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ORIGINAL ARTICLES

A comparative study of the Schizontocidal efficacy and safety of artemether versus chloroquine in uncomplicated malaria

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SUMMARY

Forty-seven patients with uncomplicated falciparum malaria were randomly assigned to receive either artemether (n=24), 9,6 mg/kg body weight intramuscularly over five days or chloroquine (n=23), 25 mg/kg body weight orally. Patients were kept in hospital for seven days followed by review on days 14, 21 and 28. Five patients on chloroquine were withdrawn before day seven due to treatment failure.

Of the remaining patients, parasite clearance time was 33.0 ± 13.6 hours for the artemether group and 63.3 ± 14.7 hours for patients on chloroquine (p<0,001). No significant difference was recorded in fever clearance time between the two groups of patients.

Recrudescence rate for patients on artemether was 14,3 pc compared to 57,1 pc for the chloroquine group (p<0,05). No major adverse events were recorded for either treatment group although five patients on artemether had a transient spike of temperature after clearance of parasitaemia.

In conclusion, our study has shown that no major adverse events were experienced by patients on artemether and the rate of parasite clearance for the artemether group was superior to that of patients on chloroquine.

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INTRODUCTION

Artemether is a lipid soluble derivative of Qinghaosu (Artemisinin), an anti malarial compound isolated from the Chinese herb Qinghao (Artemisia annual L.) Although a number of reports have been documented regarding the safety and efficacy of artemether in the treatment of falciparum malaria, many of these studies have been uncontrolled and were conducted in China where the parent drug has been in use for over a thousand years.[1]

Given the rapidly spreading problem of resistance to standard antimalarials by falciparum malaria world wide, the need to assess artemether and other derivatives of artemisinin in different parts of the world has assumed an urgent importance.

MATERIALS AND METHODS

(a) Study Location: The study was conducted at the Gokwe District Hospital in Gokwe. Gokwe District is situated in the Midlands Province of Zimbabwe and records one of the highest incidences of malaria in Zimbabwe.[2]

(b) Patient Selection: Between the months of April to July 1991, all patients presenting to hospital

with a positive blood smear for *P. falciparum* and a temperature of greater than 38°C were eligible to participate.

Patients with the following conditions were excluded: those below the age of 14 years and those aged above 60; pregnant or breast feeding women; evidence of impairment of renal, hepatic or cardio-vascular systems; a history of antimalarial ingestion two weeks before presentation and/or a positive Dill Glasko urine test for 4-aminoquinolines; those unwilling to give informed written consent.

All patients satisfying the entry criteria were admitted to the medical wards of the hospital for an initial seven day observation period followed by an outpatients review on days 14, 21 and 28.

The possibility of reinfection was minimised by giving each patient an insect repellant to use all over the body on discharge.

(c) **Drug Administration:** The study was an open comparative trial and patients were randomly assigned to receive either artemether or chloroquine.

Artemether was obtained from the Kunning Pharmaceutical Company of Yunan, China and was given at an initial dose of 160mg intramuscularly (IM), followed by 80mg IM daily over the next four days, a total dose equivalent to 9,6mg/kg body weight (BW).

Chloroquine phosphate (Norolon) was given orally at an initial dose of 10mg/kg BW followed by 5mg/kg BW after six hours and then 5mg/kg BW daily for two days, a total dose equivalent to 25mg/kg BW.

Paracetamol was the only analgesic allowed during the trial and those patients whose parasitaemia did not respond to the trial drugs were treated with either sulfadoxine/pyrimethamine (FANSIDAR) or quinine.

(d) Assessment Criteria: (i) Sensitivity to chloroquine: Sensitivity of *P. falciparum* to chloroquine was determined by an *in vitro* micro test before treatment.[3]

(ii) Parasitological response: Parasite count per microlitre of blood was determined before treatment by counting the number of parasites per 200 White Blood Cells (WBC) and then multiplying the figure obtained by 30 (assuming a normal WBC of 6 000/ul in the population). Blood smears were then taken and examined 12 hourly until day seven. The time taken from the first dose of the drug to the first negative smear was counted as the "time to parasite clearance".

(iii) Body temperature was taken four hourly after commencement of a treatment until day seven. "Time to fever clearance" was defined as the time taken for the temperature to return to normal (37,4°C) for eight hours after the first dose of the drug.

(iv) Recrudescence: After discharge, blood slides were repeated on day 14, 21 and 28. The recrudescence rate was then calculated.

(v) Adverse events: All patient were asked daily for any adverse reactions experienced. Routine laboratory and biochemical examination was done before treatment and on days one, four and 28.

(vi) Statistical analysis: Mean values and standard deviation of the time to fever clearance, and time to parasite clearance were calculated and comparisons made using parametric statistical methods. Recrudescence rates were determined for each group and then compared by non-parametric testing.

