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 parasiticidal 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-pyrimethamine, 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 so far 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 Artemesia 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, artemether, arteether, dihydroartemisinin, and arteficin acid (fig 1). These compounds have variously been formulated for oral, rectal, and parenteral administration. The sodium salts of artesunate and artelinate 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 (ab arteether, E-mail) and the Netherlands (β-artether, Artemotil (Articef)). Arteficin acid (a water soluble derivative) was developed by Walter Read Army Institute for Research. Although artelinic 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 (90%) 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
Artemisinins kill all species of plasmodium that infect humans. In vitro *P. falciparum* IC₅₀ 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. 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. 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.

Parenteral artesunate is pharmacokinetically superior to artemether for the treatment of severe malaria, whether given intravenously or by the intramuscular route (to children), a fact that escaped attention in a later study on artesunate. 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% (table 1). Severity of malaria infection seems to have no significant influence on artesunate pharmacokinetics 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%. Rectal artesinin may have a comparatively slower absorption profile in volunteers and patients with uncomplicated malaria. Intrarectal DHA has been studied in only a small number of patients and its behaviour seems comparable to intrarectal artesinin.

Unfortunately very few pharmacokinetic studies have focused on the variation in artemisinin 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 artemether and lumefantrine.

**ANTIMALARIAL PROPERTIES**

Artemisinins kill all species of plasmodium that infect humans. In vitro *P. falciparum* IC₅₀ 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. 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. 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 (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 levels after ARTS</th>
<th>Age (y)</th>
<th>Sev</th>
<th>Number</th>
<th>Dose</th>
<th>Cmax (μM)</th>
<th>T1/2 (min)</th>
<th>AUC0–24 (μM min)</th>
<th>V/F (l/kg)</th>
<th>CL/F (l/kg/h)</th>
<th>Tabs (min)</th>
<th>B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARTS</strong></td>
<td>7 Adults</td>
<td>U</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 (1.12)</td>
<td>2.9 (1.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 1.5–10</td>
<td>S</td>
<td>14</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 (0.3–20.4)</td>
<td>2.7 (0.87–5.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>2.4 mg/kg</td>
<td>1.72 (0.7–10.11)</td>
<td>8 (3.9–78.9)</td>
<td>48.2 (13.4–319.7)</td>
<td>84.9 (39.2–2264.7)</td>
<td>2.1 (0.3–6.4)</td>
<td>3.48 (0.18–10.2)</td>
<td>2.5 (1.28–4.152)</td>
<td></td>
</tr>
<tr>
<td><strong>DHA</strong></td>
<td>7 Adults</td>
<td>U</td>
<td>11</td>
<td>120 mg</td>
<td>4.1 (3.2–4.6)</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>
</tr>
<tr>
<td></td>
<td>26 1.5–10</td>
<td>S</td>
<td>14</td>
<td>1.2 mg/kg</td>
<td>1.2 (0.1–2.9)</td>
<td>25.9 (10.8–71.9)</td>
<td>31.9 (18.2–110.4)</td>
<td>83.6 (17.4–298.2)</td>
<td>1.2 (0.4–6.3)</td>
<td>2.16 (0.06–10.8)</td>
<td>15.4 (3.8–47.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>2.4 mg/kg</td>
<td>2.2 (0.8–3.6)</td>
<td>40.5 (11.5–88.2)</td>
<td>40.2 (1.4–148.8)</td>
<td>236.9 (46.7–582.7)</td>
<td>1.2 (0.03–3.2)</td>
<td>1.5 (0.36–7.8)</td>
<td>25.1 (5.1–47.3)</td>
<td></td>
</tr>
<tr>
<td><strong>ARTM</strong></td>
<td>27 Adults</td>
<td>S</td>
<td>11</td>
<td>160 mg</td>
<td>0.84 (0.56–1.81)</td>
<td>4 (2–6)</td>
<td>5.7 (4.2–6.6)</td>
<td>811 (431–1702)</td>
<td>8.6 (4.2–12.3)</td>
<td>1.1 (0.5–1.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>26 1.5–10</td>
<td>S</td>
<td>14</td>
<td>1.2 mg/kg</td>
<td>1.2 (0.1–2.9)</td>
<td>25.9 (10.8–71.9)</td>
<td>31.9 (18.2–110.4)</td>
<td>83.6 (17.4–298.2)</td>
<td>1.2 (0.4–6.3)</td>
<td>2.16 (0.06–10.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td>2.4 mg/kg</td>
<td>2.2 (0.8–3.6)</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 (0.03–3.2)</td>
<td>1.5 (0.36–7.8)</td>
<td>25.1 (5.1–47.3)</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\textsubscript{max}, peak drug concentration in plasma; T\textsubscript{max}, observed time to C\textsubscript{max}; T\textsubscript{1/2}, elimination half life; AUC, area under the plasma concentration-time curve; V/F, fractional volume of the central compartment; CL/F, fractional clearance; Tabs, 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>Cmax (μM)</th>
<th>T\textsubscript{max} (h)</th>
<th>T\textsubscript{1/2} (h)</th>
<th>AUC (μM min)</th>
<th>V/F (l/kg)</th>
<th>CL/F (l/kg/h)</th>
<th>Tabs (h)</th>
<th>B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARN</strong></td>
<td>32 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 (0.5–2.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 Adults</td>
