Simvastatin prevents steroid-induced osteonecrosis by lowering serum lipid level and inducing hepatic CYP3A in a rabbit model

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Introduction: Despite widely spread use of corticosteroids for inflammatory diseases, the pathomechanism of development of osteonecrosis of the femoral head (ONFH) has not been identified. Statins are effective in preventing ONFH by lowering intravascular lipid levels [1].

Recent studies have shown that levels of hepatic cytochrome P4503A (CYP3A), a major drug metabolizing enzyme, are consistently low in patients with steroid-induced ONFH [2] and an increase in CYP3A activity reduced the onset of steroid-induced osteonecrosis in the same experimental model [3].

In the present study, we have examined the effects of individual statin on plasma lipid levels, hepatic CYP3A activity and the incidence of steroid-induced osteonecrosis to elucidate the contribution of CYP3A to preventing osteonecrosis.

Materials and Methods: Female Japanese white rabbits were randomly allocated to receive probucol (group P), pravastatin (group PS), simvastatin (group SS), or saline (group C) for 6 weeks (n = 15 in groups P, PS and SS, and n = 30 in group C). Probucol, pravastatin and simvastatin each have lipid-lowering effects. Probucol and pravastatin do not induce hepatic CYP3A, while simvastatin is a CYP3A inducer [4]. Each agent was administered for 6 weeks. Methylprednisolone (20 mg/kg) was injected at 3 weeks to induce osteonecrosis, and the femurs were histologically examined bilaterally 3 weeks after methylprednisolone injection to detect the incidence of osteonecrosis [5]. Midazolam clearance was measured before treatments and before methylprednisolone injection to determine hepatic cytochrome P4503A (CYP3A) levels [6]. Low-density lipoprotein cholesterol (LDL), triglycerides (TG), free fatty acids (FFA), and total cholesterol (Tcho) levels were measured before treatment (day 0) and at 7, 14, 21, 24, 28, 31, 35, and 42 days after starting treatment.

Results: The incidence of osteonecrosis, distribution profile of midazolam clearance, and serum lipid levels in each group were shown in figure 1,2, and 3.

Discussion: The incidence of steroid-induced osteonecrosis was significantly lower in rabbits receiving statins than in control rabbits. Furthermore, an increase in hepatic CYP3A activity by simvastatin significantly lowered the rate of osteonecrosis in rabbits compared with those treated by pravastatin, not a CYP3A inducer. It may be possible to reduce the risk of osteonecrosis by adjusting the dose of corticosteroids to the hepatic CYP3A activity in individual patients.


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Figure 1: The incidence of osteonecrosis in four groups. The incidence of osteonecrosis in groups P (47%) and SS (13%) was significantly lower than in group C (83%). It was significantly lower in group SS than in groups PS. * p < 0.05, ** p < 0.0001.

Figure 2: Distribution profile of midazolam clearance before (0 week) and after 3 weeks’ treatment in groups P , PS, and SS. Values are shown as individual values (open circles) and the mean ± SD (solid circles and whiskers). There were no differences in midazolam clearance among groups P, PS and SS before treatments. Midazolam clearance in group SS was significantly increased after treatment, whereas it was unchanged in groups P and PS.

Figure 3: Sequential changes in the levels of low-density lipoprotein (LDL) (A), triglyceride (TG) (B), free fatty acid (FFA) (C) and total cholesterol (Tcho) (D) in all groups. There were no differences in the levels of LDL, TG, FFA or Tcho among groups P, PS and SS at any time points. * p < 0.05 compared with group C at the same time points.