Artemisinins were discovered to be highly effective antimalarial drugs shortly after the isolation of the parent artemisinin in 1971 in China. These compounds combine potent, rapid antimalarial activity with a wide therapeutic index and an absence of clinically important resistance. Artemisinin containing regimens meet the urgent need to find effective treatments for multidrug resistant malaria and have recently been advocated for widespread deployment. Comparative trials of artesunate and quinine for severe malaria are in progress to see if the persistently high mortality of this condition can be reduced.

Artemisinins are derived from a plant called sweet wormwood (or sweet Annie: Artemisia annua). In China, where they were first discovered, “qinghao” extracts were reported to have antipyretic properties more than 1500 years ago. In 1967 an outstanding coordinated programme was started by the Chinese government to discover antimalarial principles in various medicinal herbs including qinghao. In 1971, a highly active chemical from qinghao, known as qinghaosu was obtained and is now called artemisinin. Since this initial discovery, an array of semi-synthetic oil and water soluble derivatives of artemisinin have been developed, with a variety of formulations entering clinical studies. These compounds have impressive parasitidal properties in vitro, rapidly arresting parasite metabolism in concentrations within the lower nanomolar range, and killing parasites more quickly than other antimalarial drugs. These and other properties described below make artemisinins our most important class of antimalarial agent, and a mainstay against otherwise multidrug resistant Plasmodium falciparum. Their use in many countries has been severely restricted by cost, because artemisinins in combination are several-fold more expensive than the now almost useless chloroquine, or sulfadoxine-pyrimeethamine, whose efficacy is also waning. However, providing mechanisms and the political will to subsidise and control the use of artemisinins can be implemented, it is probable that some regimens combining artemisinins with other antimalarials will supersede cheaper and now ineffective alternatives.

Registration of artemisinins for use in developed countries is being actively pursued but only one fixed dose oral combination (artemether-lumefantrine) is currently available to treat uncomplicated malaria. If available, parenteral artemisinins can be used to treat severe malaria in the UK on a named patient basis.

CHEMISTRY AND SYNTHESIS
Artemisinin is comparatively easily purified by crystallisation after extraction from Artemisia annua plants but is extremely difficult to synthesise de novo. Artemisinin is a sesquiterpene lactone structure in which antimalarial activity is inextricably linked to an unusual endoperoxide trioxane moiety (fig 1). Artemisinin itself is a highly crystalline compound that does not dissolve in oil or water and so can only be given by the enteral route. Artemisinin is the parent compound for semi-synthetic derivatives that have been chemically modified at the C10 position to produce artesunate, arteether, artelene, dihydroartemisinin, and artelanic acid (fig 1). These compounds have variously been formulated for oral, rectal, and parenteral administration. The sodium salts of artesunate and artelinic are used for parenteral administration of these derivatives.

Arteether was developed under the aegis of the World Health Organisation despite lacking clear advantages over artemether, for which a much larger clinical experience already exists; arteether is no longer being investigated as an antimalarial agent. However, locally formulated products are used in India (β-artether, Artecol) and the Netherlands (β-artether, Arteotil (Articef)). Artelanic acid (a water soluble derivative) was developed by Walter Read Army Institute for Research. Although artelinate will not be further developed, various formulations and combinations of artesunate with other antimalarials are under active development.

METABOLISM AND PHARMACOKINETICS
Once absorbed, the artemisinin derivatives are converted primarily to dihydroartemisinin (DHA) and thence to inactive metabolites via hepatic cytochrome P-450 and other enzyme systems. DHA is itself a potent antimalarial with an elimination half life of about 45 minutes. The extent of conversion to DHA differs between derivatives. Artemisinin itself is not metabolised to DHA but acts as the primary antimalarial, while artesunate is rapidly (within minutes) hydrolysed to DHA and its antimalarial activity is largely mediated by DHA. Artemether and arteether contribute to antimalarial activity, probably to a similar extent as DHA, to which they are converted more slowly. DHA is mostly bound to plasma proteins.

