

THE ITALIAN ARMY STANDPOINT ON MALARIA CHEMOPROPHYLAXIS

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ABSTRACT • Soldiers on duty in tropical areas are at high risk of malaria and need chemoprophylactic regimens which may ensure the best efficacy, tolerability and compliance. Current Italian Army guidelines are based on recent military experiences in tropical areas, where mefloquine prophylaxis was as well tolerated as combination treatment with chloroquine and proguanil but more effective and easier to comply with, at least among soldiers. Chloroquine alone (300 mg base once/week) is prescribed for areas without chloroquine-resistant *Plasmodium falciparum*, while mefloquine (250 mg once/week) is recommended for areas with chloroquine-resistance. Doxycycline is the first choice regimen for mefloquine-resistant areas and an alternative to mefloquine when this medication is contraindicated or not tolerated. The combination chloroquine-proguanil represents the alternative chemoprophylactic regimen when mefloquine and doxycycline are contraindicated or not tolerated.

KEY WORDS • Malaria - Chemoprophylaxis - Mefloquine - Chloroquine - Proguanil - Doxycycline - Army.

LE POINT DE VUE DE L'ARMÉE ITALIENNE SUR LA CHIMIOPROPHYLAXIE ANTIPALUDIQUE

RESUME • Hautement exposées au risque de paludisme, les troupes en opérations dans les régions tropicales doivent bénéficier des régimes chimioprophylactiques les plus performants en termes d'efficacité, de tolérance et d'observance. A cet égard, les dispositions actuelles de l'armée italienne s'appuient sur les récentes expériences dans des régions tropicales qui montrent que la chimioprophylaxie par la méfloquine est aussi bien tolérée que l'association chloroquine/proguanil, avec une efficacité et un taux d'observance meilleurs, au moins parmi les militaires. La chimioprophylaxie est assurée par une prise hebdomadaire de 300 mg de chloroquine base dans les zones sans chloroquinorésistance et de 250 mg de méfloquine dans des zones de chloroquinorésistance. La doxycycline (100 mg/jour) est utilisée en première intention dans les zones de méfloquinorésistance ou en option si la méfloquine est contre indiquée ou non tolérée.

MOTS-CLES • Paludisme - Chimioprophylaxie - Méfloquine - Chloroquine - Proguanil - Doxycycline - Armée.

Troops deployed in tropical areas are at particular high risk of malaria, since military operations often expose soldiers to infecting bites where and when mosquito activity is particularly intense. Moreover, soldiers operating in malaria-endemic regions are usually non-immune and face the risk of malaria for longtime, since the average deployment period is usually 3-6 months. Finally, military missions take place in areas where malaria control measures are usually impaired or collapsed, because of ongoing conflicts. Although the regular use of preventive measures can reduce man-vector contact (skin-repellents, bed nets) and suppress or eradicate plasmodial infections (chemoprophylaxis), the risk of contracting malaria by troops in the field has been particularly important even in recent years (Table I).

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The four chemoprophylactic regimens used by Italian troops for malaria prevention are chloroquine, mefloquine, doxycycline and chloroquine+proguanil

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(Table II). Chloroquine alone is prescribed for areas without chloroquine-resistant *Plasmodium falciparum* infections. Mefloquine is recommended for all areas with *Plasmodium falciparum* infections resistant to chloroquine. Doxycycline is the first choice regimen for mefloquine-resistant areas in SE Asia and an alternative to mefloquine when this medication is contraindicated or not tolerated. The combination chloroquine+proguanil (C+P) represents the alternative chemoprophylactic regimen when mefloquine and doxycycline are contraindicated or not tolerated. Finally, no terminal mass prophylaxis with primaquine is usually recommended for the eradication of *Plasmodium vivax/ovale* infections in asymptomatic subjects.

Operational tasks may not always consent medical consultations or laboratory tests within 24 hours from the onset of symptoms suspicious of malaria; so it is particularly important that soldiers use chemoprophylactic regimens which may ensure the best effectiveness, tolerability and compliance. The choice of mefloquine even in areas with low or moderate chloroquine-resistance is based on our recent experience on malaria chemoprophylaxis among troops deployed for humanitarian missions in sub-Saharan Africa. The effectiveness of C+P was 94 % in Somalia (1992-94) and only 45 % in Mozambique (1993), where this regimen was subsequently changed to mefloquine, which showed a 97 % effectiveness in preventing malaria (13).

