ORIGINAL ARTICLE

A Randomized, Controlled Trial of Artemisinin-piperaquine *vs* Dihydroartemisinin-piperaquine Phosphate in Treatment of Falciparum Malaria*

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ABSTRACT **Objective:** The study aimed to evaluate and compare the efficacy and safety of dihydroartemisinin-piperaquine phosphate (Artekin) and artemisinin-piperaquine (Artequick) in the treatment of uncomplicated falciparum malaria. **Methods:** A total of 103 uncomplicated falciparum malaria patients were enrolled and randomly assigned to two groups: 52 cases in the Artequick group, and 51 cases in the Artekin group. The patients in the Artequick group were administered with Artequick, twice in 24 h, whereas the patients in the Artekin group were given Artekin 4 times in 2 days. The mean parasite clearance time, mean fever clearance time, 28-day cure rate and parasite recrudescence rates of the two groups were then compared. **Results:** The mean parasite clearance time and the mean fever clearance time were 43.2±13.9 h and 24.7±9.9 h, in the Artequick group, and 36.5±17.1 h and 22.7±11.2 h, in the Artekin group. In both groups the 28-day cure rate was 100%, and the parasite recrudescence rate was 0. **Conclusion:** Both medicines had high cure rates, low recrudescence rates, and no serious adverse reactions. The administration of Artequick, however, was more convenient and lower incidence of gastrointestinal side effects than that of Artekin, so as to increase the efficacy in the malaria population.

KEY WORDS plasmodium falciparum, malaria, artemisinin, piperaquine, antimalarials, randomized controlled trial

Resistance to antimalarial drugs is emerging throughout tropical regions. Southeast Asia is a serious area with most resistant malaria parasites in the world, with the choice of treatments limited in this region[(1)]. WHO recommends the use of artemisinin combination therapies (ACTs) to improve the clinical effectiveness of antimalarial drugs and keep the selection of drug-resistant parasites to a minimum[(2)]. A combination of antimalarial drugs is advocated for the treatment of Plasmodium falciparum malaria because it may not only fight the prevalence of drug resistance, but also further prevent the development of drug resistance. At present, more than 60 countries have changed their strategies for antimalarial drug and have used ACTs. Although ACTs have been strongly recommended and encouraged, their adoption has been limited by high cost[(3)]. Recently dihydroartemisinin-piperaquine (Artekin) in a fixed-dose preparation of 40 mg dihydroartemisinin and 320 mg piperaquine phosphate, which has been studied in China, Vietnam, Cambodia, and elsewhere, showed an efficacy of over 90% and has the advantages of administration once a day for three days and low cost (about US$1 per treatment course). Artemisinin-piperaquine (Artequick), which has been recently developed by Chinese scientists, showed good efficacy and safety in a two-day treatment course. Artequick included two components: arteminisin and piperaquin. In clinical trials in Cambodia, the results showed that the regimen was more convenient (with the medicine taken at 0 h and 24 h once), led to the lower incidence of gastrointestinal side effects, and had similar efficacy to that of Artekin (to be published in other papers). The objective of this study was to further evaluate the efficacy and safety of Artequick tablets and Arrtekin tablets in the treatment of uncomplicated falciparum malaria.

METHODS

General Information

A total of 103 patients came from Ninh Hai county, Ninh Thuan province, the multi-resistant falciparum malaria endemic areas in central Vietnam.

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The inclusion criteria were: (1) clinical symptoms of malaria such as fever (axillary temperature ≥ 37.5 ℃), (2) age ranging from 7 to 65 years old, (3) peripheral blood smears showing falciparum malaria asexual parasites at 1 000-100 000/μL, and (4) no antimalarial used within 7 days prior to onset or admission, including sulfonamide, tetracycline or trimethoprim. The exclusion criteria were pregnant women, children younger than 7 years old, senior persons older than 65 years old, and patients with severe vomiting or diarrhea, or other complications and diseases.

At enrollment, a medical history was taken, a comprehensive physical examination, which included a neurological examination, was performed, and blood samples for quantitative parasite counts and routine hematology were collected. All information was recorded in a standard case record form.

The plan in the protocol was to admit 104 uncomplicated falciparum malaria patients, but 103 cases were in fact enrolled. The block randomized design was adopted in the clinical trial. A total of 103 cases were assigned, 52 to the Artequick group and 51 to the Artekin group. The baselines of patients before treatment in the two groups had no significant difference in gender, age, duration of fever, axillary temperature, asexual parasite density, and splenomegaly rate (P>0.05, Table 1).

The clinical trial strictly followed the Declaration of Helsinki ethical principles related to human medical research. The study was approved by the Ethics Conmittee, Guangzhou University of Chinese Medicine. The informed consent form was signed by adult patients or parents of enrolled children.

