Efficacy of chloroquine—proguanil malaria prophylaxis in a non-immune population in Bangui, Central African Republic: a case—control study

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Summary A case—control study was conducted to evaluate the efficacy of the combination of chloroquine plus proguanil as malaria prophylaxis in a non-immune population living in the Central African Republic. Cases were patients presenting with a malaria attack confirmed by a positive blood film and/or an HRP2 positive antigen test at the Pasteur Institute of Bangui. Two control subjects were included per case: one was a relative or close friend and the other was matched to the patient with respect to the length of stay. A questionnaire assessing malaria prophylaxis habits and malarial risk factors over the 2-month period prior to inclusion in the study was given to 48 cases and 96 controls. A conditional logistic regression was used to identify risk factors. The efficacy of the chloroquine plus proguanil regimen was found to be high (95.5%, 95% CI 74.0—99.2%) in this country known for high chloroquine resistance. Our data lend some support to the use of chloroquine plus proguanil in Bangui, and the protective efficacy of chloroquine plus proguanil should now be studied prospectively as part of a randomised controlled trial of various prophylactic drugs.

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1. Introduction

Malaria is a threat for the increasing number of non-immune people travelling to endemic areas. Prophylactic measures are recommended to prevent malaria attacks. Primary prophylaxis consists of personal and environmental protection against mosquito bites. Second, travellers are advised to take an appropriate antimalarial chemoprophylaxis regularly (WHO, 2004).

Most experts recommend the use of mefloquine when travelling throughout sub-Saharan Africa (Bradley and Warhurst, 1997; CDC, 2004; Groupe Suisse de Travail pour les Conseils Médicaux aux Voyageurs, 2004; WHO, 2004). Although mefloquine is highly effective in preventing malaria, it has been associated with neuropsychiatric side effects. These side effects can be severe and thus may restrict the use of the drug (Bradley and Warhurst, 1997), particularly among subjects exposed for long periods such as expatriates. As a result, recommendations become vague for stays longer than 3 months (Barrett et al., 1996; Carme et al., 1997; Comité des Maladies liées aux Voyages et des Maladies d'Importation, 2003; Croft and Garner, 1997; Steffen et al., 1993). In Bangui, the capital city of Central African Republic, French experts have recommended mefloquine for short- and long-term chemoprophylaxis for visitors (Bergeri et al., 2003; Groupe de Travail ‘Santé des Voyageurs’, 2000). A study of antimalarial attitudes and practices conducted in 2002 by the French Embassy Medical Centre among French expatriates in Bangui showed that 52% of them were taking antimalarial chemoprophylaxis. Chloroquine plus proguanil was used by 94% of the individuals taking chemoprophylaxis, and mefloquine was used by only 2% (D’Ortenzio, 2002). This study estimated that expatriates taking chemoprophylaxis had a three-fold lower risk of contracting malaria than those not taking any chemoprophylaxis \((P < 10^{-3})\). These results suggested that the combination of chloroquine plus proguanil was an efficient chemoprophylaxis in the Central African Republic. It is therefore necessary to update the information given to healthcare providers advising expatriates regarding the efficacy and tolerability of the chloroquine and proguanil regimens. The Pasteur Institute of Bangui, in collaboration with the French Embassy Medical Centre, conducted a case–control study to evaluate the efficacy of chloroquine plus proguanil as a malarial prophylaxis in non-immune subjects visiting the Central African Republic for more than 3 months.

2. Materials and methods

2.1. Study population and data collection methods

A case–control study was conducted with incident cases of *Plasmodium falciparum* malaria. There were no age criteria for the study. The subjects were expatriates (long-term visitors) staying in the Central African Republic for more than 3 months. All subjects had access to the Medical Centre of the French Embassy and the Pasteur Institute of Bangui. Case subjects were defined as incident patients whose diagnosis of *P. falciparum* malaria had been confirmed by a positive malaria film and/or an HRP2 antigen test (Core Malaria pf®; Core Diagnostics Ltd, Birmingham, UK) at the Pasteur Institute. The controls were subjects for whom no presumptive or confirmed diagnosis of malaria had been made during the 2 months preceding the febrile episode of the patient to which they were matched. Two control subjects were chosen for each patient: the first was a relative or close friend and the second was matched to the patient with respect to the duration of stay (duration of stay was used as a proxy for partial malaria immunity that may have been acquired during prolonged stays; since there is no way to measure such protective immunity, matching by duration of stay was used pre-emptively to prevent confounding by such a variable).

All subjects were asked to complete a structured questionnaire regarding their sociodemographic characteristics and malaria prophylaxis habits over the last 2 months: personal protective measures (use of repellents, chloroquine plus proguanil prophylaxis, impregnated or untreated bed nets, clothes covering arms or legs) and environmental protective measures (air-conditioning, electric vapouriser systems or smoke spirals, window screens, house-spraying, treatment of home or garden with insecticides). The questionnaire also requested information regarding any recent travel to bush areas or to other malaria-endemic countries, concomitant infections and intense professional or sporting activities (more intense than usual) conducted in the 2 weeks prior to inclusion in the study.

