Interspecies Allometric Scaling of Antimalarial Drugs and Potential Application to Pediatric Dosing

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Pharmacopeial recommendations for administration of antimalarial drugs are the same weight-based (mg/kg of body weight) doses for children and adults. However, linear calculations are known to underestimate pediatric doses; therefore, interspecies allometric scaling data may have a role in predicting doses in children. We investigated the allometric scaling relationships of antimalarial drugs using data from pharmacokinetic studies in mammalian species. Simple allometry ($Y = a \times W^b$) was utilized and compared to maximum life span potential (MLP) correction. All drugs showed a strong correlation with clearance (CL) in healthy controls. Insufficient data from malaria-infected species other than humans were available for allometric scaling. The allometric exponents ($b$) for CL of artesunate, dihydroartemisinin (from intravenous artesunate), arteether, artemisinin, clindamycin, piperaquine, mefloquine, and quinine were 0.71, 0.85, 0.66, 0.83, 0.62, 0.96, 0.52, and 0.40, respectively. Clearance was significantly lower in malaria infection than in healthy (adult) humans for quinine (0.07 versus 0.17 liters/h/kg; $P = 0.0002$) and dihydroartemisinin (0.81 versus 1.11 liters/h/kg; $P = 0.04$; power = 0.6). Interpolation of simple allometry provided better estimates of CL for children than MLP correction, which generally underestimated CL values. Pediatric dose calculations based on simple allometric exponents were 10 to 70% higher than pharmacopeial (mg/kg) recommendations. Interpolation of interspecies allometric scaling could provide better estimates than linear scaling of adult to pediatric doses of antimalarial drugs; however, the use of a fixed exponent for CL was not supported in the present study. The variability in allometric exponents for antimalarial drugs also has implications for scaling of fixed-dose combinations.

The World Health Organization and standard pharmacopeial sources recommend that antimalarial drugs be administered at the same weight-based (mg/kg of body weight) or linear dose for children and adults (1). However, this linear method of dosage calculation is known to underestimate the optimum pediatric dose of many drugs (2–5). Recent clinical reports indicate that higher doses of sulfadoxine-pyrimethamine (6, 7), chloroquine (6, 8, 9), quinine (10), piperaquine (11–14), and artesunate (15, 16) are required for effective antimalarial therapy in children.

Allometric scaling is a well-established technique for relating physiological or pharmacokinetic parameters to body weight (17–22), and allometric relationships have been demonstrated for a wide range of drugs, including antimicrobial agents (23–27). The conventional applications of interspecies allometric scaling include prediction of human doses by extrapolation from preclinical animal studies and dose estimates for other mammalian species in veterinary medicine (18, 23, 26, 28). Increasing interest has been shown in the application of interspecies allometric scaling data to predict pharmacokinetic parameters or drug doses in children (27, 29, 30). Despite a paucity of reports on antimalarial drugs (31, 32), interpolation of allometric scaling of chloroquine supports recommendations from clinical studies for higher chloroquine doses in children (8, 9, 33).

The rationale for using scaling techniques to estimate pharmacokinetic parameters in children is that relatively few pediatric pharmacokinetic investigations are conducted, compared to adult studies, and sparse sampling is normally required because there are practical and ethical limitations to obtaining rich pharmacokinetic data sets from pediatric subjects (34). One alternative to conventional interspecies scaling is fixed-exponent scaling from human adult pharmacokinetic data (2–5, 34–37). The principle of scaling with a fixed exponent (e.g., 2/3 or 3/4) may provide some consistency and practical advantages; however, the validity of a universal exponent in pharmacokinetics is subject to conflicting evidence and debate (3, 5, 27, 34–40). Regardless of the scaling method that is used, caution is required for recommendations for very young children, due to immature clearance mechanisms, and for disease states for which there are limited data available or evidence that clearance may be altered in compromised patients (30, 35, 36).

We sought to investigate the allometric scaling relationships of antimalarial drugs using data from pharmacokinetic studies of healthy and malaria-infected mammalian species. Our hypothesis was that linear scaling (i.e., exponent of 1.0) would not apply and that interpolation of interspecies allometric scaling would be suitable for estimating pediatric doses of antimalarial drugs.

