**Drivers and Determinants of Variation in Albendazole Pharmacokinetics: Insights from a Systematic Review and Meta-Analysis**

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In this supplementary document we outline the methods and data used to explore and analyse the drivers of variation in Albendazole (and Albendazole Sulfoxide) pharmacokinetics. In Supplementary Information 1, we present further information on the systematic review conducted, including details of the collated references and information on the metadata (population characteristics, infection status, co-administration of other drugs etc) available for each study. In Supplementary Information 2, we detail the statistical methodologies employed to process this extracted data whose output forms the basis for the results presented in the main text. This includes further details on the pharmacokinetic model, the Bayesian fitting process and the linear regression relating results from the fitting to study metadata. Finally, in Supplementary Information 3, we present an array of figures to support the work detailed in the main text.

**Supplementary Information 1: Systematic Review References & Associated Metadata**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **#** | **Reference** | **Alb** | **AlbSO** | **Dose** | **Age** | **Weight** | **Sex** | **State** | **Disease** | **Drugs** | **n** |
| 1 | Awadzi 2003 | 0 | 1 | 400 | 36 | 56 | 1 | Fasted | Onchocerciasis | None | 14 |
| 2 |  | 0 | 1 | 400 | 39 | 61.5 | 1 | Fasted | Onchocerciasis | Ivermectin | 14 |
| 3 | Awadzi 2004 | 0 | 1 | 400 | 36 | 56 | 1 | Fasted | Onchocerciasis | None | 14 |
| 4 |  | 0 | 1 | 400 | 43 | 53.4 | 1 | Fasted | Onchocerciasis | Levamisole | 22 |
| 5 | Awadzi 1994 | 0 | 1 | 1200 | 34 | NA | 1 | Fatty Meal | Onchocerciasis | None | 14 |
| 6 |  | 0 | 1 | 1200 | 34 | NA | 1 | Fasted | Onchocerciasis | None | 14 |
| 7 | Ceballos 2018 | 1 | 1 | 400 | 34 | 64 | 0.5 | Fatty Meal | None | None | 8 |
| 8 | Chen 2004 | 1 | 1 | 400 | NA | NA | 1 | NA | None | None | 20 |
| 9 | Chhonker 2018 | 1 | 1 | 400 | NA | NA | NA | Fasted | NA | DEC & Ivermectin | 7 |
| 10 | Corti 2009 | 1 | 1 | 400 | 31 | 73 | 1 | Fasted | None | None | 8 |
| 11 |  | 1 | 1 | 400 | 31 | 73 | 1 | Fasted | None | Short Ritonavir | 8 |
| 12 |  | 1 | 1 | 400 | 31 | 73 | 1 | Fasted | None | Long Ritonavir | 8 |
| 13 | Cotting 1990 | 0 | 1 | 400 | NA | NA | 0 | Fatty Meal | Echinococcosis | None | 1 |
| 14 | Jung 1992 | 0 | 1 | 998 | 45 | 67 | 0.75 | Fasted | Neurocysticercosis | None | 8 |
| 15 | Jung 1997 | 0 | 1 | 393 | 7 | 26.2 | 0.63 | Fatty Meal | Neurocysticercosis | None | 8 |
| 16 | Kitzman 2002 | 1 | 1 | 400 | NA | NA | NA | NA | None | None | 1 |
| 17 | Lange 1988 | 0 | 1 | 400 | 43 | 70.8 | 0.83 | Fatty Meal | Echinococcosis | None | 6 |
| 18 |  | 0 | 1 | 400 | 43 | 70.8 | 0.83 | Fasted | Echinococcosis | None | 6 |