Pharmacokinetic studies on artemisinins have been limited by difficulties of assay; several techniques with differing accuracies have been used by various groups. Furthermore, studies must necessarily take into account active metabolites (mostly DHA). Bioassay techniques measuring total antimalarial activity account for...
In uncomplicated malaria, when artemisinins are used orally, most pharmacokinetic information is now available for artsunate followed by artemether. The absolute bioavailability of antimalarial activity after a single dose of oral artesunate in uncomplicated adult malaria is about 60%\textsuperscript{12} although there is greater interpatient variation than in healthy volunteers.\textsuperscript{11} Time to maximum DHA concentration is typically one to two hours.\textsuperscript{13–16} Studies suggest that clearance after artesunate is reduced during acute infection compared with recovery, either via disease effects on pharmacokinetics or enzyme autoinduction.\textsuperscript{11}–\textsuperscript{13} 19

Although absolute bioavailability studies for artemether, artemisinin, and DHA are not possible given lack of intravenous formulations, pharmacodynamic activity (parasite clearance) after oral dosing of these derivatives is satisfactory. When studied, oral formulations show appropriately reliable and rapid absorption in the treatment of uncomplicated malaria.\textsuperscript{20–22} As for artesunate, studies of oral artemether\textsuperscript{23} and artemisinin\textsuperscript{24, 25} show increasing clearance with multiple dosing and during recovery from acute infection.

In severe malaria, the delayed and variable absorption of the oil soluble derivatives artemether and arteether when given by the intramuscular route is of great potential clinical relevance. Table 1 gives the pharmacokinetic data from studies on intramuscular artemether and artesunate in malaria patients.

In uncomplicated malaria, the relative bioavailability of intramuscular artemether appears poor compared with the oral route\textsuperscript{26} and in most studies absorption is extremely variable with maximum concentrations only being achieved many hours after administration.\textsuperscript{20–22} Most worryingly, a significant number of patients (5 of 26 in one study and 7 of 97 in another) had no detectable antimalarial present as ascertained by both conventional\textsuperscript{27} 28 and bioassay techniques\textsuperscript{29} and this phenomenon was associated in one study with impaired parasite clearance kinetics.\textsuperscript{29} These properties point to pharmacokinetic disadvantages for intramuscular artemether in severe malaria. Intramuscular artemether may be absorbed even more slowly than artemether.\textsuperscript{30} These pharmacokinetic findings also have relevance to our understanding of neurotoxicity seen in animal models receiving oil based artemisinins (see below).

**Figure 1** QTing hào su or artemisinin 1 and derivatives dihydroartemisinin 2, artemether 3, arteether 4, artesunic acid (artesunate) 5, and artemolate 6. The numbering scheme is that used by Chemical Abstracts.

Parenteral artesunate is pharmacokinetically superior to artemether for the treatment of severe malaria, whether given intravenously\textsuperscript{30–34} or by the intramuscular route (to children),\textsuperscript{35} a fact that escaped attention in a later study on artemether.\textsuperscript{36} Absorption from the intramuscular site in both adults with uncomplicated malaria and children with severe malaria is rapid with peak DHA concentrations achieved within one hour and DHA bioavailability over 80%.\textsuperscript{27} (Table 1). Severity of malaria infection seems to have no significant influence on artsunate pharmacokinetics\textsuperscript{11} but age may have.

Table 2 gives the pharmacokinetic data from studies on intrarectal administration of artemisinins to malaria patients. Rectal artesunate in African children with moderate malaria (defined as being unable to take oral medications or prostration/obtundation) shows rapid but variable absorption with peak plasma DHA concentrations appearing in about two hours and bioavailability of between 20% and 60%.\textsuperscript{34, 36} Rectal artemisinin may have a comparatively slower absorption profile in volunteers and patients with uncomplicated malaria.\textsuperscript{32, 34, 37} Intrarectal DHA has been studied in only a small number of patients and its behaviour seems comparable to intrarectal artesumin.\textsuperscript{7}

Unfortunately very few pharmacokinetic studies have focused on the variation in artesumin profiles in different populations of patients, particularly children and pregnant women. There are also comparatively few studies of interactions between artemisinins and other antimalarial or groups of drugs, although there seem to be no significant interactions between artesunate and mefloquine or arteether and lumefantrine.\textsuperscript{38}

