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Background

- Ivermectin has been used for treatment of several parasitic diseases, such as onchocerciasis, Lymphatic Filariasis, and scabies.
- Ivermectin has been shown to have promising mosquito killing properties.
- Ivermectin has been shown to have altered mosquito-lethal effects after administration to human volunteers [1].
- Ivermectin could be used in studies with the aim to eradicate malaria.

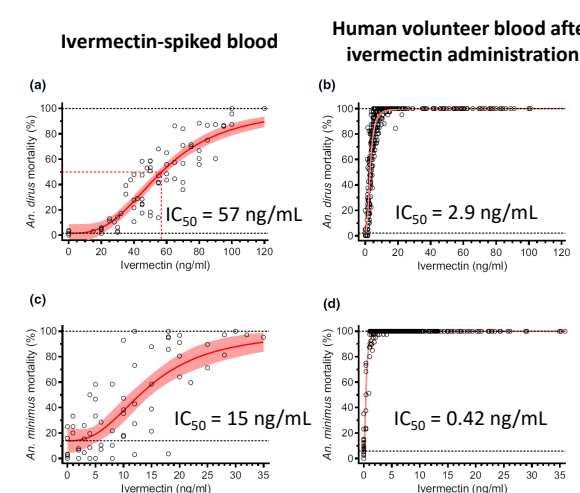


Fig 1. Relationship between mosquito mortality and ivermectin concentration after membrane (a and c) and direct feeding (b and d) in *Anopheles dirus* (a and b) and *Anopheles minimus* (c and d) [1].

Objectives

- Develop a pharmacokinetic-pharmacodynamic model describing mosquito mortality after treatment with ivermectin
- Simulate different treatment regimens

Methods

- The model was constructed using data from two different healthy volunteer trials conducted at Clinical Therapeutic Unit at the faculty of tropical medicine, Mahidol University, Thailand.
- The first study was a drug-drug interaction trial with 16 healthy volunteers designed to evaluate interactions between ivermectin and different antimalarials. A single oral dose of ivermectin was given (400 µg/kg) on four separate occasions.
- The second was ivermectin metabolite trial with 10 healthy volunteers. A single oral dose of ivermectin was given (400 µg/kg).
- Dense pharmacokinetic samples were collected for 10 (drug-drug interaction trial) and 41 days (metabolite trial).
- Concentrations of ivermectin and its metabolites (M1, M3, and M6) were quantified [2].
- The pharmacokinetic parameters were fixed when estimating the pharmacodynamic model.
- It was assumed that the sum of ivermectin and three of its metabolites drove the mosquito lethal effect.
- Effects on *Anopheles dirus* and *Anopheles minimus* were evaluated in parallel for up to 15 days after drug administration.
- The mosquito mortality at day 10 after blood meal was used as the pharmacodynamic outcome.
- The mosquito mortality was modeled with sigmoid Emax model with estimated baseline.
- All modelling and simulation was carried out in NONMEM v7.43.

Results & Discussion

- The pharmacokinetic of ivermectin was initially evaluated alone.
- Potential drug-drug interactions had been evaluated in an earlier project using data from only the drug-drug interaction study. The covariate effect was re-estimated using all data.
- Ivermectin was described by a two-compartment disposition model with transit absorption and body weight as an allometric function on all clearance and volume parameters. Concomitant treatment with dihydroartemisinin-piperquine increased the absorption of ivermectin (increased bioavailability by 33% and mean transit time by 24%).
- The model for ivermectin was fixed and the metabolite data was added. M1 and M3 were described by two-compartment disposition models and M6 by a one-compartment disposition model.

