Drug-resistant *Plasmodium falciparum* malaria in the eastern Transvaal

H. E. Deacon, J. A. Freese, B. L. Sharp

In March 1993, a study was undertaken in the Komatipoort/Malelane area to monitor the *in vitro* sensitivity of *Plasmodium falciparum* to antimalarial drugs currently in use in South Africa. Of the 12 isolates collected, 7 were successfully tested for sensitivity to chloroquine and quinine, 6 for mefloquine susceptibility, and 5 for sensitivity to Fansidar. Four of the isolates were resistant to chloroquine at RIII level, 1 at RII level, and 2 were sensitive. All isolates were found to be sensitive to both quinine and mefloquine. Results suggested possible resistance to Fansidar. These findings have implications for tourists travelling to this area.

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Resistance to chloroquine was first detected in 1958 in both South America and south-east Asia.[1]

It was first reported from Africa in 1979, from both Kenya[2] and Tanzania.[3] Reports of *in vivo* and *in vitro* resistance to chloroquine then followed in the 1980s from all the southern African countries, including Botswana,[4] Mozambique,[5] Angola,[6,7] Namibia,[7] Zimbabwe[8] and Swaziland.[9] Chloroquine resistance was first reported in South Africa in 1985. Bac *et al.*[10] reported on an *in vivo* resistant case from Venda which was confirmed *in vitro;* Visagie and Sieling[11] reported on an *in vivo* case of chloroquine resistance from Louis Trichardt, and Herbst *et al.*[12] reported on 6 *in vitro* chloroquine-resistant isolates from the KwaZulu/Natal area. A number of further studies have been completed in KwaZulu/ Natal confirming the presence of highly chloroquine-resistant *Plasmodium falciparum.*[13-15]

Other than some case reports of chloroquine resistance in the Transvaal,[10,11] no further published data from *in vivo* studies or *in vitro* tests of field isolates exist for the area. Freese *et al.*[16] reported on the *in vitro* sensitivity of 5 culture-adapted isolates collected in the eastern Transvaal. Four of the 5 isolates studied were found to be resistant to chloroquine. Although the culture conditions may have resulted in the selection of resistant clones in these isolates, the results of the investigation nevertheless indicated the presence of chloroquine-resistant parasites in the local *P. falciparum* population.

National Malaria Research Programme of the South African Medical Research Council (Natal), Durban

H. E. Deacon, B.SC. HONS

J. A. Freese, B.SC. HONS

B. L. Sharp, PH.D.

It should be borne in mind that more than 40% of cases are classified as imported into the eastern and northern Transvaal provinces, of which a high percentage originate from other southern African countries where drug resistance is known to occur (Department of National Health and Population Development — notification data).

The South African Medical Research Council recently initiated an investigation into the drug susceptibility of *P. falciparum* in the Transvaal area. In a survey carried out in March 1993 in the Komatipoort/Malelane area of the eastern Transvaal, the *in vitro* sensitivity of *P. falciparum* to antimalarial drugs currently in use in South Africa was monitored.

Materials and methods

Blood containing *P. falciparum* was obtained from patients reporting to local clinics and doctors in the area (i.e. passively detected cases)[17] and tested within 6 hours of collection for sensitivity to chloroquine, quinine, mefloquine and sulphadoxine/pyrimethamine (Fansidar), using a modification of the WHO *in vitro* microtechnique.[14]

Isolates were considered to be suitable for the test if they contained 500 - 80 000 ring forms of *P. falciparum* per microlitre blood. Patients with mixed malarial infections and those who had received antimalarial drugs during the 14 days prior to the test were excluded from the investigation.

The minimum inhibitory concentration (MIC) of each isolate, defined as the lowest concentration at which schizont maturation (SM) was completely inhibited, was determined for each drug. The discriminating MICs for resistant isolates are: chloroquine > 0,16 μmol/l, quinine > 5,12 μmol/l, and mefloquine > 0,64 μmol/l.[18]

Results

Of the 12 isolates found to be suitable for the test, 7 were successfully tested for sensitivity to chloroquine and quinine, 6 for mefloquine susceptibility, and 5 for sensitivity to Fansidar. Four of the isolates were resistant to chloroquine at RIII level (with MICs ranging from 0,64 to 1,28 μmol/l); 1 at RII level (MIC 0,32 μmol/l);[1] and 2 were sensitive (MICs 0,04 and 0,16 μmol/l) (Table I). All isolates were found to be sensitive to both quinine (MIC 1,28 μmol/l for all 7 isolates) and mefloquine (MICs ranging from 0,04 to 0,16 μmol/l). The Fansidar MICs ranged from 0,2 to 60 μmol/l.