<td>U</td>
<td>15</td>
<td>500 mg</td>
<td>0.66 (0.33)</td>
<td>4.0 (2–10)</td>
<td>2.0 (1.4)</td>
<td>184 (110)</td>
<td>1 (0.5–2.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33 Adults</td>
<td>U</td>
<td>8</td>
<td>600 mg</td>
<td>0.47 (0.1–0.6)</td>
<td>6.5 (2–14)</td>
<td>257 (26–406)</td>
<td>1063 (756–1806)</td>
<td>0.3 (0.3–0.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DHA</strong></td>
<td>7 Adults</td>
<td>U</td>
<td>11</td>
<td>160 mg</td>
<td>0.75 (0.55–1.11)</td>
<td>4.0 (2.3–6.3)</td>
<td>204 (78)</td>
<td>16 (13–25)</td>
<td>16 (13–25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ARTS</strong></td>
<td>34** 5–10</td>
<td>U††</td>
<td>47</td>
<td>12.7 (0.9) mg/kg</td>
<td>1.085 (0.21)</td>
<td>0.9 (0.27)</td>
<td>0.13 (0.27)</td>
<td>2.3 (1.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>DHA</strong></td>
<td>35 Adults</td>
<td>U††</td>
<td>10</td>
<td>9.3 mg/kg (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 (84–1692)</td>
<td>4.4 (1.8–14.4)</td>
<td>2.6 (1.1–22.3)</td>
<td>0.69 (0.3–1.24)</td>
<td>0.63 (0.13–3.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>18.9 mg/kg (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 (6–78)</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\textsubscript{max}, peak drug concentration in plasma; T\textsubscript{max}, observed time to C\textsubscript{max}; T\textsubscript{1/2}, elimination half life; AUC, area under the plasma concentration-time curve; V/F, fractional volume of the central compartment; CL/F, fractional clearance; Tabs, absorption half time; Tlag, time to quantifiable drug in plasma; B, relative bioavailability. Interquartile range, †0–8, *0–5. **Population pharmacokinetic study, ††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-butyliperoxide) 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 peroxodic 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 Fe2+ or by ferroprotoporphyrin IX (reduced haem). Carbon centred free radicals have been put forward as principal intermediates in the parasitidic process, but this theory is not without its critics as artemisinins kill 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 from CH2 groups on the periphery of the artemisinin by the O-centred radicals. Fe2+ is a catalyst that can generate free radicals from peroxodic 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 Fe2+ or by ferroprotoporphyrin IX (reduced haem). Carbon centred free radicals have been put forward as principal intermediates in the parasitidic process, but this theory is not without its critics as artemisinins kill 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 from CH2 groups on the periphery of the artemisinin by the O-centred radicals. Fe2+ is a catalyst that can generate free radicals from peroxodic 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 Fe2+ or by ferroprotoporphyrin IX (reduced haem). Carbon centred free radicals have been put forward as principal intermediates in the parasitidic process, but this theory is not without its critics as artemisinins kill 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 from CH2 groups on the periphery of the artemisinin by the O-centred radicals. Fe2+ is a catalyst that can generate free radicals from peroxodic 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 Fe2+ or by ferroprotoporphyrin IX (reduced haem). Carbon centred free radicals have been put forward as principal intermediates in the parasitidic process, but this theory is not without its critics as artemisinins kill 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 from CH2 groups on the periphery of the artemisinin by the O-centred radicals. Fe2+ is a catalyst that can generate free radicals from peroxodic 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 Fe2+ or by ferroprotoporphyrin IX (reduced haem). Carbon centred free radicals have been put forward as principal intermediates in the parasitidic process, but this theory is not without its critics as artemisinins kill 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.
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 artesunate for severe infection in both south east Asia and Africa. Despite improved parasite clearance parameters in most trials, definitive evidence for improved mortality with artesunate 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 artesunate. Secondly, the frequency of dosing (more with quinine) also adds extra demands on scarce nursing resources. Most significantly, artesunate may not have been the best choice of artemisinin to study in the first place, as suggested more than a decade ago (Dr Hien, Cho Quan Hospital, Vietnam, personal communication). Compared with artesunate, artesunate is less completely biotransformed to the more potent dihydroartesunate and has slow, erratic absorption after intramuscular administration (see above); in fact the ability of artesunate to provide equivalent benefit to quinine is probably testament to the antimalarial potency of the artemisinin 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 artesunate, 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 artesunate 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 artesinins**

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 artemisinins that require discussion.

