Treatment of imported malaria in adults: a multicentre study in France


From the Service des Maladies infectieuses et tropicales, Hôpital Nord, Assistance Publique-Hôpitaux de Marseille, Marseille, and 1INFECTIO-SUD Formation et Recherche, Nice, France

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Summary

Background: Data about anti-malarial drugs prescription practices in Europe and the safety of imported malaria treatments are scanty. In 1999, a French consensus development conference published guidelines for the prevention and treatment of imported P. falciparum malaria. The impact of these guidelines has not been evaluated.

Aim: To investigate the impact of these guidelines on the prescription of anti-malarials, and to evaluate the incidence of acute drug events (ADEs) leading to discontinuation of treatment.

Design: Cross-sectional survey.

Methods: Members of the medical staff in 14 French infectious and tropical disease wards completed a standardized form for each patient treated for imported malaria in 2001. A propensity score matching technique was used to estimate the risk of ADEs leading to discontinuation of the regimen.

Results: In the 474 patients studied, quinine was the first-line anti-malarial most often prescribed. Only 3% of patients received halofantrine. Mefloquine was associated with a RR of 4.9 (95%CI 3.2–7.4, p < 0.00001) risk of discontinuation of treatment due to ADEs.

Discussion: The very limited use of halofantrine indicates that the main practice recommendations of the guidelines have been taken into account. Mefloquine was associated with a substantial risk of discontinuing the treatment because of ADEs. This is a serious limitation for the use of mefloquine in the treatment of out-patients with imported malaria.

Introduction

Malaria remains an important infection in Europe, with approximately 16,000 cases imported each year. Of these, more than 5000 are reported from France, for the most part due to Plasmodium falciparum infections. In malaria-endemic areas, where reasons of cost often preclude the use of effective anti-malarials for routine treatment, P. falciparum drug resistance is a critical limitation to appropriate management of clinical malaria. In Europe and other industrialized countries, by contrast, travellers who have contracted malaria in endemic countries are commonly treated with...
highly effective anti-malarials when they return home.

In April 1999, a French expert consensus development conference issued practice guidelines for the prevention and treatment of imported \textit{P. falciparum} malaria.\textsuperscript{2} The experts were asked the following questions about imported \textit{P. falciparum} malaria: (i) how to shorten delays in the diagnosis of malaria; (ii) how to assess severity and manage treatment; (iii) how to treat and monitor an uncomplicated attack; (iv) how to treat and monitor a severe attack; (v) how to choose appropriate anti-malarial prophylaxis.

The aim of our study was to investigate the impact of these practice guidelines on the prescription of anti-malarial drugs in France after a period of 2 years. We also assessed the incidence rate of adverse drug events (ADEs) severe enough to prompt premature discontinuation of first-line curative anti-malarial regimens, with consequent switching to another anti-malarial.

The recommendations

We shall briefly describe the major recommendations issued for the first four issues regarding adults. Recommendations for the management of malaria in children will not be discussed here.

Shortening delays in the diagnosis of malaria

This requires improving information and education about malaria for both travelers and health professionals. The biological diagnosis of malaria is always an emergency; it should primarily rely on the examination of a thin blood slide.

Assessing the severity of a malaria attack

The ten criteria for severe malaria defined by the WHO\textsuperscript{3} were developed in malaria-endemic areas, and have not been validated in non-immune populations. For imported malaria, the experts therefore highlighted the four criteria: coma, shock, acidosis and respiratory distress as being the most relevant, in view of their frequency and predictive value. In the absence of any other criterion of severity, a high level of \textit{P. falciparum} parasitaemia (>5% of erythrocytes infected) should not in itself be considered a criterion of severe malaria.

Managing a \textit{P. falciparum} malaria attack

Malaria, severe or otherwise, should always be considered as an emergency. Out-patient treatment of malaria is possible if the following conditions are met: (i) the parasitological diagnosis is confirmed on the day of clinical examination; (ii) the malaria attack is uncomplicated (no signs of severe malaria, see above); (iii) there are no disorders of the gastrointestinal tract; (iv) \textit{P. falciparum} parasitaemia affects less than 5% of erythrocytes; (v) there are no sociocultural factors that could affect compliance with the treatment; (vi) there are no external risk factors (age, living alone, a history of splenectomy, current pregnancy, underlying cardiac disorders); (vii) the patient lives near a hospital; (viii) the patient has immediate access to the prescribed anti-malarial drug, which should be available from a pharmacy.

