**Factors Associated With Variation in Single-Dose Albendazole Pharmacokinetics: A Systematic Review and Modelling Analysis**

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**Outline of Document**

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 and tables to support the work detailed in the main text.

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

We searched the Web of Science and PubMed databases on 4th July 2019 using the keywords “albendazole” AND (treatment\* OR dose\* OR pharma\* OR “half-life” OR “half life”) in order to identify references containing temporally disaggregated data detailing the concentration of albendazole and/or albendazole sulfoxide in the blood following treatment with a single dose of the drug. References were selected for Inclusion/Exclusion according to the following criteria:

**Inclusion Criteria:**

* Reference contains data from human subjects describing the concentration of albendazole and/or albendazole sulfoxide in the blood following receipt of a single, orally administered dose of albendazole.

**Exclusion Criteria:**

* The study was carried out in animals or *in vitro* i.e. not in humans.
* The study administered multiple doses of albendazole and does not contain information on blood drug concentration following receipt of the very first dose.
* Reference does not contain temporally disaggregated information on albendazole/albendazole sulfoxide concentrations in the blood.
* The article is not in English.

A total of 7862 records were identified, with 2172 duplicates excluding leaving 5690 unique records retained for title and abstract screening. title and abstract screening excluded 5483 references, leaving a total of 207 articles for full text screening. Studies lacking the required information on blood concentration levels over time, not in English, that utilised non-standard formulations of albendazole (e.g. oral suspension), or that had been carried out *in vitro* or in non-human subjects were subsequently excluded. A total of 32 references were subsequently retained and included for data extraction. For each reference, we extracted all relevant albendazole and albendazole sulfoxide concentration data over time that was available, yielding 92 time-series describing the evolution of blood concentrations of albendazole (n=15) and/or albendazole sulfoxide (n=92) in individuals or groups of individuals following treatment with a single dose. For each time series, we also extracted relevant metadata and characteristics of the individual/group of individuals receiving treatment. These metadata were:

* **Sex:** The sex of the individual, or composition of sexes in the case of groups of individuals. This was subsequently converted into a categorical variable based on the collated responses, with levels “Males” (where the entire population were male), “Mixture” (where the population were a mixture of males and females) and “Unclear” (where sex of the individual/group was not provided), for use in the regression analyses
* **Age:** The age of the individual, or in the case of groups of individuals, the average age of the individual. This was subsequently converted into a binary indicator according to whether the age of individuals was >18 (“Adults”) or not (“Children”), for use in the regression analyses.
* **Dose Amount:** Both thetotal dose amount (in mg) and the dose per kilogram of bodyweight was collected. Where the latter was not directly provided but the weight of participants provided, the dose per kilogram of bodyweight was calculated manually.
* **Feeding State:** Whether or not the individual or group of individuals had received a fatty/oily meal prior to receiving the albendazole.
* **Co-Administered Drugs:** Details on whether or not the reference reported any drugs that either 1) co-administered alongside albendazole or 2) which the individuals were receiving prior to receiving the albendazole, and continued to take following receipt of the albendazole dose. This was subsequently converted into a binary indicator denoting whether or not any drugs were being taken alongside albendazole (“Yes”/“No”).
* **Infection Status:** Details on whether or not the individual or group of individuals receiving the albendazole were doing so because they currently had a parasitic infection (as defined by the reference); and if so, what parasite they were infected with. As with co-administered drugs, this was also converted into a binary indicator denoting whether or not the individual or group of individuals had a reported parasitic infection.
* **Weight:** Where available, we also collated and extracted information on the weight of an individual, or the average weight of a group of individuals.

We extracted albendazole and albendazole sulfoxide blood concentration data at the individual level where possible, only extracting for groups of individuals where individual-disaggregated data was not available. Where data were presented at the individual level but only group-level characteristics (such as age, sex or weight) were present, we associated each individual-level time-series with the relevant group-level average characteristic. Where individuals had received multiple doses of Albendazole but where there was pharmacokinetic data describing blood concentrations following the first dose, we extracted information on blood concentrations for all timepoints up until receipt of the second dose.