**ANTIMALARIAL PROPERTIES**

Artemisinins kill all species of plasmodium that infect humans.\textsuperscript{1} 29–47 In vitro *P. falciparum* IC\textsubscript{50} values (median and range) have been reported as 4.2(0.5–34.6), 4.3(0.5–23.2), and 16.2(1.3–58.3)nM for artesunate, dihydroartemisinin, and artemether respectively.\textsuperscript{48} The asexual stages of infection are the most susceptible, with artemisinins inducing up to a 10 000-fold reduction in parasite biomass per asexual cycle.\textsuperscript{48} In common with other antimalarials, artemisinins are particularly active against the large ring stage of infection when parasites are beginning to become most metabolically active. However, in contrast with other currently useful antimalarials, artemisinins also target tiny ring stages of infection\textsuperscript{48, 49} (present only a few hours after red cells are invaded by merozoite stages). This killing results in removal of parasites from within infected cells, probably by the reticuloendothelial system, which returns these “pitted” erythrocytes to the
### Table 1: Single dose conventional pharmacokinetic studies of intramuscular artemisinin derivatives given to patients with *Plasmodium falciparum* malaria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ref</th>
<th>Age (y)</th>
<th>Sev</th>
<th>Number</th>
<th>Dose</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µM)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (min)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (min)</th>
<th>AUC&lt;sub&gt;0-24h&lt;/sub&gt; (µM min)</th>
<th>V/F (l/kg)</th>
<th>CL/F (l/kg/h)</th>
<th>T&lt;sub&gt;abs&lt;/sub&gt; (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARTS levels after ARTS</strong></td>
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<td></td>
</tr>
<tr>
<td>Adults</td>
<td>U</td>
<td>7</td>
<td>11</td>
<td>120 mg</td>
<td>2.3 (2.0-4.8)</td>
<td>12 (10-15)</td>
<td>41 (18)</td>
<td>1.56 (1.14)</td>
<td>2.6 (1.2)</td>
<td>2.9 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S+RF</td>
<td></td>
<td>26</td>
<td>1.5-10</td>
<td>S</td>
<td>11</td>
<td>120 mg</td>
<td>2.4 (2.0-2.9)</td>
<td>7.2 (4.1-11.4)</td>
<td>25.2 (4.2-501)</td>
<td>83.5 (9.2-747.3)</td>
<td>1.3 (0.5-3.2)</td>
<td>3.4 (2.0-20)</td>
</tr>
<tr>
<td><strong>DHA levels after ARTS</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>U</td>
<td>7</td>
<td>11</td>
<td>120 mg</td>
<td>4.1 (3.4-6.4)</td>
<td>45 (34-60)</td>
<td>64 (21)</td>
<td>522 (204)</td>
<td>1.1 (0.4)</td>
<td>0.73 (0.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S+RF</td>
<td></td>
<td>26</td>
<td>1.5-10</td>
<td>S</td>
<td>11</td>
<td>120 mg</td>
<td>2.4 (2.8-3.6)</td>
<td>40.5 (11.5-68.2)</td>
<td>40.2 (1.4-148.8)</td>
<td>236.9 (46.7-582.7)</td>
<td>1.2 (0.03-6.4)</td>
<td>1.0 (0.36-10.8)</td>
</tr>
<tr>
<td><strong>ARTM levels after ARTM</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>U</td>
<td>11</td>
<td>160 mg</td>
<td>0.84 (0.56-1.81)</td>
<td>4 (2-6)</td>
<td>3.7 (4.2-6.6)</td>
<td>811 (431-1702)</td>
<td>25.9 (10.8-71.9)</td>
<td>31.9 (18.2-110.4)</td>
<td>45.6 (7.4-298.2)</td>
<td>1.2 (0.4-6.3)</td>
<td>1.6 (0.06-10.8)</td>
</tr>
<tr>
<td>S+RF</td>
<td></td>
<td>26</td>
<td>1.2 mg/kg</td>
<td>1.6 (0.6-2.97)</td>
<td>7.2 (4.1-11.4)</td>
<td>25.2 (4.2-501)</td>
<td>83.5 (9.2-747.3)</td>
<td>1.3 (0.5-3.2)</td>
<td>2.4 (0.2-20)</td>
<td>2.7 (0.87-5.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S+RF</td>
<td></td>
<td>27</td>
<td>1.2 mg/kg</td>
<td>2.4 (1.0-2.97)</td>
<td>7.2 (4.1-11.4)</td>
<td>25.2 (4.2-501)</td>
<td>83.5 (9.2-747.3)</td>
<td>1.3 (0.5-3.2)</td>
<td>2.4 (0.2-20)</td>
<td>2.7 (0.87-5.99)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Data are presented as median (range) or mean (SD) unless otherwise indicated. Bioassay values are DHA equivalents. ARTS, artesunate; DHA, dihydroartemisinin; ARTM, artemether; U, uncomplicated malaria; S, severe malaria; RF, acute renal failure; C<sub>max</sub>, peak drug concentration in plasma; T<sub>max</sub>, observed time to C<sub>max</sub>; T<sub>1/2</sub>, elimination half life; AUC, area under the plasma concentration-time curve; V/F, fractional volume of the central compartment; CL/F, fractional clearance; T<sub>abs</sub>, absorption half time. Interquartile range.

