# DOSE FINDINGS OF DIHYDROARTEMISININ IN TREATMENT OF *FALCIPARUM* MALARIA

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**Abstract.** Forty patients with uncomplicated *P. falciparum* malaria were respectively treated in an open randomized comparative study of dihydroartemisinin tablets given at total doses of 480 mg over 5 days and 640 mg over 7 days in a drug-resistant malaria endemic area in Hainan, China. The result showed that all patients were clinically cured. In 5-day and 7-day groups, the mean fever clearance times(FCT) were 26.1± 10.2 and 21.1.1±11.8 hours respectively; the mean parasite clearance times (PCT) were 58.7±20.9 and 59.4±20.9 hours respectively, which showed no significant difference. 28-day follow-ups were accomplished on 39 and 37 cases respectively in two groups, the recrudescence rates were 20.5% (8/39) in 5-day group, while 2.7%(1/37) in 7-day group with significant difference ($\chi^2$=4.19, p<0.05). No clinical drug-related side effect was found in two groups during treatment.

## INTRODUCTION

Dihydroartemisinin is one of the derivatives of artemisinin, a new antimalarial with good therapeutic effect on *falciparum* malaria, especially drug-resistant *falciparum* malaria. A considerable high recrudescence rate was on observed in a short course regimen of monotherapy of artemisinin derivatives (Guo *et al,* 1989). An open randomized comparative study of dihydroartemisinin tablet given at total doses of 480 mg over 5 days and 640 mg over 7 days have been carried out in a drug-resistant malaria endemic area in Hainan, China (Cai *et al,* 1986), in an attempt to find out a dose regimen with high cure rate.

## METHODS

### Selection and grouping of patients

Including criteria : Patients aged from 7 to 65 with clinical symptoms of malaria; *Falciparum* parasite asexual form ≥ 1,000/μl or large ring form ≥ 300/μl with high fever. No antimalarial has been used since this onset, including tetracycline or sulfonamide.

Excluding criteria : Age < 7 years or > 65 years; Pregnant women; Severe vomiting, severe complications.

Eighty patients were randomly allocated to the two dose groups.

### Dose regimen

Dihydroartemisinin tablets, each tablet contains 20mg, manufactured by the Sixth Beijing Pharmaceutical Factory, China; Batch No: 930811. 80 mg was given once daily with the first dose doubled, and a total dose of 480 mg over 5 days and 640 mg over 7 days. The children's dose was reduced by fractions (Table 1). The drug was given by supervision of the investigators. The additional dose was given to those with vomiting within 2 hours after medication. Patients with repeated vomiting were excluded.

### Observation of patients

All patients were hospitalized for 28 days. Armpit temperature was taken once every 6 hours until the patients remained afebrile for 24 hours and then it was taken once daily in the afternoon until discharge. Investigation of the patients for side effect was done twice daily and the results were recorded in

Table 1
Dose regimens of dihydroartemisinin in two groups.

| Age | Daily dose(mg) | | Total dose(mg) | |
|---|---|---|---|---|
| (y) | D0 | Dl-D6 | 5-day | 7-day |
| ≥ 16 | 160 | 80 | 480 | 640 |
| 11-15 | 120 | 60 | 360 | 480 |
| 7-10 | 80 | 40 | 240 | 320 |

detail in the relevant forms. Evening ward inspection was also done for patients' compliance of hospitalization.

**Laboratory examination**

Blood smears were taken for asexual parasite counts at 7.00 am and 7.00 pm every day from D0 to D4, and at 7.00 am every morning from D5 to D7, and then it was taken on D10, D14, D17, D21 and D28. No asexual parasite found in 200 fields of thick smear was regarded as negative. Blood smear was also taken for examination of parasitemia whenever the patients had fever. White blood cell and hematocrit were examined on D0 and D7.

**Efficacy evaluation**

It is based on the Four-week Clinical Observation Method of Chloroquine Sensitivity Assessment recommended by WHO (1973). Fever clearance time, parasite clearance time, cure rate and recrudescence rate were used as the parameters for evaluation of the efficacy.

## RESULTS

**Patients' conditions**

40 patients in 5-day regimen group included 30 males and 10 females, age ranged from 7 to 50 years, with 6 patients ≤ 15 years and the average age was 24.8 ± 9.9 years. All patients had fever on admission, with the mean body temperature of 38.8 ± 0.9°C. The mean parasite count was 27,210 ± 58,055/μl. Hepatomegaly was found in 10 patients and splenomegaly in 15 patients, including 9 patients with both.

Forty patients in 7-day regimen group included 33 males and 7 females, age ranged from 7 to 65 years, with 4 patients ≤ 15 years and the average age was 24.8 ± 2.0 years. Thirty-six patients had fever on admission, with the mean body temperature of 38.9 ± 0.9°C; The mean parasite count was 29,137 ± 46,916/μl, and 10,742 ± 3,628/μl in 4 afebrile patients on admission. Hepatomegaly was found in 19 patients and splenomegaly in 20 patients, including 16 patients with both.

No significant difference was found in patients' conditions of the two groups ($p > 0.05$, Table 2).

**Efficacy**

All patients had rapid control of clinical symptoms. The mean fever clearance times were 26.1 ± 10.2 hours and 21.1 ± 11.8 hours; and the mean parasite clearance times were 58.7 ± 20.9 hours and 59.4 ± 20.9 hours in 5-day and 7-day regimens respectively. In 39 patients in 5-day and 37 in 7-day regimens with follow-up for 28 days, the recrudescence rates were 20.5% (8/39) and 2.7% (1/37), the cure rates were 79.5% and 97.3% respecively, which showed significant difference($\chi^2=4.19$, $p < 0.05$). The efficacy of the two groups was shown in Table 3. No obvious drug-related side effect was found in the two groups.

Table 2
Patients' conditions of the two groups.

| Group | No.of cases | Age (yrs) | Temperature (°C) | Parasitemia (l/μl) | Splenomegaly (%) |
|---|---|---|---|---|---|
| 5-day | 40 | 24.8 ± 9.9 | 38.8 ± 0.9 | 27,210 ± 58,055 | 37.5 |
| 7-day | 40 | 24.8 ± 12.0 | 38.9 ± 0.9 | 29,137 ± 46,916 | 50.0 |

Table 3
Efficacy of dihydroartemisinin in two regimen groups.

| Group | No.of cases | FCT(h) X ± SD | PCT(h) X ± SD (%) | Cure (%) | Recrudescence (%) | p |
|---|---|---|---|---|---|---|
| 5-day | 40 | 26.1 ± 10.2 | 58.7 ± 20.9 | 79.5 | 20.5 | <0.05 |
| 7-day | 40 | 21.1 ± 11.8 | 59.4 ± 20.9 | 97.3 | 2.7 | |

## DISCUSSION

The study showed that 5-day regimen of dihydroartemisinin tablet with a total dose of 480 mg in treatment of *falciparum* malaria resulted in 79.5% cure rate; A prolonged 7-day regimen with an increased total dose of 640 mg provided a significantly higher cure rate of 97.3%. Most of the patients in this study were non-immune to malaria as they had stayed in the malaria endemic area for a short period of time. This result is similar to that provided by Fu LC (Clinical trial phase III of dihydroartemisinin, 1995), in which 5-day regimen with a total dose of 480mg in treatment of 73 patients with *falciparum* malaria provided 82.2% of cure rate. No side effect was found. It indicates that 7-day regimen of dihydroartemisinin tablets with a total dose of 640 mg is a safe and high effective dose regimen which can be recommended as a standard dose regimen.

## REFERENCES

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