**Supplementary Table 1:** Studies collated through the systematic review and their associated metadata. Further details and disaggregation of metadata by each specific time-series (rather than reference) is available in the supplementary data associated with this manuscript, and also available here: <https://github.com/cwhittaker1000/albendazole_pk>. Abbreviations: IVM = Ivermectin, DEC = diethylcarbamazine, PZQ = praziquantel. Alb = albendazole, AlbSO = albendazole sulfoxide.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Year** | **# Time-Series** | **Total Number of Individuals** | **Drug Blood Concentration Information** | **Dose mg** | **Dose per kg** | **Sex** | **Age** | **Fatty Meal?** | **Co-Drugs** | **Infection** |
| Awadzi | 2003 | 2 | 28 | AlbSO Only | 400 | Various | All Males | Various (Adults) | None | Various (None; IVM, DEC & PZQ) | Onchocerciasis |
| Awadzi | 2004 | 1 | 22 | AlbSO Only | 400 | 7.49 | All Males | 43 (Adults) | None | Levamisole | Onchocerciasis |
| Awadzi | 1994 | 2 | 28 | AlbSO Only | 1200 | NA | All Males | NA (Adults) | Various | None | Onchocerciasis |
| Ceballos | 2018 | 1 | 8 | Alb & AlbSO | 400 | 6.25 | Mixture | NA (Adults) | None | None | None |
| Chen | 2004 | 1 | 20 | Alb & AlbSO | 400 | NA | All Males | NA (Adults) | NA | None | None |
| Chhonker | 2018 | 1 | 7 | Alb & AlbSO | 400 | NA | Mixture | NA (Adults) | None | Ivermectin | Mixture (None; Lymphatic Filarisis) |
| Corti | 2009 | 3 | 24 | Alb & AlbSO | 400 | 5.48 | All Males | 31 (Adults) | None | Various (None; Ritonavir) | None |
| Cotting | 1990 | 3 | 3 | AlbSO Only | 200 | Various | All Females | Various (Adults) | Fatty Meal | Various (Amoxicillin & Gentamicin; Metronidazole and Ceftriaxone) | Echinococcosis |
| Delatour | 1991 | 1 | 4 | AlbSO Only | 725 | 10 | All Males | Various (Adults) | None | None | None |
| Edi | 2019 | 2 | 56 | Alb & AlbSO | 400 | NA | Mixture | Various (Adults) | NA | DEC & Ivermectin | Various (None; Lymphatic Filariasis) |
| Hoaksey | 1991 | 2 | 32 | AlbSO Only | Various | Various | All Males | 37 (Adults) | Fatty Meal | None | Onchocerciasis |
| Jung | 1992 | 8 | 8 | AlbSO Only | Various | 15 | Mixture | Various (Adults) | Fasted | None | Neurocysticercosis |
| Jung | 1997 | 8 | 8 | AlbSO Only | Various | 15 | Mixture | Various (Children) | Fatty Meal | None | Neurocysticercosis |
| Kitzman | 2002 | 1 | 1 | Alb & AlbSO | 400 | NA | NA | NA | NA | None | None |
| Lange | 1988 | 2 | 12 | AlbSO Only | 400 | 5.65 | Mixture | 43.5 (Adults) | Various | None | None |
| Monteiro | 2010 | 2 | 18 | AlbSO Only | 400 | 6.23 | Mixture | 26 (Adults) | None | Various (None; PZQ) | None |
| Marriner | 1986 | 10 | 10 | AlbSO Only | 400 | 5.93 | NA | 27.5 (Adults) | Various | None | None |
| Mingjie | 2002 | 1 | 7 | AlbSO Only | 830 | 12.5 | All Males | 29.3 (Adults) | NA | None | Echinococcosis |
| Mirfazaelian | 2002 | 3 | 30 | AlbSO Only | Various | Various | Mixture | 32.5 (Adults) | None | None | None |
| Mirfazaelian | 2003 | 2 | 12 | AlbSO Only | 800 | 11.81 | Mixture | 30 (Adults) | Fasted | None | None |
| Na-Bangchang | 2006 | 2 | 46 | AlbSO Only | 400 | 7.53 | Mixture | 21 (Adults) | None | Various (IVM; IVM & PZQ) | None |
| Nagy | 2002 | 4 | 24 | AlbSO Only | 690 | 10 | All Males | 20 (Adults) | Various | Various (None; Cimetidine) | None |
| Okelo | 1993 | 5 | 5 | AlbSO Only | 250 | 9.33 | All Males | 9.5 (Children) | NA | None | Echinococcosis |
| Pengsaa | 2004 | 2 | 20 | Alb & AlbSO | 400 | Various | Mixture | Various (Children) | Fatty Meal | Various (None; PZQ) | Giardia |
| Rathod | 2016 | 1 | 51 | Alb & AlbSO | 400 | NA | NA | NA (Adults) | None | None | None |
| Rigter | 2004 | 1 | 1 | AlbSO Only | 400 | 7.14 | NA | 29.5 (Adults) | None | None | None |
| Sarin | 2004 | 1 | 10 | AlbSO Only | 600 | 10.03 | NA | 32.5 (Adults) | Fatty Meal | None | None |
| Schipper | 2000 | 9 | 30 | AlbSO Only | Various | Various | All Males | 20 (Adults) | None | None | None |
| Schulz | 2019 | 1 | 10 | Alb & AlbSO | 400 | NA | NA | 16.5 (Children) | None | Oxantel Pamoate | Hookworm |
| Sergio- Mares | 2005 | 2 | 32 | AlbSO Only | 800 | 12.72 | Mixture | 24.7 (Adults) | Various | None | None |
| Shenoy | 2002 | 2 | 28 | Alb & AlbSO | 400 | Various | Mixture | 31.5 (Adults) | None | Various (None; DEC) | None |
| Thomsen | 2016 | 2 | 24 | AlbSO Only | 400 | Various | Mixture | Various (Adults) | None | Various (None; DEC & Ivermectin) | Lymphatic Filariasis |

