Pharmacometric modelling to describe pharmacokinetics and exposure -response of ivermectin in adolescent patients infected with *Trichuris trichiura*

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Introduction

- Soil-transmitted helminth infections are a major public health challenge in many tropical and subtropical low-income regions.[1]
- Monotherapy with albendazole has shown good efficacy for roundworm and hookworm but not for *Trichuris trichiura* (whipworm) infection, for which the combination with ivermectin has been explored.[2]
- Studies have shown that the efficacy of the combination therapy was significantly higher in Tanzania (Pemba Island) than in Côte d'Ivoire.[3]

Objectives

- To investigate the difference between the population pharmacokinetics (popPK) of ivermectin when combined with albendazole in Tanzania and Côte d'Ivoire, to determine if an exposure-response analysis of ivermectin in combination with albendazole could explain the low efficacy in Côte d'Ivoire, and to explore, using simulations, whether higher doses might have different outcomes.

Methods

- A total of 110 microsamples were collected in the framework of a randomized controlled trial from 24 adolescents with *T. trichiura* infection in Côte d'Ivoire and Tanzania, who were treated with a combination therapy of ivermectin and albendazole.[4,5]
- A popPK model was developed with the Monolix 2023R1 software.
- A regression analysis was performed to investigate the relationship between egg reduction in the faeces and different exposure metrics of ivermectin and albendazole for each country.
- Using simulations, exposure level of the current ivermectin dose (200 µg/kg) was compared to higher doses of ivermectin (400 and 600 µg/kg).

Results PK

Figure 1: Concentration of ivermectin versus time stratified by study site: (A) linear scale. (B) semi-log scale.

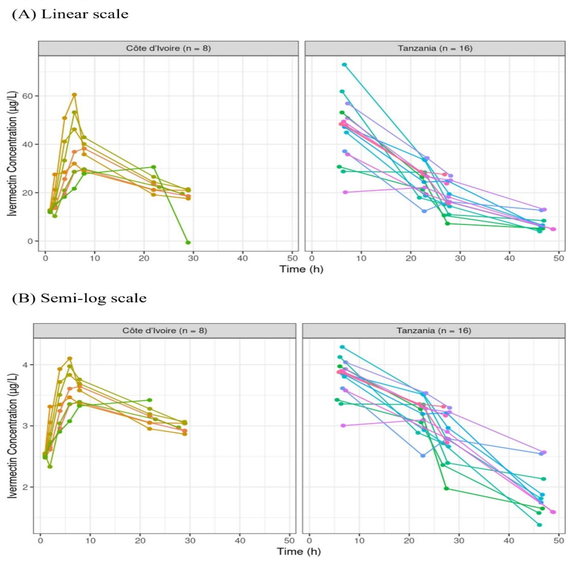
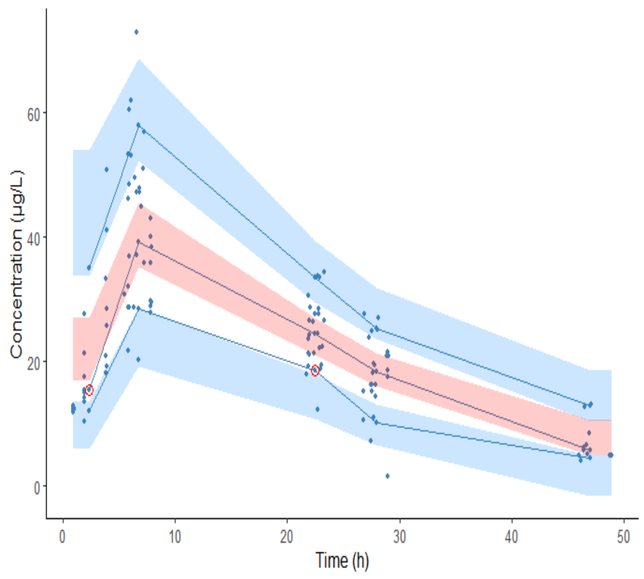


Figure 2: Visual predictive check of plasma ivermectin concentrations.



Conclusion

- A one-compartment model with first-order absorption and first-order elimination fitted the PK data of ivermectin collected from adolescent patients with *T. trichiura* in Tanzania and Côte d'Ivoire with good adequacy, and the PK parameters were not significantly different across both study sites.
- There was a relationship between relative egg count and peak concentration of ivermectin co-administered with albendazole in Côte d'Ivoire, although not statistically significant.
- Model-based simulations indicate that higher doses such as 400 and 600 µg/kg may be associated with reduced egg count.