**MATERIALS AND METHODS**

**Data collection.** A comprehensive literature search was conducted via PubMed, OvidSP, Google Scholar, and citation records, using relevant key words, including the specific antimalarial drugs and mammalian species. The initial target list of antimalarial drugs was determined from WHO treatment guidelines (1): artemisinin, artesunate, arteether, dihydroartemisinin, mefloquine, amodiaquine, piperaquine, chloroquine, quinine, primaquine, lumezantrine, sulfadoxine-pyrimethamine, atovaquone, proguanil, tetracycline, doxycycline, and clindamycin. Exclusions comprised fixed-dose combinations where data for individual drugs were not
readily available (sulfadoxine-pyrimethamine, arteether-lumefantrine, atovaquone-proguanil), drugs for which pharmacokinetic data were available from fewer than three mammalian species (amodiaquine and lumefantrine), and drugs that are contraindicated in children (tetracycline and doxycycline). Chloroquine (33) and doxycycline (41) had been studied previously and were excluded.

The pharmacokinetic studies were screened for suitability of the data, with a focus on uniformity of biological matrix (especially for quinolines with high blood-plasma ratio), period over which blood and plasma samples were collected for the pharmacokinetic study (preferably >3 half-lives), route of administration, and use of validated analytical methods. Although pharmacokinetic parameters from studies with intravenous (or parenteral) drug administration are preferred for allometric scaling, other routes of administration were more appropriate for some antimalarials, such as those which are available only as oral formulations. The final list of drugs (and routes of administration) was as follows: artemisinin (intravenous [IV], intraperitoneal, and oral), arteether (intravenous [IV], oral), mefloquine (oral), piperaquine (oral), quinine (IV), and clindamycin (IV). Pharmacokinetic parameters. Clearance (CL), volume of distribution during terminal phase (Vₜ), and half-life (t½) data were collated or determined from the available data using model-independent equations (CL = k × Vₜ; Vₜ = CL/k). Comprehensive pharmacokinetic data (e.g., mean residence time [MRT] and steady-state volume of distribution [Vₜss]) were reported in a limited range of studies and therefore were not included in the present analysis. In studies where different doses were administered to the same subjects and there was no evidence of dose-dependent variability, the mean value of the pharmacokinetic parameter was used. However, if separate groups were given different doses within a study, the data were treated independently except when the results were reported as group data. In human studies where body weight was not reported, 60 kg was used for Asian and African subjects, whereas 70 kg was used for Caucasian subjects, based on standard references and other reports used in the present study. The body weight of animals was not provided in some nonhuman studies; hence, published standard body weights of the respective species were used for the allometric scaling (17, 25, 28, 42).

Allometric scaling. Simple allometry was the principal method of interspecies scaling, using the equation

\[ Y = a \times W^b \]  

where Y is the pharmacokinetic parameter (e.g., CL or Vₜ), W is the body weight of the species, a is the coefficient, and b is the allometric exponent (19, 24, 38).

The pharmacokinetic parameter data were plotted against body weight on a log-log scale (SigmaPlot version 12.5; Systat Software, Inc., Chicago, IL) to determine the allometric coefficient and exponent by regression analysis. Data from healthy control subjects were used for the allometric scaling, as there were insufficient pharmacokinetic studies in malaria-infected nonhuman species for each antimalarial drug that was investigated. However, pharmacokinetic parameters from human (adults) studies of malaria infection were compared to the healthy-control data, as a guide to the application of allometric interpolation to decisions on pediatric doses.

Maximum life span potential (MLP) correction. Several alternative methods of scaling and use of correction factors have been proposed and reviewed (17–19, 26, 43, 44), although the physiological relevance and application of some methods were not applicable in the present study. The most relevant and best-studied method for our consideration was MLP correction, which is an integral feature of the “rule of exponents” approach (26, 44). According to the rule of exponents, simple allometry is the best predictor for exponents in the range from 0.50 to 0.70, whereas CL × MLP provides the best prediction method when the range is 0.71 to 0.99 (44). As the CL exponent from simple allometry was <1 for all antimalarial drugs, we compared MLP correction to simple allometry.

The maximum life span potential (MLP) was calculated from the equation (17)

\[ MLP = 10.839 \times BW^{0.636} \times B^{-0.225} \]  

where BW is brain weight in grams and B is body weight in grams (the coefficient 10.839 is replaced with 185.5 if the brain and body weights are in kg [44]). Brain and body weight data for mammalian species are well established (17, 42, 45).

