Original Article

Efficacy and safety of Artemehter-Lumefantrine in uncomplicated falciparum malaria in Liberia

Abdul Rasheed,[1] Sabir Mehmood Khan,[2] Muhammad Younis Awan,[3] Umar Khurshid,[4] Kaleem Ahmad[5]

Department of Medicine,[1-3] Department of Pathology,[4] Intensive Care Unit,[5] UN Level-II Hospital, Liberia.

Abstract

Objective: To assess the in vivo efficacy and adverse effects of Artemether-lumefantrine combination in acute uncomplicated falciparum malaria.

Methods: A prospective, observational study was conducted at Department of Medicine and Pathology, Pakistan Medical level II hospital, Tubmanburg and Harper from March 2009 to September 2009.

One hundred subjects with positive Plasmodium falciparum rings on malaria slide fulfilled the selection criteria and were included in the study. Mean, minimum and maximum values along with standard deviation of age, malarial parasite index, fever clearance time and parasite clearance time were calculated. A 28 day parasitological cure rate was determined. Frequency of various adverse events observed during this study were also noted.

Results: Of 100 subjects, 70 were Africans while remaining were Asians. Mean fever clearance time in Africans and Asians were 18.9 ± 11.5 and 27.9 ± 14.3 hours respectively. The mean parasite clearance time was almost similar in both races ranging from 28 to 31 hours. A 28 day parasitological cure rate was found to be 100%. About 10% of the subjects developed mild to moderate side effects including headache, vomiting, loss of sleep, vertigo and diarrhoea. There was no mortality during the study.

Conclusion: Artemether Lumefantrine combination therapy may be used safely and effectively in the management of acute uncomplicated falciparum malaria.

Keywords: Artemether Lumefantrine combination, uncomplicated plasmodium falciparum, Malaria (JPMA 61:131; 2011).

Introduction

Malaria is a deadly mosquito-born disease, which despite years of continual efforts, is still a threat to half of the world population. In 2008, there were an estimated 243 million cases of malaria and 863000 people deaths worldwide. Of all the malaria deaths 89% were in the African region.[1]

Among the four species of malarial parasite, the protozoan plasmodium (P.) falciparum accounts for the majority of instances of morbidity and mortality. The increasing prevalence of antimalarial drug resistance is a serious public health threat to the global control of malaria, especially in poor countries like Liberia. The World Health Organization (WHO) has recommended Artemisinin-based combination therapy for the treatment of malaria in such countries. The rationale for combination therapy is to improve the cure rate of infections responding inadequately to monotherapy and possibly to prevent or delay the emergence of resistance to other drugs.[2]

Artemether-lumefantrine combination combines the benefits of a rapid short lived schizonticidal effect of artemether with a slower but longer acting schizonticidal effect of lumefantrine, a highly lipophilic aryl amino alcohol.[3] This was first made available as a four dose regimen, which was found to be safe and effective in areas where drug resistance was rare at the time,[4] but not in Thailand, an area where multi-drug resistance is common. Subsequent trials of six dose regimen in Thailand proved it to be well tolerated with a high cure rate.[3] The six dose regimen is now the global standard regimen for Artemether-lumefantrine.[5]

Considering the fact that Liberia is a highly endemic

malaria area and that a drug combination will not work everywhere due to difference in drug resistance between regions, we conducted a study to determine the in vivo efficacy and adverse events of six dose regimen of artemether-lumefantrine in two endemic regions of Liberia following WHO therapeutic efficacy protocols.[6] Moreover to our knowledge, no research work has been conducted on antimalarial drug efficacy and safety since 2001 in this war torn area despite significant morbidity and mortality due to this entity.

Patients and Methods

This in vivo prospective observational study was conducted from March 2009 to September 2009 at Department of Medicine, Pakistan Medical hospital level II Liberia. Research was conducted from March 2009 to June 2009 at Tubmanburg in collaboration with Liberian General Hospital while later portion from July onwards was done at Harper, south eastern part of Liberia. Laboratory support and medicines were provided by the Level II Hospital, Liberia which was financed by United Nations.

This study enrolled subjects presenting with typical symptoms of malaria and who had a blood smear positive for P.falciparum. Inclusion criteria were: above six months of age, weight above 5 kg, infection with P.falciparum at screening, fever (axillary temperature >37.5 ºC or history of fever in the preceding 24 hours), and subjects able to take medicine orally. Exclusion criteria were: symptoms or signs of severe malaria, serious comorbid condition or any other illness requiring treatment incompatible with study, allergy to study drugs, use of any component of study drugs within last 28 days prior enrollment, and pregnancy (clinically or with beta human chorionic gonadotrophin test (HCG)). All subjects fulfilling the said criteria during the above mentioned period were enrolled in this study after taking informed consent.