Table I - Crude attack rates of malaria among soldiers during and after deployment in some endemic areas.

Malaria endemic areas	Number of exposed soldiers	Months of duty	Number of cases* (attack rate)		Number of relapses **	Ref. Number
			during deployment	after deployment		
Somalia, 1992-4	11,700, Italian	4	18 (0.1 %)	147 (1.3 %)	15/130 (11 %)	13
Mozambique, 1993-4	4,800, Italian	3	119 (2.5 %)	40 (0.8 %)	0	13
Somalia, 1992-3	30,000, US	6	48 (0.2 %)	112 (0.4 %)	33/103 (32 %)	10,19,21
Somalia, 1993	74, Belgian	4	0	20 (27 %)	6/20 (30 %)	8
Central Africa, 1996	2,000, French	2	107 (5.3 %)	?	?	12
Cambodia, 1992-3	2,300, Dutch	5	31 (1.3 %)	33 (1.4 %)	?	9
Cambodia, 1992-3	600, Australian	12	5 (0.8 %)	3 (0.5 %)	2/6 (33 %)	18
Somalia, 1993	900, Australian	4	0	3 (0.3 %)	?	18

* Most of malaria cases occurring while on duty in endemic areas were due to *Plasmodium falciparum*, while most of cases after repatriation were primary attacks of *Plasmodium vivax* infections.

** Number of malaria cases due to *Plasmodium vivax/ovale* which relapsed once.

No cases of severe adverse effects (convulsions, psychosis) to either mefloquine or C+P were reported. Minor adverse events did occur, but chemoprophylaxis curtailment rate due to side-effects was very similar among C+P users (1.5 %) and mefloquine users (0.9 %). This rate did not change significantly after three months of continuous chemoprophylaxis. Moreover, soldiers who curtailed mefloquine prophylaxis because of adverse effects reported gastrointestinal (nausea, vomiting, diarrhea) and neuropsychiatric symptoms (headache, dizziness, vertigo) more frequently than subjects taking mefloquine regularly, but this difference was not significant. Our conclusions were that mefloquine was at least as well (if not better) tolerated as the association C+P (14).

Overall, the proportion of international travellers with any adverse effects to chemoprophylaxis is similar among mefloquine users and subjects taking the combination C+P, but an excess of neuropsychiatric adverse events has been associated with mefloquine prophylaxis (1, 4). However, this regimen has not been found to be associated with an increase of overall, neuropsychiatric or gastrointestinal side-effects among soldiers, when compared with C+P prophylaxis (7,

14). A possible explanation could be that soldiers are a selected population, which is less likely to be affected by neuropsychiatric conditions representing contraindications for mefloquine use or predisposing factors for adverse events. Moreover, soldiers are mostly male and usually younger than international travellers and mefloquine seems less well tolerated among women (1, 15) and in older subjects (9, 14).

Chemoprophylaxis compliance was 95 % for mefloquine and significantly lower (90 %) for C+P. These rates did not change significantly even after three months of continuous chemoprophylaxis. The main reasons for curtailing prophylaxis were neglecting the scheduled doses for C+P and the onset of adverse effects for mefloquine (14). Our conclusions were that mefloquine regimen (1 tablet/week) is much easier to comply with than C+P (16 tablets/week).

Doxycycline seems as effective as mefloquine for prevention of chloroquine-resistant *Plasmodium falciparum* malaria (11, 16), but tolerability of several current formulations (hydrate) is still unsatisfactory (2) and compliance is lower (17). Moreover, doxycycline is not currently licensed for antimalarial prophylaxis in some countries and long-term safety (>3 months) of this regimen has not yet been established.

Table II - Chemoprophylactic regimens prescribed for Italian soldiers deployed in malaria-endemic areas.

Chemoprophylaxis	Dose	Duration	Indications
Chloroquine	300 mg base once/week	From 1-2 weeks before exposition until 4 weeks after leaving the endemic area	Areas without doxycycline-resistant <i>Plasmodium falciparum</i> strains (WHO : group A ; French CSHP: group 1)
Mefloquine	250 mg once/week	From 2-3 weeks before exposition (*) until 4 weeks after leaving the endemic area	Areas with chloroquine-resistant <i>Plasmodium falciparum</i> strains (WHO : groups B & C ; French CSHP: groups 2 & 3)
Doxycycline	100 mg once/day	From 1-2 days before exposition until 4 weeks after leaving the endemic area	Areas with mefloquine-resistant <i>Plasmodium falciparum</i> strains (Thailand-Myanmar/Laos/ Cambodian border) ; Alternative regimen when mefloquine is contraindicated or not tolerated
Chloroquine + proguanil	Cq 100 mg + Pg 200 mg once/day	From 1-2 days before exposition until 4 weeks after leaving the endemic area	Alternative regimen if mefloquine and doxycycline are contraindicated or not tolerated

