Drivers of the variability in albendazole pharmacokinetics and their consequences for anti-helminthic treatment: a systematic review and meta-analysis

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What is the research?

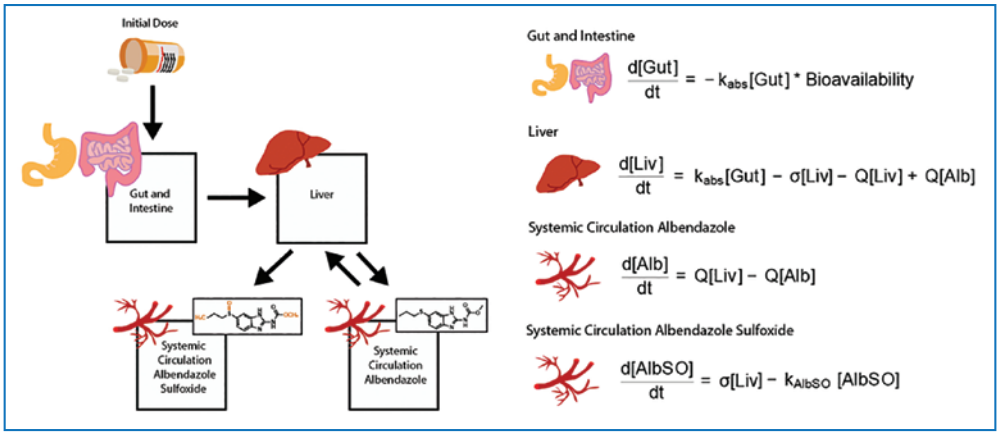
Albendazole (a benzimidazole) is an anti-parasitic medication used in a wide array of both clinical and programmatic contexts to treat (neuro-)cysticercosis, echinococcosis, infection with soil-transmitted helminths, lymphatic filariasis and loiasis, amongst others. The drug is characterised by extensive pharmacokinetic variability, with this variation likely to have important consequences for treatment success both at the individual and population level. In order to better characterise the determinants of this variation, we carried out a systematic review to identify references containing information on the pharmacokinetics (PK) of albendazole following a single oral dose of the drug. These results were then integrated into a mathematical modelling framework in order to infer key PK parameters, including the maximum concentration reached (C_{Max}), the area under the curve (AUC, reflecting total drug exposure), the bioavailability of albendazole and the half-life of its pharmacologically-active metabolite, albendazole sulfoxide. Using a regression-based approach, we related the values of these parameters to characteristics of the populations receiving treatment. Specifically, we assessed, on albendazole PK parameters, the effect of age, weight, sex, dosage, infection and co-infection status, whether patients had received a fatty meal prior to treatment and co-administration of other drugs.

Why is this research necessary?

The therapeutic efficacy of albendazole has been investigated against a wide array of helminth parasites, but its PK features are characterised by extensive variation. This variation has implications for treatment and is thought to contribute to the failure of cure in some treated patients. For example, whereas some patients typically require only one course of treatment, others require a multiple treatment regimen and in a number of instances, complete treatment failure has been observed in clinical settings. Similar results have been recorded in field studies, where for example, cure rates (the proportion of those treated who achieve parasitological clearance) for hookworm infection have been observed to vary from 53% to 95% across different communities in Ghana. Similar variability in albendazole's efficacy has also been observed for programmes treating lymphatic filariasis in the Democratic Republic of the Congo. Transmission dynamics models tend to assume fixed efficacy values when making projections of the impact of treatment in populations or population groups, but variation in efficacy among these groups is seldom considered. Although some studies have explored the drivers of this variation in the literature, our understanding of the phenomenon remains for the most part, incomplete. Frequently, these studies have focussed on a single factor and so a systematic understanding of the precise determinants and drivers of albendazole's extensive PK variation, their comparative impact and whether they interact with one-another, remains outstanding.

What is the research impact?

This research provides insight into the mechanisms underlying the variation in albendazole's PK suggesting potential avenues for clinical and programmatic optimisation of drug delivery, the outcome of which, it is hoped, will be more consistent pharmaceutical efficacy of the drug when deployed to treat parasitic infections. Additionally, the research highlighted key biases relating to which populations and individuals have previously been studied during research into albendazole, a finding which should motivate further research into key groups (such as children and women) currently underrepresented within the literature. Ultimately, we advocate for a better collection, collation, curation and understanding of individual patient data regarding the efficacy, pharmacodynamics and pharmacokinetics of albendazole for the treatment of human helminthiases.



Schematic of the pharmacokinetic model of Albendazole and Albendazole Sulfoxide: A compartmental model consisting of a series of linked ordinary differential equations (ODEs) was developed to simulate the pharmacokinetics of Albendazole and its pharmacodynamically active metabolite, Albendazole Sulfoxide, in the blood following a single oral dose of the drug