RESULTS

A total of 47 patients were enrolled in the study. Twenty-four patients received artemether whilst 23 were treated with chlorquine. There was no significant difference in age, sex, body weight and height between the two groups of patients (Table I).

(a) Parasitology Response: (i) *In vivo* findings: The mean parasite count in the artemether group was 9 950/ul and 8 337/ul for the chloroquine patients ($p>0,05$) (Table II.i.i).

Five patients treated with chloroquine did not complete the initial seven days observation period; three, due to positive smear and pyrexia 72 hours after initiation of therapy and the other two due to a persistent parasitaemia. All four were successfully treated with either sulfadoxine/pyrimethamine (FANSIDAR) or quinine.

Table I: Demographic Characteristics of 47 Malaria Patients, Gokwe 1991.

I.i Age distribution

Age class (years)	*Artemether*	*Treatment chloroquine*	*Total*
14–19	4	9	13
20–25	7	4	11
26–33	7	5	12
34+	6	5	11
Total	24	23	47

Chi-Square	D.F.	Prob.
3,15	3	0,37

I.ii Distribution of patients according to sex

Gender	*artemether*	*Treatment chloroquine*	*Total*
male	18	18	36
female	6	5	11
Total	24	23	47

Chi-Square	D.F.	Prob.	
0,07	1	0,79	
0,00	1	1.00	after Yates correction.

I.iii Mean weight (kg)

artemether	58.3(8.6)* Cases=24
chloroquine	56.9(17.2) cases=23

t value	D.F	Prob.
0,36	45	0.72

Standard deviation

I.iv Mean height

artemether	168,48(8.7)* cases=21
achloroquine	167.99(11.6) cases=20

t value	D.F.	Prob.
0,16	39	0,87

Standard deviation

Table II: Response to antimalarial treatment, Gokwe,1991

II.I Parasitological response:

II.i.i Initial mean parasitemia

artemether	9 950(6 061)* cases=24
chloroquine	8 337(4 350) cases=23

t value	D.F.	Prob.	
0,79	45	0,435	(calculated following log x + 1 transformation).

Standard deviation

II.i.ii Mean time to parasite clearance

Treatment	*Time hours*
artemether	33,0(13,6) (24 cases)
chloroquine	63,3(4,7) (18 cases)

t value	D.F.	Prob.
6,87 3	4,7	0,000***

***p<0,001*
**Standard deviation*

II.ii Clinical response

II.ii.i Mean time to fever clearance (hours)

treatment	
artemether	22,8(10,3*)
chloroquine	22,9(8,4)

t value	D.F.	Prob.
0,03	3,43	0,978

**Standard deviation*

II.i.iii *In vivo* **sensitivity of parasites to day 28**

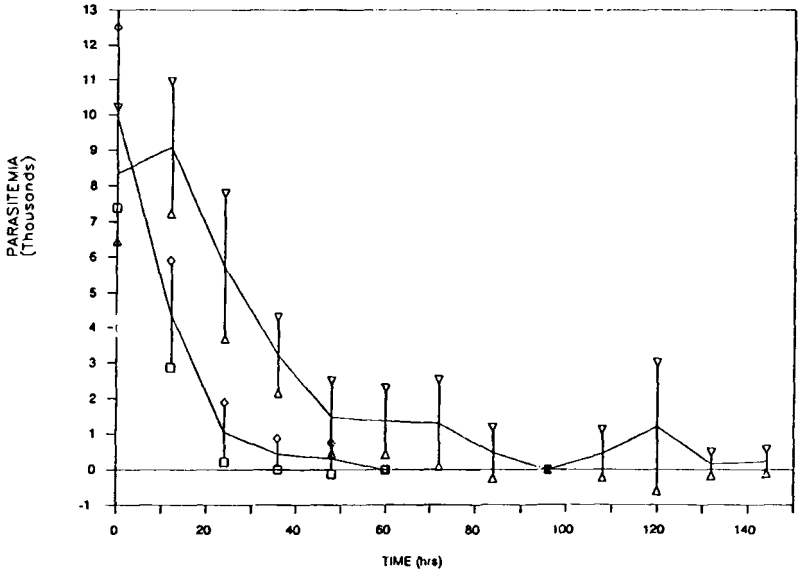
Treatment	*Sensitive(S)*	*S or RI+*	*Treatment failure*	*RI(rate°)*	*Lost before Day 7*
artemether	16	3	0	3 (14,3 pc)	2
chloroquine	5	4	6	8 (57,1 pc)	0

LEVEL OF SIGNIFICANCE FOR RATE OF RECRUDESCENCE

Chi-square	D.F.	Prob.	
7,2	1	0,0075**	
5,3	1	0,02*	(after Yates correction)

***p<0,001*
***P<0,05*
+represents patients sensitive up to seven but subsequently lost to follow up
°rate is based on 21 artemether patients seen after day seven and 14 chloroquine patients seen after day seven.

