doses (2,4,8,16 and 32/ml bath) produced no effect on the isolated rabbit's aortic strip and basal myocardial contractility of isolated rabbit's heart. Also, it did not antagonize angiotensin-II induced contractions in isolated rabbit's aortic strip or rabbit's heart. In conclusion, both candesartan and perindopril have cardioprotective effect against acute MI and HF as well as marked nephroprotective effect in diabetic nephropathy with no significant difference between both drugs. So, the choice of either drug in these disease states depend on which of them has low side effects.