Title: *Pemba Island, Tanzania, versus Côte d'Ivoire – Population effect on apparent clearance of active albendazole metabolites*

Author: Veshni Pillay-Fuentes Lorente (1), Jacinta Nwogu (2), Britta Steffens (3), Dominic Bräm (3), Daniela Hofmann (4,5), Marc Pfister (3,6), Jennifer Keiser (4,5)

Institution: (1) Stellenbosch University, Cape Town, South Africa; (2) Lead City University, Ibadan, Nigeria; (3) Pediatric Pharmacology and Pharmacometrics Research, University of Basel Children's Hospital (UKBB), University of Basel, Basel, Switzerland; (4) Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, University of Basel, Basel, Switzerland; (5) University of Basel, Basel, Switzerland; (6) Department of Clinical Research, University of Basel and University Hospital Basel, Basel, Switzerland

Abstract

Introduction: Soil transmitted helminth infections affect an estimated 24% of the world's population [1]. Communities with poor access to sanitation and proper hygiene in tropical and sub-tropical areas are most infected with sub-Saharan Africa being reported as one of the highest prevalent areas [1,2]. Trichuriasis, a soil transmitted helminth infection caused by the human whipworm, *Trichuris trichura*, is a public health problem, particularly in children [2], As proposed by The World Health Organisation, morbidity related to worm burden may potentially be reduced by periodic medicinal treatment of individuals at high risk living in endemic areas [1]. Albendazole and ivermectin are anti-helminthic agents used in the treatment of trichuriasis. Studies conducted in Côte d'Ivoire and Pemba Island, Tanzania have reported different cure rates on combination therapy of albendazole and ivermectin with Pemba Island showing higher cure rates compared to Cote d'Ivoire [3]. Goal of this pharmacometric work was (i) to develop a population pharmacokinetic model for albendazole and its active metabolites (albendazole sulfoxide and albendazole sulfone), and (ii) to explore the population effect and comedication effects of ivermectin on the pharmacokinetics of albendazole.

Methods: Pooled pharmacokinetic (PK) data from two single dose clinical studies in adolescents infected with trichuriasis in Côte d'Ivoire and Pemba Island were used to develop a pharmacometric model. Participants received either albendazole, 400 mg alone or albendazole, 400 mg in combination with ivermectin, 200 mcg/kg. Blood samples were collected up to 27 and 48 hours post-dose for Côte d'Ivoire and Pemba Island, respectively, and albendazole and its two active metabolites (albendazole sulfoxide and albendazole sulfone) concentrations were determined with LC/MS-MS. Population effect (Côte d'Ivoire versus Pemba Island) and comedication (ivermectin) were evaluated as covariates on clearance parameters. Non-linear mixed effects modelling was conducted using Monolix Suite 2021R2 (Lixoft, Orsay, France).

Results: A population PK model was developed for two active albendazole metabolites (albendazole sulfoxide, albendazole sulfone). Parent drug (albendazole) serum concentrations were excluded from the model development due to a large portion of values below limit of quantification (35%). Concentration-time profiles were best described with a two-distribution compartment on albendazole sulfoxide, one distribution compartment on albendazole sulfone, and a transit compartment assuming first order oral absorption and linear elimination. Co-administered ivermectin did not influence population PK of albendazole. Interestingly, apparent clearance of

albendazole sulfoxide and albendazole sulfone were 75% and 46% higher in the Pemba Island population, respectively.

Conclusions: Addition of ivermectin to albendazole in the treatment of Trichuriasis had no effect on albendazole PK. A population difference on apparent clearance of albendazole sulfoxide and albendazole sulfone exists and could in part be an explanation for the difference in cure rates between the two countries. Since albendazole sulfoxide is excreted through biliary elimination [4], more active metabolite becomes available at the site of action which is the gastrointestinal tract. Studies evaluating pharmacodynamic aspects and resistance patterns are needed to further explain observed differential cure rates in the two investigated populations.

Number of characters (including spaces) **3,512**

References:

[1] https://www.who.int/news-room/fact-sheets/detail/soil-transmitted-helminth- infections
[2] https://www.cdc.gov/parasites/whipworm/epi.html
[3] Hürlimann, E., Keller, L., Patel, C., Welsche, S., Hattendorf, J., Ali, S. M., et al. (2022). Efficacy and safety of co-administered ivermectin and albendazole in school-aged children and adults infected with Trichuris trichiura in Côte d'Ivoire, Laos, and Pemba Island, Tanzania: a double-blind, parallel-group, phase 3, randomised controlled trial. The Lancet Infectious Diseases, 22(1), 123-135.
[4] https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=0a4ce2e1-db3d-4b24-98aa-0519fbaff547&type=display