EXTENDED CLEARANCE TIME AFTER TREATMENT OF INFECTIONS WITH PLASMODIUM MALARIAE MAY NOT BE INDICATIVE OF RESISTANCE TO CHLOROQUINE

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Abstract. A retrospective examination was made of archival data on the response of Plasmodium malariae infections in humans to chloroquine. The clearance time for P. malariae was longer than that for P. falciparum and P. vivax. Of 100 P. malariae–infected patients treated with 1,500 mg of chloroquine given over 3 days, 15 had detectable parasites for 7 days, 4 for 10 days, and 1 for 15 days after treatment. Of 17 patients treated intramuscularly with 450 mg of dihydrochloroquine, parasites persisted in 1 patient for 11 days. Of patients with chloroquine-sensitive P. falciparum, 44 cleared parasites by 6 days after treatment; 37 patients with P. vivax infections cleared parasites by day 5. The confirmation of chloroquine resistance may depend on the adaptation of isolates to nonhuman primates in which controlled drug trials can be made.

INTRODUCTION

Resistance of Plasmodium falciparum to treatment with chloroquine has been recognized since the 1960s and is now widespread throughout much of the tropical world. In the 1990s, Plasmodium vivax resistance also was documented, primarily in Indonesia, New Guinea, and Southeast Asia. There is continued vigilance for the appearance of resistance of the other 2 human-infecting malaria parasites, Plasmodium malariae and Plasmodium ovale. Often the first suggestion of resistance has been the failure of the standard treatment to clear parasites rapidly from the peripheral blood.

Young and Eyles1 reported the progressive clearance of P. malariae from the peripheral blood after standard treatment of patients with 1,500 mg of chloroquine given over 3 days. One of 18 patients treated still had parasites 10 days after initiation of treatment. When patients with higher numbers of parasites (2,000–9,900/μL) were compared with patients with lower parasite counts (50–1,310/μL), the cumulative percentages of parasites removed daily from each group were essentially the same. Subsequently, McLendon and Young2 reported on the clearance time for 12 patients with initial parasite counts of 2,140–29,825/μL to be 2–10 days after a single intramuscular injection of 450 mg of dihydrochloroquine (approximately 400-mg base). It is apparent from these observations that clearance time for P. malariae infections after treatment can be greatly extended. The presence of P. malariae many days after treatment may not indicate developed resistance.

We present a retrospective examination of archival data from P. malariae–infected patients for whom records were available3 who were treated with chloroquine. A database was extracted from parasitologic records acquired between 1949 and 1963 at National Institutes of Health installations then located at the South Carolina State Hospital, Columbia, South Carolina, and the Georgia State Hospital, Milledgeville, Georgia. An historical perspective on the use of malarialotherapy for the treatment of patients with neurosyphilis has been presented previously.4

MATERIALS AND METHODS

Patient management. Consent for which treatments the hospital staff determined necessary was granted by the fami-
Data presentation. The parasite counts from the 2 hospitals have been combined. Reported here are data recorded for 100 patients. These patients were infected with *P. malariae* for the treatment of paresis and other mental disorders associated with tertiary syphilis.

RESULTS

Group I consisted of 62 patients with initial parasite counts >1,000/μL who received 1,500 mg of chloroquine over 3 days (Figure 1A). By day 7, 12 patients still had detectable parasitemia; by day 10, 3 still had detectable parasitemia; the last patient cleared parasites on day 16. This was compared with the clearance time for 41 patients with *P. falciparum* (Figure 2A) and 37 patients with *P. vivax* (Figure 2B) with initial parasite counts >1,000/μL. All infections with *P. falciparum* were cleared by day 7; infections with *P. vivax* were cleared by day 5.

Group II consisted of 38 patients with initial parasite counts <1,000/μL who were given 1,500 mg of chloroquine over 3 days (Figure 1B). By day 7, 3 were still detectable; the last patient was cleared of detectable parasitemia by day 13. One patient was not included in the figure. This patient had an initial parasite count of 648/μL. After initiation of treatment, parasites persisted for 17 days; 12 days after initiation, the count was 633/μL. The parasite count eventually cleared, and there was no recrudescence of parasitemia.

There were 17 patients treated with 450 mg of dihydrochloroquine (Figure 3A); the last patient cleared detectable parasitemia on day 12. This compares with 13 patients infected

![Figure 1](image-url) - Decreases in asexual parasite count after treatment with 1,500 mg of chloroquine (base) given over 3 days. (A) 62 patients with *P. malariae* having initial parasite counts >1,000/μL. (B) 38 patients having initial parasite counts <1,000/μL.
with *P. falciparum* in whom parasites were all cleared by day 6.

**DISCUSSION**

Archived records on induced infections in humans with different species of *Plasmodium* provide biologic data on the course of parasitemia, the immune response, and the response to treatment with various antimalarial drugs, some of which are still being used. The objective in conducting this retrospective analysis of the parasitologic response of infections with *P. malariae* to treatment with chloroquine was to determine the reliability and predictability of parasite counts after treatment with chloroquine as an indication of drug resistance. In contrast to infections with *P. falciparum* and *P. vivax*, in which the continued presence of parasites on a thick blood film for ≥1 week would be suggestive of resistance, infections with *P. malariae* may require much longer periods for parasite clearance. The presence of parasites >10 days after initiation of treatment occurred in some patients given either 450 mg of dihydrochloroquine intramuscularly or 1,500 mg of chloroquine orally over 3 days.

These observations suggest that another criterion for documentation of resistance of *P. malariae* is needed. Strains of *P. malariae* have been adapted to grow in New World monkeys and in chimpanzees.8–13 Controlled drug studies in these nonhuman hosts may be useful or even necessary to confirm resistance with this parasite. The adaptation of *P. malariae* to *in vitro* culture could be a major contribution in efforts to determine resistance. Infections of *P. ovale* respond to chlo-

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**FIGURE 2.** Decreases in asexual parasite count after treatment with 1,500 mg of chloroquine (base) given over 3 days. **(A)** 41 patients with *P. falciparum* having initial parasite counts >1,000/µL. **(B)** 37 patients with *P. vivax* having initial parasite counts >1,000/µL.
roquine in a manner similar to that of P. vivax. In this species, failure to clear parasitemia by 7 days after treatment would be indicative of drug resistance.

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REFERENCES


FIGURE 3. Decreases in asexual parasite count after treatment with 450 mg of dihydrochloroquine (400-mg base) given intramuscularly. (A) 17 patients with P. malariae having initial parasite counts >1,000/μL. (B) 13 patients with P. falciparum.