Discussion

Although multiresistant *P. falciparum* is an increasing problem, reports of *P. vivax* resistant to chloroquine have been few. The above case reports document the presence of chloroquine-resistant *P. vivax* in India, and show that P. vivax may not be as rare as it is presumed to be. Also, the number of drug resistant strains is probably increasing. Antimalarial drugs other than chloroquine used for *P. vivax* have limitations of their own: sulfadoxine-pyrimethamine is not as effective as chloroquine, quinine is difficult to administer, and tetracyclines are contraindicated in children and pregnant women and are not tolerated by many patients. Non-availability and cost limits the use of mefloquine and halofantrine.

Further population-based epidemiological studies will be needed to define the extent of chloroquine resistant *P. vivax* and identify suitable alternative treatments. If this problem were to become widespread, there would be significant implications for the treatment and prophylaxis of malaria in India.

Acknowledgements

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Activity in vitro of chloroquine, cycloguanil, and mefloquine against African isolates of *Plasmodium falciparum*: presumptive evidence for chemoprophylactic efficacy in Central and West Africa

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Antimalarial chemoprophylaxis is one of the important means to protect nonimmune travellers visiting malaria endemic areas. At present, there is no consensus on the prophylactic regimens, especially for West and Central Africa, where chloroquine resistance is present but is generally of low level (type R1 and RII). The World Health Organization (WHO) and the American Centers for Disease Control recommend mefloquine for most of sub-Saharan Africa (CDC, 1990; WHO, 1995). European experts generally recommend either mefloquine or chloroquine plus proguanil, on a case-to-case basis, for Central and West Africa (Bradley & Warhurst, 1995; CSHP, 1995). For East Africa, it is generally agreed that mefloquine is the drug of choice. Whether chloroquine plus proguanil or mefloquine should be prescribed for Central and West Africa is still debated, largely because no randomized, prospective study on the effectiveness of these 2 regimens has been conducted.

Previous studies have been based on retrospective questionnaires distributed to returning travellers or Peace Corps volunteers (Lobel et al., 1993; Steffen et al., 1993). These investigators have concluded that mefloquine is well tolerated and more effective than chloroquine plus proguanil for chemoprophylaxis in travellers visiting Africa. However, the design of these studies cannot lead to firm conclusions due to the subjective answers of the tourists to questionnaires concerning compliance, tolerance, and effectiveness and the statistical bias involving a significantly smaller sample size for the chloroquine-proguanil group.

Another indirect approach to evaluate the efficacy of antimalarial drugs is the determination of their activity in vitro against fresh clinical isolates of *Plasmodium falciparum*. Between 1992 and 1994, we have analysed the drug sensitivity patterns of more than 300 isolates obtained from malaria-infected travellers returning to France from sub-Saharan Africa, mostly from the francophone countries in central and western parts of the continent. The activity in vitro of chloroquine, cycloguanil (biologically active metabolite of proguanil), and mefloquine was determined using the isotopic semi-microtest (Basco et al., 1994). Based on previous in vitro/in vivo correlation studies (Le Bras & Ringwald, 1990), the threshold 50% inhibitory concentration (IC50) value for resistance to chloroquine was set at 100 nM. The threshold value for cycloguanil resistance was fixed at 50 nM (Basco et al., 1994). Most malaria-infected patients receiving correct chloroquine–proguanil or mefloquine prophylaxis provided isolates with cycloguanil IC50 values above this threshold value. The cut-off value for mefloquine resistance was estimated to be >30 nM, based on the analysis of drug sensitivity patterns of more than 300 isolates obtained from malaria-infected travellers returning to France from sub-Saharan Africa, mostly from the francophone countries in central and western parts of the continent. The activity in vitro of chloroquine, cycloguanil (biologically active metabolite of proguanil), and mefloquine was determined using the isotopic semi-microtest (Basco et al., 1994). Based on previous in vitro/in vivo correlation studies (Le Bras & Ringwald, 1990), the threshold 50% inhibitory concentration (IC50) value for resistance to chloroquine was set at 100 nM. The threshold value for cycloguanil resistance was fixed at 50 nM (Basco et al., 1994). Most malaria-infected patients receiving correct chloroquine–proguanil or mefloquine prophylaxis provided isolates with cycloguanil IC50 values above this threshold value. The cut-off value for mefloquine resistance was estimated to be >30 nM, based on the analysis of drug sensitivity patterns of more than 300 isolates obtained from malaria-infected travellers returning to France from sub-Saharan Africa, mostly from the francophone countries in central and western parts of the continent. The activity in vitro of chloroquine, cycloguanil (biologically active metabolite of proguanil), and mefloquine was determined using the isotopic semi-microtest (Basco et al., 1994). Based on previous in vitro/in vivo correlation studies (Le Bras & Ringwald, 1990), the threshold 50% inhibitory concentration (IC50) value for resistance to chloroquine was set at 100 nM. The threshold value for cycloguanil resistance was fixed at 50 nM (Basco et al., 1994). Most malaria-infected patients receiving correct chloroquine–proguanil or mefloquine prophylaxis provided isolates with cycloguanil IC50 values above this threshold value. The cut-off value for mefloquine resistance was estimated to be >30 nM, based on the analysis of drug sensitivity patterns of more than 300 isolates obtained from malaria-infected travellers returning to France from sub-Saharan Africa, mostly from the francophone countries in central and western parts of the continent.
tivity patterns of isolates from cases of prophylactic failure (RINGWALD et al., 1990). Overall, resistance in vitro to chloroquine, cycloguanil, and mefloquine was observed in 51%, 33% and 5% of the isolates, respectively (Table 1). The mechanisms of action of chloroquine and cycloguanil and the mechanisms of resistance to these drugs are different. Furthermore, since cycloguanil has additional high activity against the hepatic stages, the drug combination should be more effective in vitro than chloroquine alone (HOWELLS et al., 1985). Several clinical studies have suggested the superiority of chloroquine plus proguanil over chloroquine alone (SARKOY et al., 1991; GARIN et al., 1993), contradicting the opinion of LOBEL et al. (1993). In comparison with cycloguanil and chloroquine, mefloquine resistance in vitro was observed in only a few isolates. Thus, assuming full compliance with the recommended regimens, we should expect to see less breakthrough in travellers on mefloquine than in those on chloroquine-proguanil.