Two follow-up consultations, three and seven days after the beginning of treatment, are mandatory.

Patients who do not meet the above criteria for out-patient management must be referred to a hospital (emergency room or reference ward). In the emergency room, treatment should be started without delay according to the standard operating procedure for the management of patients with malaria, which must be easily accessible and regularly updated. Curative treatment must be initiated as soon as the diagnosis of malaria has been confirmed.

Hospitalization in an intensive care unit is mandatory if the patient presents with any sign of severe malaria. Patients with uncomplicated malaria should be treated in an ordinary medical ward. Hospitalization for at least 24 h is recommended in order to assess treatment tolerability and compliance. On discharge from hospital, the patient’s family doctor must be informed of the need for a follow-up visit on the seventh day.

The experts recommended that anti-malarial treatment be started when clinical presumption of malaria is convincing, even if the patient presents no sign of severe or complicated malaria and/or the initial thin blood film examination has been reported as negative or is not available. In such cases, the initial blood smear (if available) should be reviewed and further smears taken. If possible, investigations should include another technique that can detect lower levels of parasitaemia.

Treating and monitoring an uncomplicated \textit{P. falciparum} malaria attack

The choice of anti-malarial should be based on the risk benefit ratio for the drugs considered. Availability, effectiveness against the \textit{Plasmodium} isolate concerned, toxicity and rapidity of action, as well as other characteristics of patients, such as expected compliance with the treatment, must be
taken into account. Only three anti-malarial drugs were in regular use in 1999 in France: quinine, mefloquine and halofantrine. Each has been associated with potentially severe adverse effects, either due to intrinsic toxicity or overdose. The drug’s safety depends on the strict respect of dosage, administration route, and contraindications. Halofantrine has been associated with lethal cardiac complications, although the experts declared that insufficient relevant pharmacovigilance data about halofantrine were available. The most important adverse effects of mefloquine are neuropsychiatric; their frequency ranges from 1/200 to 1/1700 curative treatments, and can be severe. Quinine is associated with lethal complications only in the case of IV overdose. Oral quinine is usually well tolerated, but patients who do not adhere to the oral regimen have an increased risk of therapeutic failure.

On the basis of an analysis of the risk/benefit ratio, the experts recommended quinine or mefloquine as the first-line treatment of uncomplicated malaria for adults. The choice of either quinine or mefloquine depends on the patient’s expected compliance with treatment, respective contra-indications and the socio-economic context. The experts recommended that halofantrine should be used with extreme caution. At that time, the atovaquone-proguanil combination was considered an alternative whose importance remained unclear. The experts also stressed that great caution should be applied when anti-malarials were used simultaneously or in succession.

The recommended anti-malarial regimens for imported uncomplicated *P. falciparum* malaria in adults were as follows.

**Quinine**

Oral route: quinine 8 mg/kg tid for 7 days. Intravenous route: quinine 8 mg/kg diluted in serum glucose 5%, administered in a 4-h infusion tid or a continuous infusion over 24 h for 7 days. If the patient recovers quickly, the treatment can shift to oral administration of quinine or mefloquine, in order to avoid prolonged use of the intravenous route.

**Mefloquine**

A total of 25 mg/kg, split in two or three doses at 6- to 12-hourly intervals.

**Halofantrine**

Three doses of 24 mg/kg each, at 6-hourly intervals, to be taken well outside meal-times. This should be repeated on day 7 in order to avoid a relapse (but there is an increased risk of cardiac toxicity at the time of the second dose and the patient should thus be monitored for cardiac manifestations).

**Special cases**

Pregnant women should receive quinine only. Treatment of a patient who contracted malaria in an area where multi-resistant *P. falciparum* is endemic should rely on a 7-day intravenous or oral quinine regimen, in combination with either doxycycline 100 mg bid or clindamycin 10 mg/kg tid. The experts recommended clinical monitoring on day 3 and day 7 after the beginning of treatment. Prophylactic anti-malarial regimen is of no benefit and should not be prescribed after the completion of curative treatment.

**Treating and monitoring of a severe malaria attack**

All patients presenting with severe malaria must be hospitalized in an intensive care unit. Treatment with intravenous quinine must start as soon as the diagnosis is suspected (IV quinine must therefore be available in all hospitals). IV quinine treatment is administered with a loading dose of 17 mg/kg as a infusion over four hours, followed with 8 mg/kg tid either in continuous infusion or in a four-hour infusion. The objective is to reach a quinine blood level ranging from 10 to 15 mg/l as soon as possible, and to maintain this level. A shift to the oral route should occur as soon as possible. The total duration of treatment is 7 days.

