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A comparative study of anti-arrhythmic and hemodynamic effects of dihydropyridines and oxidized dihydropyridines in the model of ischemia- and reperfusion- induced arrhythmias in rats

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Our previous studies have established cardio-protective effects of furnidipine, a dihydropyridine, and its active metabolites. Privileged pharmacophore as the dihydropyridines are named, are known to protect the heart from ventricular arrhythmias also. Furnidipine, is oxidatively metabolized in the body and M-2 is known to be such a major metabolite of it. We therefore decided to study 1) the influence of furnidipines' three metabolites (M-2, M-3, M-8 administered 24 and 1 h before LAD occlusion in the dose of 20 mg/kg p.o. each) in ischemia-and reperfusion- induced arrhythmias Sprague-Dawley rats' model, and 2) the effects of chronic treatment after experimental infarction (from 6^{th} to 35^{th} day) with M-2 (4 mg/kg p.o.) in rats. In the first series of experiments, mortality was significantly reduced in M-2 and M-3 treated groups with M-3 preventing animal mortality entirely. All three examined substances significantly reduced the ventricular fibrillation (VF) incidence and its duration with M-3 completely preventing VF. Through the occlusion and reperfusion, M-8 was strongly hypotensive as compared to control while such a drastic effect was not seen with M-2 or M-3. Among the tested metabolites, M-2 and M-3 exhibited the most pronounced anti-arrhythmic effect at same time being the most normotensive and therefore were considered as the most cardio-protective.

While our other studies have established three phases of non-treated myocardial infarction in rats, in the second series the rats were treated with M-2 during the longest period and a marked increase of coronary flow (CF) without a significant increase of myocardial oxygen consumption was observed in working heart study (60 min). We conclude, therefore, that the earliest and the longest oral administration of M-2 after myocardial infarction reveals the most beneficial effects on hemodynamic parameters in a model of physiological perfusion of the isolated rat heart mainly due to CF increase without a significant cardio-depressive effects.

Furthermore, unlike furnidipine, M-2 do not only possess calcium channel blocking activities, therefore is a potentially promising cardio-protective agent representing a new structural class of drugs Our previous studies have established cardio-protective effects of furnidipine and its active metabolites. We therefore decided to compare the influence of oral and intravenous administration of furnidipine, nifedipine, nitrendipine and nimodipine to examine their effects on hemodynamics and arrhythmias in model of ischemia- and reperfusion- induced arrhythmias of rats. Since dihydropyridines are oxidatively metabolised in the body and these metabolites can be thought to be final products, we studied also the influence of four oxidized dihydropyridines (oxy nifedipine, oxy nimodipine, oxy nitrendipine and oxy nisoldipine) on the same parameters. Dihydropyridines were administered 5 mg/kg orally (24 and 1h before LAD occlusion for 7 min) or 5 µg/kg intravenously (10 min before ischemia), whereas 20 mg/kg of the oxidized dihydropyridines each was given orally in the same protocol. The dihydropyridines exhibited significant anti-arrhythmic actions after both forms of administration but their influence on blood pressure was different and dependent from the route of administration. The oxidized dihydropyridines strongly protected against lethal arrhythmias exerting various influence on blood pressure (oxy nifedipine and oxy nisoldipine were hypertensive and oxy nitrendipine the most normotensive).

The differential effects observed with the dihydropyridines after the two routes of administration led us strength to the hypothesis that their metabolites may play a significant role in mediating the actions of the parent drug. The strong anti-arrhythmic action of the oxidized dihydropyridines along with disparity effect on blood pressure could indicate their potential use as cardio-protective drugs in better defined groups of patients.