

## UNDERSTANDING DRUG/STATIN INTERACTIONS

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have emerged as the most valuable of the cholesterol-lowering drugs because they have wide therapeutic indices and are generally well tolerated. However, the combination of statins with triglyceride-lowering fibrates, especially nicotinic acid or gemfibrozil, or potent cytochrome P4503A/ p-glycoprotein inhibitors significantly increases the risk to develop myopathy such as potentially fatal rhabdomyolysis. A recent example stressing the clinical importance of statin drug interactions is the removal of cerivastatin from the market on August 8, 2001, after at least 40 fatal cases of rhabdomyolysis were reported when cerivastatin was co-administered with the fibrate gemfibrozil. Interestingly, the molecular mechanisms underlying statin rhabdomyolysis are largely unknown and have never systematically been studied. Although for each statin an equilibrium between both acid and lactone form exists *in vivo*, very little attention has been paid to the potential role of the lactones of statins administered as open acids (atorvastatin, cerivastatin, fluvastatin, pravastatin) in pharmacokinetic and pharmacodynamic drug interactions and toxicity.

We hypothesize that statin lactones play a key role in drug-drug interactions and skeletal muscle toxicity of statins and are evaluating the role of statin lactones in the pharmacokinetics and toxicity of statins. It is our aim to assess the mechanistic role of statin lactones in the pharmacokinetics and toxicity of statins in comparison to their corresponding acids. Our studies will allow us to rank the statins in terms of their risk for toxic drug-drug interactions, will allow important new insights in the mechanism of statin drug-drug interactions and toxicity that will allow a risk-assessment of new statins already during pre-clinical development and will significantly contribute to the development of safer statins.

Assays to predict the clinical risk of drug-statin combinations as early as the pre-clinical development phase would be highly desirable, especially for cardiovascular drugs. Such a test is not available and will require more detailed knowledge of the mechanisms underlying statin drug-drug interactions and toxicity. It is our goal to provide the mechanistic basis for such preclinical assessments and we expect that our studies will suggest the required experimental algorithms and setups. Considering today's costs for the clinical development of new drugs and the compensations sought in lawsuits, it seems reasonable to estimate that the results of our study will help to prevent economic damage in the billion US\$ range.

