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Research Note

Decreasing Resistance of *Plasmodium falciparum* to Chloroquine in Hainan Island, China

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The development and spread of multiple drug resistance in *falciparum* malaria have created increasing difficulties in malaria control measures in the tropics. Hainan Island has been one of the most serious endemic areas of malaria in China. A record high incidence was in 1955; the morbidity was 286,745 with a mortality of 287 in 2.77 million population. The introduction of residual spraying with D.D.T. in 1959 showed very promising results in morbidity and the incidence of malaria was successively reduced every year thereafter. In 1965, the incidence of parasitic infection was less than 0.9% and a 0.2% level has been maintained for the last decade (Cai *et al.*, unpublished results). However chloroquine-resistant *P. falciparum* was discovered in 1974 at Sanya (South coast of the Island) and by 1978 it had spread to all areas of the Island (Cai *et al.*, 1986). More than 80% of cases were resistant to chloroquine, 1/3 of which were RII to RIII grade and 500,000 individuals were involved. In 1979, a 4-amino-quinoline derivative, piperaquine, was introduced as a replacement for chloroquine prevention and treatment. In 1982, however, piperaquine-resistant *P. falciparum* appeared. The resistance fraction is about 30% at present which is still lower than that of chloroquine resistance and 10% of cases showed RII to RIII resistance. One of the authors has examined the drug resistance of *P. falciparum* by the *in vitro* WHO micro-method in Ledong county (Central part of the Island) for the last several years. The results show that the degree of resistance to chloroquine is still high but is decreasing annually. In contrast, that of piperaquine is increasing continuously (Cai *et al.*, 1989). At the same time, it was found that the chloroquine-resistant *P. falciparum* has developed drug resistance to other antimalarials including amodiaquine (Huang *et al.*, 1988), quinine and mefloquine (Huang *et al.*, unpublished results), pyronaridine and artesunate (Cai *et al.*, unpublished results).

Since the use of chloroquine for treatment and prevention of *falciparum* malaria has been stopped in 1979, the sensitivity of the parasites to the drug has increased each year. Cai *et al.*, (1986) showed that IC_{50} of isolates examined by the *in vitro* micro test for 3 years (1981–1983) dropped from 1.21 to 0.57 μM. We have examined sensitivity of *P. falciparum* isolates to

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Table 1 Fifty percent inhibitory concentration (Mean $IC_{50} \pm$ standard deviation) of antimalarials for *Plasmodium falciparum* isolates from Hainan Island during a five-year period

Year	Number of samples	IC_{50} concentration (μM/L)			
		Chloroquine	Piperaquine	Artemether	Pyronaridine
1987	11	0.24 ± 0.08*			
1989	12	0.13 ± 0.08	0.15 ± 0.13	0.05 ± 0.05	
1990	10	0.08 ± 0.05	0.10 ± 0.08	0.04 ± 0.04	0.06 ± 0.05
1991	8	0.08 ± 0.09	0.20 ± 0.12	0.04 ± 0.03	0.07 ± 0.04

*The data was cited from Waki *et al.* (1989).

antimalarials by the modified WHO standard *in vitro* method (Waki *et al.*, 1989, 1992) for the last several years in order to establish a new method for standardization of drug sensitivity test in Sanya City, Hainan Island. Malaria patients, sent to the hospital by village doctors, were routinely examined by means of blood smears. Blood samples from untreated patients showing more than 0.1% parasitemia were subjected to the tests. The results show that the sensitivity of *P. falciparum* isolates to the drugs except chloroquine have not changed significantly based on the number of samples examined but a further reduction in IC_{50} from 0.24 to 0.08 μM ($P<0.01$ by Student's t-test) has been demonstrated for chloroquine during the last 5 years (1987–1991). Although it should be necessary large scale surveys to be carried out for more accurate evaluation, the current degree of resistance is quite low since sensitive isolates show suppression of their maturation at a concentration of 0.08 μM/L or less (WHO, 1984). Those isolates show resistance to piperaquine but are sensitive to artemether and pyronaridine.

In recent years many antimalarials have been successfully used in combination for treatment and prevention of chloroquine resistant *falciparum* malaria (Huang *et al.*, 1986). If sensitivity of the parasites to those drugs can be properly monitored, it might be possible to use a limited number of antimalarials by rotation in combination.

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