After enrollment, all participants were prescribed artemether lumefantrine (AL) combination therapy. AL tablets were a fixed combination, each containing 20 mg of artemether and 120 mg of lumefantrine. AL was administered orally according to body weight (5-14 kg: one tablet, 15-24 kg: two tablets, 25-34 kg: three tablets, >35 kg: four tablets), Six doses were given at hours 0, 8, 24, 36, 48, and 60. Paracetamol and dimenhydrinate were provided, as needed, for symptoms of fever/headache/myalgias and nausea/dizziness, respectively. Other medications or intravenous fluids were provided only as prescribed by the treating physician.

Treatment was directly observed by the study team in the hospital till patients fever and parasitaemia resolved, later they were monitored as outdoor. A full drug dose was re-administered if the patients either spat out or vomited the AL tablets within 30 minutes. Half the drug dose was re-administered if the patient vomited between 30 minutes to one hour.

All the patients were followed up on days 1, 2, 3, 7, 14, and 28 days or at any time if patient felt unwell. Their signs and symptoms, medication history, and adverse events were recorded in a previously designed proforma.

Blood smears for malaria parasites were obtained twice a day until the smear cleared followed by weekly or as clinically warranted. Parasite counts were done on Giemsa-stained thick films and the number of parasites per 500 RBC were counted by light microscopy and divided by 5. A thick smear was regarded as negative on initial review if no parasite was seen in 100 high power fields. Complete blood count was done at baseline.

The efficacy of therapy in every subject was determined by fever clearance time, parasite clearance time and parasitological cure rates at days 7, 14 and 28. Fever clearance time was defined as the time from drug administration until temperature fell below $\leq$ 37.4°C and remained there for at least an additional 48 hours. Parasite clearance time was defined as time from the start of treatment until the first negative blood smear for asexual stages, which remained negative for an additional 24 hours. Parasitological cure rates were defined as the proportion of patients cleared of asexual parasitaemia within the specified time intervals of initiation of treatment with AL. All information was recorded in a previously designed proforma. All patients were evaluated daily for the reporting of adverse events during treatment that were new in onset or aggravated in severity or frequency after administration of the study drugs. An adverse event was considered to be drug related if its relationship to treatment was rated definite or probable by a study clinician.

Statistical analysis:

The data was entered and analyzed in the SPSS 11.0 software. Mean, median, minimum and maximum values along with standard deviation of malarial parasite index, fever clearance time and parasite clearance time were calculated. Frequencies of various adverse events noted during this study were calculated.

Results

In all, one hundred subjects fulfilled the selection criteria and were included in the study. Out of these, 70 were Africans while remaining 30 were Asians. The mean age of participants was 21.76 ± 7.31 years with majority in 1st, 3rd and 4th decade of life. Patients were predominantly male (70%).

Fever was present in all subjects at the time of enrollment from Asian and African races. Other main

Table-1: Parasitaemia and efficacy of artemether-lumefantrine combination.

Parameters	African n = 70	Asian n = 30	P value
Malarial parasite index	Mean 2.1113 ± 2.64 Median 1.00 Range .01-12	Mean 1.1120 ± 1.32 Median 1.00 Range .01-5	0.713
Fever clearance time (hours)	Mean 18.91 ± 11.5 Median 14.00 Range 4-64	Mean 27.93 ± 14.32 Median 29.00 Range 4-54	0.13
Parasite clearance time (hours)	Mean 28.39 ± 10.41 Median 26.00 Range 8-57	Mean 31.17 ± 11.05 Median 31.50 Range 12-52	0.594

symptoms were chills, vomiting and headache. Splenomegaly was the leading sign. Thrombocytopenia (less than 150 x 109/l) was present in 33% and 28% of subjects from Asian and African races respectively.

Parasite density was generally relatively low. The mean malarial parasite index was 2.11 in Africans while 1.112 in Asian races. The mean fever clearance times were significantly different between Asian and African subjects. It was 27.93 ± 14.32 hours and 18.91 ± 11.5 hours respectively. The mean parasite clearance times in both races were almost identical with mean of 31.17 ± 11.05 and 28.39 ± 10.42 hours in Asian and Africans respectively. The difference in the response in two populations was not statistically significant

Parasitological cure rate at day 7, 14 and 28 was 100%. Parasitaemia and therapeutic efficacy of study drugs are shown in Table-1.

About 90% individuals in this study tolerated six dose regimen of Artemether Lumefantrine without any adverse effects. Only 10 subjects developed mild to moderate side effects including headache, vomiting, loss of sleep, diarrhoea, vertigo, loss of appetite and malaise. The detailed account of adverse effects of this drug combination can be seen in Table-2.