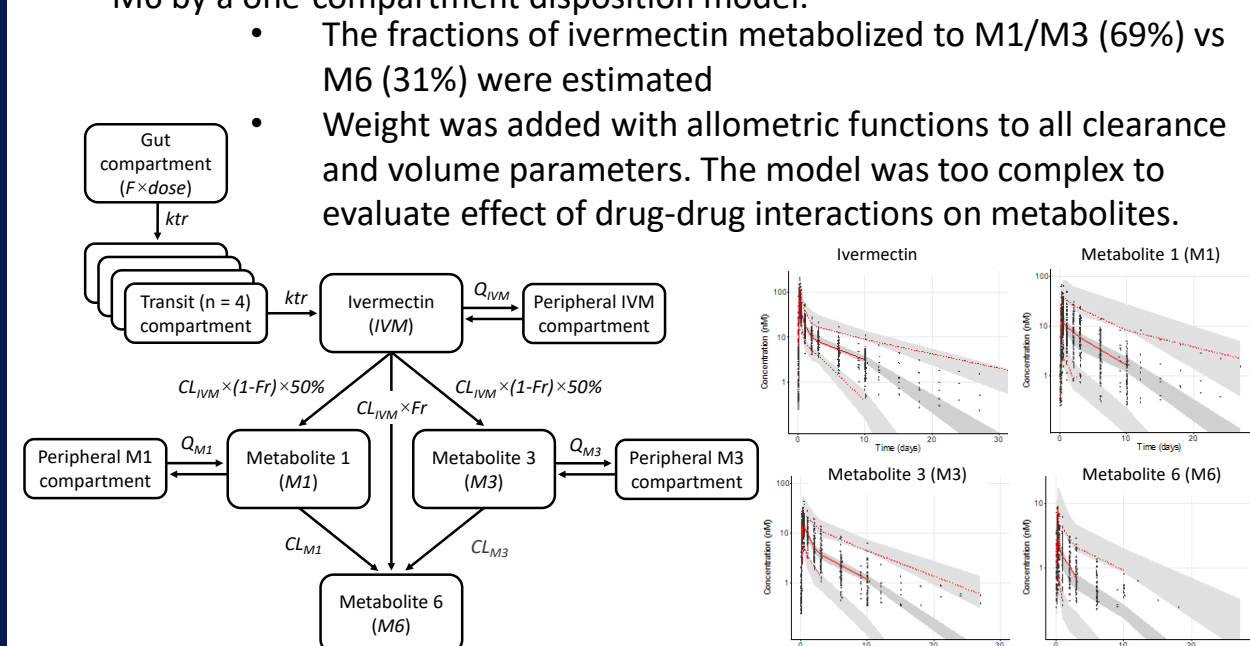


Fig 2. Final pharmacokinetic model

- Mosquito mortality was successfully described by the sigmoid Emax model.
- Feeding method had an impact on baseline mosquito mortality for *An. dirus* (lower baseline after membrane feeding).
- An. minimus* had slightly lower EC₅₀ after membrane feeding compared to direct feeding, and ivermectin was twice as effective in killing mosquitos in males compared to females.

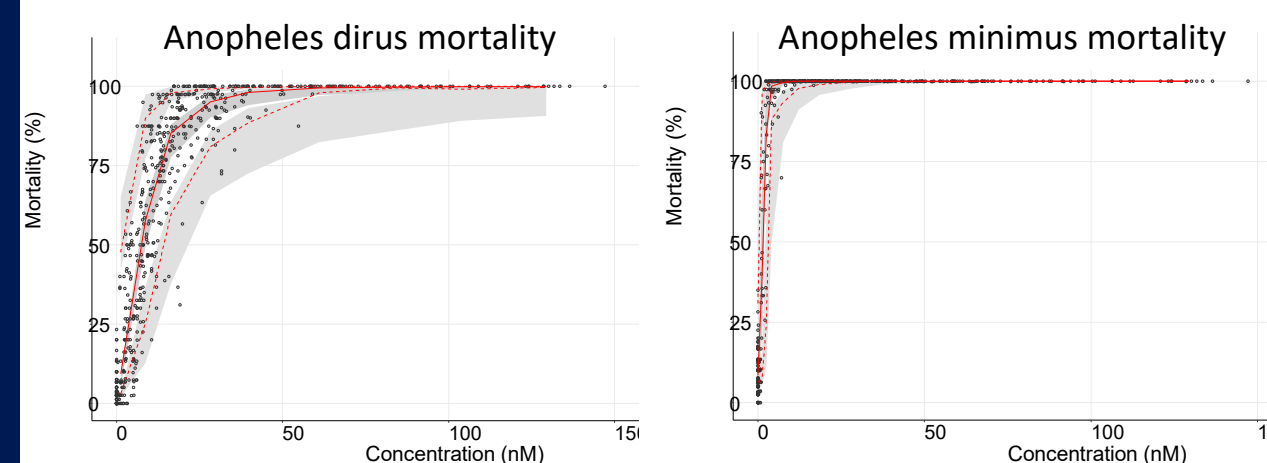
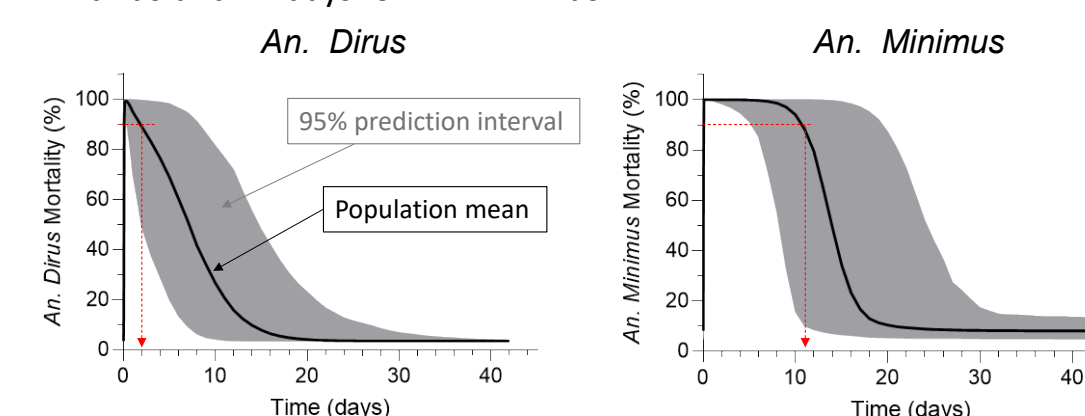


