Congrès

THE MALARIA THREAT

A.M. Croft, K.G. Geary

ABSTRACT • The British experience of the past two decades indicates that fixed-schedule chemoprophylaxis is difficult because of the variety of epidemiological situations and increasing incidence of drug resistance. Of the 110 cases of malaria contracted in Kenya between 1982 and 1996, 74 % were due to *Plasmodium falciparum.* Of the 45 malaria infections contracted in Belize, 84 % were due to *Plasmodium vivax.* In 1985 the fixed drug combination of chloroquine base 300 mg weekly plus proguanil 200 mg daily was adopted as standard chemoprophylaxis for use in all parts of the world where chemoresistant *Plasmodium falciparum* had been observed. Mefloquine was recommended as first-line prophylaxis in Papua New Guinea in 1986 and in East Africa in 1993. Doxycycline hyclate was prescribed in September 1999 when a Gurkha company was deployed on peacekeeping duties to East Timor, but its effectiveness has not yet been evaluated. Chemoprophylaxis must be combined with non-drug antimalaria technologies, especially insecticide-treated bed nets.

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

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LA MENACE DU PALUDISME

RESUME • Selon l'expérience britannique des vingt dernières années, la chimioprophylaxie ne peut pas être figée, en raison de la variété des situations épidémiologiques et de l'augmentation des chimiorésistances. Sur les 110 cas de paludisme contractés au Kenya entre 1982 et 1996, 74 % étaient dus à *Plasmodium falciparum*. Sur les 45 paludismes contractés au Belize, 84 % étaient dus à *Plasmodium vivax*. L'association chloroquine (300 mg par semaine) plus proguanil (200 mg par jour) a été adoptée en 1985 comme chimioprophylaxie standard partout où a été rapportée une résistance de *Plasmodium falciparum* à la chloroquine. La méfloquine a été recommandée en première intention en Papouasie-Nouvelle-Guinée en 1986 et en Afrique de l'est en 1993. L'hyclate de doxycycline a été prescrite en septembre 1999 à une compagnie de Gurkha déployée au Timor Oriental en maintien de la paix : son efficacité n'est pas encore évaluée. La chimioprophylaxie doit être associée à des actions autres que médicamenteuses, en particulier à l'utilisation des moustiquaires de lit imprégnées d'insecticide.

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

As at January 2000, British troops were deployed in 27 locations worldwide. Malaria is a threat in seven of these locations, namely Belize, Brunei, East Timor, Kenya, Nepal, Sierra Leone and Turkey (1).

The British experience of the past two decades was that soldiers were more likely to contract malaria than sailors or airmen. Figure 1 gives a breakdown of confirmed cases of malaria in the British Army between 1982 and 1996, by geographical source of infection. Kenya was the largest single source (2) : of the 110 cases of malaria in the British Army that were contracted in Kenya between 1982-1996, 74 % were due to *Plasmodium falciparum* ; 45 malaria infections were contracted in Belize, and of these, 84 % were due to *Plasmodium vivax* (2).

Thanks to prompt diagnosis and treatment, there have been no malaria fatalities in British soldiers during the past two decades. There have however been two recent fatalities in Royal Air Force personnel. In 1995 a Royal Air Force officer contracted *Plasmodium falciparum* infection during UN monitoring duties in Cambodia, and subsequently died. In 1999 a Royal Air Force officer contracted *Plasmodium falcipanum* infection during off-duty travel to the Gambia, and also died.

PREVENTING MALARIA - CURRENT DRUG OPTIONS

Chloroquine and proguanil.

The fixed drug combination of chloroquine base 300 mg weekly plus proguanil 200 mg daily was adopted by the British Army in 1985 as the standard chemoprophylaxis for use in all parts of the world where there was recorded *Plasmodium falciparum* resistance to chloroquine. This included Southeast Asia and East Africa.

A cohort study carried out in 1985 in 120 British soldiers taking chloroquine plus proguanil during a 7-week jungle training exercise in the Sepik district of Papua New Guinea found five cases of breakthrough *Plasmodium falciparum* malaria, despite strict anti-mosquito discipline and close monitoring of adherence to chemoprophylaxis (3). This rate of infection was considered unacceptably high, and from 1986 chloroquine plus proguanil was no longer used as first-line prophylaxis for Papua New Guinea.