* At least 3 doses of mefloquine should be taken before entering the malarious area; if less than 15 days are available before the beginning of exposition, a loading dose of mefloquine is prescribed (one tablet on day -7, -6, -5 and the regular weekly dose thereafter), in order to change chemoprophylaxis if adverse effects occur.

shed. This medication is a good alternative for subjects intolerant to mefloquine or when this medication is contraindicated and represents the first line chemoprophylactic regimen only for areas where mefloquine-resistance is widespread.

The C+P association still withholds considerable effectiveness in areas with low to moderate chloroquine-resistance, but this medication is not better tolerated than mefloquine, while its compliance is significantly lower (14). C+P may represent an alternative chemoprophylaxis when mefloquine and doxycycline are contraindicated or not tolerated. The new formulation of this association (1 tablet of chloroquine 100 mg + proguanil 200 mg), recently licensed in some European countries for daily prophylaxis, should be preferred to the standard regimen (2 tablets of chloroquine weekly + 2 tablets of proguanil daily), since it is more easily taken and more strictly complied with (20).

Plasmodium falciparum infections represent most of malaria risk among troops deployed in endemic areas, but a considerable number of *Plasmodium vivax* malaria occur after repatriation, usually several weeks or months after curtailment of chemoprophylaxis. In our recent experience in Somalia, the attack rate of imported *Plasmodium vivax/ovale* malaria was 1.3 % (3 cases/1,000/month of exposition); 15/130 (11 %) primary attacks relapsed once and 2/15 relapsed twice (13). Considering the low attack rate of *Plasmodium vivax/ovale* malaria and the small proportion of cases which relapsed, we are oriented to avoid mass terminal treatment of asymptomatic soldiers and to limit primaquine treatment to clinical cases, after G6PD-deficiency has been ruled out by laboratory testing.

PERSPECTIVES CONCERNING HARMONISATION OF CHEMOPROPHYLAXIS AMONG THE MILITARIES

Harmonisation concerning malaria chemoprophylaxis among the military is difficult, due to national different experiences and standpoints about the elective prophylactic regimens and the tolerability of the mostly used medications. The CDC recommend weekly mefloquine for all areas with chloroquine-resistant *Plasmodium falciparum* malaria (5). Otherwise, C+P is recommended by WHO for areas where chloroquine-resistant *Plasmodium falciparum* strains are present or even widespread but the global risk of malaria is low or intermediate, as in some parts of Africa (Mauritania, Namibia), the Indian subcontinent, most of Indonesia and the Philippines (22). The British recommendations are more restrictive about the use of mefloquine: although this medication is considered the first choice chemoprophylactic regimen for most of Sub-Saharan Africa, where highly chloroquine-resistant strains of *Plasmodium falciparum* are widespread and the risk of malaria is high, C+P is however recommended for travellers to these areas if the duration of the exposition is <2 weeks (3). The French standpoint is even more cautious on mefloquine prophylaxis, since C+P and not mefloquine is the preferred regimen for most of West Africa and some other African countries (Somalia, Madagascar); moreover, mefloquine should not be taken for more than 3 months (6).

The harmonisation of chemoprophylactic regimens is however not impossible, at least for the military. Adverse effects recently reported among international travellers taking mefloquine have not been registered among soldiers. If we consider that soldiers are groups at particular high risk of malaria, the preferred option for chemoprophylaxis for all areas with chloroquine-resistant malaria could reasonably be represented by mefloquine, because of its higher efficacy, tolerability and compliance. The only exception could be represented by the areas with mefloquine-resistance, where doxycycline should be the preferred prophylactic regimen. Moreover, mefloquine can be safely taken at least up to six months of continuous prophylaxis.

Finally, current prophylactic regimens are however ineffective in preventing malaria caused by liver hypnozoites of *Plasmodium vivax* and *Plasmodium ovale*. Further development of new prophylactic regimens both causal and/or suppressive of malaria infections, such as atovaquone+proguanil or WR 238605 (tafenoquine), may represent a good chance for the harmonisation of malaria chemoprophylaxis among the military.

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