



The role of pharmacokinetic studies in development of drugs, containing endogenous compounds

Oleg Medvedev, Elena Kalenikova,
Eugenia Gorodetskaya, Alexander
Ivanov, Ekaterina Charitonova

School of Medicine, Lomonosov Moscow State
University, Russia

Final phase of preclinical development of the new drug includes pharmacokinetic and pharmacodynamic studies in laboratory animals. There are additional requirements for the endogenous molecules, developed as new drug. Pharmacokinetic studies should pay attention on the endogenous level of the compound during the whole duration of blood sampling period. It is important to know the influence of pathological process on the endogenous levels of compound in plasma and in the target organ and to correlate its pharmacological effect with the amount of compound delivered to the target organ. To provide the optimal transport of endogenous compound to the target organ it is necessary to determine the optimal dose, formulation, route and time schedule of its administration. The aim of our study was preclinical study of coenzyme Q10, as cardioprotective agent.

Methods: In experiments on male Wistar rats we used ligation of the left coronary a. for modeling acute and chronic regional cardiac ischemia. Levels of CoQ10 in plasma and myocardium were measured by HPLC with electrochemical detection in normal rats and in rats with myocardial ischemia. It was shown, that zone of postischemic necrosis of myocardium and the tissue level of CoQ10 are inversely correlated. Pharmacokinetics of CoQ10, administered per os (tablets), intramuscularly (im) and intravenously (iv) (solubilised form of CoQ10) were studied.

Results: It was shown that administration of Q10 via different routes could increase its level in the myocardium, but after different delay time. The fastest increase by 20% was observed in 30 min after iv administration. In the following experiments solution of solubilised form of CoQ10 (Kudesan - "Akvion" Company, Moscow, Russia) was used. Daily administration of CoQ10 (10 mg/kg/day) (3 weeks before the coronary a. occlusion and 3 weeks after) was followed by increase in its level in myocardium by 17%, decrease in necrosis zone by 40% and decrease in left ventricle (LV) hypertrophy from 2,38 g/kg (control group) to 2,18 g/kg (CoQ10 treated group). Single iv administration of CoQ10 after occlusion of coronary a. was followed by decrease in LV hypertrophy from 2,17 to 2,03 g/kg. In Q10-treated rats development of postinfarct LV aneurism and hypertrophy of the right ventricle. Levels of CoQ10 in plasma and myocardium were increased by 87 and 23%. Single iv administration of CoQ10 during ischemic period but before the reperfusion, decreased the infarct zone by 30% and diminished the occurrence of reperfusion arrhythmias.

In conclusion: The results of our study confirmed the pathogenetic role of CoQ10 deficit in ischemia-reperfusion conditions and proved the positive effect of replenishment of its myocardial tissue levels. Such data may serve as the prove of necessity to develop iv form of CoQ10 containing cardioprotective drug.

Biography

Oleg Medvedev has completed his PhD at the age of 26 years from the 1st Medical Institute in Leningrad and postdoctoral studies from the Institute of Pharmacology, Moscow. He is the Chairman of the Department of Pharmacology at the Lomonosov Moscow State University. He published more than 200 papers in reputed journals.