Daily chlorproguanil is an effective alternative to daily proguanil in the prevention of *Plasmodium falciparum* malaria in Kenya

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Abstract

To test the efficacy of chlorproguanil prophylaxis, 156 malaria-free schoolchildren in the coastal region of Kenya were allocated at random to receive either 7·5 mg chlorproguanil daily, 50 mg chlorproguanil weekly, 100 mg proguanil daily, or 100 mg calcium lactate weekly (placebo). The children were followed up daily for 169 d, by which time *Plasmodium falciparum* parasitaemia had occurred in 92% of the placebo group, 31% of the daily proguanil group, 38% of the daily chlorproguanil group and 55% of the weekly chlorproguanil group. There was significant reduction ($P<0·001$) in the risk of parasitaemia in all the groups receiving chemoprophylaxis. Daily chlorproguanil and daily proguanil were equally effective, and significantly more effective than weekly high dose chlorproguanil. No significant toxicity was reported or observed. Thus daily chlorproguanil 20 mg/60 kg is a cheap and effective alternative to proguanil for chemoprophylaxis.

Introduction

Daily proguanil, a biguanide antimalarial, has remained an effective, non-toxic chemoprophylactic agent against chloroquine-resistant falciparum malaria (CRPF) (NEVILL *et al.*, 1988; MANN & PHILLIPS-HOWARD, 1989). However, weekly chlorproguanil, a chlorinated analogue of proguanil, gave poor protection against *Plasmodium falciparum* (see COOSEMANS *et al.*, 1987; WATKINS *et al.*, 1987a), despite the greater activity *in vitro* of its metabolite chlorcycloguanil against *P. falciparum* compared to that of cycloguanil (WATKINS *et al.*, 1987a). This failure may have been due to an inappropriate dosage interval since the half-life of chlorproguanil is less than 10 h (WATKINS *et al.*, 1987b), or to reduced sensitivity of the parasite to chlorcycloguanil.

We therefore investigated these possibilities in children by comparing chlorproguanil in a weekly dose of 50 mg (2 mg/kg) and a daily dose of 7·5 mg (0·3 mg/kg), which amounted to approximately the same total weekly dose and is equivalent to the previously recommended weekly dose of 20 mg for an adult weighing about 60 kg.

Methods

Trial procedure

One hundred and fifty-six schoolchildren attending Konjora primary school, 60 km north of Mombasa on the coast of Kenya, were recruited by class with informed parental consent in June 1986. The children were examined (by J.D.L.) and thick and thin blood films made from a finger prick. All children were given chloroquine, 25 mg/kg, plus pyrimethamine/sulfadoxine, 25 mg/kg, to clear any malaria parasites before sequential allocation at random to one of the following 4 regimens. A: 7·5 mg chlorproguanil hydrochloride daily (syrup; 7·5 mg of Lapudrine® per 5 mL prepared immediately before use; B: 50 mg chlorproguanil hydrochloride once weekly (Lapudrine® tablets); C: 100 mg proguanil hydrochloride daily (Paludrine® tablets); D: 100 mg calcium lactate (placebo) weekly (tablets).

Administration was started on day 14 when all children had confirmed negative blood films for asexual forms of *P. falciparum*. A daily school visit ensured compliance and the follow-up of missing children. Any child that reported sick was also examined, investigated by means of a blood film and managed accordingly, if necessary at the district hospital. In addition, all children were screened for malaria parasites every 14 d throughout the study. Any child with a blood film showing asexual forms of *P. falciparum* was treated with a single dose of pyrimethamine/sulfadoxine, removed from the study and followed-up to confirm clinical recovery and parasite clearance.

All thick and thin blood films were stained with 4% Giemsa's stain for 30 min and examined with the aid of an oil immersion objective. Asexual parasites were counted per 300 white blood cells and a slide was reported as negative after examination of the complete film; the microscopist was unaware of the origin of the slides.

Statistics

The first subject was randomly assigned to his/her preventive protocol and the remainder sequentially. Log rank significance levels were applied to life tables constructed for risk of parasitaemia on the 170th day of the study, after removal of all subjects who had suffered a 'terminal event' (PETO *et al.*, 1977). Recruitment characteristics were assessed between the groups with Student's *t* test.