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

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

A mathematical model describing the evolution of albendazole and albendazole sulfoxide concentrations in the blood following receipt of a single dose, based on series of linked ordinary differential equations (ODEs). This model includes a number of pharmacokinetic dynamics known to be relevant to albendazole, including its limited bioavailability (which is thought to be due to its poor solubility along the gastrointestinal tract21) as well as first-pass metabolism of albendazole to albendazole sulfoxide known to occur via the liver22. In brief, following administration of an oral dose of albendazole, we model the amount of drug in the gut, and its subsequent absorption into the body – we model the newly absorbed albendazole as passing directly through a liver compartment that converts some proportion of passaged albendazole into the metabolite albendazole sulfoxide via first-pass metabolism. Subsequent circulation and exchange of peripheral and hepatic blood leads to further conversion of albendazole into albendazole sulfoxide. Additionally, we model both albendazole and albendazole sulfoxide as being metabolised by enzymatic processes and leading to gradual removal over time. The model is specified mathematically as follows:

where , refers to the amount of albendazole in the gut, and refer to the concentrations of albendazole in the liver and peripheral blood respectively, and the concentration of the metabolite albendazole sulfoxide in the peripheral blood. is the rate of absorption of Albendazole from the gut into the bloodstream (and implicitly includes a conversion translating the absolute amount of Albendazole absorbed from the gut to the corresponding concentration in the liver compartment), references the rate at which albendazole is converted to albendazole sulfoxide by the liver. and are the rates at which albendazole and albendazole sulfoxide respectively are processed and cleared in the body. references the rate of exchange between the liver and the peripheral blood, and for the purposes of the results presented here is set to 15 (reflecting the approximate extent of exchange anticipated per hour between the two compartments1). The dose of Albendazole used is further modified by another parameter, , which corresponds to the proportion of the albendazole dose received that is available for absorption.

