METABOLIC PROPERTIES OF OPEN ACID FORM AND LACTONE FORM OF STATINS
Tsuyoshi Saito, Hideki Fujino, Yoshihiko Tsunenari, and Junji Kojima
Tokyo New Drug Research Laboratories I, Kowa Company Ltd., 2-17-43 Noguchicho, Higashimurayama, Tokyo, Japan

To gain a better understanding of the metabolic properties between the open acid and lactone form of HMG-CoA reductase inhibitors (statins), the investigation focused primarily on characterizing the metabolic properties of statins. We compared the metabolism of the acid form and lactone form of several statins, such as atorvastatin, cerivastatin, fluvastatin, simvastatin, pitavastatin and rosuvastatin in regard to metabolic clearance, CYP enzymes involved and drug-drug interactions. The metabolic switching of CYP between acids and lactones was noted in the metabolism of cerivastatin, fluvastatin and pitavastatin. CYP2Cs were critically involved in the metabolism of these acids. In contrast, CYP2Cs were not involved in the metabolism of these lactones and CYP3A4 was closely involved. Also, a remarkable increase of metabolic clearance was noted in all lactones except for pitavastatin lactone. The metabolic clearances of lactone for atorvastatin, simvastatin, cerivastatin, fluvastatin and rosuvastatin were 73-, 69-, 30-, 7- and 71-fold higher, respectively, than these of acids. Moreover, quite a difference in the metabolic inhibition of statins was found between acids and lactones. These results reminded us to pay close attention to the metabolic properties of lactones. The present study demonstrates that CYP-mediated metabolism of lactones is also a common metabolic pathway for statins and CYP3A4-mediated metabolic properties of lactone form clearly will need to be taken into account in assessing mechanistic aspects of drug-drug interaction involving statins.