Treatment

Drug regimens were the following: (1) In the Artequick group, for the adults aged ≥16 years, 4 tablets as the total dosage, twice a day (at 0 h and 24 h) for a total 2-day treatment; 3 tablets for patients' ages 11 to 15; and 2 tablets for patients ages 7 to 10. (2) In the Artekin group, 2 tablets given respectively at 0 h, 8 h, 24 h and 32 h, for adults aged ≥16, a total of 8 tablets; for patients ages 11 to 15, 1.5 tablets each time, totaling 6 tablets; for patients ages 7 to 10, 1 tablet each time, 4 tablets in total.

Artequick tablets were provided by Artepharm Co., Ltd., China (batch No. 20030820). Each tablet contains 62.5 mg artemisinin and 375 mg piperaquine. Artekin tablets were provided by Guangzhou Holleykin Pharmaceutical Co., Ltd., China (batch No. 20030301). Both Artequick and Artekin were fixed-dose compound tablets. The study design was accordant with the guideline of WHO on the Assessment and Monitoring of Antimalarial Drug Efficacy for the Treatment of Uncomplicated Falciparum Malaria[4].

Items and Methods of Observation

All patients were observed in the treatment center for 7 days, and symptoms were observed on day 14, day 21, and day 28, home visiting to diagnose the recrudescence. Standard date tables were completed to record demographic information including age, sex, race, height, weight and others. Illness histories included past medical history, drug using history, hypersusceptibility history, and family history. General conditions were recorded, such as vital signs, systematic inspection, clinical symptoms, etc.

The formula "compliance index = the actual dose/the selected dose × 100%" was used to calculate the compliance, and to check the actual dose. This result expressed the treatment compliance.

Axillary temperature was measured every 6 h if the patients had fever, and examined once daily in the afternoon after the temperature became normal, until leaving hospital. Ward inspection was conducted twice in the morning and afternoon separately each day, and clinical symptoms were inquired about and recorded according to the adverse reaction record form.

Thick blood films were taken at 7 a.m. and 5

Table 1. The Baseline of Patients before Treatment

Group	Case	Sex (Case, M/F)	Age [Year, M(Q_R)]	Day of fever (day, $\bar{x}\pm s$)	Axillary temp. (℃, $\bar{x}\pm s$)	Asexual parasite density [number/μL, M(Q_R)]	Splenomegaly rate (%)
Artequick	52	34/18	25.8 ± 13.9	3.0 ± 1.4	38.7 ± 0.9	20428 ± 23826	5.8
Artekin	51	29/22	26.4 ± 14.0	3.1 ± 1.6	38.8 ± 0.9	30561 ± 54391	3.9
P value			0.83	0.74	0.57	0.22	0.98

p.m. from day 0 to day 4, and the ratio of asexual parasites number to 200 white blood cell (WBC) count was calculated. If the parasites numbered less than 1/200 WBC, the parasite clearance rate was checked in 200 fields. Blood films were taken at 7 a.m. from day 5 to day 7, and three consecutive negative blood films predicated the clearance of parasites. Blood films were taken and checked on day 14, day 21, and day 28 to investigate the recrudescence. Once patients got fever, they were taken back to the hospital for an examination of blood films. If the blood film was positive on day 0 and day 28 follow-up study, the blood blots were analyzed by PCR genotyping qualitative analysis, in order to differentiate re-infection from the recrudescence.

WBC count, differential count, and hematocrit (HCT)/red blood cell (RBC) count were checked on day 0 and day 7. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), direct bilirubin (DBil), and creatinine (Cr), were examined on day 0 and day 7. Abnormal items found at day 4 were re-examined on day 7 then every week until it normal. Electrocardiogram examinations were examined on day 0 and day 7.

Our study referred to "Assessment and Monitoring of Antimalarial Drugs Efficacy for the Treatment of Uncomplicated Falciparum Malaria"[4]. The following indexes were used to assessed efficacy: mean fever clearance time (h), mean parasite clearance time (h), cure rate (%), parasite recrudescence rate (%) and mean recrudescence time (day).

Adverse Reaction

The occurrence rate of adverse reaction (symptoms and signs appeared or aggravated after the administration) was observed. The functions of the liver, kidney and the electrocardiogram before and after treatment were examined in order to evaluate the toxicity and side effects on the main organs of the human body. The safeties of Artkequick and Artekin were evaluated according to adverse reactions and hematology and biochemical tests results on day 0 and day 7.

Statistical analysis

Statistical analysis was conducted through SAS 6.12 software. Data were expressed as means ± standard deviation. The measurement data were treated with analysis of variance or *t*-test, and qualitative data were treated with χ^2 test. All statistical tests were two-tailed, and a significance level of 0.05 was used.

RESULTS

All follow-up studies were conducted normally and showed a good compliance. Only one case dropped out, on the 14th day.

