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A comparative study of the effects of furnidipines' metabolites (M-2, M-3, M-8) in the model of ischemia- and reperfusion- induced arrhythmias and with M-2 chronic oral treatment after myocardial infarction 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.