None of the patients died during the study.

Table-2: Adverse effects of Artemether-lumefantrine combination.

Parameters	African n=70	Asian n=30
Headache n (%)	7(10)	3(10)
Vomiting n (%)	7(10)	3(10)
Loss of sleep n (%)	6(8.6)	3(10)
Diarrhoea n (%)	5(7.14)	2(6.66)
Vertigo n (%)	5(7.14)	1(3.33)
Loss of appetite n (%)	4(5.7)	1(3.33)
Malaise n (%)	3(4.29)	1(3.33)

Discussion

This study has demonstrated in vivo efficacy and safety of artemether lumefantrine combination therapy in uncomplicated falciparum malaria in two different parts of Liberia (Tubmanburg and Harper, Maryland). Although various studies have been conducted in different parts of the world on this topic with favourable outcome but to our knowledge this is the only study which enrolled otherwise healthy subjects from both Asian and African races. Moreover this is perhaps the first study which analyzed artemether lumefantrine combination in this part of the world. However efficacy of artesunate amodiaquine combination was assessed in 2001 in Harper, Liberia.[7]

This study reported mean fever clearance time in P.falciparum infected subjects to be about 19 hours in Africans as compared to about 28 hours in Asians. This disparity in two races may be due to the partial immunity of individual's resident of Africa that resulted in early clearance of fever. However this duration is much less than that observed in some of the international studies assessing AL efficacy reported as 26 to72 hours.[8-11]

Even, one of the Artesunate-amodiaquine combination efficacy determining trials conducted in Nigerian children showed mean duration of about 28 hours in African population which is longer than this study.[9] This disparity in mean fever clearance time in existing documented data may be due to the fact that their fever was not monitored in hospital as we did in this study.

Mean parasite clearance time in this study was 28 and 31 hours in African and Asian races respectively. This outcome was almost identical in both races but less than the existing data on this aspect ranging from 34 to 51 hours.[8,12,13]

Parasitaemia was reduced within 24 hours of commencement of therapy in 100% of both races. This was achieved in 95% of cases with similar drug combination as compared to 93% noted with Artesunate amodiaquine combination in a previous study.[9]

A 28 day parasitological cure rate was seen in 100% cases in this study as compared to 90 to 98% in previous studies on a similar drug combination.[8-16]

Treatment with other drug combinations like ASAQ was also found less effective ranging from 91 to 96%[8-11,15] in previous studies as compared to AL in this study.

Artemether-Lumefantrine was well tolerated and no serious adverse reaction was observed in any of the enrolled subjects in this study. Only mild to moderate side effects were seen in 10% individuals. This outcome is similar to few documented studies[11-13,15] but dissimilar to other AL safety determining trials in which adverse effects were observed in higher number of subjects(29%).[8-11,15] The adverse effects

observed in this study were successfully managed with supportive treatment.

Other artemisinin based combinations like artesunate amodiaquine trial showed adverse effects in upto 70%of subjects.[8-10]

This disparity in adverse reactions may be due to the fact that all antimalarial drugs were administered as per recommended protocols under close supervision of clinicians in the hospital.

None of the patients died during the study as compared to previous studies determining safety of AL[11,15] and ASAQ[11] combination in which one individual died in each study.

Clinical implication and limitations of the study:

This study highlighted the importance of six dose regimen of Artemether Lumefantrine in uncomplicated falciparum malaria in this part of the world particularly in the backdrop of reports of growing resistance in various parts of the world and emerging more expensive antimalarial drug combinations like Atovaquone proguanil.

All participants were successfully treated with AL combination with rapid resolution of parasitaemia and higher parasitological cure rate as compared to existing documented data regarding efficacy of different artemisinin based combination including AL and ASAQ. Adverse events were less as compared to few previous studies assessing safety of both similar and artesunate amodiaquine combination.

Considering aforementioned advantages, cheaper price and low economic capacity of the people in the poor socioeconomic communities like our region; AL may be used as the treatment of choice in uncomplicated falciparum malaria.

The main limitation was nonavailability of molecular markers which are used to differentiate the recrudescence and reinfection among the study subjects. Other limitation as designated earlier was exclusion of pregnant women. Although there is no difference in artemether metabolism between pregnant and non-pregnant women, but lumefantrine is contraindicated in pregnancy.

Limitations of this study require further attention from future researchers.

Conclusion

Artemether-lumefantrine combination therapy may be used safely and effectively in the management of uncomplicated falciparum malaria in liberia and could make a substantial contribution to malaria control, however the drug efficacy must be carefully monitored periodically.

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