International TB workshop 2024 Abstract Submission

Pharmacokinetics and dosing of dispersible moxifloxacin formulation in children with rifampicin-resistance tuberculosis

Yuanxi Zou1, Megan Palmer2, Anneke Hesseling2, Mats O Karlsson1, Paolo Denti3, Anthony J. Garcia-Prats 2,4, Elin M Svensson1,5

Institution

1) Department of Pharmacy, Uppsala University, Uppsala, Sweden
2) Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University
3) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa
4) Department of Pediatrics, University of Wisconsin-Madison, Madison, Wisconsin, USA
5) Department of Pharmacy, Radboud University Medical Center, Nijmegen, The Netherlands

(Limit for main text below (w/o reference):500/500 words)

Objectives

Moxifloxacin is a priority drug for the treatment of rifampicin-resistant tuberculosis (RR-TB). The standard 400mg tablet formulation is poorly palatable and non-dispersible, posing difficulties for accurate dosing in young children. It has been previously reported that pediatric exposures are substantially lower than in adults given the World Health Organization (WHO) recommended doses. We assessed the pharmacokinetics (PK) of a new 100mg child-friendly dispersible-tablet formulation of moxifloxacin against the standard tablet formulation in children treated for RR-TB and evaluated the dosing recommendations for moxifloxacin in children.

Methods

The CATALYST study was a multisite trial to investigate the new child-friendly formulations of TB drugs including moxifloxacin. Participants <15 years were enrolled in South Africa, India, and the Philippines. All participants underwent a first study visit (PK1) while taking the standard formulation, then switched to the new dispersible formulation at the second visit (PK2) after PK1, both following WHO-guided dosing. At each visit, six blood samples were drawn over 24h.

The data were analyzed with nonlinear mixed effect modelling, using a published model as starting point developed by Radtke *et.al.* from children with RR-TB. Covariates tested included formulation type, metabolic maturation with age, HIV status, and nutritional measures. To compare with the standard bioequivalence criterion of 80-125%, a 90% confidence interval (CI) of the formulation effect on bioavailability in the final model was obtained with log-likelihood profiling (LLP). Simulations were made to evaluate the current WHO pediatric dosing and an alternative higher dosing (Radtke dosing) by comparing area under concentrations ($AUC_{0\text{-}24}$) to adult values for efficacy and max concentration (C_{max}) for safety. The reference value (median with 95% population coverage for $AUC_{0\text{-}24}$ and C_{max}) was summarised by weighting 10 adult studies where the standard dose 400mg daily was given.

Results

Thirty-six children were enrolled with 16 <15kg and 7 <2years. In total, 434 observations were obtained. The final model was a two-compartment model with first-order elimination. Three transit compartments captured the absorption described by mean absorption time (MAT); interoccasion variability was introduced on bioavailability and MAT to account for multiple dosing occasions in the study; interindividual variability was included on clearance. All disposition parameters were allometrically scaled using weight with fixed theoretical factors. No other covariate was found significant.

The new formulation was not significantly different in bioavailability or MAT. The estimated bioavailability ratio of the new to standard formulations was 105 (LLP-CI, 95-115) %, fulfilling the preset criterion. With the final model, the dosing simulation showed that the current WHO pediatric dosing yielded exposures similar to the summarised adult level for children >10kg, but lower exposures in the smallest children. The Radtke doses were predicted to generate relatively high exposures compared to the summarised adult level.

Conclusions

The new 100mg dispersible formulation of moxifloxacin has similar PK to the standard 400mg non-dispersible formulation in children with RR-TB across three countries. The findings support the use of the new formulation of moxifloxacin in children. Simulations with our updated model suggest that children below 10kg may benefit from increased doses of WHO recommendations.