If an infection with *P. falciparum* with a decreased sensitivity to quinine is suspected, it is advisable to add doxycycline (100 mg IV bid) or, if doxycycline is contra-indicated, clindamycin (10 mg/kg IV tid). Artemether should only be used in the case of an infection with *P. falciparum* where resistance is proven or in the case of a genuine contra-indication to quinine. Empirical antibiotic treatment is justified if a bacterial infection is suspected.

The therapeutic index of quinine is narrow, and dosage can be optimized by measuring quinine blood levels. An initial measurement after administration of the loading dose is advisable to check the accuracy of initial dosage. For patients at risk (e.g. with hepatic and/or renal insufficiency, for children and for pregnant women), later measurements of quinine blood level are advisable. Parasite counts should be performed only before the start of treatment and on the third day thereafter. If the patient does not improve, the interpretation of a therapeutic failure will rely both on the differential parasite count (from day 0 to day 3) and on the quinine blood level. With this information, it is
possible to adapt dosage. Because hypoglycaemia commonly occurs, intravenous infusion with glucose solution should be used, and the glucose blood level should be monitored every 4 h. Electrocardiograms must be undertaken at regular intervals.

The main new recommendation included in the guidelines is the need to use halofantrine with extreme caution to treat uncomplicated \textit{P. falciparum} malaria in adults, because of its cardiotoxicity. The conference also highlighted the need to gather more data concerning the safety of curative anti-malarial regimens. Although their effectiveness may be the same, anti-malarial drugs may differ in their safety profile. The fact that adverse drug events (ADEs) may ultimately result in treatment failure because regimens are not completed is the main rationale for the systematic hospitalization of patients presenting with imported \textit{P. falciparum} malaria, a much-debated topic.\footnote{4}

\section*{Methods}

A multicentre cross-sectional study was set up within the infrastructure of the Infectio-Sud group, an association of French infectious and tropical diseases specialists based in 14 teaching hospitals located in 11 cities in the South of France. Infectio-Sud focuses on training and research in tropical and infectious diseases.

All patients diagnosed in 2001 with malaria (i.e. with a \textit{Plasmodium} sp. infection) were included in the study. The diagnosis of malaria infection relied on the presence of parasites in the blood under microscope examination; other criteria, such as parasite antigenemia or PCR, were not considered in this study. Members of the medical staff in each centre completed a standardized form for each patient. To limit memory bias, we only used straightforward items aiming at answering our research question, and only covered data that could readily be found in the patient’s medical record. Briefly, we recorded: centre; patient’s gender, age and outcome; \textit{Plasmodium} species concerned; whether or not the patient presented with signs of severe or complicated malaria (according to the WHO criteria\footnote{5}); whether the patient had been managed as in- or out-patient; first-line anti-malarial drugs administered; duration of treatment and, if relevant, of hospitalization; incidence of ADEs prompting discontinuation of the first-line anti-malarial treatment and; if relevant, the second-line anti-malarial drugs used. Any unwanted harmful or abnormal effects plausibly related to anti-malarial administration were referred to as ADEs.

As in the above-mentioned guidelines, it is common practice among French practitioners to start the treatment of imported malaria using the IV route before switching to the oral route as soon as both fever and parasitaemia are cleared. The systematic hospitalization of uncomplicated \textit{P. falciparum} malaria is also common practice, although it is neither a national recommendation nor a legal obligation in France. The switching from a first-line IV regimen to a second-line oral regimen is usually undertaken in order to prevent infusion-related adverse events and improve patient comfort, and is rarely a consequence of ADEs or treatment failure. The details of ADEs were not specified in our questionnaire, but whether the treatment had been stopped because of ADEs was explicitly investigated. Even mild ADEs, such as vomiting, are important when considering the out-patient treatment of potentially life-threatening disease; ADEs prompting the discontinuation of the first-line anti-malarial treatment are thus a useful proxy of tolerability.