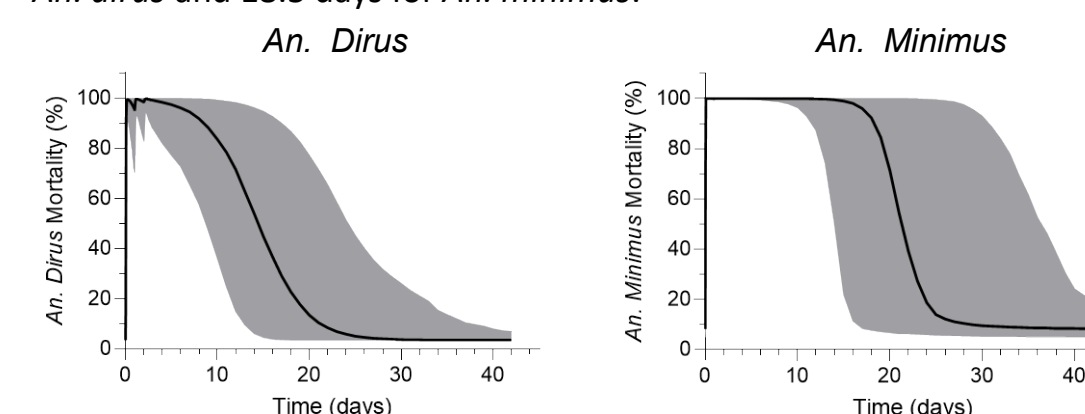
Fig 3. Visual predictive check of the final pharmacokinetic-pharmacodynamic model

Simulations

- After administration of a single oral dose of ivermectin (400 µg/kg) simulations predicted a sustained killing (>IC₉₀) for an average of 2 days for *An. dirus* and 11 days for *An. minimus*.



- After administration of 3-day daily oral dose of ivermectin (400 µg/kg/day) simulations predicted a sustained killing (>IC₉₀) for an average of 8.7 days for *An. dirus* and 18.5 days for *An. minimus*.



Conclusions

- The pharmacokinetic-pharmacodynamic properties showed rapid killing of both *An. dirus* and *An. minimus*, but *minimus* was more sensitive.
- A three-day treatment of ivermectin resulted in sustained killing of mosquitos for more than 7 days according to simulations from the final pharmacokinetic-pharmacodynamic model
- The developed model can help guide future mass drug administration trials with the aim of malaria eradication.

References

- [1] Kobylinski KC et al. Safety, Pharmacokinetics, and Mosquito-Lethal Effects of Ivermectin in Combination With Dihydroartemisinin-Piperaquine and Primaquine in Healthy Adult Thai Subjects. Clin Pharmacol Ther. 2020
- [2] Tiphara P et al. Identification of the metabolites of ivermectin in humans. Pharmacol Res Perspect. 2021

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