The CL × MLP data were plotted against body weight on a log-log scale (SigmaPlot) to determine the coefficient and exponent by regression analysis. Clearance exponents from simple allometry and MLP correction were used to determine interpolated CL for children and compared to available clinical study data.

Pediatric doses. A standard allometric model for pediatric dosing is to use one of the following equations:

\[ \text{dose}_{\text{child}} = \text{dose}_{\text{adult}} \times \left( \frac{\text{weight}_{\text{child}}}{\text{weight}_{\text{adult}}} \right)^b \]  

\[ CL_{\text{child}} = CL_{\text{adult}} \times \left( \frac{\text{weight}_{\text{child}}}{\text{weight}_{\text{adult}}} \right)^b \]  

where \( \text{dose}_{\text{child}} \) is the total dose for a child at the specified weight (weight child), \( \text{dose}_{\text{adult}} \) is the standard total dose for an adult at the specified weight (weight adult), and \( \text{CL}_{\text{child}} \) and \( \text{CL}_{\text{adult}} \) are the total CL of the drug.

The exponent derived by allometric scaling (equation 1) was applied in the present study (equation 3) to compare calculated doses to pharmacopelar or reference doses for arbitrary weights of 15 kg and 25 kg (children approximately 4 and 8 years of age, respectively). Dose estimates for children less than 2 years were not considered, due to the known physiological and pharmacokinetic differences between very young infants and adults (35, 36).

Statistical analyses. Data analysis and representation were performed with SigmaPlot version 12.5 (Systat Software, Inc., Chicago, IL). Data are means ± standard deviations (SD) unless otherwise indicated. The 95% confidence interval (CI) was determined for the allometric exponent [95% CI = mean ± (1.96 × standard error)]. The Student t test was used for two-sample comparison as appropriate, with significance at a P value of <0.05.

RESULTS
Simple allometry. Simple allometric scaling data for CL and Vₜ are shown in Tables 1 and 2 respectively. A strong correlation was found for both CL and Vₜ for all antimalarials except Vₜ for the prodrug arteether (Tables 1 and 2). Arteether (Fig. 1) is normally administered by intramuscular injection, but the inclusion of IV data from a rodent and rabbit study did not significantly alter the allometric parameters. Artemisinin was given parenterally in the studies of mice and rats, but as oral administration was used in human studies, CL data were corrected for oral bioavailability to facilitate scaling (Table 1). Due to the mixed sources of data, artemisinin was excluded from subsequent analyses.

The 95% CI for CL of piperaquine, mefloquine, and quinine did not encompass 2/3 or 3/4, hence the application of these fixed exponents could not be supported by the present data (Table 1, Fig. 1). Linear dosing of piperaquine could be supported, based on the 95% CI for CL in the present analysis (Table 1).

The 95% CI for Vₜ encompassed unity for three of the seven drugs: arteether, piperaquine, and quinine (Table 2). Volume of distribution is normally used in calculations of loading dose and in pharmacokinetic modeling; therefore, no further analysis of Vₜ was undertaken for the purposes of the present study.

