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Of pregnant women and mice: Maternal-fetal disposition of glyburide during pregnancy and implications for the treatment of gestational diabetes mellitus

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Gestational diabetes mellitus is a major complication of human pregnancy. The clearance (CL) of glyburide, an oral anti-diabetic drug, increases 2-fold in pregnant women during late gestation versus non-pregnant controls. However, the mechanism behind this pharmacokinetic change has not been fully understood. Therefore, in the present study,we examined gestational age-dependent changes in maternal-fetal pharmacokinetics (PK) of glyburide and metabolites in a pregnant mouse models. Non-pregnant and pregnant FVB mice were given glyburide by retro-orbital injection. Maternal plasma was collected over 240 min on gestation days (gd) 0, 7.5, 10, 15 and 19; fetuses were collected on gd 15 and 19. Glyburide and metabolites were quantified using HPLC-MS, and PK analyses were performed using a pooled data bootstrap approach. It was found that maternal CL of glyburide increased ~50% on gd 10, 15, and 19 compared to non-pregnant controls. Intrinsic clearance (CL_{int}) of glyburide in maternal liver microsomes also increased as gestation progressed. Although total fetal exposure to glyburide was < 5% of maternal plasma exposure, it doubled on gd 19 compared to gd 15. This is the first evidence of gestational age-dependent changes in glyburide PK. Increased glyburide clearance during pregnancy is attributable to increased hepatic metabolism. In the mouse model, fetal exposure to glyburide is gestational age-dependent, which can be explained by gestational-age dependent expression in the placenta of BCRP, a drug transporter that mediates efflux of glyburide from the fetal compartment back to the maternal circulation. These results suggest that adjusting maternal glyburide dosing regimens according to gestational age should be considered to achieve optimal efficacy and safety of the drug if the same PK changes occur in pregnant women.

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