Statistical analyses used SAS v. 8.2 (SAS Institute). Data are reported as percentages or as means ± SD. Univariate comparisons used ANOVA or Fisher’s exact test, as appropriate. All tests were two-sided. Multivariate stepwise logistic regression analysis was used to determine significant independent predictors of treatment with mefloquine vs. any other anti-malarial drug, and to build mefloquine treatment propensity scores; i.e. the probability of being treated by mefloquine in terms of known prior covariates.\footnote{6} Patients were then matched by propensity score. In an observational study, this approach is a way of ensuring that the effect of treatment is compared only between individuals who are equally likely to have received it. A logistic regression analysis predicting ADEs was then computed on the basis of estimating equations, to take into consideration the correlation between matched sets when computing estimates.

\section*{Results}

In the 14 participating centres, 474 patients were diagnosed with a \textit{Plasmodium} sp. infection. The mean age of patients was 38 ± 14 years; 68% were males; 93% were in-patients. The mean duration of hospital stay was 5 ± 4 days, and 8% of patients presented with symptoms of severe or complicated malaria. No treatment failure was recorded: clinical recovery was recorded in 92% of patients, and the remainder were lost to follow-up. Of the 72 (15%) patients followed up for 1 month after treatment,
all were parasitologically cured, i.e. showed no *Plasmodium* parasitaemia by day 28.

*P. falciparum* infected 402 patients (85% of all *Plasmodium* infections). In 10 (2%) of these, *P. falciparum* was associated with another species. Infection with a *Plasmodium* species other than *P. falciparum* occurred in 78 patients (including the 10 patients with a mixed infection): 37 (47%) of these were infected with *P. vivax*, 30 (38%) with *P. ovale* and 11 (14%) with *P. malariae*. In 4 patients the *Plasmodium* species was not determined. Eight (12%) of the 68 infected with *Plasmodium* species other than *falciparum* and 25 (6%) of the 402 patients infected with *P. falciparum* were out-patients, the others were in-patients. Severe or complicated malaria attacks occurred in 39 patients infected with *P. falciparum*. The symptoms recorded (more than one symptom could occur in the same patient) included: cerebral manifestations (*n* = 19); acute renal failure (*n* = 9); respiratory distress (*n* = 8); hyperparasitaemia with >5% of parasitized erythrocytes (*n* = 7); disseminated intravascular coagulation (*n* = 4); hypoglycaemia (*n* = 3); purpura (*n* = 2); haemodynamic shock (*n* = 1). A spleen infarct occurred in one patient infected with *P. vivax*.

Table 1 summarizes the first-line anti-malarial drugs prescribed. Intravenous quinine, mefloquine, atovaquone-proguanil, chloroquine and oral quinine were those most often prescribed, totalling 88% of all first-line and 93% of all second-line prescriptions (data not shown). Halofantrine (3%) ranked seventh among all first-line anti-malarials prescribed. The most often prescribed oral anti-malarials were mefloquine and the atovaquone-proguanil combination. Quinine-clindamycin combinations were prescribed in only one centre, halofantrine in 7, and mefloquine in 8. Only one patient was treated with an artemisinin derivative, as none of these anti-malarials have been commercialized in France to date. Second-line anti-malarial regimens (data not shown) were usually given orally; it was common practice to start the treatment of imported malaria using the IV route before switching to oral administration. Of the 137 patients treated with a first-line IV quinine regimen who switched after the first few days to a second-line regimen, 71% received oral quinine in order to complete the seven-day standard regimen without the inconvenience of the IV route. Second only to oral quinine as a second-line treatment, mefloquine shortens the total duration of the anti-malarial regimen. Although less often used than mefloquine, the single dose sulfadoxine-pyrimethamine fixed combination shares the same advantage and is used as a second-line treatment to shorten the standard quinine regimen. Four patients developed a severe or complicated *P. falciparum* malaria attack after the initiation of a first-line oral regimen; they were then switched to second-line IV quinine regimen. Among patients infected with *P. vivax*, *P. ovale*, or *P. malariae*, the reference drug chloroquine was the most often prescribed (71%).