Figure I: Comparison of artemether and chloroquine phosphate with respect to asexual parasite count through time.



The figure compares mean asexual parasite counts as determined by thick smears taken at 12 hour intervals over seven days. Top line (chloroquine phosphate group), and bottom line (artemether group) showing mean parasite count and 95 pc confidence limits.

II.ii.ii Adverse events reported by patients

Event	Treatment	
	artemether	chloroquine
pruritis	0	7^
insomnia	4	4^
diarrhoea	3	0^
vomiting	0	3^
dizziness	6	6^
myalgia	3	1^
headache	16	14
vertigo	1	1^
tinnitus	1	1^
body hotness	1	1^
inflammation at site of injection	1	0^
abdominal pain	12	8
Total	48	46

^Indicates where expected frequencies were below the accepted limit for significance tests.

Of the remaining patients the mean time to parasite clearance was 33,0 ± 13,6 hours for artemether (n = 24) and 63,3 ± 14,4 hours for patients treated with chloroquine (n = 18) (p<0,001) (Table II.i.ii and Figure I).

Two patients on artemether withdrew before day seven for personal reasons; both were slide negative at the time. Of the 22 artemether patients seen up to day seven, one never returned after discharge and two did not complete the 28-day observation period. Three of the 21 (14,3 pc) patients on artemether seen after day seven had a recrudescence of RI response and 16 were fully sensitive up to day 28, (Table II.i.iii.)

Amongst the 18 chloroquine patients who were seen up to day seven, one recrudesced on day seven three were never seen again and one was lost to follow up after day 14. A total of eight out of 14 (57,1 pc) chloroquine patients seen after day seven had a recrudescence or RI response and five were fully cured of their parasitaemia when seen on day 28 (Table II.i.iii.).

(ii) *In vitro* Findings: Seven *in vitro* micro tests were successful out of which four isolates were found to be resistant to chloroquine.

(b) Clinical Response: There was no difference in time to fever clearance between the two groups of patients (Table II.ii.i.).

No major adverse or toxic effects were recorded in either group of patients. Seven patients treated with chloroquine experienced pruritis, an event not recorded in the artemether group. Only one patient had a mild inflammation at the site of injection in the artemether group and this subsequently resolved without treatment (Table II.ii.ii.).

Five patients on artemether had a transient temperature spike after clearance of parasitaemia. Twelve patients on artemether complained of abdominal pains compared to eight on chloroquine. This finding however was not significant and resolved uneventfully.

DISCUSSION

Our study was the first one to use artemether for the treatment of falciparum malaria in Zimbabwe. To our knowledge, only two other studies of artemether have been reported in Africa.[4,5] Overall, artemether was well tolerated and no major adverse events were recorded.

Five patients treated with artemether had a transient spike of temperature after clearance of parasitaemia. Transient pyrexia has been reported in previous artemether studies[6] and although no explanation has been offered for it, we believe that this effect could be an idiosyncratic reaction to the drug itself as normal temperature is obtained within hours.

Parasite clearance was significantly faster with artemether than with chloroquine. Although the mode of administration of drug could affect the therapeutic outcome, it is a well-known fact that chloroquine is well absorbed orally and peak plasma concentrations of 250ug/litre have been obtained within two hours following a dose of 10mg/kg body weight.[7]

On the other hand limited studies with artemether which is available as a suspension in peanut oil indicate that peak concentrations of 220ug/litre are attained six hours after a single intramuscular injection of 10mg/kg body weight.[8] Our findings therefore compare well with those obtained by other workers.[1,4,5,9] Eight of the 14 (57,1 pc) chloroquine

patients seen to day 28 had a recrudescence or RI response compared to only three (14,3 pc) of the 21 artemether patients seen up to day 28 ($p<0,001$). In the absence of a mechanism to exclude entirely the possibility of reinfection, our figures may be higher than the actual situation prevailing in the district. However, when compared to previous studies, our recrudescence rate for artemether is much lower than the rate of up to 41,2 pc reported in China.[10]

Six chloroquine patients did not complete the study due to treatment failure. This finding when taken together with the chloroquine recrudescence rate of 57,1 pc and the *in vitro* chloroquine resistance in four out of seven isolates, suggests that chloroquine resistant malaria is now established in the district.

No significant difference was found in mean time to fever clearance between the two groups of patients.This finding is similar to that found in Chinese and Nigerian studies where mean time to fever clearance for patients treated with artemether was less than 24 hours.[1,4]

Or study has therefore demonstrated that there was no major adverse event recorded in patients on artemether and more rapid clearance of parasitaemia was obtained with artemether when compared to that of chloroquine.

In Zimbabwe, quinine is the drug of choice for the treatment of severe or complicated malaria; we are therefore planning studies to compare artemether with quinine in this condition. The need for alternative drugs in the light of the ever increasing problem of drug resistant malaria cannot be over emphasised.

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