**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 an adaptive Metropolis-Hastings Markov Chain Monte Carlo (MH-MCMC) sampling algorithm. Prior distributions for the estimated parameters were defined as follows:

truncated at 0 so that only positive parameter values were accepted. Weakly informative priors were set over and (i.e. the two parameters where further inference and association with collated metadata in the form of multiple linear regression was not being carried out). For the other parameters, , , and , uninformative priors were set as described above. 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:

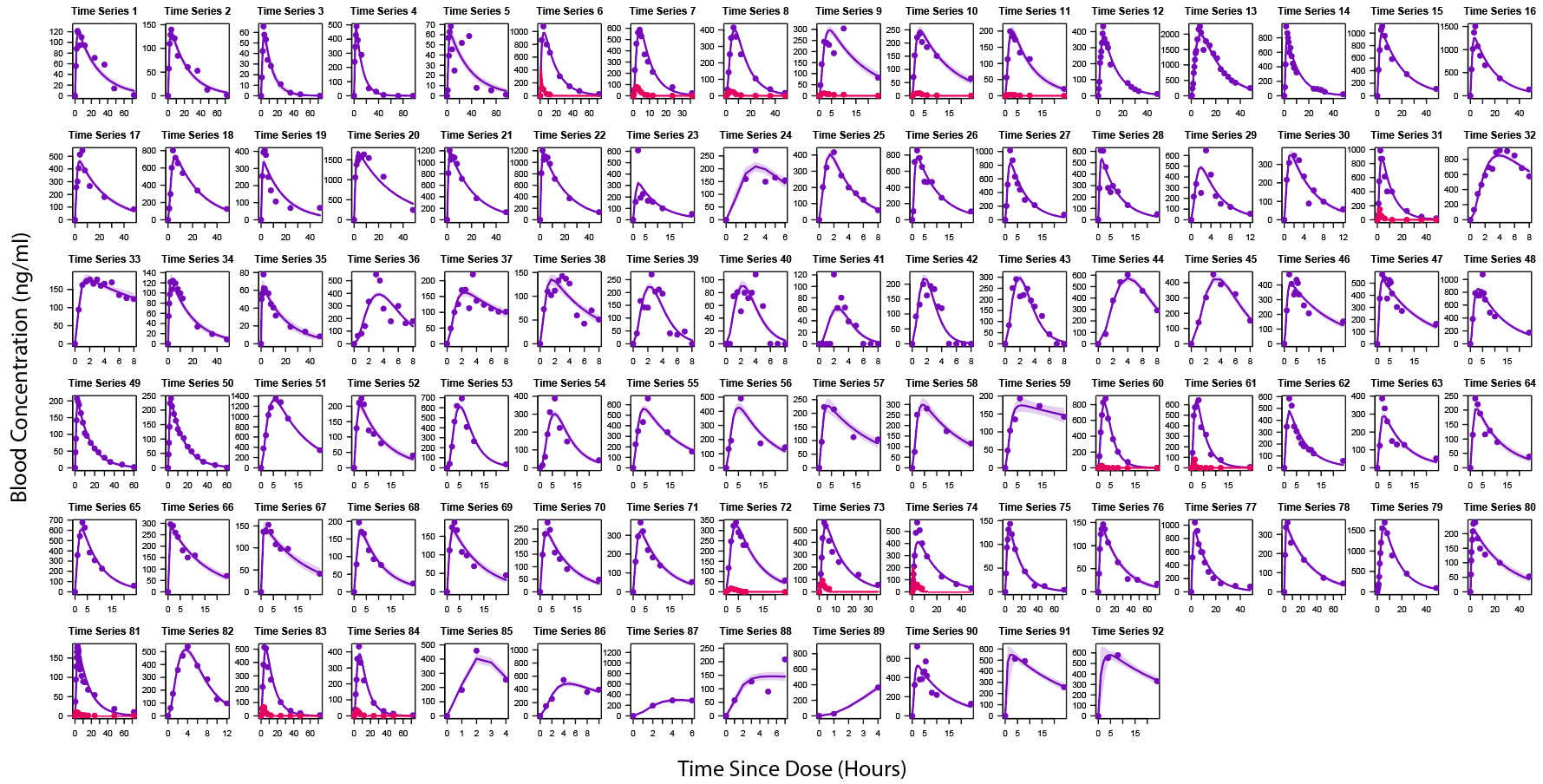
where and represent the empirically observed blood concentrations of albendazole and albendazole sulfoxide respectively at timepoint . and represent the modelled blood concentrations of Albendazole and Albendazole Sulfoxide respectively at timepoint. For each of the 92 time-series, a total of 50,000 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**