**Poor cure rate of monotherapy**

Artemisinins reliably reduce initial malaria parasitaemia by a factor of 10^4 per 48 hour asexual cycle and modelling studies therefore suggest that six days of treatment should cure parasite burdens of up to 10^22 parasites. This model is difficult to reconcile with the high recrudescence rates (10%–15%) seen with artesunate monotherapy. This poor efficacy of cure (which is not due to resistance) is usually attributed to the intrinsically short half life of artemisinins, which is further shortened by the increased drug clearance that develops during repeat dosing and/or convalescence with various oral artemisinin derivatives (see above). Blaming pharmacokinetic factors alone for the poor efficacy of artesunate 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 artesunate 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 artemisinin therapy, necessitating a second (albeit less visibly effective) antimalarial. Although it has been strongly argued that, in any case, combination therapy has long term benefit in preventing resistance, the poor efficacy of monotherapy with the current generation of artemisinins remains a troubling and poorly explained phenomenon.

**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 and pathologically. This discrepancy between animal and human toxicity has been attributed to the comparatively high and prolonged dosing regimens used in certain animal studies. 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 concerns, artemisinin derivatives have less major toxicity vulnerable neurological systems and where therapeutic duration of exposure to artemisinins that determines neurotoxicity rather than the maximum concentrations reached. 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. A recent claim that arteether-lumefantrine induces mild but significant hearing loss 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. Concern with regard to neurotoxicity should also be maintained in the context of children who have more vulnerable neurological systems and where therapeutic experience is more limited. Even taking into account these concerns, artemisinin derivatives have less major toxicity than other available antimalarial drugs.

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 or haemolysis. 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. In addition, there are few stability studies for many of the formulations of artemisinins (mainly artesunate) 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. In this regard, fully synthetic trioxalones under drug development may help rapidly to expand the repertoire of new antimalarials. They have the advantage of independence from artemisinin as a raw material for synthesis. On the other hand newer semi-synthetic artemisinins such as artesinnone (http://www.mmv.org/) have been developed from a much larger base of medicinal chemistry and clinical experience suggesting that both approaches to improving our stock of antimalarials should be pursued.

USES OUTSIDE MALARIA
Oral arteether has been known for some time to possess activity against immature worms of Schistosoma japonicum and Schistosoma mansoni, and has proved an efficacious chemoprophylactic agent against both infections. It should be noted that the long term consequences of arteether use in this context potentially include selection for resistant plasmodia. Artesunate shows antitumour cell activity, although it has yet to enter clinical trials.

CONCLUSION
Like many drugs, artemisinins have been used empirically for many years during which their mechanism of action and pharmacokinetic properties have been unclear. Empirical judgements of efficacy and optimal administration have tended to be influenced by their undoubtedly impressive parasite clearance kinetics, which are superior to other commonly used antimalarials. However if the only fundamental and reliable measures of efficacy are cure and mortality rates for uncomplicated and severe malaria respectively, current artemisinins have some way to go before they can be said to provide a clear cut advantage over other antimalarial combinations in some geographical locations. Artemisinins are poorly efficacious at curing malaria as monotherapy, a phenomenon that is not well understood. Some concerns over neurotoxicity and its mechanism also remain. No regimen has yet proved superior to quinine for reducing mortality of severe malaria, although artemisinins certainly reduce the incidence of hypoglycaemia. Despite these issues, no time should be wasted in deploying artemisinins as part of combination therapy for multidrug resistant malaria when judged appropriate, with rectal administration permitting community based treatment of moderate malaria. If trial evidence can be obtained for improved outcome compared with quinine, parenteral artemether may finally take its place as the optimum treatment for the ever present problem of severe malaria.

YES/NO QUESTIONS (ANSWERS AT END OF REFERENCES)
1. True or false:
   (A) Artemisinins have very high efficacy in terms of cure rate when administered as monotherapy
   (B) There are several independent reports of human brainstem neurotoxicity induced by artemisinins
   (C) Parenteral artemisinins have been definitively shown to reduce mortality in severe malaria compared with quinine
   (D) Oral artemisinins are not used in prophylactic regimens
   (E) Artemisinin resistance has developed rapidly in south east Asia in the past decade
   (F) Manufacture of current artemisinin formulations is now entirely synthetic

2. Which formulations of artemisinin show most promise in the context of severe malaria?
Artemisinins

Authors’ affiliations
C J Woodrow, S Krishna, Department of Cellular and Molecular Medicine, Infectious Diseases, St George’s Hospital Medical School, Tooting, London, UK
R K Haynes, Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong

Funding: none.

Conflicts of interest: none declared.

REFERENCES

Artemisinins

C J Woodrow, R K Haynes and S Krishna

*Postgrad Med J* 2005 81: 71-78
doi: 10.1136/pgmj.2004.028399

Updated information and services can be found at:
http://pmj.bmj.com/content/81/952/71

These include:

**References**
This article cites 100 articles, 20 of which you can access for free at:
http://pmj.bmj.com/content/81/952/71#BIBL

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/