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Since 2008, the French guidelines have promoted the systematic use of 30 mg/day of primaquine for the radical cure of *Plasmodium vivax* and *Plasmodium ovale* infections. We observed three relapses in 10 patients with *P. vivax* acquired in French Guiana. No relapses were seen in West African *P. ovale* patients.

In 2008, the French guidelines promoted the systematic use of 30 mg/day of primaquine for the radical cure of *Plasmodium vivax* and *Plasmodium ovale* infections.¹ Few data have been published on the indications, dosage, tolerability, and outcomes in returning travelers with *P. vivax* and *P. ovale* infections treated with primaquine.² The most recent *P. vivax* infections managed in our university hospital were characterized by a high unusual rate of relapses in comparison with the English scientific literature.³ Therefore we conducted a systematic analysis of the records of all the patients who were given primaquine for radical cure of *P. ovale/P. vivax* malaria treated in our teaching hospital since 2008.

Methods

The survey included the medical records of patients treated from November 2008 to December 2010 (in order to select records with a minimum follow-up period of 1 year after radical cure).

The data included the following items: age, gender, body weight, parasite species, number of malaria attacks before treatment, schizontocidal treatment before radical cure, time between schizontocides and first primaquine cure, primaquine dosage, compliance to treatment, tolerance, hematologic (hemogram) and biochemistry (creatinine and alanine aminotransferase), before and after treatment. Glucose-6-phosphate dehydrogenase (G6PD) deficiency testing is mandatory before any prescription according to the national guidelines and therefore no patient was G6PD deficient.

Active surveillance (phone call and mailing) was performed 1 year after the last cure to obtain information on the outcome. A relapse was defined by the identification of a further non-falciparum infection during follow-up in the absence of exposure to malaria.

Results

Primaquine was prescribed to 14 male patients (13 adults and 1 child) during the study period. Detailed information on age, body weight, parasite species, number of malaria attacks before treatment, schizontocidal treatment before primaquine, time between schizontocides and first primaquine cure, primaquine dosage, and outcome are presented in Table 1. The parasitological diagnosis before the first radical cure was based in all cases on both blood smears and *Plasmodium* lactate dehydrogenase rapid diagnostic tests. Polymerase chain reaction (PCR) was performed in 13 patients.
All *P. vivax* infections from French Guiana were observed in soldiers who had completed a 3-month mission overseas. Three patients developed a PCR-confirmed relapse (Table 1) and were all returning from French Guiana. The first one was a 23-year-old male (body weight: 105 kg), with a recent history of two *P. vivax* infections. He was given his first radical cure 47 days after the last malaria attack and had a relapse 40 days later. The second patient was a 30-year-old male (body weight: 100 kg), with a recent history of two *P. vivax* infections. He was given his first radical cure 16 days after the last malaria attack and had a relapse 70 days later. The third was a male aged 29 years (body weight: 70 kg), with a recent history of two *P. vivax* infections. He was given his first radical cure 29 days after the last malaria attack and had a relapse 8 months later. The three patients were given 30 mg/day of primaquine at their first radical cure and roughly 0.5 mg/kg/day (52.5, 45, and 37.5 mg/day, respectively) at their second radical cure. No further relapse was observed.

Compliance to treatment was declared suboptimal (85%) in one case (first course). One patient reported dizziness and headache (first and only course), but took all his dosages. All patients completed the course of primaquine despite presumed side effects.

No significant variations were observed in hematologic and biochemistry parameters (eight patients assessed before and after therapy).

Active surveillance was unsuccessful in six cases, including two relapsing cases. No further relapse was detected in eight patients.

### Discussion

Primaquine was first synthesized six decades ago but remains the only effective treatment for the hypnozoites of *P. ovale* and *P. vivax*. The aggravated hematotoxicity of primaquine in G6PD-deficient patients as well as the low oral bioavailability of the compound have been obstacles to its widespread use.

