Drugs for treatment and prevention, and other novel therapies

OC - (8510) - BIOTRANSFORMATION OF PRAZIQUANTEL FOR THE PHARMACOKINETIC OPTIMIZATION OF PRAZIQUANTEL USE IN MASS DRUG ADMINISTRATION AND DEVELOPMENT OF NEW PEDIATRIC FORMULATIONS.

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_Beckground:_ Praziquantel (PZQ) is the only drug available for the treatment of all forms of schistosomiasis. New pediatric formulations for the active enantiomer R-PZQ and the racemate PZQ are currently under development. There is however limited drug metabolism and pharmacokinetic data on PZQ available to support these initiatives. Detailed knowledge of PZQ metabolism will enable the use of PBPK modeling to determine appropriate doses for the new formulations in pediatric patients and to predict risks for drug-drug interactions in mass drug administration.

_Methods:_ Biotransformation studies on PZQ were conducted in human liver microsomes and recombinant CYPs. Structure elucidation was inferred from mass spectra. Enzyme kinetic studies to determine the Michaelis-Menten kinetics, Km and Vmax, of the formation of the main metabolites and analysis of clinical samples were determined by LC-MS/MS.

_Results:_ CYP reaction phenotyping studies with HLM and r-CYPs indicate major involvement of CYP1A2, 2C19, 2D6 and 3A4/5 in the metabolism of R- and S-PZQ. Biotransformation studies showed that PZQ is metabolized to cis-4-OH-PZQ mainly by CYP1A2 and CYP2C19. CYP3A4/5 metabolizes PZQ to a mono-hydroxyl metabolite (X-OH-PZQ) whilst CYP2D6 metabolizes PZQ to minor novel mono-hydroxyl metabolite (Y-OH-PZQ) both pending structural elucidation by NMR. R-PZQ was more rapidly cleared than S-PZQ with variable interindividual AUC and Cmax.

_Discussion & Conclusions:_ The differential role of CYP1A2 & CYP2C19 and of CYP3A4 & CYP3A5 in the formation the 4-OH-PZQ and the novel X-OH-PZQ respectively are intriguing findings as this has not been reported before in humans. _In vitro_, cis and not trans 4-OH-PZQ formation has been observed contrary _in vivo_ reports in humans which indicate trans 4-OH-PZQ as the main metabolite. The data will enable us to understand the rapid clearance of PZQ and predict potential drug-drug-gene interactions which may explain the inter-individual variability of PZQ pharmacokinetics.