GW23-e2670  
EFFECTS OF SIMVASTATIN IN A RABBIT MODEL OF Atherosclerosis: role of HO-1/CO-CGMP Pathway and Related Anti-Oxidative Enzyme Expression

doi:10.1136/heartjnl-2012-302920a.11

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Objectives  Clinical and experimental observations indicated that HMG-CoA reductase inhibitors (statins) have pleiotropic effects. The present study was designed to elucidate the status of cyclic adenosine monophosphate (c-GMP), Cyclooxygenase-2 (COX-2),
Carbon Monoxide Haemoglobin (COHb) and haem oxygenase-1 (HO-1) to the antioxidative effects of Simvastatin in the hypercholesterolemic rabbit.

**Methods** Twenty four male Japanese white (JW) rabbits weighing approximately 2.0 kg were used in this study. The animals were randomised into three groups of eight animals each: one control group and other two groups which were maintained on high-cholesterol diet (HCD) for 24 weeks. After 8 weeks on this diet, the animals were divided into two groups: non-treated group and simvastatin group; the animals were euthanised with an overdose of sodium pentobarbital at the end 24th week. The aorta were excised, placed in ice-cold sterile saline, and cleaned of connective tissue. Blood was taken through cardiac puncture and plasma was used for biochemical assay of lipid peroxides. Levels of HbCO, COX-2 and cGMP were measured by Enzyme-Linked Immunosorbent Assay (ELISA) kits. HO-1mRNA in arterial were analysed using Real Time Quantitative PCR methods, and expression of MMP-9 protein was measured by immunohisto-chemical assay, serum malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were also measured.

**Results** Twenty-four weeks of atherogenic diet significantly increased the levels of MDA cytotoxic (19.72±2.60 vs 14.24 ±1.87 ng/ml control group), and SOD (1.31±0.45 vs 7.92±1. μg/ml control), cGMP (18.66±1.47 vs 12.54±1.45 nmol/l control group) decreased in serum; HO-1mRNA expression of non-treated group is no different than the control group (1.75±1.02 vs 1.34±0.65), but is showing the tendency to increase (3.22±1.67 vs 1.75±1.02 non-treated group, p=0.062) after treatment with Simvastatin. SOD, NO and cGMP were as well as increased (p<0.01 or p<0.05), but MMP-9 and HbCO (56.12±11.67 vs 101.0±41.55 μg/ml non-treated group) decreased significantly than the non-treated group (p<0.01 or p<0.05) after treatment with Simvastatin. Simvastatin partially restored the HO-1, SOD and NO, decreased MDA and HbCO levels, but to COX-2(67.69±6.39 vs 68.90±9.04 U/l non-treated group), no differences among groups were observed.

**Conclusions** Atherosclerosis induced an oxidative damage and simvastatin had significant anti-atherogenic and anti-oxidation effects in an animal model with rabbits fed a hypercholesterolemic diet, maybe it mediated by HO-1, restoring the SOD and NO levels and reducing cytotoxic MDA levels.