| 19 | Monteiro 2010 | 0 | 1 | 400 | 26 | 64.2 | 0.44 | Fasted | None | Praziquantel | 9 |
| 20 |  | 0 | 1 | 400 | 26 | 64.2 | 0.44 | Fasted | None | None | 9 |
| 21 | Marriner 1986 | 0 | 1 | 400 | 27 | 67.4 | 0.5 | NA | None | None | 8 |
| 22 |  | 0 | 1 | 400 | NA | NA | 0.75 | Fatty Meal | None | None | 4 |
| 23 |  | 0 | 1 | 400 | NA | NA | 0.75 | Fasted | None | None | 4 |
| 24 | Mirfazaelian 2003 | 0 | 1 | 800 | 30 | 67.7 | 0.67 | Fasted | None | None | 12 |
| 25 | Mirfazaelian 2002 | 0 | 1 | 400 | 33 | 64 | 0.6 | Fasted | None | None | 10 |
| 26 |  | 0 | 1 | 800 | 33 | 64 | 0.6 | Fasted | None | None | 10 |
| 27 |  | 0 | 1 | 1200 | 33 | 64 | 0.6 | Fasted | None | None | 10 |
| 28 | Na-Bangchang 2006 | 0 | 1 | 400 | 21 | 53.1 | 0.52 | Fasted | None | Ivermectin | 23 |
| 29 |  | 0 | 1 | 400 | 21 | 53.1 | 0.52 | Fasted | None | Ivermectin & Praziquantel | 23 |
| 30 | Nagy 2002 | 0 | 1 | 690 | 20 | 69 | 1 | Fatty Meal | None | None | 6 |
| 31 |  | 0 | 1 | 690 | 20 | 69 | 1 | Fasted | None | None | 6 |
| 32 |  | 0 | 1 | 690 | 20 | 69 | 1 | Fasted | None | None | 6 |
| 33 |  | 0 | 1 | 690 | 20 | 69 | 1 | Fasted | None | Cimetidine | 6 |
| 34 | Okelo 1993 | 0 | 1 | 467 | 9 | 26.8 | 1 | NA | Hydatid | None | 5 |
| 35 | Pengsaa 2004 | 1 | 1 | 400 | 8.5 | 21 | 0.7 | Fatty Meal | Giardiasis | None | 10 |
| 36 |  | 1 | 1 | 400 | 9.1 | 24 | 0.7 | Fatty Meal | Giardiasis | Praziquantel | 10 |
| 37 | Rigter 2004 | 0 | 1 | 400 | 29 | 83 | 0.4 | Fasted | None | None | 10 |
| 38 | Schipper 2000 | 0 | 1 | 385 | 20 | 77 | 1 | Fasted | None | None | 6 |
| 39 |  | 0 | 1 | 770 | 20 | 77 | 1 | Fasted | None | None | 6 |
| 40 |  | 0 | 1 | 1540 | 20 | 77 | 1 | Fasted | None | None | 6 |
| 41 |  | 0 | 1 | 2310 | 20 | 77 | 1 | Fasted | None | None | 6 |
| 42 |  | 1 | 1 | 1540 | NA | NA | 1 | Fasted | None | Cimetidine | 1 |
| 43 | Schulz 2019 | 0 | 1 | 400 | 16 | 55 | 1 | Fatty Meal | Hookworm | Oxantel Pamoate | 10 |
| 44 | Shenoy 2002 | 1 | 1 | 400 | 35 | 36.5 | 0.81 | NA | None | None | 14 |
| 45 |  | 1 | 1 | 400 | 35 | 36.5 | 0.81 | NA | None | DEC | 14 |
| 46 | Thomsen 2016 | 1 | 1 | 400 | 34 | 49 | 0.5 | Fatty Meal | Lymphatic Filariasis | DEC | 12 |
| 47 |  | 0 | 1 | 400 | 39 | 53 | 0.5 | Fatty Meal | Lymphatic Filariasis | DEC & Ivermectin | 12 |
| 48 | Mingjie 2002 | 0 | 1 | 830 | 29 | 66.4 | 1 | NA | Echinococcosis | None | 7 |
| 49 | Sarin 2004 | 0 | 1 | 600 | 32 | 59.8 | NA | Fatty Meal | None | None | 10 |
| 50 | Sergio-Mares 2005 | 0 | 1 | 800 | 25 | 62.9 | 0.56 | Fatty Meal | None | None | 16 |
| 51 |  | 0 | 1 | 800 | 25 | 62.9 | 0.56 | Fasted | None | None | 16 |
| 52 | Rathod 2016 | 0 | 1 | 400 | NA | NA | NA | Fasted | None | None | 51 |
| 53 | Delatour 1991 | 1 | 1 | 725 | NA | 72 | 1 | NA | None | None | 4 |
| 54 | Edi 2019 | 0 | 1 | 400 | 44 | NA | 0.63 | NA | Lymphatic Filariasis | DEC & Ivermectin | 32 |
| 55 |  | 1 | 1 | 400 | 36 | NA | 0.5 | NA | None | DEC & Ivermectin | 24 |