### Table 2: Single dose pharmacokinetic studies of intrarectal artemisinin derivatives administered to patients with *Plasmodium falciparum* malaria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ref</th>
<th>Age group</th>
<th>Severity</th>
<th>Number</th>
<th>Dose</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µM)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;0-24h&lt;/sub&gt; (µM min)</th>
<th>V/F (l/kg)</th>
<th>CL/F (l/kg/h)</th>
<th>T&lt;sub&gt;abs&lt;/sub&gt; (h)</th>
<th>T&lt;sub&gt;lag&lt;/sub&gt; (h)</th>
<th>B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARN after ARN</strong></td>
<td></td>
<td>Adults</td>
<td>U</td>
<td>8</td>
<td>600 mg</td>
<td>0.37 (0.21)</td>
<td>7.2 (3.9)</td>
<td>3.1 (2.1)</td>
<td>80.8 (61.9)</td>
<td>1.0 (0.5-2.5)</td>
<td>0.3 (0.3-0.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>U</td>
<td>25</td>
<td>500 mg</td>
<td>0.86 (0.33)</td>
<td>4.0 (2-10)</td>
<td>2.0 (1.4)</td>
<td>184 (110)</td>
<td>184 (110)</td>
<td>98.0 (61.9)</td>
<td>1.0 (0.5-2.5)</td>
<td>0.3 (0.3-0.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>U</td>
<td>33</td>
<td>600 mg</td>
<td>0.47 (0.1-0.6)</td>
<td>6.5 (2-14)</td>
<td>4.4 (4)</td>
<td>1063 (756-1806)</td>
<td>1139 (708-1702)</td>
<td>5.4 (3.2-6.9)</td>
<td>0.4 (0.3-0.8)</td>
<td></td>
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<tr>
<td><strong>DHA after DHA</strong></td>
<td></td>
<td>Adults</td>
<td>U</td>
<td>11</td>
<td>160 mg</td>
<td>0.75 (0.55-1.11)</td>
<td>4.0 (2.63-6)</td>
<td>204 (78)</td>
<td>190 (78)</td>
<td>16 (13-25)</td>
<td>16 (13-25)</td>
<td>16 (13-25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ARTS after ARTS</strong></td>
<td></td>
<td>Adults</td>
<td>U</td>
<td>11</td>
<td>160 mg</td>
<td>0.75 (0.55-1.11)</td>
<td>4.0 (2.63-6)</td>
<td>204 (78)</td>
<td>190 (78)</td>
<td>16 (13-25)</td>
<td>16 (13-25)</td>
<td>16 (13-25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>U</td>
<td>26</td>
<td>12.7 (0.9) mg/kg</td>
<td>1.0858</td>
<td>0.98</td>
<td>0.27</td>
<td>2.3 (1.0)</td>
<td>23 (10)</td>
<td>25 (10)</td>
<td>23 (10)</td>
<td>23 (10)</td>
<td>23 (10)</td>
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<tr>
<td><strong>DHA after ARTS</strong></td>
<td></td>
<td>Adults</td>
<td>U</td>
<td>11</td>
<td>160 mg</td>
<td>0.75 (0.55-1.11)</td>
<td>4.0 (2.63-6)</td>
<td>204 (78)</td>
<td>190 (78)</td>
<td>16 (13-25)</td>
<td>16 (13-25)</td>
<td>16 (13-25)</td>
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<td></td>
</tr>
<tr>
<td>Adults</td>
<td>U</td>
<td>35</td>
<td>10</td>
<td>9.3 mg/kg</td>
<td>6.9-11.8</td>
<td>2.4 (0.8-5.8)</td>
<td>1.7 (0.9-3.2)</td>
<td>0.79 (0.41-2.69)</td>
<td>588 (81-1692)</td>
<td>4.4 (1.8-14.4)</td>
<td>2.6 (1-22.3)</td>
<td>0.69 (0.3-1.24)</td>
<td>0.63 (0.06-10.8)</td>
<td>15.4 (3.8-47.9)</td>
</tr>
<tr>
<td>Adults</td>
<td>M</td>
<td>16</td>
<td>18.9 mg/kg</td>
<td>15.4-22.9</td>
<td>3.1 (0.7-6.8)</td>
<td>1.8 (0.6-3.3)</td>
<td>0.85 (0.09-2.5)</td>
<td>792 (174-1572)</td>
<td>5.9 (1.1-11.7)</td>
<td>3.9 (1.7-19.6)</td>
<td>1.1 (0.6-2.7)</td>
<td>0.37 (0.09-0.93)</td>
<td>23 (6.8-78)</td>
<td></td>
</tr>
</tbody>
</table>