Control versus malaria. In the absence of pharmacokinetic data from malaria-infected nonhuman species for each antimalarial drug, a direct comparison of pharmacokinetic parameters from human (adult) healthy controls and malaria-infected patients was
TABLE 1 Simple allometric scaling data for clearance (CL) of antimalarial drugs in healthy mammals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration</th>
<th>No. of species</th>
<th>Allometric exponent (95% CI)</th>
<th>Allometric coefficient</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artesunate</td>
<td>IV</td>
<td>4 (r, d, p, h)</td>
<td>0.92</td>
<td>0.71 (0.33–0.88)</td>
<td>7.0</td>
</tr>
<tr>
<td>Dihydroartemisinin (from IV artesunate)</td>
<td>IV</td>
<td>4 (r, d, p, h)</td>
<td>0.94</td>
<td>0.85 (0.68–1.03)</td>
<td>3.3</td>
</tr>
<tr>
<td>Artemether</td>
<td>IM</td>
<td>3 (r, d, h)</td>
<td>0.98</td>
<td>0.66 (0.38–0.93)</td>
<td>3.3</td>
</tr>
<tr>
<td>Artemether</td>
<td>IM or IV</td>
<td>4 (r, rb, d, h)</td>
<td>0.99</td>
<td>0.66 (0.56–0.75)</td>
<td>3.3</td>
</tr>
<tr>
<td>Artemisin</td>
<td>IV, IP, oral×P</td>
<td>3 (m, r, h)</td>
<td>0.92</td>
<td>0.83 (0.69–0.96)</td>
<td>4.2</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>IV</td>
<td>3 (d, r, h)</td>
<td>0.98</td>
<td>0.62 (0.55–0.69)</td>
<td>1.4</td>
</tr>
<tr>
<td>Piperaquine</td>
<td>Oral</td>
<td>3 (m, r, h)</td>
<td>0.99</td>
<td>0.96 (0.86–1.05)</td>
<td>1.6</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>Oral</td>
<td>3 (m, r, h)</td>
<td>0.90</td>
<td>0.52 (0.43–0.61)</td>
<td>0.2</td>
</tr>
<tr>
<td>Quinine</td>
<td>IV</td>
<td>3 (r, d, h)</td>
<td>0.89</td>
<td>0.40 (0.33–0.47)</td>
<td>1.9</td>
</tr>
</tbody>
</table>

* IV, intravenous; IM, intramuscular; IP, intraperitoneal.
* Species: m, mouse; r, rat; d, dog; p, pig; rb, rabbit; h, human.

**TABLE 2 Simple allometric scaling data for volume of distribution (Vz) of antimalarial drugs in healthy mammals**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration</th>
<th>No. of species</th>
<th>Allometric exponent (95% CI)</th>
<th>Allometric coefficient</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artesunate</td>
<td>IV</td>
<td>4 (r, d, p, h)</td>
<td>0.69</td>
<td>0.54 (0.22–0.85)</td>
<td>3.2</td>
</tr>
<tr>
<td>Dihydroartemisinin (from IV artesunate)</td>
<td>IV</td>
<td>4 (r, d, p, h)</td>
<td>0.99</td>
<td>0.86 (0.78–0.94)</td>
<td>4.2</td>
</tr>
<tr>
<td>Artemether</td>
<td>IM</td>
<td>3 (r, d, h)</td>
<td>0.99</td>
<td>0.93 (0.82–1.05)</td>
<td>12.4</td>
</tr>
<tr>
<td>Artemether</td>
<td>IM or IV</td>
<td>4 (r, rb, d, h)</td>
<td>0.96</td>
<td>1.06 (0.75–1.38)</td>
<td>6.7</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>IV</td>
<td>3 (d, r, h)</td>
<td>0.98</td>
<td>0.81 (0.72–0.91)</td>
<td>2.5</td>
</tr>
<tr>
<td>Piperaquine</td>
<td>Oral</td>
<td>3 (m, r, h)</td>
<td>0.94</td>
<td>1.16 (0.87–1.45)</td>
<td>280</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>Oral</td>
<td>3 (m, r, h)</td>
<td>0.91</td>
<td>0.78 (0.66–0.90)</td>
<td>39.8</td>
</tr>
<tr>
<td>Quinine</td>
<td>IV</td>
<td>4 (r, rb, d, h)</td>
<td>0.92</td>
<td>0.88 (0.74–1.01)</td>
<td>4.61</td>
</tr>
</tbody>
</table>

* IV, intravenous; IM, intramuscular.
* Species: m, mouse; r, rat; d, dog; p, pig; rb, rabbit; h, human.
and evidence of a power law relationship between biological parameters and body weight; however, there are conflicting reports on the application of fixed exponents and correction factors (20, 35, 36, 38–40, 46, 47). Historical research on basal metabolic rate established a 2/3 power scaling of body mass and is supported by the concept of scaling surface area to volume of 3-dimensional objects (20, 39). The “1/4 power law” is based on seminal studies that scaled the metabolic rate of animals using an exponent of 3/4 and is reported to be consistent with structure and function observations in biology (20, 21, 38, 39). This power law has been translated to the use of an exponent of 3/4 for drug clearance, 1/4 for elimination half-life, and 1 for volume of distribution (21, 22, 35, 36, 38, 39). It has recently been argued that the small numerical difference between 2/3 and 3/4 powers is of little clinical relevance in pharmacokinetics (36).