Ethical issues

The study was approved by the scientific and ethical committees of KEMRI. Children were recruited with informed parental consent and were monitored daily by trained staff because of (i) the lack of data on cumulative effects of daily chlorproguanil and (ii) the higher than normal weekly dose.

Results and Analysis

The numbers of children recruited to the groups A, B, C and D were 40, 40, 39 and 37 respectively. Their mean weights and ages were within the ranges 24·3–24·9 kg and 8·6–9·1 years, and 70–82% were parasitaemic at recruitment. There was no significant difference between the groups with respect to mean weight, age, or the number parasitaemic at the outset ($P>0·1$). The 118 children (76%) parasitaemic at recruitment were successfully cleared of malaria parasites by the combination of chloroquine and pyrimethamine/sulfadoxine and remained parasite-free to day 28.

The cumulative frequency of malaria episodes by group during the study is illustrated in the Figure; the 'natural' infection rate in the placebo group was at least 3·7 episodes of parasitaemia per year. All 83 of these *P. falciparum* episodes were treated successfully with pyrimethamine/sulfadoxine alone.

The probability of parasitaemia by day 170 was 0·359 for daily proguanil, 0·412 for daily chlorproguanil, 0·592 for weekly chlorproguanil, and 0·932 for weekly placebo. Paired group life tables were analysed on day 170. There was significantly less risk of parasitaemia in all the biguanide groups compared to the placebo group ($\chi^2=16·4$, 55 degrees of freedom (d.f.); 28·5, 48 d.f.; and

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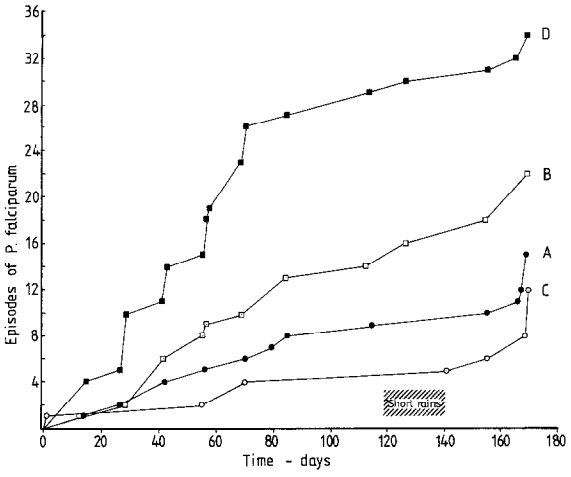

Figure. Cumulative episodes of *P. falciparum* parasitaemia in each of the 4 study groups of schoolchildren in Kenya. A: 7·5 mg chlorproguanil daily; B: 50 mg chlorproguanil weekly; C: 100 mg proguanil daily; D: 100 mg calcium lactate weekly.

37·3, 45 d.f., respectively; $P<0·001$), and in the daily proguanil group compared to the weekly chlorproguanil group ($\chi^2=5·15$, 33 d.f.; $P<0·05$). However, there was no difference in risk between weekly chlorproguanil and daily chlorproguanil ($\chi^2=2·24$, 36 d.f.; $P>0·1$), nor between daily chlorproguanil and daily proguanil ($\chi^2=0·51$, 26 d.f.; $P>0·3$). No adverse reaction was observed or reported.

Discussion

This study confirmed that daily proguanil and chlorproguanil gave adequate protection in this area of high infection pressure with *P. falciparum* resistant to 4-aminoquinolines (NEVILL *et al.*, 1990). Weekly administration of chlorproguanil gave inadequate protection even at increased dosage. The failure of the higher weekly regimen of chlorproguanil and the success of the daily regimen support the hypothesis that the drug's half-life is too short for weekly administration and that decreased parasite sensitivity was not responsible for the poor efficacy; this is further supported by sensitivity tests *in vitro*, which show little change in actual sensitivity of the parasite to biguanide over the last decade (WATKINS *et al.*, 1987b; MBERU *et al.*, 1993).