We next sought to associate the estimates of pharmacokinetic parameters from the above model fitting to collected metadata associated with each time-series (describing aspects of the patient population and treatment regimen received), to assess the influence of these factors on variation in albendazole and albendazole sulfoxide’s pharmacokinetics. These pharmacokinetic parameters were (related to the half-life of albendazole sulfoxide), the bioavailability of albendazole (the proportion of administered albendazole absorbed from the gut into the blood), (the peak concentration of the drug in the blood) and (reflecting the total exposure to the drug after administration of the dose, calculated over a time-period of 50 hours).

For each time-series, we calculated the median value of and directly from the MCMC chains generated during model fitting. We could not calculate and directly from the fitted model output however as studies differed significantly in the size of the dose administered (which would directly effect estimates of these two quantities). We therefore used the median estimates of each model parameter from the model fitting process described above, and for each time-series, simulated a hypothetical pharmacokinetic curve assuming a standardised dose of 400mg. From this hypothetical curve, standardised to have the same dose as all other time-series, we then calculated and – we subsequently refer to these quantities as and

Using a multiple linear regression-based approach, we then associated each of these pharmacokinetic parameters with the suite of collated individual/group metadata described in further detail above. When examining the impact of different specific diseases, we replaced the infection status variable with binary indicators for onchocerciasis, echinococcosis and neurocysticercosis (where 1 indicates that individual or group of individuals has that disease and 0 indicates an absence of the particular disease).

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

**Supplementary Figure 1: Results of model fitting and calibration to data collated through the systematic review.** The systematic review identified a total of 92 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.

**Supplementary Table 2: Multiple linear regression results relating pharmacokinetic properties to study characteristics when controlling for dosage per kilogram of body weight instead of raw dosage amount in milligrams.** Inferred pharmacokinetic parameters, specifically albendazole bioavailability, albendazole sulfoxide half-life, CMax and AUC were regressed onto various characteristics of the study populations controlling for sex, feeding status, age, dose per kilogram of body weight, presence of other infection (including breakdown by whether or not that infection is onchocerciasis, echinococcosis or neurocysticercosis) and co-administration of other drugs.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Bioavailability** | **AlbSO Half-Life** | **AUC (For Standardised 400mg Dose)** | **CMax (For Standardised 400mg Dose)** |
| **Sex**  **(Male = Ref)** | p=0.27 | p=0.67 | p=0.51 | p=0.22 |
| **Fatty Meal** | p=0.003 | p=0.93 | p=0.005 | p<0.001 |
| **Age Group**  **(Adults = Ref)** | p=0.43 | p=0.008 | p=0.22 | p=0.52 |
| **Dose (Per kg body weight)** | p=0.09 | p=0.20 | p=0.19 | p=0.11 |
| **Parasitic Infection**  **(Ref = None)** | p=0.73 | p=0.06 | p=0.51 | p=0.95 |
| **🡺 Onchocerciasis** | p=0.31 | p=0.42 | p=0.94 | p=0.28 |
| **🡺 Echinococcosis** | p=0.006 | p=0.37 | p<0.001 | p<0.001 |
| **🡺 Neurocysticercosis** | p=0.96 | p=0.07 | p=0.10 | p=0.23 |
| **Co-Administered Drugs**  **(Ref = None)** | p=0.43 | p=0.97 | p=0.56 | p=0.43 |

**References**

1. Eipel, C., Abshagen, K. & Vollmar, B. Regulation of hepatic blood flow: the hepatic arterial buffer response revisited. *World J. Gastroenterol.* **16**, 6046–6057 (2010).