Table I. In vitro sensitivity of eastern Transvaal isolates of *Plasmodium falciparum* to four antimalarial drugs

Isolate No.	Chloroquine MIC (μmol/l)	Quinine MIC (μmol/l)	Mefloquine MIC (μmol/l)	Fansidar MIC (μmol/l)
1	0,32	1,28	NS	NS
5	1,28	1,28	0,16	0,6
6	0,64	1,28	0,16	20,0
9	0,64	1,28	0,04	60,0
14	1,28	1,28	0,08	0,2
15	0,16	1,28	0,16	0,2
16	0,04	1,28	0,16	NS

NS — tests with SM less than 5% were considered not to be successful.[19]

Discussion

These results confirm the presence of chloroquine-resistant *P. falciparum* in the eastern Transvaal. No information is, however, available concerning the *in vivo* response of the same parasites to chloroquine. There was a wide range of susceptibility to sulphadoxine/pyrimethamine (MICs ranged from 0,2 to 60 μmol/l). The isolates fell into two distinct groups, those with MICs < 1 μmol/l and those with MICs ⩾ 20 μmol/l. It was not possible to draw conclusions regarding the Fansidar resistance status of these isolates as the discriminatory MIC values for resistant isolates in the WHO sulphadoxine/pyrimethamine *in vitro* test have not yet been determined. Various authors have found that resistant and sensitive isolates can easily be distinguished by their MICs[20] and it is therefore possible that 2 isolates in this study with MICs ⩾ 20 μmol/l may in fact be resistant to Fansidar.

Since all the cases were classified as local transmission by the authorities, the results indicate that there is transmission of chloroquine-resistant and possibly Fansidar-resistant *P. falciparum* malaria in this region. These data are considered important to the planning of malaria control strategies for the area. Continued monitoring of the susceptibility to Fansidar (both *in vivo* and *in vitro*) should be seen as a priority. Immunity to malaria is known to shorten the duration of individual infections and to enhance the effect of antimalarial drugs.[21] Chloroquine may still have a role to play in malaria control but resistance to this drug would pose a threat to non-immune tourists travelling to this area.

As outlined earlier, chloroquine-resistant *P. falciparum* is widespread in southern Africa. A large number of our malaria cases are imported into the country (> 30%) (Department of National Health and Population Development — notification data) and it is therefore not surprising that chloroquine resistance should be detected in our malarious areas. Currently, the eastern Transvaal is still documented as a low-risk area where chloroquine alone or no prophylaxis is recommended.[22] We believe that the eastern Transvaal should be reclassified as a moderate to high-risk area (mainly from November to May) where prophylaxis such as chloroquine plus proguanil or mefloquine or doxycycline should be recommended to tourists.

This study will continue in the next malaria season.

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Antimalarial measures — type, sources of advice and compliance among tourists to Natal/KwaZulu

G. B. Wilken, L. Baker

Typical advice on antimalarial measures provided by pharmacies as well as actual behaviour in this regard and sources of advice accessed by tourists to northern Natal/KwaZulu were canvassed by telephonic interviews with 70 pharmacies and 53 'care providers' (members of travel parties). Doctors (26%) and pharmacists (40%) were the most commonly approached sources of antimalarial advice. Professional recommendations frequently involved chloroquine-based drugs (80% of recommended drugs), despite the chloroquine-resistant status of the study area. Drug choice reflected the limited availability of new alternatives to chloroquine at the time the study was conducted, as well as ignorance of drug resistance in the area. Possible reasons for the inappropriate nature of many of the reported recommendations, as well as an approach to the dissemination of future prophylactic policy documents, are discussed.

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National Malaria Research Programme of the South African Medical Research Council, Durban

G. B. Wilken, M.SC.

TPS Drug Information Services, Johannesburg

L. Baker, DIP. PHARM.