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Identification of CYP3A7 for glyburide metabolism in human fetal livers

Qingcheng Mao
University of Washington, USA

Glyburide is commonly prescribed for the treatment of gestational diabetes mellitus; however, fetal exposure to glyburide is not well understood and may have short- and long-term consequences for the health of the child. Glyburide can cross the placenta; fetal concentrations at term are nearly comparable to maternal levels. Whether or not glyburide is metabolized in the fetus and by what mechanisms has yet to be determined. In this study, we determined the kinetic parameters for glyburide depletion by CYP3A isoenzymes; characterized glyburide metabolism by human fetal liver tissues collected during the first or early second trimester of pregnancy; and identified the major enzyme responsible for glyburide metabolism in human fetal livers. CYP3A4 had the highest metabolic capacity towards glyburide, followed by CYP3A7 and CYP3A5 (Clint,u = 37.1, 13.0, and 8.7 ml/min/nmol P450, respectively). M5 was the predominant metabolite generated by CYP3A7 and human fetal liver microsomes (HFLMs) with approximately 96% relative abundance. M5 was also the dominant metabolite generated by CYP3A4, CYP3A5, and adult liver microsomes; however, M1-M4 were also present, with up to 15% relative abundance. CYP3A7 protein levels in HFLMs were highly correlated with glyburide Clint, 16α-OH DHEA formation, and 4`-OH midazolam formation. Likewise, glyburide Clint¬ was highly correlated with 16α-OH DHEA formation. Fetal demographics as well as CYP3A5 and CYP3A7 genotype did not alter CYP3A7 protein levels or glyburide Clint. These results indicate that human fetal livers metabolize glyburide predominantly to M5 and that CYP3A7 is the major enzyme responsible for glyburide metabolism in human fetal livers.

Biography

Qingcheng Mao is an Associate Professor of Pharmaceutics at the University of Washington, Seattle, Washington. He received his PhD in Biochemistry from the University of Berne in Switzerland, and completed Postdoctoral training at the University of North Carolina and Queen's University in Canada before joining the faculty of the University of Washington in 2002. His research mainly focuses on mechanistic understanding and prediction of drug/xenobiotic disposition during pregnancy including fetal exposure to drugs and xenobiotics. He has published over 50 peer-reviewed papers and has been serving as an Editorial Board Member for "*Drug Metabolism and Disposition*".

qmao@u.washington.edu