Anti-malarial-induced ADEs leading to discontinuation of treatment occurred in 16 patients (3%);

Table 1  Drugs prescribed as first-line anti-malarials in patients with either severe or uncomplicated *P. falciparum* malaria or non-falciparum infections

<table>
<thead>
<tr>
<th>Anti-malarial</th>
<th>Falciparum malaria</th>
<th>Non falciparum malaria</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severe (<em>n</em> = 39)</td>
<td>Uncomplicated (<em>n</em> = 367)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>IV quinine</td>
<td>30 (77%)</td>
<td>152 (41%)</td>
<td>9 (13%)</td>
</tr>
<tr>
<td>Oral quinine</td>
<td>2 (5%)</td>
<td>32 (9%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Atovaquone-proguanil</td>
<td>0</td>
<td>51 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>1 (3%)</td>
<td>65 (18%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>1 (3%)</td>
<td>14 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>IV quinine + clindamycin</td>
<td>2 (5%)</td>
<td>24 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Oral quinine + clindamycin</td>
<td>0</td>
<td>11 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>IV quinine + doxycycline</td>
<td>3 (8%)</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>0</td>
<td>4 (1%)</td>
<td>48 (71%)</td>
</tr>
<tr>
<td>Other (&lt;1% each)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>7 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>No anti-malarial</td>
<td>0</td>
<td>5 (1%)</td>
<td>2 (3%)</td>
</tr>
</tbody>
</table>

Data are numbers (%).

<sup>a</sup>Including four patients for whom the *Plasmodium* species was not determined, who were managed as uncomplicated *P. falciparum* malaria. <sup>b</sup>Other anti-malarial drugs were: Oral quinine plus doxycycline; arthemether; sulfadoxine-pyrimethamine. <sup>c</sup>These patients, hospitalized in one centre, did not receive any anti-malarial drug and recovered.
Discussion

Our data highlight the marginal use of halofantrine for adult malaria patients in France, 2 years after the consensus development conference. This is in agreement with the striking decrease supported by the French National Reference Centre for Imported and autochthonous Malaria (CNREPIA, Centre National de Référence de l’Épidémiologie du Paludisme d’Importation et Autochtone) data (F. Legros, personal communication). In 1998, the year preceding the French expert consensus development conference, 47% of the 2005 adults ascertained with imported malaria through CNREPIA had been treated with halofantrine, which ranked first among the prescribed anti-malarials. Findings two years after the conference show that only 8% of the 2598 adults ascertained with imported malaria through CNREPIA and 3% of the 474 in our sample were treated with this anti-malarial. Clinicians thus appear to have taken the recommendations of the French expert consensus development conference into account.

Less than 12% of the patients infected with a Plasmodium species other than P. falciparum were out-patients. Chloroquine (the reference drug) was prescribed in 71% of first-line treatments and 75% of both first-line and second-line (data not shown) treatments in these patients. This low level of out-patient care was an unexpected finding since hospitalization is not recommended, and so was the relatively low level of chloroquine use, since chloroquine remains the reference drug for treating patients with non-falciparum malaria, despite occasional reports of chloroquine resistance in P. vivax.

The standardized initial management of acute malaria is the most likely explanation for the very low number of out-patients recorded in this group. Another explanation may be that in several cases treatment was started before knowing which Plasmodium species infected the patients (i.e. before a senior parasitologist confirmed the diagnosis), the patients being initially managed as if they were infected with P. falciparum.

ADEs leading to discontinuation of treatment occurred in 11% of the patients treated with mefloquine; five times more often than among those treated with any other anti-malarial. Stopping the treatment is not always indicative of particularly severe ADEs. Even though mefloquine is known to induce somatic and psychiatric effects, it is usually well tolerated: most adverse events are mild and restricted to gastrointestinal side-effects. However, vomiting and diarrhoea are both associated with reduced oral bioavailability and an increased risk of subsequent treatment failure. These ADEs, although mild, are therefore important when considering the treatment of a potentially life-threatening disease; this is particularly true for mefloquine treatment of acute P. falciparum malaria in out-patients.

Evidence on the relatively poor safety profile of mefloquine is accumulating, and our observations are in keeping with others. Yet, to our knowledge, no comparative study has been explicitly designed to address the safety of anti-malarials used to treat imported malaria. In French practice, now that halofantrine has been superseded for the treatment of imported malaria in adults, three equally effective first-line oral anti-malarials are advocated: quinine, mefloquine, and the newer atovaquone-proguanil fixed combination. Oral atovaquone-proguanil appears to have an excellent therapeutic index (reviewed in reference 13), and is now extensively used to treat uncomplicated imported malaria in France. However, evidence-based data on the treatment of imported malaria remain limited. A prospective study comparing mefloquine with another oral anti-malarial regimen as regards tolerance rather than effectiveness may be more suitable for identifying which drug should be recommended for the treatment of acute imported P. falciparum malaria in adults. Meanwhile, we suggest that mefloquine only be used very cautiously to treat out-patients with imported malaria.

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References