* Data are presented as median (range) or mean (SD) unless otherwise indicated. ARN, artemisinin; DHA, dihydroartemisinin; ARTS, artesunate; U, uncomplicated malaria; M, moderate malaria; C<sub>max</sub>, peak drug concentration in plasma; T<sub>max</sub>, observed time to C<sub>max</sub>; T<sub>1/2</sub>, elimination half life; AUC, area under the plasma concentration-time curve; V/F, fractional volume of the central compartment; CL/F, fractional clearance; T<sub>abs</sub>, absorption half time; T<sub>lag</sub>, time to quantifiable drug in plasma; B, relative bioavailability. Interquartile range, † includes patients with *P vivax* infection, ‡ modelled mean values.
circulation carrying an immunological marker of the presence of the parasite on its surface (an early stage antigen called RESA). Artemisinins also inhibit metabolism of parasites more quickly than other antimalarials used to treat severe malaria, a pharmacodynamic property that is of potential benefit given that most deaths in African children occur in the first 12 to 24 hours after admission. They also reduce cytoadherence of infected red cells, a recognised virulence determinant.

Artemisinins do not interfere with hepatic stages of parasite development and therefore have no causal prophylactic value. They do kill early gametocyte stages of development and have the potential to interfere with mosquito transmission. This property may be useful in areas where transmission rates for malaria are comparatively low, but has not provided benefit in areas of high transmission despite reported reduction of gametocyte rates.

MECHANISM OF ACTION

For several decades, the antimalarial action of artemisinins has been attributed to their chemical capability to generate free radicals. This mechanism of action has been suggested partly on the grounds that well recognised sources of free radicals (such as tert-butylperoxide) can themselves kill malaria parasites, albeit in comparatively high (mM) concentrations. The peroxide structure (essential for antimalarial activity) has been studied in detailed chemical experiments aiming to decipher exactly how it may act as an antimalarial. It is held by many workers that artemisinins upon reaction with Fe²⁺ are converted first into oxygen centred free radicals derived by reductive cleavage of the peroxide bridge, which are then converted into carbon centred free radicals by intramolecular hydrogen abstraction from CH₂ groups on the periphery of the artemisinin by the O centred radicals. Fe²⁺ is a catalyst that can generate free radicals from peroxidic structures in other peroxides, but in the case of the antimalarial action or artemisinins, this is further maintained to take place in the food vacuole by either free Fe³⁺ or by ferroprotoporphyrin IX (reduced haem). Carbon centred free radicals have been put forward as principal intermediates in the parasitidical process, but this theory is also the first to see artemisinins killing parasites via an indiscriminate process, a view that is hard to integrate with the exceptionally high in vitro activities of artemisinins and stands in pronounced contrast with the mechanism of action of most bioactive molecules where activity is mediated by high affinity binding to an active site.