A cohort study carried out in 1993 in 150 British sol-

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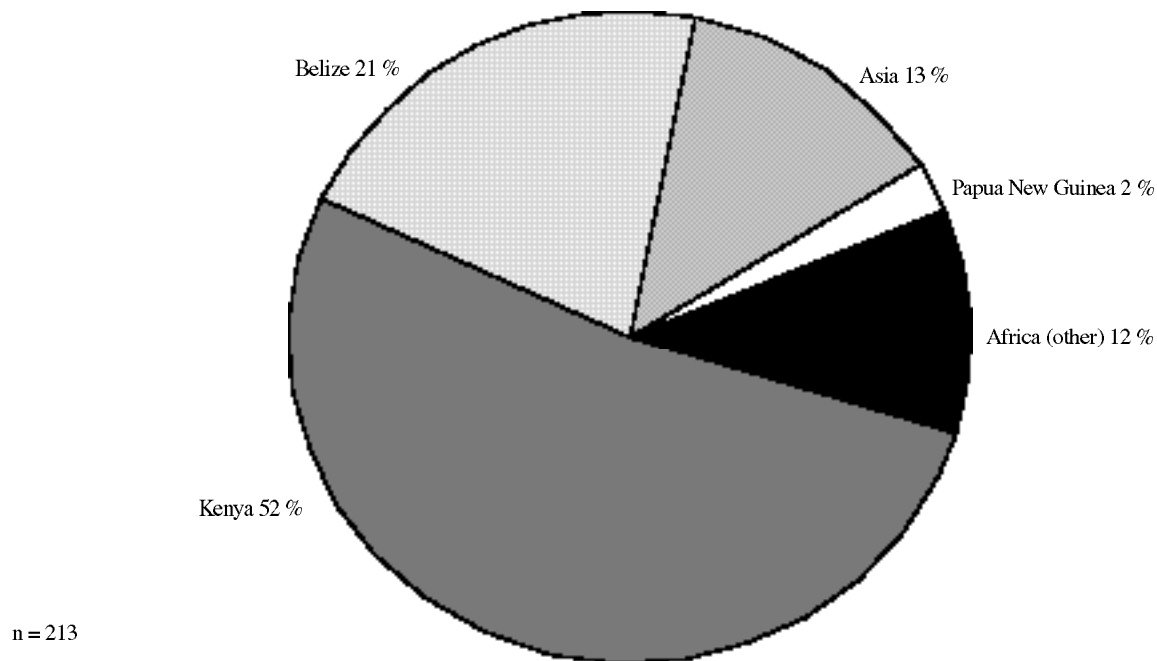
• *Actes du congrès*

Figure 1 - British Army malaria cases 1982-1996 by source of infection (Source : Miller S. et al. 1999, reproduced with permission).

diers taking chloroquine plus proguanil during a 5-week training exercise in central Kenya found seven cases of breakthrough *Plasmodium falciparum* malaria, although the investigators did not monitor adherence to chemoprophylaxis (4). In keeping with new guidelines issued in 1993 by the UK Public Health Laboratory service, the British Army's recommended first-line prophylaxis for East Africa was changed to mefloquine in July 1993 (5).

In a randomised controlled trial (RCT) in British troops in Kenya in 1995, the adverse effects most commonly associated with chloroquine plus proguanil prophylaxis were abdominal pain (19 %), nausea (16 %), anorexia (12 %), abnormal dreams (8 %), sleeplessness (8 %), mouth ulcers (7 %), fever (3 %), depression (3 %), pruritus (2 %) and tremor (2 %) (6).

A cohort study in 470 British soldiers in Belize found that the risk of mouth ulcers almost doubled with chloroquine plus proguanil compared with proguanil alone (relative risk 1.9, P = 0.025) (7).

Mefloquine.

Mefloquine hydrochloride is a 4-quinoline methanol which has been used in prophylaxis since 1985 (8). The normal maintenance dose is 250 mg taken once weekly (1).