Our extrapolation from the in vitro data to the expected effectiveness in vitro must be treated with caution. The limitations of the present study include the exclusion of pharmacokinetic factors, evaluation restricted to the blood schizontocidal activity of cycloguanil, and lack of complete information concerning compliance, side effects, and prophylactic effectiveness in patients from whom the isolates were obtained. Inter-individual variability in drug absorption as well as biotransformation of proguanil to cycloguanil in extensive and poor metabolizers may possibly result in prophylactic failure even with drug-sensitive parasites. Since cycloguanil is more active against the hepatic stages than against the intra-erythrocytic stages, an isolate that is cycloguanil-resistant during the intraerythrocytic stages may in fact be cycloguanil-sensitive in the hepatic stages (HOWELLS et al., 1985). This observation implies that our study may have underestimated the efficacy of cycloguanil in vitro. In addition, possible bias in our collection of African isolates must be considered since our hospitals (in Paris and Marseille) tend to recruit patients who are severely ill or in whom chemoprophylaxis or previous treatment has failed, thus increasing the proportion of drug-resistant isolates.

Nevertheless, our study suggests that cycloguanil alone has high activity in vitro against most African isolates of *P. falciparum*, that there are a few isolates that are resistant in vitro to both chloroquine and cycloguanil, and that mefloquine-resistant isolates are rare in Africa. Despite the uncontestably high activity in vitro and proven clinical efficacy of mefloquine, the chloroquine-cycloguanil combination is active in vitro against a considerable proportion of African isolates and still has a place in the chemoprophylaxis of travellers visiting Africa, especially the western part of the continent.

**References**


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**Short Report**

Japanese poor metabolizers of proguanil do not have an increased risk of malaria chemoprophylaxis breakthrough

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Because proguanil is metabolized to a much more active triazine derivative, it has been assumed that effective malarial chemoprophylaxis depends upon the extent of Table. Concentration of proguanil and cycloguanil in urine of Japanese volunteers 6 h after an oral dose of 200 mg proguanil

<table>
<thead>
<tr>
<th>Proguanil metabolizer statusa</th>
<th>Extensive</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>102</td>
<td>23</td>
</tr>
<tr>
<td>Mean concentration (µg/mL)</td>
<td>5-5±3-6</td>
<td>10-1±6-6</td>
</tr>
<tr>
<td>Cycloguanil (µg/mL)</td>
<td>1-1±1-3</td>
<td>0-4±1-0-45</td>
</tr>
<tr>
<td>Proguanil/cycloguanil ratio</td>
<td>4.2±0-2</td>
<td>41.6±32-9</td>
</tr>
<tr>
<td>Mean Range</td>
<td>0-48-0-91</td>
<td>12-9-100b</td>
</tr>
</tbody>
</table>

aAll differences are significant at P<0.05.
bFive of the poor metabolizers had urinary cycloguanil concentrations below the minimum detection limit (0-001 µg/mL), and their proguanil/cycloguanil ratio was ascribed a maximal value of 100.
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