Title: Population pharmacokinetics of delamanid in adults treated for rifampicin-resistant tuberculosis: effect of pregnancy.

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Background and introduction: Delamanid is a WHO-recommended drug for the treatment of RR-TB [1]. Delamanid has a terminal half-life of 30-38 h and is mainly metabolized by albumin into DM-6705, which exhibits a longer half-life of 5-13 days [2], [3]. The pharmacokinetics (PK) of delamanid and DM-6705 in adults are well described [3]–[5], although no PK information is currently available for pregnant women. We developed a joint model of delamanid and DM-6705 in patients with RR-TB, and evaluated the effect of pregnancy, body size, HIV status, and albumin concentrations on delamanid exposure.

Methods: We pooled data from two studies in South African adults treated for RR-TB with regimens including delamanid 100 mg twice daily, administered orally. Blood samples were drawn pre-dose, and at 2, 4, 6, 8, 10, and 24 h post-dose. Delamanid and DM-6705 concentrations were assayed using HPLC-MS/MS, both with a lower limit of quantification of 0.001 mg/L. In pregnant women, sampling was performed during the third trimester and again approximately 6-weeks postpartum. Albumin concentrations were measured close to the respective pharmacokinetic visits. The data were analysed using non-linear mixed effects modelling in NONMEM. Allometric scaling of all disposition parameters, including those for the metabolite was tested using either total body weight or fat-free mass (FFM) [6]. We assessed the effect of covariates on the PK of delamanid and DM-6705 including pregnancy, albumin, HIV status, and morning versus evening dosing.

Results: PK samples were available for 24 participants. The median (range) age was 34 (19-60) years, weight 55 (37-104) kg, and albumin concentrations 29 (20-43) g/L. Fifteen (63%) participants had HIV, mostly treated with dolutegravir-based antiretroviral therapy. Of the 16 female participants included, 7 (44%) were pregnant, of whom 4 (57%) contributed matched antepartum and postpartum PK profiles. Albumin concentrations were 3.40% lower in pregnant women compared to non-pregnant participants. Delamanid and DM-6705 PK were best described by two-compartment disposition models. The typical values for clearances, best allometrically scaled using weight, were 33.7 L/h for delamanid, and 137 L/h for DM-6705. We found an increase of 25% in bioavailability of the evening dose compared with the morning dose of delamanid. Notably, no statistically significant effect of pregnancy, albumin, or HIV status was found on the PK of delamanid or DM-6705.

Conclusions: We developed a joint model, which adequately described the PK of delamanid and its main metabolite DM-6705. Our findings are in line with previous research [4], [5], highlighting total body weight as a better body size descriptor for drug disposition than FFM. The observed values for clearances were comparable to those reported in adult populations [4], [5]. Similarly, our study aligns with prior reports indicating a higher bioavailability for the evening dose, possibly attributable to variations in absorption of delamanid influenced by food quantity and composition [4], [5]. Reassuringly, no pregnancy effect was found on the PK of delamanid or DM-6705, thus alleviating concerns for dose adjustments in pregnancy – although additional research with a larger sample size of pregnant women is required.

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