More recently, an alternative mechanism of action for artemisinins based on inhibition of the malarial parasite’s calcium ATPase (sarcoplasmic endoplasmic reticulum calcium ATPase, SERCA) has been suggested. This work has reconciled some intriguing observations on actions of artemisinins, and also proposed new directions for further studies and drug development pathways. The arguments for and against these different mechanisms have been discussed in detail in current reviews.

CLINICAL APPLICATIONS

Artemisinin derivatives are used for treatment of uncomplicated and severe malaria in both adults and children. After some initial concerns, evidence for the safety of artemisinins in pregnant women (a population that is particularly at risk from malaria) is emerging: in a study of over 500 women treated with artemisinins in Thailand, there was no increase in rate of abortion, congenital abnormality, or stillbirth compared with background incidences in this population. When artesunate was added to an intermittent pyrimethamine-sulfadoxine regimen in pregnant women in the Gambia, there was again no significant adverse effect after gestational exposure. However, data on artemisinin use in the first trimester of pregnancy remain scanty, and more experience is needed before recommendations can be made on a firm basis.

Artemisinins are unique among antimalarials in that there is still no evidence of significant resistance in clinical isolates. Their short half life renders them inappropriate for prophylaxis.

Uncomplicated malaria

Uncomplicated malaria can be managed by oral antimalarial and symptomatic therapy, in contrast with moderate or severe disease. Particular combinations have been reviewed recently. The emergence of resistance to chloroquine and pyrimethamine-sulfadoxine has led to the introduction of artemisinin containing combinations, particularly in south east Asia where resistance to mefloquine also emerged rapidly. In this location combination of artemisinins with mefloquine provided much improved cure rates. Successful use of artemisinin derivatives with sulfadoxine-pyrimethamine has recently been described in Africa but addition of artesunate to chloroquine did not prevent treatment failure. The combination approach has been discussed extensively elsewhere and is now being implemented in a variety of national policies as well as by international organisations. However, with ready availability on the open market, the reality is that artemisinins are certainly being applied in inappropriate regimens including monotherapy (see below); furthermore trading of fake artesunate represents a significant threat to malaria initiatives. Artemether-lumefantrine is the only fixed dose artemisinin containing combination that is registered for use in Europe, and is licensed as a six dose regimen over 60 hours in patients weighing over 35 kg.

Very few dose ranging/frequency studies have been carried out to ensure that current regimens for uncomplicated malaria have been truly optimised. In adults, different doses of artesunate, given under cover of the slower acting agent mefloquine, suggested to the authors that a dose of 2 mg/kg artesunate was sufficient to reduce parasitaemia rapidly. However, results from only two to three patients probably skewed the inherently variable pharmacodynamic data obtained in this small study, and make more tentative the conclusions drawn from this study about oral dosing regimens in general. Most physicians currently use an oral dose of artemate of 4 mg/kg per day for three days for patients with uncomplicated malaria when in combination with a second antimalarial. Despite the generally rapid elimination kinetics of artemisinins, daily dosing of oral artemate results in parasite clearance kinetics indistinguishable from twice daily dosing. This suggests that constant drug levels are not necessary for satisfactory parasite clearance; the biological effects of artemisinins extend beyond their presence at therapeutic concentrations in plasma. In some ways analogous to a post-antibiotic effect.