**Note:** Sex denotes the proportion of Males comprising the study i.e. 1 means that the study was carried out solely with Male participants. Dose refers to the amount of Albendazole given as a single oral dose, in milligrams (mg). NA means that the study either did not contain information on that particular factor, or the study population comprised a mixture of individuals (e.g. Healthy and Infected individuals) and no disaggregation into two distinct populations was possible. DEC stands for diethylcarbamazine.

**NOTE GIVEN THE LAST SCHIPPER TIME SERIES (#42 HERE, #55 IN EXCEL DATA) WAS ADDED LAST, MIGHT NEED TO RE-JIG THE EXCEL AROUND SO THAT IT MATCHES WHAT I’VE PUT HERE.**

**Supplementary Information 2: Description of Statistical Methodologies Utilised**

In this supplementary document we outline the methods and data used to explore and analyse the drivers of variation in Albendazole (and Albendazole Sulfoxide) pharmacokinetics. In Supplementary Information 1, we present further information on the systematic review conducted, including details of the collated references and information on the metadata (population characteristics, infection status, co-administration of other drugs etc) available for each study. In Supplementary Information 2, we detail the statistical methodologies employed to process this extracted data whose output forms the basis for the results presented in the main text. This includes further details on the pharmacokinetic model, the Bayesian fitting process and the linear regression relating results from the fitting to study metadata. Finally, in Supplementary Information 3, we present an array of figures to support the work detailed in the main text.

**Mathematical Model of Albendazole and Albendazole Sulfoxide Pharmacokinetic Dynamics**

**Brief model overview.**

**Description of the model in words. Assumptions etc etc.**

**Together this can be described using the following series of linked Ordinary Differential equations.**

A physiologically inspired pharmacokinetic model was developed in order to explore and assess the pharmacokinetic profile of Albendazole and its metabolites. Briefly, this model consists of a series of linked Ordinary Differential Equations (ODEs) describing the concentration of Albendazole and Albendazole Sulfoxide in the blood following an orally taken dose of Albendazole. It incorporates a number of pharmacokinetic phenomena relevant to Albendazole, including its well-established, limited bioavailability (thought to be a product of its poor solubility along the gastrointestinal tract20) and the extensive first-pass metabolism of Albendazole to Albendazole Sulfoxide known to occur in the liver21. This model was fitted individually to each of the 55 collated datasets using an adaptive Metropolis-Hastings based Markov Chain Monte Carlo sampling scheme. In a small number of studies, both Albendazole and Albendazole Sulfoxide blood concentrations over time were reported – where this was the case, the model was fitted to both time series simultaneously. Uninformative priors were used for each of the parameters being inferred. For each dataset, a total of 80,000 iterations were run, with the first 60,000 discarded as burn in, and leaving 20,000 iterations available for parameter inference. Further information on the exact formulation of the model and the fitting process is available in Supplementary Information: Model Construction, Fitting and Inference

where each describes the change in concentration of a metabolite in a compartment over time and where **DESCRIPTION OF PARAMETERS. Describe the use of ODIN for model running.**

**Model Fitting and Inferential Framework**

The above pharmacokinetic mathematical model was fitted within a Bayesian framework. Specifically, the model was fit to each dataset individually, using a bespoke adaptive Metropolis-Hastings Markov Chain Monte Carlo (MCMC) sampling algorithm. Prior distributions for the estimated parameters were defined as follows:

using Truncated Normal distributions in order to avoid non-sensical and negative parameters. Weakly informative priors were set over and i.e. the two parameters where further inference and regression was not being carried out. For the other parameters, , , and , uninformative priors were set.