The physiological origins of interspecies relationships provide some context for the limitations of allometric scaling in pharmacokinetics, which have been the subject of detailed review (39, 48–50). One limitation of scaling pharmacokinetic parameters that we encountered was a small range of mammalian species and low number of subjects in each study (typically 6 to 16 in human studies and 6 to 8 in other species). We were able to obtain data from only two or three nonhuman species, a finding that is consistent with similar previous investigations (24, 31, 33). However, some pharmacokinetic studies, especially veterinary reports, were compiled with data from at least 8 species (17, 19, 23, 51), and interspecies scaling of physiological parameters, such as basal metabolic rate, comprises data from over 20 species (21). A larger range of animal studies would therefore enhance the quality of allometric scaling data in future studies.

Further limitations may occur if there are species differences in the pharmacokinetic properties of drugs that lead to unpredictable and weak allometric scaling outcomes (39, 49, 50). Highly protein-bound drugs (>98% in humans), such as mefloquine (52) and piperaquine (53), may have inconsistent scaling if binding is substantially lower in other species. Bioavailability and renal or hepatic clearance mechanisms also may have species differences which could be relevant for antimalarial drugs that are subject to hepatic metabolism and commonly administered as oral formulations. However, there is generally a paucity of relevant data to address these potential limitations in the scaling of pharmacokinetic parameters (49, 50).

Notwithstanding the limitations of interspecies scaling and the power law relationship debate, allometric scaling data indicate that fixed exponents of 2/3 or 3/4 may not be universally applicable in pharmacokinetics (24, 28, 29, 31, 33, 38, 44, 47). Our analyses showed that the 95% CI encompassed both 2/3 and 3/4 for CL of artemether and artemisinin, whereas the upper limit of the 95% CIs for mefloquine, quinine, and chloroquine (0.63, based on re-analysis of a previous study [33]) were all <0.65 (Table 1). In contrast, the allometric exponents for dihydroartemisinin and piperaquine CL were 0.85 and 0.96, respectively, and the 95% CI of the exponent spanned unity. Hence, the use of a fixed exponent for CL of antimalarial drugs is not supported by the present study.

The influence of allometric exponents on interpolated dose predictions can be substantial and varies according to body weight. For example, if the recommended adult dose of a drug is 10 mg/kg (for a 70-kg adult), arbitrary exponents of 0.6 and 0.75 would lead to predicted doses of 18.5 mg/kg and 14.7 mg/kg, respectively, for a 15-kg child and of 15.1 mg/kg and 12.9 mg/kg, respectively, for a 25-kg child. The differential between adult and
child doses will decrease for children with higher body weights and will also decrease as the exponent approaches unity. The potential effect of these inverse relationships on dose predictions demonstrates the importance of high-quality data for allometric scaling.

It was evident from our detailed literature search that an extensive range of interspecies scaling for antimalarial drugs was precluded by several factors. In particular, the target list of antimalarials was limited by a paucity of data for individual drugs within some common, fixed-dose combinations, and we could not obtain pharmacokinetic data from a minimum of three mammalian species for amodiaquine and lumefantrine. Studies with intravenous (or parenteral) drug administration would have been optimal, but inclusion of other routes of administration was necessary for artemisinin, artemether, mefloquine, and piperaquine. An important issue was the small body of pharmacokinetic research in malaria-infected nonhuman species for the antimalarial drugs, and this limitation was addressed by comparing drug clearance from studies in malaria-infected human adults with that reported for healthy controls (Table 3). Consistent with previous reports, only quinine was shown conclusively to have significantly different clearance in malaria infection (54). Our data indicate that dihydroartemisinin clearance was higher in healthy controls than patients with malaria infection (Table 3); however, the power of the analysis was inconclusive. The apparent clearance (CL/F) of piperaquine and mefloquine could be higher in malaria infection than in healthy controls (Table 3) and may be a function of altered bioavailability, as has been reported for dihydroartemisinin (55).

Our investigation of the relevance of correction factors for allometric scaling was to ascertain if the more sophisticated approaches to interpolation of interspecies scaling would be beneficial for antimalarial drugs. Some of the techniques require raw concentration-time data (17, 18, 43), which were not available in most reports, and we therefore confined our analysis to maximum life span potential (MLP). This correction method has been incorporated in the rule of exponents, whereby simple allometry is used for exponents in the range from 0.50 to 0.77 and scaling CL/H against body weight is recommended when the exponent from simple allometry is in the range from 0.71 to 0.99 (44).