Efficacy of Artequick and Artekin

The clinical symptoms of malaria were rapidly controlled, the parasite clearance time and fever clearance time were relatively shorter after treatment in both the Artequick and the Artekin groups. The mean fever clearance times were not significantly different between the two groups (P=0.339). The parasite clearance time in the Artekin group was shorter than that in the Artequick group (P=0.031). The fever and other symptoms in the two groups disappeared in two days after taking medicines. No recrudescence was found after the 28-day follow-up, and the cure rate was 100 % in both groups (Table 2).

Adverse Reaction

The tolerance in patients was good, and there were no serious drug-related adverse reactions recorded in the two groups. Only 9 (17.3%) in the Artequick group and 16 (31.4%) in the Artekin group had minor adverse reactions related to the trial medications. The occurrence rate of dizziness in the Artequick group was similar to that of the Artekin group (9.6% *vs* 7.8%, P=0.976). It was slight dizziness, which may be disease-related, and did not influence the normal activities. The appearance of nausea in patients treated by Artekin had higher rates than those treated by Artequick, but there was no significant difference (9.8% *vs* 5.8%, P=0.692). There was no vomiting in the Artequick group, but in the Artekin group the occurrence rate was 9.8% (P=0.063), which might be related with the irritation

Table 2. Efficacy of Artequick and Artekin

Group	Case	Mean fever clearance time (h, $\bar{x} \pm s$)	Mean parasite clearance time (h, $\bar{x} \pm s$)	Cure rate (%)	Parasite recrudescence rate (%)
Artequick	52	24.7 ± 9.9	43.2 ± 13.9*	100	0
Artekin	51	22.7 ± 11.2	36.5 ± 17.1	100	0

Note: *P<0.05, compared with the Artekin group

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Table 3. Results of Hematological and Biochemical Tests before and after Treatment ($\bar{x} \pm s$)

Group	Case	Time	WBC ($\times 10^6$/L)	RBC ($\times 10^{12}$/L)	TBil (μmol/L)	DBil (μmol/L)	ALT (U/L)	AST (U/L)	Cr (μmol/L)
Artequick	52	Day 0	7.34 ± 2.26	4.08 ± 0.52	1.10 ± 0.35	0.30 ± 0.16	28.8 ± 11.2	32.7 ± 11.5	0.98 ± 0.17
		Day 7	8.21 ± 2.31	3.99 ± 0.43	0.77 ± 0.19	0.19 ± 0.08	32.8 ± 14.9	30.9 ± 11.2	0.93 ± 0.15
Artekin	51	Day 0	7.25 ± 2.70	3.96 ± 0.52	1.00 ± 0.34	0.26 ± 0.14	28.1 ± 8.0	31.2 ± 11.1	0.97 ± 0.18
		Day 7	7.65 ± 2.01	3.85 ± 0.50	0.72 ± 0.19	0.18 ± 0.05	34.5 ± 15.6	33.5 ± 13.4	0.92 ± 0.21

of phosphate to the gastric mucosa. There was no anorexia in the Artequick group, but one case in the Artekin group (P=0.992). No serious neuropsychiatric reactions or other evidence of serious central nervous system toxicity in this study were found, and no fatality happened. There were no significant changes in hematological and biochemical tests before and after the treatments in the both groups (Table 3).

DISCUSSION

Resistance to antimalarial drugs is a global problem. WHO recommends the use of ACTs to improve artemisinin effectiveness. Vietnam is the one of the first countries where ACTs were used as the first-line medicine. China-Vietnam 8 (CV8) compound, being of the first generation ACTs, was developed by Chinese and Vietnamese scientists cooperatively, based on the continuous improvement of CV8, the new drugs, Artequick and Artekinare, were made. The cure rate of Artekin for falciparum malaria is quite high, with the lower rate of adverse reactions[5-8]. In Artequick, piperaquine was used as a compatible drug of artemisinin that belongs to 4-aminoquinolines, and it had been used widely in China in the 1970-1980s as the replacement of chloroquine. The tolerance of piperaquin in clinic is superior to its phosphate[9]. So piperaquin was to be a compatible drug; in order to guarantee the curative effect, increasing a single administration and reducing the dosing frequency could be conducted to shorten the treatment course. This clinical trial is at the phase Ⅱ stage. It is the first clinical comparison trial among ACTs conducted in the middle drug resistant endemic areas of falciparum malaria in Vietnam, aiming to observe the clinical efficacy and safety of the Artequick compound. The effectiveness and safety of Artekin had been evaluated in Vietnam, and the report showed its good profile of efficacy and tolerance[10]. Then Artekin has been chosen as a control in this study.

The results showed that the 28-day cure rate of the uncomplicated falciparum malaria patients treated with Artequick was not inferior to that in the Artekin group. Artequick had a simpler regimen, however, and lesser gastrointestinal reactions than Artekin. The patients had a good tolerance to Artequick with the recommended dose, which made it easier for malarial patients, especially for children patients, to accept the full treatment, thus optimizing the whole population efficacy. And expansion of the trial is recommended.

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