For both Albendazole and Albendazole Sulfoxide blood concentrations, a Poisson likelihood (reflecting the assumption that the drugs are well-mixed within each of our modelled compartments) was used, such that the model likelihood could be constructed as follows:

where and represent the empirically observed blood concentrations of Albendazole and Albendazole Sulfoxide respectively at timepoint . and represent the modelled blood concentrations of Albendazole and Albendazole Sulfoxide respectively at timepoint. For each dataset, a total of 50,000 iterations of the MCMC sampling algorithm were run for purposes of model fitting and parameter inference. Half of each chain’s iterations were discarded as burn-in/the adaptive phase of the sampling, leaving a total of 25,000 iterations available for inference.

**Pharmacokinetic Parameter Estimation and Linear Regression Modelling**

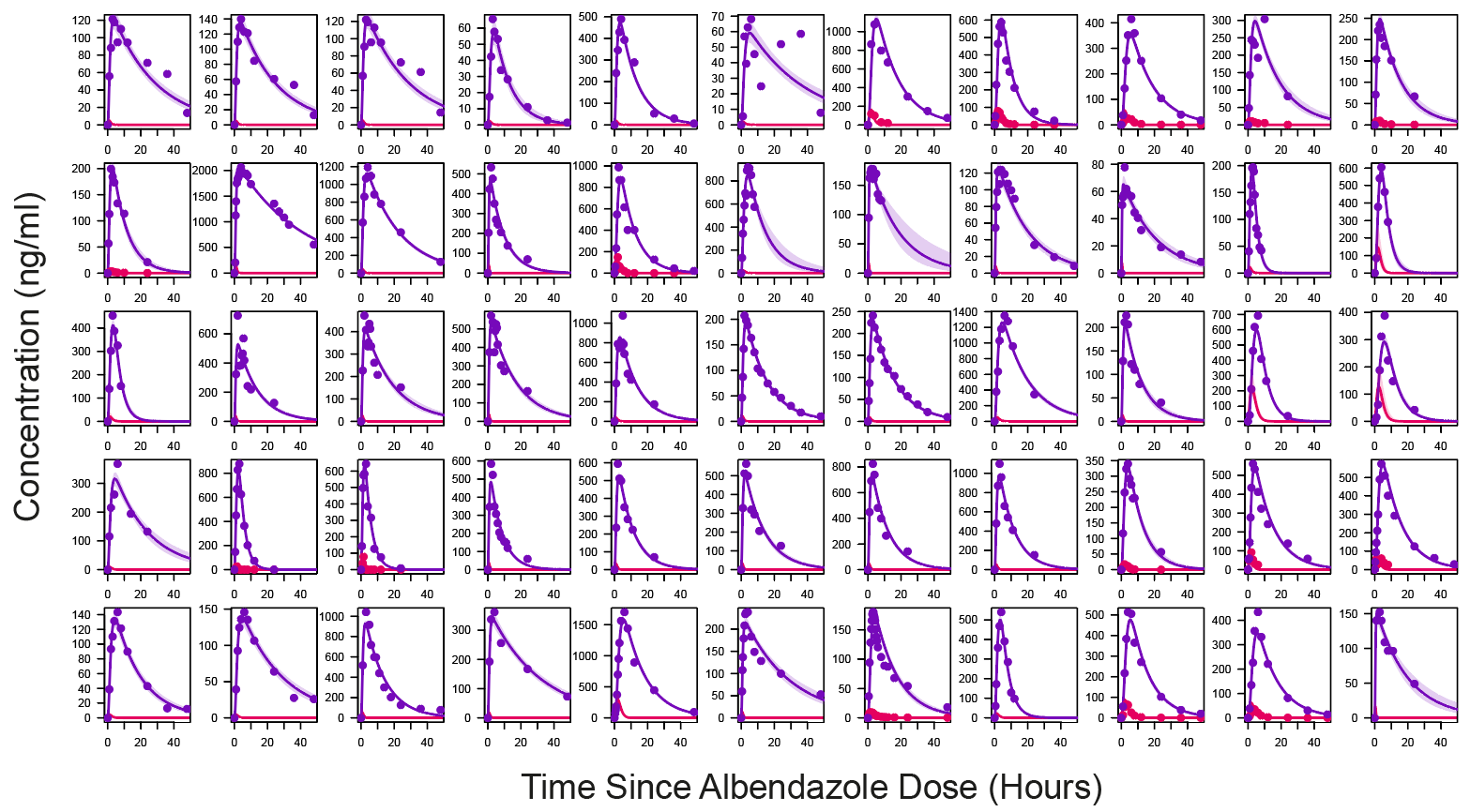
* Take the mean estimate of each parameter from the MCMC fitting. Then run using this parameter set.
  + Take Albendazole Sulfoxide Half-Life and Bioavailability. Then run the model using the parameter set and take AUC and CMax­­.
  + Collate set of PK parameters for every dataset.
* Regression analyses – univariate followed by multivariate analyses.