The anti-relapse efficacy of primaquine depends not only on the timing of radical cure and patient compliance but also on the dosage of the prescribed regimen. The initial standard recommended regimen for primaquine was 15 mg/day for 14 days. However, full elimination of the hypnozoites of some *P. vivax* strains was shown to require a daily dose of 30 mg. The report from the Centers for Disease Control and Prevention (CDC) expert meeting on malaria in 2006 recommends a presumptive anti-relapse therapy at doses of 30 mg daily for 14 days with an expected efficacy of about 95%.

The formerly recommended daily primaquine dosage of 15 mg/day has been used in the three adult patients treated for *P. ovale* infections during the study period and no further relapse was observed. This may reflect the lower trend of *P. ovale* infections compared with *P. vivax* to relapse after a radical cure. To our knowledge, only five case reports of treatment failure with unsupervised primaquine in *P. ovale* malaria have been published in the English scientific literature, among which primaquine total dose/kg was available in four cases. In three cases, total dose ranged between 2.5 and 3 mg/kg (from Ghana, Nigeria, and Ethiopia). One relapse from Uganda was observed after a 5 mg/kg total dose (45 mg weekly for 6 weeks).

As illustrated by this study, relapses occur in the case of *P. vivax* infections. These relapses could be attributed to poor compliance, which cannot be ruled out, but this also applies to the weight-adapted regimen. *Plasmodium vivax* sensitivity to primaquine differs from one geographic area to another. Studies performed on *P. vivax* strains from Ethiopia and Brazil showed that primaquine total doses >3.5 mg/kg were successful, while another study based on *P. vivax* strains from

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**Table 1** Patients and malaria attack characteristics, drug dosage, and outcome of the first primaquine cure

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Species</th>
<th>Number of malaria attacks</th>
<th>Country</th>
<th>Schizontocide</th>
<th>PQ daily dose (14 days, mg)</th>
<th>Time to PQ (days)</th>
<th>Relapse</th>
<th>Total dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>71</td>
<td>PO</td>
<td>1</td>
<td>Guinea</td>
<td>AL</td>
<td>15</td>
<td>21</td>
<td>N</td>
<td>2.9</td>
</tr>
<tr>
<td>29</td>
<td>77</td>
<td>PO</td>
<td>3</td>
<td>Ivory Coast</td>
<td>Mefloquine</td>
<td>15</td>
<td>39</td>
<td>N</td>
<td>2.9</td>
</tr>
<tr>
<td>31</td>
<td>64</td>
<td>PO</td>
<td>1</td>
<td>Ivory Coast</td>
<td>Chloroquine</td>
<td>15</td>
<td>45</td>
<td>N</td>
<td>3.2</td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>PO</td>
<td>1</td>
<td>Cameroon</td>
<td>Chloroquine</td>
<td>11.25</td>
<td>47</td>
<td>N</td>
<td>6.3</td>
</tr>
<tr>
<td>23*</td>
<td>105</td>
<td>PV</td>
<td>2</td>
<td>French Guiana</td>
<td>AP</td>
<td>30</td>
<td>47</td>
<td>Y</td>
<td>4.0</td>
</tr>
<tr>
<td>30*</td>
<td>100</td>
<td>PV</td>
<td>2</td>
<td>French Guiana</td>
<td>Chloroquine</td>
<td>30</td>
<td>47</td>
<td>Y</td>
<td>4.2</td>
</tr>
<tr>
<td>29*</td>
<td>105</td>
<td>PV</td>
<td>2</td>
<td>French Guiana</td>
<td>Quinine</td>
<td>30</td>
<td>27</td>
<td>Y</td>
<td>6.0</td>
</tr>
<tr>
<td>20</td>
<td>72</td>
<td>PV</td>
<td>3</td>
<td>French Guiana</td>
<td>Chloroquine</td>
<td>30</td>
<td>32</td>
<td>N</td>
<td>5.8</td>
</tr>
<tr>
<td>23</td>
<td>65</td>
<td>PO+PV</td>
<td>3</td>
<td>French Guiana, Ivory Coast</td>
<td>Quinine</td>
<td>30</td>
<td>180</td>
<td>N</td>
<td>6.4</td>
</tr>
<tr>
<td>34</td>
<td>87</td>
<td>PV</td>
<td>2</td>
<td>French Guiana</td>
<td>AP</td>
<td>30</td>
<td>30</td>
<td>N</td>
<td>4.8</td>
</tr>
<tr>
<td>23</td>
<td>75</td>
<td>PV</td>
<td>2</td>
<td>French Guiana</td>
<td>Chloroquine</td>
<td>30</td>
<td>22</td>
<td>N</td>
<td>5.6</td>
</tr>
<tr>
<td>30</td>
<td>75</td>
<td>PV</td>
<td>1</td>
<td>French Guiana</td>
<td>AP</td>
<td>30</td>
<td>37</td>
<td>N</td>
<td>5.6</td>
</tr>
<tr>
<td>32</td>
<td>80</td>
<td>PV</td>
<td>1</td>
<td>French Guiana</td>
<td>AP</td>
<td>30</td>
<td>36</td>
<td>N</td>
<td>5.2</td>
</tr>
<tr>
<td>28</td>
<td>65</td>
<td>PV</td>
<td>2</td>
<td>French Guiana</td>
<td>AP</td>
<td>15</td>
<td>110</td>
<td>N</td>
<td>3.2</td>
</tr>
</tbody>
</table>

