**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 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 206 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 X 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=X) and/or albendazole sulfoxide (n=X) 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 n=X), “Mixture” (where the population were a mixture of males and females n=X) and “Unclear” (where sex of the individual/group was not provided, n=X), 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”, n=X) or not (“Children”, n=X) , 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; 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.

**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 |
| Jung | 1992 | 16 | 16 | AlbSO Only | Various | 15 | Mixture | Various (Mixture) | Various | 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 |
| Mirfazaelian | 2002 | 3 | 30 | AlbSO Only | Various | Various | Mixture | 32.5 (Adults) | None | 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 |
| Rigter | 2004 | 1 | 1 | AlbSO Only | 400 | 7.14 | NA | 29.5 (Adults) | None | 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 |
| 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 |
| Mingjie | 2002 | 1 | 7 | AlbSO Only | 830 | 12.5 | All Males | 29.3 (Adults) | NA | None | Echinococcosis |
| Sarin | 2004 | 1 | 10 | AlbSO Only | 600 | 10.03 | NA | 32.5 (Adults) | Fatty Meal | None | None |
| Sergio- Mares | 2005 | 2 | 32 | AlbSO Only | 800 | 12.72 | Mixture | 24.7 (Adults) | Various | None | None |
| Rathod | 2016 | 1 | 51 | Alb & AlbSO | 400 | NA | NA | NA (Adults) | None | None | None |
| 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 |

**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.

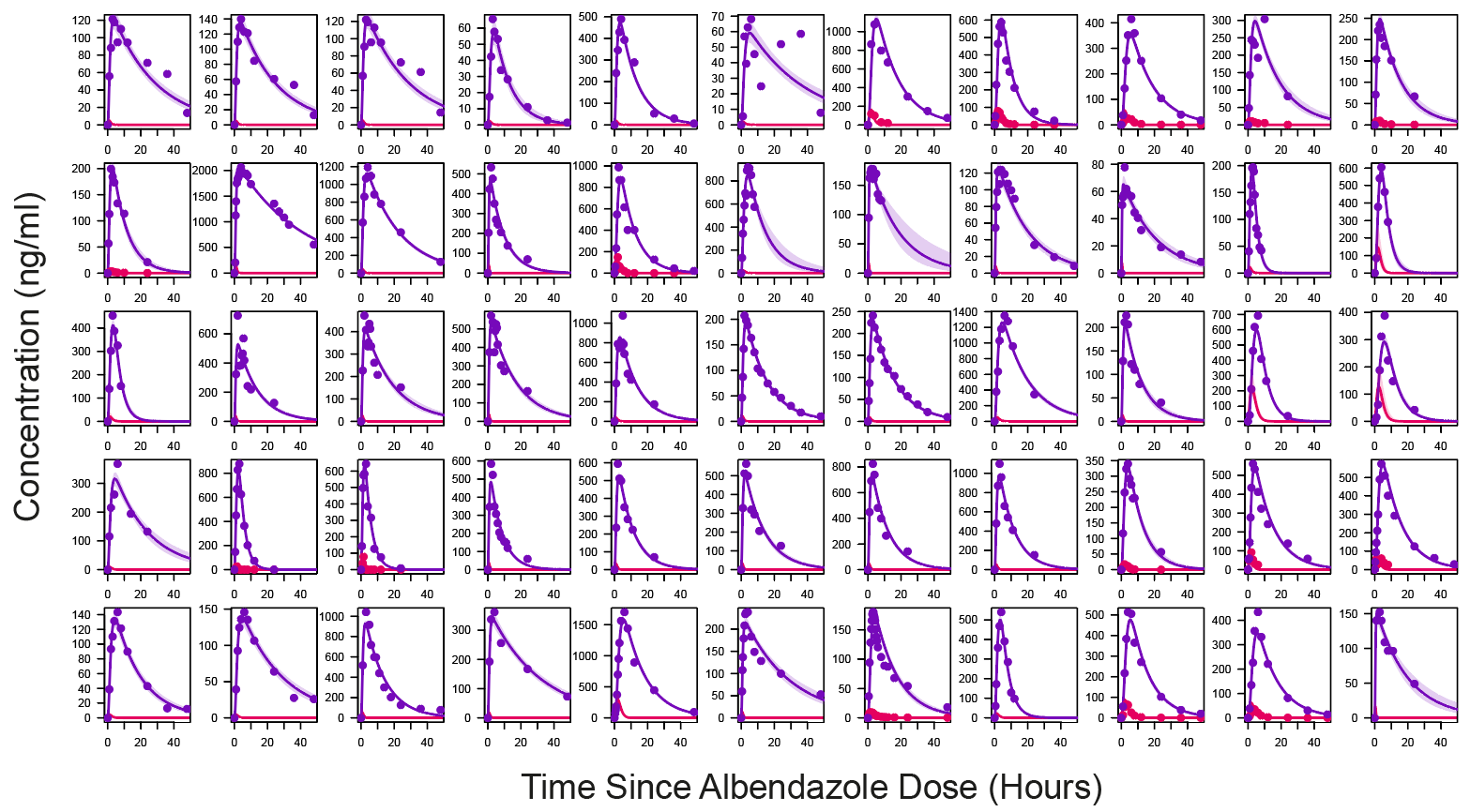
For both Albendazole and Albendazole Sulfoxide blood concentrations, a Poisson likelihood (reflecting the assumption that the drugs are well-mixed within each of our modelled compartments) was used, such that the model likelihood could be constructed as follows:

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 Figure X: 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=0.25 | p=0.90 | p=0.44 | p=0.15 |
| **Fatty Meal** | p=0.001(+14%) | p=0.93 | p=0.01  (+6141) | p<0.001  (+330) |
| **Age Group**  **(Adults = Ref)** | p=0.67 | p=0.19 | p=0.12 | p=0.95 |
| **Dose (Per kg body weight)** | p=0.03  (-1.1% per 100mg increase) | p=0.19 | p=0.30 | p=0.10 |
| **Parasitic Infection**  **(Ref = None)** | p=0.41 | p=0.10 | p=0.46 | p=0.95 |
| **🡺 Onchocerciasis** | p=0.09 | p=0.48 | p=0.51 | p=0.08 |
| **🡺 Echinococcosis** | p=0.04  (+14%) | p=0.15 | p<0.001  (+15604) | p<0.001  (+538) |
| **🡺 Neurocysticercosis** | p=0.74 | p=0.047  (-1.5 hours) | p=0.32 | p=0.14 |
| **Co-Administered Drugs**  **(Ref = None)** | p=0.09 | p=0.48 | p=0.58 | p=0.27 |