**Supplementary Information 3: Additional Figures and Results**

**Supplementary Table 1: Univariate Regression Outputs Relating PK Properties to Study Characteristics.** Inferred pharmacokinetic parameters, specifically Albendazole Bioavailability, Albendazole Sulfoxide Half-Life, CMax and AUC were regressed onto various characteristics of the study populations. These include Sex (defined here by the proportion of Male participants in each study), Feeding Status (describing whether individuals were Fasted or received a Fatty Meal prior to receiving the single oral dose or not), Dose (the amount of Albendazole given, in milligrams), Drug Co-Administration, Age (in years, representing the mean age of the study population), Weight (in kilograms, representing the mean weight of the study population) and Co-Infection Status (describing whether the study population consisted of healthy individuals or whether they had parasitic infections). Each of these characteristics were individually regressed onto the pharmacokinetic parameters, with the results of this univariate regression analysis presented below.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Sex** | **Feeding Status** | **Dose** | **Drug Co-Administration** | **Age** | **Weight** | **Co-Infection** |
| **Bioavailability** |  |  |  |  |  |  |  |
| **Half-Life** |  |  |  |  |  |  |  |
| **AUC** |  |  |  |  |  |  |  |
| **C­­Max** |  |  |  |  |  |  |  |

**Supplementary Figure 1: Histogram of Inferred Pharmacokinetic Parameter Values.** The model of Albendazole’s pharmacokinetic dynamics was fitted to each of the 55 time series individually using a Bayesian MCMC based framework and the mean parameter estimates of Albendazole Bioavailability and Albendazole Sulfoxide Half-Life for each time-series collated. Also, for each time series, the pharmacokinetic model was run using the mean estimates of each of the parameter values to generate a pharmacokinetic curve – from this curve, two relevant quantities, CMax (the maximum blood concentration of Albendazole Sulfoxide reached) and AUC (area under the curve, reflecting total exposure to the drug) were also calculated. Histograms of each of these parameters for each time series are displayed, specifically **(A)** Albendazole Bioavailability, **(B)** Albendazole Sulfoxide Half-Life, **(C)** CMax and **(D)** AUC.

**Figure 3: Model Fitting Results for All Time Series**

**Figure 3: Results of model fitting and calibration to data collated through the systematic review.** The systematic review identified a total of 55 time series containing information on the concentration of Albendazole and/or Albendazole Sulfoxide in the blood following treatment with a single oral dose. The pharmacokinetic model was fitted to these data individually using a Bayesian MCMC-based framework. This fitting was carried out in order to estimate the various pharmacokinetic parameters governing the model. For the results presented above, points represent empirical data and the lines represent model output, with the results for Albendazole in pink and those for Albendazole Sulfoxide in purple. Pale shaded area represents the 95% Credible Interval.