References

1. Pullan & Brooker,2012. *Parasites and Vectors*. doi:10.1186/1756-3305-5-81
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3. Hürlimann *et al*, 2022. *Lancet Infect Dis*. doi:10.1016/S1473-3099(21)00421-7
4. Sprecher *et al*., 2023. *Clin Infect Dis*. doi:10.1093/cid/ciad387
5. Welsche et al., 2023. *Lancet Infect Dis*. doi:10.1016/S1473-3099(22)00589-8

Model-based simulations indicate that *higher doses* such as 400 and 600 µg/kg may be associated with reduced egg count

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Results PK/egg counts

Figure 3: Simulated peak concentration of ivermectin and (B) Simulated relative egg counts with doses 200, 400, and 600 µg/kg ivermectin.

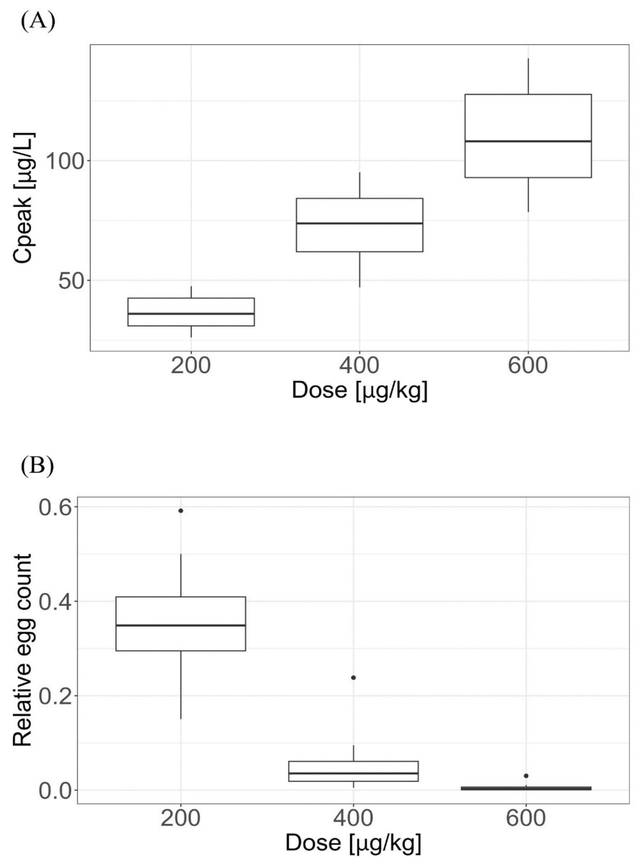

Table 2: Bivariate analysis of covariates with cure

Covariate	Cure		P-value
	No	Yes	
Sex			
Male	10 (62.5)	6 (37.5)	0.673
Female	4 (50.0)	4 (50.0)	
Study site			
Côte d'Ivoire	8 (100.0)	0 (0)	0.006
Tanzania	6 (37.5)	10 (62.5)	
Age (years)	15.21 ± 2.04	15.90 ± 1.60	0.371
Body weight (kg)	46.41 ± 10.61	51.37 ± 8.29	0.235

Table 3: Regression analysis of ivermectin and albendazole exposure

Parameters	Estimate	P-value
β_0	2.81	0.21
β_1	0.07	0.20
β_2	0.002	0.48
$\bar{\beta}_0$	2.16	0.26
$\bar{\beta}_1$	0.05	0.23
$\bar{\beta}_2$	0.07	0.35

Table 1: Parameter Estimates for the Final Population Pharmacokinetic Model

Parameter	Estimate (%RSE)
Population parameter	
K_a (h^{-1})	0.26 (11.7)
V/F (L)	162.43 (9.7) x (WT/50)
Cl/F (Lh^{-1})	7.82 (4.9) x $(WT/50)^{0.75}$
Inter-individual variability (IIV, %)	
IIV k_a	10.0 (fixed)
IIV V/F	29.0 (23.7)
IIV Cl/F	16.8 (42.0)
Residual error	
Additive error	3.21 (42.6)
Proportional error	0.18 (32.2)