

## Minocycline and Tetracycline Treatment of Acute *Falciparum* Malaria in Thailand

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**OBJECTIVE:** Recent investigations of both natural and experimentally induced *falciparum* malaria in man have shown that tetracycline is highly effective in terminating infections of chloroquine resistant strains of this parasite. However, its relatively delayed onset of action and prolonged course of administration limit its value as a suitable antimalarial agent.

Minocycline (7-dimethylamino-6-demethyl-6-deoxytetracycline) is a new synthetic addition to the tetracycline family of antibiotics. Its preparation, structure and some of its properties have been reported by Martell and Booth (1967). Preliminary investigations of this new analogue have shown that minocycline is more potent and has a broader antibacterial spectrum than tetracycline. The purpose of our studies was to evaluate the therapeutic efficacy of minocycline in acutely ill subjects naturally infected with *Plasmodium falciparum*.

**DESCRIPTION:** The study was conducted at Prapokklao Hospital in the capital city of Chantaburi Province, which is located approximately 300 km southeast of Bangkok and 10 km north of the Gulf of Thailand. This area was selected because of the occurrence of year round transmission of *falciparum* malaria. During 1970, over 3,000 patients with confirmed *P. falciparum* infections were treated and followed on the wards or in the outpatient department. Personal observations of the staff physicians indicated that radical cures of *P. falciparum* infections following conventional doses of chloroquine were infrequent. Moreover, chloroquine resistant strains of *P. falciparum* are highly endemic in Trat Province which is only 35 km east of Chantaburi City.

Acutely ill male subjects, aged 14-60 years, infected with *P. falciparum* were considered for study. Those with renal or cerebral complications and those with a history of antimalarial drug intake during the preceding 7 days were excluded. Selected subjects were alternately assigned to one of 2 treatment groups. Individuals in one group were given 640 mg of quinine sulfate, thrice daily for 3 days, followed by 100 mg of oral minocycline twice daily for 7 days. Those in the other treatment group were administered a similar course of quinine followed by 250 mg of tetracycline, 4 times daily for 10 days. Control of initial symptoms with quinine was indicated because of the relatively delayed onset of action of tetracycline. Seven subjects in the quinine-minocycline (QM) group and 8 in the quinine-tetracycline (QT) group were initially hospitalized for 6-8 days. The others were treated and followed on an outpatient basis.

During the treatment phase, all subjects were examined daily for clinical manifestations and appropriate medications were dispensed. Blood smear examinations in subjects among both treatment groups were performed daily for the first ten days and then at weekly intervals for the next 3 weeks. When subjects were available, blood smears were also obtained 2 months after commencement of therapy. Quantification of asexual and sexual parasitemias was performed by the method of Earle and Perez (1932). Serum specimens for determinations of bilirubin, and alkaline phosphatase and glutamate-oxaloacetate transaminase activities were obtained before treatment, and on the 10th and 31st days of observation.

**PROGRESS:** Twenty-nine subjects were chosen for the QM regimen. Treatment and follow-up examinations were successfully completed in 28, aged 15 to 50 years (mean 25.2). Asexual parasitemias among individuals in the QM group upon admission to the study ranged from 390 to 90,650 per cmm with a

geometric mean of 8,670 per cmm. Of 33 subjects chosen for the QT regimen, treatment and follow-up examinations were successfully completed in 29, whose ages ranged from 14 to 57 years (mean 31.7). The levels of asexual parasitemias in subjects of the QT treatment group at the onset of study ranged from 425 to 238,700 per cmm with a geometric mean of 14,170 per cmm.

Table 1 shows the presumptive radical cure rates and the parasite clearance times obtained with both treatments. The single subject who experienced a treatment failure with the QM combination became symptomatic 24 days after commencement of therapy and exhibited asexual parasites 3 days later. Infections with *P. vivax* were observed on the 31st day of follow-up examination in 5 subjects treated with QT and in 3 treated with QM. Sixteen and eight individuals in the QM and QT groups, respectively, were available for follow-up blood smear examinations 2 months after commencement of therapy. No parasites of *P. falciparum* were observed.

None of the 28 subjects treated with QM and only 1 of 29 subjects treated with QT exhibited gametocytemia upon admission to the study and circulating gametocytes were observed during the follow-up period in specimens from 18 of the 57 subjects among both treatment groups. The levels of sexual parasites were generally low in density and persisted for a period longer than 12 days in only 6 subjects of whom 4 were treated with QM and 2 with QT.

Daily doses of both tetracycline and minocycline were generally well tolerated. Transient complaints of mild nausea, vomiting and weakness were occasionally observed during minocycline treatment after clearance of patent parasitemia. Abnormalities in one or more of the liver function tests possibly attributable to minocycline or tetracycline were observed in 9 patients. Six patients in the QM group and 3 patients in the QT group, who had normal pretreatment serum values, had an abnormal elevation in the serum transaminase and/or alkaline phosphatase tests on the 10th day of observation. These abnormalities were mild and were still demonstrable on the 31st day in 4 patients treated with QM, but in none treated with QT. In 7 subjects among both treatment groups who had an abnormal liver function test(s) on the first day of observation, none exhibited significant increases during the treatment and follow-up period.

**SUMMARY:** The purpose of this study was to evaluate the antimalarial action of a new tetracycline analogue, minocycline, which is more potent and has a broader antibacterial spectrum than tetracycline. The study was conducted in an endemic area for chloroquine resistant falciparum malaria. Acutely ill residents infected with *P. falciparum* were alternately assigned to 1 of 2 treatment groups. Subjects in one group were given 540 mg of quinine base, thrice daily for 3 days followed by 100 mg of minocycline, twice daily for 7 days. Subjects in the other group were given a similar course of quinine followed by 250 mg of tetracycline, 4 times daily for 10 days. Presumptive radical cures were achieved in all 29 patients treated with quinine-tetracycline and in 27 of 28 treated with quinine-minocycline. No significant toxic side effects were observed. Although both treatments were highly effective, further studies are warranted to determine the optimal duration and dosage of minocycline and its potential human toxicity.

Table 1.  
Presumptive radical cure rates and mean parasite clearance times  
with 2 treatments of acute falciparum malaria

Treatment*	No. subjects	% cure	Mean parasite clearance
Quinine-Tetracycline	29	100.0	3.0
Quinine-Minocycline	28	96.4	3.1

\* See text for dosage.