Mefloquine prophylaxis has been evaluated rigorously, through a placebo-controlled randomised trial in non-immune Indonesian soldiers deployed to a malaria-endemic setting (9). Mefloquine ingestion was directly observed, and the drug was found to have a protective efficacy of 100 % (95 % Confidence Interval 96 % to 100 %).

In randomised controlled trial carried out in British troops in Kenya, 31 % of participants admitted that their adherence to chemoprophylaxis was not complete (10). It was presumed that this was due to adverse effects. The adverse effects most commonly associated with mefloquine prophylaxis were abdominal pain (15 %), nausea (12 %), anorexia (9 %), abnormal dreams (8 %), mouth ulcers (8 %), pruritus (7 %), sleeplessness (6 %), paranoid feelings (3 %), depression (2 %) and anxiety attacks (1 %) (6).

The neuropsychiatric adverse effects of mefloquine are a matter for concern, and their aetiology has not as yet been rigorously investigated (11). There is one published case report of a deployed British soldier who experienced an acute psychotic reaction to mefloquine prophylaxis (12). There are four other published case reports of military personnel experiencing neuropsychiatric adverse effects secondary to mefloquine prophylaxis (13, 14). In a 12-week randomised controlled trial carried out by Boudreau and colleagues in US marines stationed in a non-endemic area, two out of 203 mefloquine recipients were withdrawn from the study on account of depression and suicidal thoughts. Marines using mefloquine had more problems with sleep disturbances and significantly increased vivid dreams and nightmares than those receiving chloroquine (15).

Doxycycline hyclate.

Doxycycline hyclate is an antibiotic of the tetracycline group which is not licensed in the UK for antimalaria prophylaxis, but which is recommended in the UK national guidelines as a chemoprophylaxis option for travel to those parts of the world (such as South East Asia) where there is recorded resistance to mefloquine (1). Doxycycline is prescribed as a once-daily 100 mg dose.

In a placebo-controlled randomised trial in non-immune Indonesian soldiers deployed to a malaria-endemic setting, doxycycline was found to have a protective efficacy against *Plasmodium falciparum* malaria of 99 % (95 % Confidence Interval 94 % to 100 %). Commonly-reported adverse effects were unspecified dermatological problems (33 %), cough (31 %) and headache (16 %) (9).

The first large-scale use of doxycycline hyclate by a British force was in September 1999, when a Gurkha company deployed on peacekeeping duties to East Timor was prescribed this drug as malaria prophylaxis. Its effectiveness will be evaluated and reported in due course.

Other drug options.

The fixed drug combination of dapsone 4mg or 12.5 mg daily plus proguanil 200 mg daily was evaluated in 1990-1991 in a randomised controlled trial in Thai soldiers on the Thai-Cambodian border. Adherence to chemoprophylaxis was 69 %. The *Plasmodium falciparum* attack rate over the 40-day study period was 10.3 p. 100 and the *Plasmodium vivax* attack rate was 1.6 p. 100. Fewer than 2 % of participants reported any drug-related symptom (16).

The fixed drug combination of dapsone 100 mg weekly plus pyrimethamine 12.5 mg weekly was evaluated in the same randomised controlled trial. Adherence to chemoprophylaxis was 74 %. The *Plasmodium falciparum* attack rate over the 40-day study period was 11.3 p. 100 and the *Plasmodium vivax* attack rate was 12.4 p. 100. Fewer than 2 % of participants reported any drug-related symptom (16).

Neither of these two drug regimens has been evaluated in British troops.

PREVENTING MALARIA - CANDIDATE ANTIMALARIA DRUGS

Two candidate drugs are currently of great interest to the British Army, for possible future use in malaria chemoprophylaxis.

Doxycycline monohydrate (Tolexine®) is a newly-developed doxycycline salt which is described as a rapidly-disintegrating multiparticulate tablet. It is prescribed as a once-daily 100 mg dose. In a controlled clinical trial in 524 French soldiers in Gabon, the malaria attack rate over the 4-month study period was 2.8 p. 100 in doxycycline monohydrate users and 9 p. 100 in chloroquine plus proguanil users (P=0.003). The drug was reportedly well-tolerated (17).