Our study showed that MLP correction led to substantially lower interpolated CL estimates, compared to simple allometry.
and data from clinical reports, except for one group of children treated with mefloquine (Table 4). We conclude that the application of MLP correction for antimalarial drugs is not supported by the present study. By comparison, simple allometry overestimated the CL/F of mefloquine in children with uncomplicated falciparum malaria, which could lead to excessive dose predictions, and therefore, this requires more detailed, contemporary clinical investigations. Conversely, interpolation from simple allometry provided good estimates of CL for dihydroartemisinin and artemether (Table 4). The piperaquine data appear to be conflicting; however, there were several clinical differences between the two populations and no conclusive explanation for the findings (56, 57). Two recent reports of piperaquine pharmacokinetics showed lower CL/F values, suggesting that the rule of exponents may be applicable to piperaquine, but as noted in Table 4, these data could not be included in the present study due to the use of pooled results from different partner drugs (12) and use of capillary blood analysis to determine the pharmacokinetic parameters (13).

Quinine predictions are problematic, due to the difference in CL (and Vz) between healthy subjects and patients with malaria, and the reported lower CL in children than adults (Table 3). Therefore, cautious interpretation of allometric scaling results are required for quinine, due to the complex and multifactorial effects of malaria infection on the pharmacokinetic properties of this drug.

The final component of our study was to translate the allometric scaling results to dose estimates (Table 5). The recommendations for dihydroartemisinin (as IV artesunate) and clindamycin

### Table 4: Antimalarial drug clearance from clinical studies in children compared to interpolated CL from simple allometry and MLP correction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Allometric exponenta</th>
<th>Interpolated CL (liters/h/kg)b</th>
<th>Clinical studyb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simple allometry</td>
<td>MLP correction</td>
<td>Simple allometry</td>
</tr>
<tr>
<td>Dihydroartemisinin</td>
<td>0.85</td>
<td>1.31</td>
<td>2.21</td>
</tr>
<tr>
<td>Artemether</td>
<td>0.66</td>
<td>1.18</td>
<td>1.52</td>
</tr>
<tr>
<td>Piperaquine</td>
<td>0.96</td>
<td>1.46</td>
<td>1.40</td>
</tr>
<tr>
<td>Piperaquine</td>
<td>0.96</td>
<td>1.46</td>
<td>1.39</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>0.52</td>
<td>1.0</td>
<td>0.068</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>0.52</td>
<td>1.0</td>
<td>0.068</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>0.52</td>
<td>1.0</td>
<td>0.045</td>
</tr>
<tr>
<td>Quinine</td>
<td>0.40</td>
<td>0.93</td>
<td>0.37</td>
</tr>
</tbody>
</table>

a Allometry was conducted in healthy controls; CL/F was determined for piperaquine and mefloquine.

b Data from studies in malaria-infected children; CL/F was determined for piperaquine and mefloquine.

c Piperaquine CL/F was determined from studies of piperaquine-dihydroartemisinin in malaria-infected children. There is no significant difference in piperaquine clearance when piperaquine is administered alone or in combination with dihydroartemisinin (148). One recent study reported a CL/F of 0.57 liter/h/kg, however, the data were pooled from a previous study of piperaquine-dihydroartemisinin (57) and an investigation of piperaquine-artemisinin (12). A report of a piperaquine CL/F of 0.42 liter/h/kg from capillary blood samples could not be compared directly to investigations using venous plasma samples for determination of piperaquine pharmacokinetic parameters (13).

d Mefloquine CL/F was determined from studies of mefloquine-sulfadoxine-pyrimethamine in malaria-infected children. Mefloquine clearance may be lower when mefloquine is administered in combination with sulfadoxine and pyrimethamine (101).

e Malaria-infected children were all <2 years of age in these studies; the mean age was 1.6 years.

f All quinine data are from studies in healthy controls.

