LETTERS TO THE EDITOR

Dear Sir:

We read with interest the recent report on the pharmacokinetics of artemisinin (ART) and artesunate (ARTS) in healthy volunteers.\(^1\) We would like to comment on the data analysis and interpretation of the results because several assertions are unsubstantiated and ignore available literature.

With respect to the pharmacokinetic data, the authors apply a compartmental approach yet plasma concentration-time profiles for ART and dihydroartemisinin (DHA) have insufficient data for accurate and precise estimation of model parameters. When non-linear regression is used to analyze pharmacokinetic data, it is customary to describe the different models tested and the method used to discriminate between them. The variance of parameter estimates should also be reported. Because none of these details were provided, the reader can have limited confidence in the estimates presented in the paper.

The “biotransformation half-life” presented for the formation of DHA is a misnomer because the in vivo appearance of DHA after oral ARTS is unlikely to be governed by systemic hydrolysis alone but also by rates of gastrointestinal tablet transit, absorption of ARTS across the gut wall, and pre-systemic and systemic hydrolysis. The claim that DHA is formed by reductive pathways is contrary to earlier findings\(^2\) and unsupported by experimental results.\(^3\) The view that elevated area under the curve (AUC) values could be “due to slower distribution” is contrary to pharmacokinetic principles, as is the statement that data from single dose studies give “most exact . . . pharmacokinetic parameters”. Furthermore, the assumption that there is complete bioavailability of ART is inconsistent with the report by Titulaer and others,\(^4\) who demonstrated a relative bioavailability (oral to intramuscular administration) of only 32%. With one exception,\(^5\) comparisons with previously reported studies\(^6\)–\(^11\) were conspicuously absent.

We strongly contest the assertion that high-performance liquid chromatography (HPLC) with electrochemical (EC) detection is the only valid analytical method for the artemisinin drugs. We have reported appropriately validated HPLC-UV methods, applicable to human pharmacokinetic studies, employing derivatization under acidic\(^12\)–\(^13\) and alkaline conditions.\(^6\)–\(^8\) In support of the authors’ contention that alkali derivatization is inapplicable because the ratio of compounds “is highly dependent on temperature, pH, and duration of the hydrolysis procedure,” the authors cite Edlund and others\(^14\) who, on the contrary, point out the high reproducibility of the on-line post-column alkali derivatization method. The HPLC-UV techniques are not only economical and efficient but are suitable for precise and accurate quantification of ART, ARTS, and DHA (but they are less for arteether and arteether) in plasma. Limits of quantification (LOQ) for ART\(^7\)–\(^8\) appear similar to those claimed for HPLC-EC although, for the latter method, only detection limits (a less meaningful parameter) have been reported.\(^1\)–\(^5\) Limits of quantification values for ARTS and DHA below 50 ng/ml are achievable but may be unnecessary in clinical studies because peak plasma concentrations in excess of 2,000 ng/ml are found after therapeutic doses.\(^6\)

Finally, the description of the analytical method does not meet criteria for valid pharmacokinetic studies.\(^6\)–\(^7\) Overall recoveries for the analytes are insufficient to validate the technique. The authors state that “only sensitive analytical techniques . . . must be used” but fail to report either LOQ or within- and between-day coefficients of variation. Such information is not provided in the reference offered in support of the above statement.\(^5\) Moreover, the authors have not identified which of the two anomers of DHA they have measured. This is important because the time-dependent change of the ratio of the α:β anomers in vitro may contribute to assay variability.\(^8\)

The study of Benakis and others\(^1\) reminds us that the credibility of pharmacokinetic research on the artemisinin drugs requires fully validated analytical procedures, appropriate methods of data analysis, and a clear acknowledgement of limitations in the data.

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REFERENCES


Dear Sir:

The pharmacokinetic approach is certainly important for artemisinin and derivative drugs since there is enough evidence that kinetics are related to the pharmacodynamic effect. It is true that for a pharmacokinetic analysis a greater number of subjects is needed to establish a better pharmacokinetic approach than was used in our study as suggested by Batty and others. It is also true that there could be confusion between the kinetic analyses of artemisinin and artesunate because for the latter, the apparition constant that is given in Table 6 should have been better expressed so that it would have included all modifications of the molecule comprising the biotransformation producing dihydroartemisinin. We do not claim that there are no other metabolites but we feel that for these drugs, dihydroartemisinin is the essential metabolite to explain the mode of action.

With regard to analytical techniques for quantification of these drugs and metabolites, we feel that HPLC with electrochemical detection in the reductive form is the most appropriate. Certainly there are other methods, but for the laboratories of developed countries working in the field, this type of equipment is affordable. In fact, many European and American laboratories, as well as some in Asian countries, are already equipped for this. Nevertheless, it is true that for many developing countries, the purchase and operation of this equipment is very expensive and often impossible.

We feel that in the area of drug metabolism and pharmacokinetics, analytical techniques are essential.

We agree with the last sentence of Batty and others and are fully aware of the limitations of our data. We continue to work in the field and recently initiated a multicentric study for the evaluation of our technique using the same biological material.

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