Daily chlorproguanil is not only an effective alternative to proguanil but may be a better choice in areas with *P. falciparum* resistant to pyrimethamine and proguanil, firstly due to the greater sensitivity *in vitro* of *P. falciparum* to chlorcycloguanil than to cycloguanil, the metabolite of proguanil (WATKINS *et al.*, 1987b), and secondly because this daily dosage gives trough concentrations of chlorcycloguanil which are approximately 50 times the 50% inhibitory dose of chlorcycloguanil to pyrimethamine resistant *P. falciparum*, compared to 5 times the corresponding value for cycloguanil derived from daily proguanil (RITSCHEL, 1986; BYGBJERG *et al.*, 1987; WATKINS *et al.*, 1987c). However, there are no data on the cumulative effects of daily chlorproguanil and, although we observed no significant toxicity during this trial, prospective studies should evaluate the toxicity of a daily dosage regimen before this can be safely recommended.

In conclusion, both biguanide antimalarials, at a daily dosage, offer relatively inexpensive, non-toxic and effective malaria prevention even in this area of high transmission pressure. Daily chlorproguanil may have some advantages over daily proguanil, but caution is advised until there are further data available on its possible cumulative effects.

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References

Bygbjerg, I., Ravan, P., Roun, A., Falchs, H. & Hvidberg, E. F. (1987). Human pharmacokinetics of proguanil and its metabolites. *Tropical Medicine and Parasitology*, **38**, 77–80.

Coosemans, M. H., Barutwanayo, M., Onori, E., Otoul, C., Gryseels, B. & Wéry, M. (1987). Double-blind study to assess the efficacy of chlorproguanil given alone or in combination with chloroquine for malaria chemoprophylaxis in an area with *Plasmodium falciparum* resistance to chloroquine, pyrimethamine and cycloguanil. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **81**, 151–156.

Mann, R. D. & Phillips-Howard, P. A., editors. (1989). Malaria in Britain: past and present. *Journal of the Royal Society of Tropical Medicine*, **82**, supplement 17, 488–492.

Mberu, E. K., Winstanley, P. A., Howells, R. E. & Watkins, W. M. (1993). Antifolate synergy against *Plasmodium falciparum in vitro*; a comparison of candidate combinations for therapeutic use in man. *Annual Meeting of British Society for Parasitology, Leeds, UK, March 1993* (abstract).

Nevill, C. G., Watkins, W. M., Carter, J. Y. & Munafu, C. G. (1988). Comparison of mosquito nets, proguanil hydrochloride and placebo to prevent malaria. *British Medical Journal*, **297**, 401–403.

Nevill, C. G., Hulleman, P., Watkins, W. M., Milner, R., Mosobo, M. & Peshu, N. (1990). Clinical rather than parasitological failure—a more appropriate measure of antimalarial resistance. A pilot study. *Proceedings of the Annual KEMRI/KETRI Conference, February, Nairobi, Kenya, February 1990.*

Peto, R., Pike, M. C., Armitage, P., Breslow, N. E., Cox, D. R. & Howard, S. V. (1977). Design and analysis of randomised clinical trials requiring prolonged observation of each patient. II Analysis and examples. *British Journal of Cancer*, **35**, 1–39.

Ritschel, W. A. (1986). *Handbook of Basic Pharmacokinetics*, 3rd edition. Hamilton, Ontario: Drug Intelligence Publications.

Watkins, W. M., Brandling-Bennett, A. D., Oloo, A. J., Howells, R., Gilles, H. M. & Koech, D. K. (1987c). Inadequacy of chlorproguanil 20 mg per week as chemoprophylaxis for falciparum malaria in Kenya. *Lancet*, **i**, 125–127.

Watkins, W. M., Chulay, J. D., Sixsmith, D. G., Spencer, H. C. & Howells, R. E. (1987b). A preliminary pharmacokinetic study of the antimalarial drugs proguanil and chlorproguanil. *Journal of Pharmacy and Pharmacology*, **39**, 261–265.

Watkins, W. M., Howells, R. E., Brandling-Bennett, A. D. & Koech, D. K. (1987c). *In vitro* susceptibility of *Plasmodium falciparum* isolates from Jilore, Kenya to antimalarial drugs. *American Journal of Tropical Medicine and Hygiene*, **37**, 445–451.

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