Severe malaria

Severe malaria in hospitalised patients is associated with a mortality of between 15% to 20%, despite appropriate antimalarial and supportive treatment. With the widespread establishment of chloroquine resistance, there are only two classes of compound that are useful to manage severe malaria, the cinchona alkaloids (quinine and quinidine) and artemisinins. In Europe and Africa, quinine remains the drug of choice, although it suffers from certain drawbacks. Quinine has a narrow therapeutic ratio, causing hyperinsulinaemic hypoglycaemia (more frequent and severe in pregnancy) and prolongs the QTc interval when given parenterally, particularly if infused too rapidly. Intramuscular
quarine is effective, but can cause local toxicity as well as hypoglycaemia in patients who may not have intravenous access. Furthermore, in south east Asia there is evidence of increasing quinine resistance so that artemisinins are now used as first line treatment for severe malaria in most units.

Several trials have compared quinine and intramuscular artesmer for severe infection in both south east Asia and Africa. Despite improved parasite clearance parameters in most trials, definitive evidence for improved mortality with artesmeter in individual trials and meta-analysis is lacking. Many important observations have emerged from these studies. Firstly, the incidence of post-admission hypoglycaemia is significantly higher with quinine compared with artesmeter. Secondly, the frequency of dosing (more with quinine) also adds extra demands on scarce nursing resources. Most significantly, artesmeter may not have been the best choice of artesminin to study in the first place, as suggested more than a decade ago (Dr Hien, Cho Quan Hospital, Vietnam, personal communication to SK). Compared with artesunate, artesmer is less completely biotransformed to the more potent dihydroartesminin and has slow, erratic absorption after intramuscular administration (see above); in fact the ability of artesmer to provide equivalent benefit to quinine is probably testament to the antimalarial potency of the artesminin derivatives as a group.

Attention has therefore switched to artesunate. Parenteral artesunate has been used in adults and children with severe malaria in south east Asia where intramuscular administration was comparable in efficacy and safety to the intravenous route. In an analogous manner to parenteral artesmer, artesunate (intravenously) shows reduced incidence of hypoglycaemia compared with quinine. Large multinational studies in south east Asia comparing artesunate and quinine using mortality as an end point are now underway (Professor N White, personal communication). Similar studies in African children are also urgently needed because of differences in natural history of severe malaria, particularly the more rapid recovery of children compared with adults as well as the incidence of quinine resistance in south east Asia, both of which may obscure mortality advantages seen with quinine in adults. Intramuscular artesunate has an acceptable pharmacokinetic profile in African children where parasite clearance kinetics seem to be comparable to the intravenous route. Trials in this area are a high priority and can properly be funded by organisations such as the EDCTP and Medicines for Malaria Ventures whose avowed aim is to improve treatments for malaria.

**Intrarectal administration**

Patients with malaria presenting in rural areas may be obtunded or vomiting and unable to take oral medications, leading to significant delay in treatment if facilities for parenteral treatment are unavailable. In such circumstances the rectal route of administration is attractive because in areas where this route is culturally acceptable, rural healthcare workers can be trained to identify moderate and severe malaria and administer rectal drugs before transfer of patients to hospital. Quinine has been tested via the intrarectal route but may still induce hypoglycaemia, which may not be recognised or treated. The wider therapeutic index of artesminin derivatives means that they are excellent choices for rectal administration despite the inevitable variability of absorption from this route. Artemisinin formulations have been used with empirical success in south east Asia for some considerable time and recently pharmacokinetic profiles have begun to be delineated. In a comparative study with parenteral quinine, rectal artesunate was efficacious in African children with moderate malaria. This study was developed from detailed pharmacokinetic characterisation of a rectal formulation of artesunate that led to rapid falls in parasitaemia that were indistinguishable from those seen after intravenous artesunate.

**LIMITATIONS OF ARTEMISININS**

Putting aside questions of cost, which may be the most important for users of antimalarials but have been comprehensively reviewed in a recent authoritative report from the Institute of Medicine, there are certain inherent problems with current artesminins that require discussion.