### Table 5: Allometric interpolation of antimalarial doses in comparison to current pharmacopeial recommendations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration</th>
<th>Standard regimenc</th>
<th>Dose (mg) for:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>15-kg child</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Referenceb</td>
</tr>
<tr>
<td>Dihydroartemisinin</td>
<td>IV</td>
<td>Dose at 0, 12, 24 h, then once/day (2.4 mg/kg/dose)</td>
<td>35</td>
</tr>
<tr>
<td>(as IV artesunate)</td>
<td></td>
<td></td>
<td>Referencec</td>
</tr>
<tr>
<td>Artemether</td>
<td>Oral</td>
<td>Twice/day for 3 days</td>
<td>40</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Oral</td>
<td>Twice/day for 7 days (10 mg/kg/dose)</td>
<td>150</td>
</tr>
<tr>
<td>Piperaquine</td>
<td>Oral</td>
<td>Once/day for 3 days (18 mg/kg/day)</td>
<td>270</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>Oral</td>
<td>2/3 total dose day 1; 1/3 total dose day 2 (25-mg/kg total dose)</td>
<td>375</td>
</tr>
<tr>
<td>Quinine</td>
<td>IV</td>
<td>Three times per day for 5–7 days (10 mg/kg/dose)</td>
<td>150</td>
</tr>
</tbody>
</table>

a As reported by the World Health Organization (1) and confirmed by reference to the British National Formulary.

b Based on mg/kg doses and practical recommendations.

c Based on reference doses and equation 3, where adult dose was according to a 70-kg body weight and the allometric exponent was from Table 1. Doses were mostly rounded to a 10-mg increment rather than the nearest practical dose.

d Current artemether dose recommendation is for body weight range (1, 2, 3, and 4 20-mg tablets for patients weighing 5 to 14 kg, 15 to 24 kg, 25 to 34 kg, and >34 kg, respectively). The adult (70 kg) dose is therefore the same as that for a child of 34 kg (80 mg), which equates to 1.1 mg/kg for adults and 2.3 mg/kg for the 34-kg child. Hence, current practical dose recommendations are higher (mg/kg) for children and vary within the weight ranges.
would be modest increases that can be achieved in the clinical setting, whereas the small predicted increase in piperaquine dose would not be practical. It is notable that recent clinical studies have recommended higher doses for piperaquine (11, 13, 14) and artemunate in children (15). Indeed, the doses proposed in the latter study closely match the allometric predictions of 3 mg/kg (15-kg child) and 2.8 mg/kg (25-kg child), based on scaling for dihydroartemisinin in the present study.

The recommended mefloquine doses were 1.6- to 2-fold higher than reference doses for adults (mg/kg), which could be viewed as excessive and to the best of our knowledge have not been proposed in any clinical studies. However, recent allometric scaling of chloroquine indicated that pediatric doses 1.6-fold higher than those for adults (mg/kg) were potentially appropriate, and these doses were exceeded by clinical studies where 2-fold-higher doses were used in children (8, 9, 33). Complementary data are available for quinine, notwithstanding our cautious interpretation of the allometric scaling. Indeed, our results from simple allometry of quinine suggest that 18 to 24 mg/kg could be more appropriate than 10 mg/kg (Table 5), and a recent study supports earlier recommendations in adults that 20 mg/kg quinine should be used as a loading dose in children (10).

An important consideration from our allometric exponent data is that disproportionate dose increases appear to apply to antimalarial drugs, and the implications for rational pediatric dosing of combination regimens are therefore significant. For example, an adult dose of a dihydroartemisinin-piperaquine (120/960 mg; approximately 2/16 mg/kg for a 60-kg patient) oral fixed-dose combination is reduced by linear calculations to 30/240 mg for a 15-kg child. However, based on our allometric interpolation, this would result in an appropriate scaled dose of piperaquine and a dihydroartemisinin-piperaquine dose that is 20% lower than the optimum. Allometric scaling of fixed-dose combinations will be valid only if the same exponent applies to both drugs (or a default-to-fixed-exponent scaling is used); however, our data indicate this is unlikely to be appropriate for artemisinin-based combination therapies, due to mismatch of the allometric exponents (Table 1).

We conclude that interpolation of interspecies allometric scaling is plausible for estimation of pediatric doses of antimalarial drugs and would be valuable in designing clinical pharmacokinetic or efficacy studies. The limitations of allometric scaling are well documented; however, the ongoing use of linear scaling of adult to pediatric doses (mg/kg) is recognized as flawed (36) and should be the subject of further investigation in antimalarial chemotherapy.

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