2.2. Sample size

It was estimated that 42 cases and 84 controls would be required to detect a three-fold reduction in the risk of malaria, assuming that 49% of the controls would be exposed to the combination
Malaria prophylaxis in a non-immune population

2.3. Statistical analysis

Data were analysed using the Epi Info version 6.04dfr (CDC, Atlanta, GA, USA) and STATA Intercooled 8.0 (Stat Corp., College Station, TX, USA) software programs. Odds ratios (OR) and their 95% CI, describing the association between cases and exposure variables, were determined by conditional logistic regression. For the multivariate analysis, variables with P-values <0.25 were initially introduced into the model and removed following a backwards-stepwise selection procedure to leave only those with a P-value <0.05 in the final model (except for age group, gender and duration of stay, which were forced into the model). The estimate of the efficacy of chloroquine plus proguanil chemoprophylaxis (%) compared with no chemoprophylaxis was calculated as follows: (1—OR) × 100, where OR describes the association between falciparum malaria and the chloroquine plus proguanil regimen, with no chemoprophylaxis as the reference exposure category.

The study was approved by the Ministry of Health, Central African Republic; no formal ethics review body existed at the time of the study.

3. Results

3.1. Description of control subjects

Subjects were recruited from 8 May 2002 to 17 November 2003. Forty-eight consecutive subjects were included as cases and 96 as controls. Nineteen percent of the controls were relatives of the patients, 31% were close friends and 50% were matched with patients according to the length of stay in Central African Republic. Controls were more often male (59.4%), with a median age of 40 years (range 0—78 years), of French citizenship (92.7%), and with mostly administrative (32.3%) and educational (22.9%) occupations.

Of the 41 controls on chemoprophylaxis, 36 (87.8%) had been using their chemoprophylaxis since their arrival in Central African Republic, which was less than 2 years ago for 29 (80.6%) of this group. During the 2 months prior to inclusion in the study, 14 (34.1%) of this control group were fully compliant, 27 (65.9%) forgot to take their chemoprophylaxis more than once and 10 (24.4%) stopped their chemoprophylaxis for several days (vacations in France). Seventeen (41.5%) suffered from side effects: eight (47.1%) nausea or abdominal pain, six (35.3%) visual disturbances, three (17.6%) mouth ulcers and two (11.8%) dizziness. Twenty-eight (68.3%) of these individuals were the only person in their family on chemoprophylaxis, but 97.6% were keen to take the chemoprophylaxis. Thirty-eight (92.7%) had never had a malaria attack.

The number of military personnel and babies was higher among controls on chemoprophylaxis than among those not taking any chemoprophylaxis (39.1% vs. 9.1%, P<0.001). Compared with those not taking any chemoprophylaxis, controls on chemoprophylaxis also used repellents more often (75.6% vs. 50.9%, P=0.01) and had fewer malaria attacks per year (0.1 vs. 0.3, P<0.001).

3.2. Risk factors for malaria attack

In the univariate analysis, the following factors were positively associated with contracting malaria: conducting excessive professional or sporting activities (OR = 5.13, 95% CI 2.29—11.51, P<0.001) and having a concomitant infection (OR = 2.53, 95% CI 1.02—6.31, P=0.046) within the 2 weeks prior to inclusion in the study. The following factors were negatively associated with malaria: taking chloroquine plus proguanil chemoprophylaxis (OR = 0.12, 95% CI 0.03—0.40, P=0.001) and having window screens at home (OR = 0.24, 95% CI 0.08—0.69, P=0.008) (Table 1). Sleeping under an impregnated bed net was also negatively associated with malaria; however this association was marginally significant.

The results of the multivariate analysis are shown in Table 2. ORs are shown only for variables remaining in the final model. The OR of the chloroquine plus proguanil chemoprophylaxis regimen (OR = 0.045, 95% CI 0.008—0.26, P=0.001) corresponds to an efficacy of 95.5% (95% CI 74.0—99.2%) of the combined drug in preventing malaria. Although not significant in the univariate analysis, wearing clothes covering arms or legs in the evening or at night had a protective effect (OR = 0.13, 95% CI 0.02—0.65, P=0.01) in the multivariate analysis. This effect was independent of that of the chloroquine plus proguanil regimen. Excessive professional or sporting activities (more intense than usual) conducted within the 2 weeks prior to inclusion in the study were an additional risk factor for
contracting malaria. This factor resulted in a 12-fold higher risk (95% CI 3.31–43.02, \( P < 10^{-3} \)). The protective effects of impregnated bed nets, window screens and repellents, and the increase in risk effects of having a concomitant infection, being single and having recently travelled to bush areas disappeared after controlling for chemoprophylaxis use.

