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Reprint of "Pharmacokinetic modelling of the anti-malarial drug artesunate and its active metabolite dihydroartemisinin"☆,☆☆

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ABSTRACT

A four compartment mechanistic mathematical model is developed for the pharmacokinetics of the commonly used anti-malarial drug artesunate and its principle metabolite dihydroartemisinin following oral administration of artesunate. The model is structurally unidentifiable unless additional constraints are imposed. Combinations of mechanistically derived constraints are considered to assess their effects on structural identifiability and on model fits. Certain combinations of the constraints give rise to locally or globally identifiable model structures.

Initial validation of the model under various combinations of the constraints leading to identifiable model structures was performed against a dataset of artesunate and dihydroartemisinin concentration–time profiles of 19 malaria patients. When all the discussed constraints were imposed on the model, the resulting globally identifiable model structure was found to fit reasonably well to those patients with normal drug absorption profiles. However, there is wide variability in the fitted parameters and further investigation is warranted.

1. Introduction

Malaria is a parasitic disease that has affected humans and animals for thousands of years [1]. Even now in the 21st century, the most deadly strain *Plasmodium falciparum* infects 200 million people and causes over half a million deaths every year, with young children being most severely affected [2].

Artemisinin and its derivatives have been used as anti-malarials with increasing frequency since the 1990s [3]. They are the most rapidly acting drugs out of the currently available anti-malarials [4], reducing the parasite biomass

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~10, 000-fold per asexual life cycle [5,4]. They are well-tolerated and produce few side-effects [4], and as such form the core part of the World Health Organisation recommended first-line treatment for many patients: artemisinin-based combination therapies [2]. Artemisinins remain as the most effective drugs to which malaria has not yet developed widespread resistance, though resistance has been confirmed in some regions [4]. It is hoped that use of these combination therapies, in favour of artemisinin monotherapies, will assist in delaying artemisinin resistance to ensure artemisinins continue to remain effective against multi-drug resistant malaria [4]. Meanwhile, there remains an urgent need to develop new antimalarials [6].

However, the behaviour of current artemisinins is still not fully understood; debate remains concerning their mechanism of action [7,8] and stage-specific effects [9]. One theory is that artemisinins decompose when activated by iron that has accumulated in malaria infected red blood cells, forming free radicals which then damage the parasites [10]. Thus in this theory, the anti-malarial action also acts as a route of elimination for artemisinins.

Further, recrudescence is frequently observed with the currently adopted dosing regimens [11], which have been derived largely empirically [4]. This recrudescence may be attributed to either resistant or arrested/dormant parasites, or the drug concentrations in blood falling below their effective levels, but such issues have not yet been fully characterised [9].

The blood plasma concentration–time profiles and thus the pharmacokinetics of artemisinins have been shown to display high inter-individual variability in the majority of studies. Further understanding of the pharmacokinetics and pharmacodynamics of artemisinins may assist in informing more effective dosing regimens, as well as the development of improved antimalarials. This work focusses on the pharmacokinetics because a pharmacodynamic model should build on a well-suited pharmacokinetic model.

Artesunate (hereafter ARS) is the most frequently used artemisinin derivative, and is rapidly and almost entirely converted to dihydroartemisinin (hereafter DHA) *in vivo*, mostly by plasma esterases and liver cytochrome P450 CYP2A6 [12–14]. DHA is the most active of all artemisinin derivatives, with activity approximately 1.4 times that of ARS [15].

ARS is water soluble, facilitating its absorption [16] (usually assumed to be fast, efficient and first-order [12]). Its rapid hydrolysis into the more active metabolite means that although ARS may make a significant contribution to parasite kill [17], it is often referred to as a pro-drug for DHA [3], and some researchers take the viewpoint that it is therefore not necessary to model the parent drug. DHA is also rapidly eliminated, again either through activation by infected red blood cells or through further metabolism (e.g. glucuronidation [4]), but the metabolites of DHA are inactive [18].

Many of the results and methods of studies involving ARS and DHA are summarised in Morris et al. [12], so no attempt is made to list them here. Instead, a brief discussion of existing models for artemisinin-class drugs in general, their features and the analyses conducted on them is provided in the next subsection.

1.1. *Existing models*

Many existing pharmacokinetic studies for artemisinins have been conducted over the last couple of decades, and have successfully provided some insights into the absorption, elimination and/or multiple dosing behaviour of these drugs, and the covariates that influence these. Some studies have restricted their interest to either healthy subjects, uncomplicated malaria, or severe malaria, and either children, adults or pregnant women, while others have been designed specifically to consider the differences between some of these groups. Each study focusses on a specific artemisinin derivative or derivatives, and a specific route or routes of administration, either alone or in combination with other antimalarial agents.

Of those that used modelling rather than non-compartmental approaches, some have been used to analyse the effects of differing dosing regimens in different contexts, including cases where the malaria has developed resistance to this class of drugs [19]. They range from being very simple, e.g. with linear absorption and exponential elimination as in Saralamba et al. [19], to being quite complicated, e.g. involving 9 compartments as in Gordi et al. [20], and of various complexities in between, e.g. 4 compartments as in Tan et al. [21].

However, such models have not been analysed to determine if they are structurally identifiable. The importance of knowing the structural identifiability of models will be reiterated in this paper. Indeed, Karunajeewa et al. [22] use a three-compartment model based on mechanistic principles but experience problems obtaining parameter estimates, perhaps due to structural identifiability issues. In many of the more complicated models, there are even more unknown parameters and many of these have to be assigned fixed values in order to estimate the remaining parameters successfully (again perhaps due to structural identifiability issues). In those cases, the selection of the parameters to fix and what values to use can be somewhat arbitrary and the effects of using other values is not always explored or reported.

When processes involved in the system being modelled are not well understood, it can be informative to perform model selection based on comparing a relative goodness of fit statistic for a variety of structural models, and indeed this approach is used to various extents for the pharmacokinetic models used for artemisinins in the literature. However, when information is known about the processes and mechanisms involved, models selected in this way can be less useful than models of process [23], and of course different models must be used for different observational situations (e.g. Gordi et al. [20] measure drug concentrations in saliva samples as opposed to the more common use of plasma samples, and so uses a model tailored for that situation). To be fully certain of model appropriateness, fits should be reported and validated on an individual patient basis in addition to any population levels of interest. (If a mixed-effects/hierarchical model is used, this means estimating the subject-specific deviation from the mean parameters.) This can help to determine whether or not there are key features of the data that are missed due to the structure of the model employed, which may go unnoticed if only population data are considered. However, pharmacokinetics on an individual patient basis are understandably of