PO = *Plasmodium ovale*; PV = *Plasmodium vivax*; AL = artemether-lumefantrine; AP = atovaquone-proguanil; PQ = primaquine; Y = yes; N = no.

*Patients in whom a relapse was observed.
Oceania stated that 6 mg/kg of primaquine was the appropriate total dose for radical cure.10

The pattern and probability of relapse also varies according to the geographical origin of malaria infection.6 In contrast to P vivax malaria acquired in temperate regions, which often relapses after long intervals (>6 months), two of the patients infected with P vivax strains from French Guiana had a relapse within 2 months (40 and 70 days) of radical cure. Data from Brazil (most of which were from Amazonia and a few from French Guiana) have identified P vivax relapse rates of 39.6% after primaquine regimens (total doses ranging from 2.2 to 4.9 mg/kg), half of which occurred within 108 days of radical cure10; the study advocates the primaquine total dose above which relapses do not occur is 3.6 mg/kg. The failure rate of the 30 mg/day regimen in the present study (roughly 30%) is not so different from those observed by Pedro and colleagues10 but higher than the other data found in the literature (efficacy of 95%).4 However, all three relapsing patients were prescribed primaquine total doses of above 3.6 mg/kg, which seems contradictory to the findings in Brazil,10 and would suggest that some strains from French Guiana need higher primaquine doses, closer to the Chesson type of P vivax. More data from records of travelers who acquired P vivax in French Guiana would be required to discern whether the high risk of relapse observed after standard radical cure on a small sample of records reflects the current risk of relapse in this area. If so, efficacy of potentially more effective alternative regimens should be comparatively assessed.

The fact that two of the patients who relapsed had body weight >70 kg (100 and 105 kg) may have played a role as the initial regimen for them was 0.3 mg/kg daily whereas the second one was 0.5 mg/kg daily. On the basis of a trend of higher risk of relapse after standard radical cure in high body weight patients with P vivax infections, Baird and colleagues6 advocated for a regimen of 0.5 mg/kg primaquine daily for 14 days for patients weighing more than 70 kg.

This recommendation has since been partially integrated by the CDC experts meeting: although the standard recommended course is still 30 mg/day over 14 days, it is now specified that for individuals weighing more than 70 kg, the treatment could be extended to provide a total dose of 6 mg/kg.3

In our case series, radical cure of P ovale and P vivax infections used primaquine alone; however, as higher efficiency of primaquine was demonstrated when given concurrently with blood schizonticides,4 an alternative could be to give a combinative treatment as first-line radical cure.

Conclusion

Relapses of P vivax infections from French Guiana were frequently observed in our experience of radical cure with primaquine at 30 mg daily. More data are needed to estimate properly the relapse rate of P vivax infections from French Guiana after primaquine radical cure and further comparative studies would be required to test suitably the hypothesis that radical cure dosage could be adapted to body weight in order to reduce the risk of relapse in this population.

Declaration of Interests

The authors state they have no conflicts of interest to declare.

References