### 4. Discussion

The main finding of this study was that the chloroquine plus proguanil combination was protective (efficacy 95.5%, 95% CI 74.0–99.2%) against *P. falciparum* malaria in a country where only mefloquine prophylaxis is recommended. No malaria episode was observed in compliant users, suggesting that lack of compliance rather than drug resistance was the main cause of prophylaxis failure. Fontanet et al. (2005) have described similar findings among short-term travellers to Africa returning to France. The policy to support the use of mefloquine instead of chloroquine–proguanil has been motivated by the reduced risk of malaria death among short-term travellers to east Africa (CDC, 2001). It was also triggered by the rapid rise in resistance to pyrimethamine–sulfadoxine, a treatment of the same antifolate family as proguanil. However, no study has documented a similar decrease in the efficacy of proguanil, and it has been shown that proguanil efficacy in the combination atovaquone–proguanil (Malarone®; GlaxoWellcome GmbH & Co., Bad Oldesloe, Germany) operates through a different non-antifolate mechanism (Thapar et al., 2003). In this regard, these results are important as they provide evidence of continuing efficacy of proguanil in central Africa.
Table 2  Multivariate (conditional logistic regression) analysis of factors associated with the presence of falciparum malaria, Bangui (Central African Republic), May 2002 to November 2003

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate OR</th>
<th>95% CI</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0—32 (reference)</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>33—40</td>
<td>0.30</td>
<td>0.06—1.42</td>
<td>0.13</td>
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<tr>
<td>41—51</td>
<td>0.25</td>
<td>0.05—1.28</td>
<td>0.10</td>
</tr>
<tr>
<td>52—78</td>
<td>0.19</td>
<td>0.03—1.23</td>
<td>0.08</td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (reference)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.98</td>
<td>0.92—9.62</td>
<td>0.07</td>
</tr>
<tr>
<td>Length of stay (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2—8 (reference)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9—14</td>
<td>4.02</td>
<td>0.59—27.37</td>
<td>0.16</td>
</tr>
<tr>
<td>15—33</td>
<td>2.78</td>
<td>0.26—30.17</td>
<td>0.40</td>
</tr>
<tr>
<td>34—550</td>
<td>3.17</td>
<td>0.20—50.11</td>
<td>0.41</td>
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<tr>
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</tr>
<tr>
<td>Yes</td>
<td>0.045</td>
<td>0.008—0.26</td>
<td>0.001</td>
</tr>
<tr>
<td>Professional or sporting activity more intense than usual</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (reference)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11.93</td>
<td>3.31—43.02</td>
<td>&lt;10^-3</td>
</tr>
<tr>
<td>Long-sleeved clothing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (reference)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.13</td>
<td>0.02—0.65</td>
<td>0.01</td>
</tr>
</tbody>
</table>

OR: odds ratio. 95% CI: 95% Confidence Interval.

Based on these results, for subjects not willing to take mefloquine, the combination chloroquine—proguanil may represent an alternative. It may be particularly relevant for long-term visitors travelling to the Central African Republic for two reasons. First, the tolerability of subjects to this combination is good and only minor side effects, such as mouth ulcers and gastrointestinal upset, have been reported (Taylor and White, 2004). In addition, these drugs are safe for prolonged use (Carme et al., 1997; Gozal et al., 1991a, 1991b). In contrast, mefloquine can induce serious neuropsychiatric side effects, although the rate of occurrence is low (1/10 600 travellers) (Carme et al., 1997). The risk of this side effect has already led to tourists and expatriates visiting zone three countries using chloroquine—proguanil as a malaria prophylaxis in preference to mefloquine (Carme et al., 1997; D’Ortenzio, 2002; Petersen et al., 2000). Second, to prevent the emergence of P. falciparum strains resistant to the drugs used to treat malaria attacks. Cross-resistance has been found between mefloquine and halofantrine: the use of subtherapeutic amounts of mefloquine during prophylaxis and the long half-life of this drug may lead to the emergence of mefloquine-resistant and, therefore, halofantrine-resistant strains (Gay et al., 1990). Cross-resistance may also occur with lumefantrine, another aminoalcohol, which is being used increasingly in combination with artemether (Coartem®/Riamet®; Novartis Group, Basel, Switzerland) as a malaria treatment.

Multivariate analysis revealed that, independently of chloroquine plus proguanil use, malaria risk was 8-fold lower in those using clothes for protection at night, and 12-fold higher in those who had conducted an excessive (more intense than usual) professional or sporting activity within the previous 2 weeks. This increased risk has, to our knowledge, not been reported before. The protective effects of impregnated bed nets, window screens and repellents, and the increase in risk effects of having a concomitant infection, being single and having recently travelled to a bush area disappeared after controlling for chemoprophylaxis use.

5. Conclusions

Our data lend some support to the use of chloroquine plus proguanil in Bangui, and the protective
efficacy of chloroquine plus proguanil should now be studied prospectively as part of a randomised controlled trial of various prophylactic drugs.

Conflicts of interest statement
The authors have no conflicts of interest concerning the work reported in this paper.

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