Atovaquone plus proguanil (Malarone®) is a fixed drug combination which has shown high chemoprophylactic efficacy in randomised controlled trials in indigenous African populations, but which has not yet been evaluated in non-immune travellers (18).

COUNTERING THE THREAT

Formulating antimalaria drug policy.

Policy decisions on malaria prevention should be based on a systematic analysis of the best available scientific evidence (19). The best sources of primary evidence for informing decisions about military chemoprophylaxis are randomised controlled drug trials carried out on military groups who are deployed or in training.

An important compendium of the best available evidence on the effects of common clinical interventions has been published jointly by the BMJ Publishing Group and the American College of Physicians. This compendium, entitled *Clinical Evidence*, includes a section on preventing malaria in travellers and is updated and expanded twice a year (18). *Clinical Evidence* is now used as a primary data source by medical planners in the British Armed Forces.

For specific military operations, evidence on the effectiveness of chemoprophylaxis needs to be supplemented by up-to-date information regarding parasite resistance locally to standard antimalaria drugs (1).

Designing and reporting military drug trials.

As new antimalaria drugs become available for use on military operations, and as the spread of parasite resistance undermines the usefulness of older drugs, the newly-developed agents will need to be evaluated through appropriately designed randomised controlled trials in military populations.

Any future military chemoprophylaxis trial should be of sufficient power to show that the new agent being evaluated is well tolerated by military users, under the anticipated conditions of use (20). When designing military trials it is convenient to use a military sub-grouping (for example, a platoon or a company) as the functional unit of allocation, but this practice should be avoided, and randomising should be according to individual trial participants (21).

The design of any malaria chemoprophylaxis trial must be such that the main study drug of interest is assessed against an appropriate comparator or comparators, and not simply against a different formulation of the drug itself (22). To facilitate comparison with other studies, the trial should be conducted according to a standardised scientific methodology (23).

Future military chemoprophylaxis trials should be reported completely, and the reporting format should be that of the CONSORT guidelines (24-26). These guidelines were developed by an international panel of investigators, epidemiologists, biostatisticians and editors, and currently provide the best available evidence on the correct reporting format for randomised controlled trials.

It is particularly important that study drop outs, and rates of adherence to different prophylactic regimens, are reported as primary outcomes in future military trials of malaria chemoprophylaxis (27).

The role of non-drug antimalaria interventions.

Randomised controlled trials show that deployed troops do not adhere fully to malaria chemoprophylaxis, even when they are aware that malaria is a serious threat (10, 16). Chemoprophylaxis therefore needs to be combined with non-drug antimalaria interventions, especially those interventions which have been shown through randomised controlled trials to be effective. Of all the possible non-drug interventions to prevent malaria, the most beneficial has been found to be the use of insecticide-treated nets (18).

REFERENCES

1 - BRADLEY D.J., WARHURST D.C. - Guidelines for the prevention of malaria in travellers from the United Kingdom. *Commun. Dis. Rep. CDR Rev.* 1997 ; **7** : R137-R152.

2 - MILLER S.A., BERGMAN B.P., CROFT A.M. - Epidemiology of malaria in the British Army from 1982-1996. *J. R. Army Med. Corps* 1999 ; **145** : 20-22.

3 - HENDERSON A., SIMON J.W., MELIA W. - Failure of malaria chemoprophylaxis with a proguanil-chloroquine combination in Papua New Guinea. *Trans. R. Soc. Trop. Med. Hyg.* 1986 ; **80** : 838-840.

4 - MILLER J.H., BYERS M., WHITEOAK R., WARRELL D.A. - Imported *falciparum* malaria in British troops returning from Kenya. *J. R. Army Med. Corps* 1994 ; **140** : 119-123.

5 - BRADLEY D. - Prophylaxis against malaria for travellers from the United Kingdom. *Br. Med. J.* 1993 ; **306** : 1247-1252.

6 - CROFT A. - Toxicity of mefloquine is similar to that of other chemoprophylaxis. *Br. Med. J.* 1995 ; **311** : 191.

