

Phase I and phase II metabolites identification of macrolactin A using human liver microsomes and API5500Q trap

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It was reported that macrolactin A, a polyene macrolides containing a 24-membered lactone ring, has been a bacteriostatic antibiotic that inhibits a number of multidrug-resistant gram-positive bacterial pathogens, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *enterococci*, and a small-colony variant of *Burkholderia cepacia*. Despite the excellent pharmacological properties of macrolactin A, to date there is no information regarding the Phase I or Phase II biological metabolites of macrolactin A. In our present study, we investigated and characterized the CYP and UGT enzymes that are responsible for the metabolism of MA. Furthermore, we predicted and identified the metabolic pathway of macrolactin A by lightsight software of API5500Q trap. Five different human cDNA-expressed UGTs (rUGT1A1, rUGT1A4, rUGT1A6, rUGT1A9, and rUGT2B7) and ten different human cDNA-expressed CYPs (rCYP1A2, rCYP2A6, rCYP2B6, rCYP2C8, rCYP2C9, rCYP2C19, rCYP2D6, rCYP2E1, rCYP3A4, and rCYP3A5) were used. Using human liver microsomes and human cDNA-expressed CYPs, and UGTs, we identified four phase I metabolite of macrolactin A, products of oxidation. Among these CYP isozymes, CYP3A4 and CYP3A5 are major enzymes for the formation of the metabolite of MA. Three O-glucuronide conjugations of macrolactin A also occurred. It is extensively glucuronized by mainly UGT2B7, and a lesser extent, UGT1A1, UGT1A4 and UGT1A9 and formed three different MA-glucuronides. To be specific, oxidation of MA via CYP3A4 and CYP3A5 is minor metabolic pathway of MA compared to the formation of MA-glucuronide. Taken together, MA is metabolized by UGT1A1, UGT1A4, UGT1A9, UGT2B7, and CYP3A4/5 and among these enzymes, UGT2B7 is major enzyme for the metabolism of MA.

Biography

Su Min Jang is now studying for a master's degree in the Catholic University of Korea. The course focuses on specialization in the field of drug metabolism and pharmacokinetics.

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