**Poor cure rate of monotherapy**

Artemisinins reliably reduce initial initial malaria parasitaemia by a factor of 10 per 48 hour asexual cycle and modelling studies therefore suggest that six days of treatment should cure parasite burdens of up to 10 parasites. This model is difficult to reconcile with the high recrudescence rates (10–15%) seen with artesminin monotherapy. This poor efficacy of cure (which is not due to resistance) is usually attributed to the intrinsically short half life of artesminins, which is further shortened by the increased drug clearance that develops during repeat dosing and/or convalescence with various oral artesminin derivatives (see above). Blaming pharmacokinetic factors alone for the poor efficacy of artesminin monotherapy may not be justified because constant drug levels are not necessary for potent pharmacodynamic effects (at least in the initial, visible phase of parasitaemia). Furthermore, if pharmacokinetic behaviour were a problem, prolongation of treatment course may be predicted to compensate, but this is not generally observed in practice; seven days of monotherapy with artesminin still only cures 80–90% of uncomplicated falciparum infections. Parasite reduction ratio models for artesunate derived on data obtained at the start of treatment may not be applicable to the process of eradication of small numbers of residual parasites, which determines eventual cure rates. Other phenomena may exist that permit escape from artesminin therapy, necessitating a second (albeit less visibly effective) antimalarial.

**Neurotoxicity**

Despite pre-clinical evidence of brainstem toxicity in animals, millions of doses in various formulations have been given to humans without significant evidence of major toxicity, even when particular attention is given to monitoring for...
neurotoxicity both clinically\textsuperscript{96, 97} and pathologically.\textsuperscript{98} This discrepancy between animal and human toxicity has been attributed to the comparatively high and prolonged dosing regimens used in certain animal studies.\textsuperscript{99} In addition, pharmacokinetic studies of parenteral artemether and arteether have showed the slow release and consequently pharmacokinetic studies of parenteral artemether and arteether have showed the slow release and consequently long exposure times seen with oil based formulations of these drugs in both animals\textsuperscript{100} and humans.\textsuperscript{101} It is probably the long duration of exposure to artemisinins that determines neurotoxicity rather than the maximum concentrations reached.\textsuperscript{102} Prolonged high concentrations of artemisinins are certainly not seen in oral regimens, which constitute the vast majority of artemisinin courses given, and there is no pathological evidence of neurotoxicity in patients exposed to an average of 76.5 hours of intramuscular artemether.\textsuperscript{103} A recent claim that arteether-lumefantrine induces mild but significant hearing loss\textsuperscript{104} seems to contradict this view but needs to be reproduced independently and the mechanism dissected, particularly in terms of the time course of hearing loss.\textsuperscript{105} Concern with regard to neurotoxicity should also be maintained in the context of children who have more significant hearing loss\textsuperscript{106} seems to contradict this view but needs to be reproduced independently and the mechanism dissected, particularly in terms of the time course of hearing loss.\textsuperscript{107} Concern with regard to neurotoxicity should also be maintained in the context of children who have more significant hearing loss\textsuperscript{108} and in the context of adults who have sustained high doses of artemisinins. Artemisinin for treatment of uncomplicated falciparum malaria: is there a place for monotherapy? Am J Trop Med Hyg 2001;65:690–5.


Other toxicity and interactions

Administration of artemisinins may be associated with transient gastrointestinal disturbance, a characteristic of acute malaria in any case, and rarely with severe allergic reactions\textsuperscript{109} or haemolysis.\textsuperscript{110} Fetotoxicity is an important concern, again based on animal studies, although artemisinins have not been shown to be teratogenic in the small human experience available. They are not advised for use in the first trimester of pregnancy, but have been used rarely when alternatives to lifesaving treatment have been exhausted. Given the plan to roll out artemisinin combination therapies, there have been few drug metabolism and interaction studies carried out for artemisinins and their combination partners.\textsuperscript{111} In addition, there are few stability studies for many of the formulations of artemisinins (mainly artemesunate) that are used today.

ARTEMISININS—THE NEXT GENERATION

Some limitations of current artemisinins may be addressed by well designed studies using available formulations of drugs. However, some issues may best be dealt with by developing the next generation of artemisinins, aiming for increased potency, reduced toxicity, and improved stability.
Artemisins

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