7 - DRYSDALE S.F., PHILLIPS-HOWARD P.A., BEHRENS R.H. - Proguanil, chloroquine and mouth ulcers. *Lancet* 1990 ; **335** : 164.

8 - HEIMGARTNER E. - Praktische erfahrungen mit mefloquin als malariaprophylaktikum. *Schweiz. Rundsch. Med. Prax.* 1986 ; **75** : 459-462.

9 - OHRT C., RICHIE T.L., WIDJAJA H. et Coll. - Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers. A randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.* 1997 ; **126** : 963-972.

10 - CROFT A.M., CLAYTON T.C., WORLD M.J. - Side effects of mefloquine prophylaxis for malaria : an independent randomized controlled trial. *Trans. R. Soc. Trop. Med. Hyg.* 1997 ; **91** : 199-203.

11 - CHOO V. - Uncertainty about mefloquine will take time to resolve. *Lancet* 1996 ; **347** : 891.

12 - CROFT A.M., WORLD M.J. - Neuropsychiatric reactions with mefloquine chemoprophylaxis. *Lancet* 1996 ; **347** : 326.

13 - GULLAHORN G.M., BOHMAN H.R., WALLACE M.R. - Anaesthesia emergence delirium after mefloquine prophylaxis. *Lancet* 1993 ; **341** : 632.

14 - PIENING R.B., YOUNG S.A. - Mefloquine-induced psychosis. *Ann. Emergency Med.* 1996 ; **27** : 792-793.

15 - BOUDREAU E., SCHUSTER B., SANCHEZ J. et Coll. - Tolerability of prophylactic Lariam regimens. *Trop. Med. Parasitol.* 1993 ; **44** : 257-265.

16 - SHANKS G.D., EDSTEIN M.D., SURIYAMONGKOL V. et Coll. - Malaria combinations using proguanil/dapsone chemoprophylaxis on the Thai-Cambodian border. *Am. J. Trop. Med. Hyg.* 1992 ; **46** : 643-648.

17 - BAUDON D., BOUTIN J-P., PAGES F. et Coll. - Determination of the tolerance and effectiveness of a new doxycycline salt in malaria chemoprophylaxis compared with chloroquine-proguanil. Proceedings of the Sixth International Conference on Travel medicine, 1999, Jun 6-10, Montréal. International Society of Travel Medicine, Montréal, 1999.

18 - CROFT A - Malaria prevention in travellers. In «Clinical evidence : a compendium of the best available evidence for effective health care». BMJ Publishing Group ed., Londres, 2000, pp 337-349.

19 - PENCHEON D. - The international Cochrane Collaboration. *Trans. R. Soc. Trop. Med. Hyg.* 1998 ; 92 : 473-474.

20 - SMITH P.G., MORROW R.H. - Field trials of health interventions in developing countries: a toolbox. Macmillan ed., Londres, 1996, 362 p.

21 - CROFT A.M., VASSALLO D.J., ROWE M. - Handsearching the Journal of the Royal Army Medical Corps for trials. *J. R. Army Med. Corps* 1999 ; **145** : 86-88.

22 - HENRY D., HILL S. - Comparing treatments. *Br. Med. J.* 1995 ; **310** : 1279.

23 - MACLEAN M., ANDERSON J., DAVIES C. - Making malaria research bite. *Nat. Med.* 1997 ; **3** : 14-16.

24 - ALTMAN D.G. - Better reporting of randomised controlled trials : the CONSORT statement. *Br. Med. J.* 1996 ; **313** : 570-571.

25 - BEGG C., CHO M., EASTWOOD S. et Coll. - Improving the quality of reporting of randomized controlled trials : the consort statement. *JAMA* 1996 ; **276** : 637-639.

26 - SCHULZ K.F. - Randomised trials, human nature, and reporting guidelines. *Lancet* 1996 ; **348** : 596-598.

27 - CROFT A., GARNER P. - Mefloquine to prevent malaria : a systematic review of trials. *Br. Med. J.* 1997 ; **315** :1412-1416.