

3rd World Congress on Bioavailability & Bioequivalence

March 26-28, 2012 Marriott Hotel & Convention Centre, Hyderabad, India

Fate of pharmacologically active isoflavones upon administration in sprague dawley rats Wahajuddin, KSR Raju and S P Singh

Division of Pharmacokinetics and Metabolism, CSIR-Central Drug Research Institute, India

F ormononetin (FMN) and Biochanin A (BCA) are methoxylated isoflavones which are the major constituent in red clover and in commercially available extracts of this plant. In this study, we investigated the parallel artificial membrane permeability assay (PAMPA) permeability, protein binding, blood uptake characteristics, pharmacokinetics and metabolism. The permeability study samples were analyzed by HPLC–PDA method; whereas the pharmacokinetic study, protein binding and whole blood partitioning samples were analyzed by LC–MS/MS method. The PAMPA permeability of FMN was found to be high at pH 4.0 and 7.0. Plasma protein binding of FMN was found to be 93.61 \pm 0.44% and 96.14 \pm 0.15% at the tested concentration of 50 and 150 ng/mL, respectively. FMN reached equilibrium fast between red blood cells (RBCs) and plasma, and the partition coefficients between RBCs and plasma (KRBC/PL) were independent of the initial rat blood concentrations of FMN. The bioavailability of unchanged/free FMN was found to be poor, i.e. approximately 3%. FMN was found to have a high clearance (5.13 L/h/kg) and a large apparent volume of distribution (14.16 L/kg). Circulating conjugates (glucuronides/sulfates) of FMN and it's metabolite daidzein (DZN) were quantified using enzymatic hydrolysis of plasma samples. The levels of isoflavone glucuronides/sulfates were found to be much greater than that of the corresponding aglycones.

The plasma concentration of BCA following intravenous administration dropped to 50% with in 15 min. The metabolite Genistein (GEN), GEN and BCA conjugates (glucuronides and/or sulfates) were detected from first time point onward. These results suggest that BCA is rapidly O-demethylated to GEN and that both BCA and its metabolite GEN are rapidly conjugated. The CL of BCA was found to be 15.70 l/h/kg which is greater than mean hepatic blood flow indicating that BCA is rapidly metabolized by the liver. The high clearance is likely due to rapid metabolism of BCA. Upon de-conjugation of plasma samples using glucuronidase/sulfatase, the AUC of BCA and GEN increased approximately 4.5 and 3.5 times, respectively. It suggests that the glucuronide/sulfate conjugates are major circulating metabolites in blood. Less than 20% of BCA was detected in plasma in free form after intravenous administration. The oral bioavailability of BCA was found to be poor (4.6%). Glucuronidase/sulfatase used for the de-conjugation of plasma samples, generated after oral administration. Upon hydrolysis, the AUC of BCA and GEN increased approximately 136 and 24 times, respectively. Reentry peaks of BCA, GEN and their conjugates were present in the plasma, likely due to enterohepatic recirculation, after oral as well as intravenous administration. The poor bioavailability of FMN and BCA may be due to extensive first-pass metabolism and biliary elimination.

wahajuddin@gmail.com