MEDICAL CHANNEL

Original Article

THERAPEUTIC EFFICACY OF ARTEMETHER-LUMEFANTRINE A FIXED COMBINATION ANTIMALARIALS IN UNCOMPLICATED PLASMODIUM FALCIPARUM MALARIA.

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ABSTRACT

Objective: To determine the therapeutic efficacy of combined anti-malarials (Artemether-Lumefantrine) in uncomplicated plasmodium falciparum malaria .
Study design: Observational descriptive study.
Place and duration of study: Children hospital larkana and Ghulam Muhammad Mahar Medical College hospital Sukkur, from July 2009 to December 2009.
Methods: 75 Children, who were 1-12 years of both sexes, were assigned to enter the study.
After obtaining the informed written consent from parents, medical histories including presenting symptoms, current medications i,e single or combined antimalarials were obtained. Patients were given standard six doses of artemether –lumefantrine and were followed-up on days 1, 2, and 3 to see clinical clearance.
Results: After start of treatment fever relieved in 69 (92%) patients, while fever persisted in 6 (8%) patients. Chills disappeared in 50 (93%) patients but remained in 4 patients (7%). 47 (90%) patients out of 52 patients got relief from nausea and vomiting after completion of therapy. Spleen size regressed in 48 (96%) patients out of 50 patients. Liver size regressed in 34 (85%) patients out of 40 patients and 34(89%) patients out of 38 got relief from malaise.
Conclusion: Current study proved the safe excellent therapeutic efficacy of artemether-lumefantrine in uncomplicated plasmodium falciparum malaria with 92% fever and parasite clearance.

Keywords: Artemethr-Lumefantrine, plasmodium falciparum, malaria.

INTRODUCTION

Malaria is of over whelming importance in the developing world to day, with an estimated 300-500 million cases and more than one million deaths each year. Most malarial deaths occur among infants and young children[1].
In Pakistan there are 1.6 million cases and 50,000 deaths / year so looking at such a high incidence it is very important to determine proper drugs resistance for malaria.
Artemether-lumefantrine (AL) is a co-formulation of artemether and lumefantrine. Multidrug resistance of plasmodium falciparum is spreading throughout Asia and is impending efforts to control malaria. The emergence of drug resistance in Plasmodium falciparum has significantly undermined malaria control programs in countries where it is endemic[2].
To ensure high cure rates and to combat this threat, the WHO has recommended the use of artemisinin combination therapy[3]. Artemisinin or Qinghaosu is an extract of the medical plant Qinghao, which together with its derivatives, artesunate and artemether are the most active antimalarial compounds to date [4].As a class, the artemisinins are potent

and fast acting antimalarials. They are particularly well suited for the treatment of severe P .falciparum malaria and now play a key role in the combination therapy of drug resistance infections. These compounds act rapidly against the asexual erythrocytic stages of P.vivax and P.falciparum. Their potency in vivo is ten to one hundred folds greater than that of other antimalarials[5]. The rationale for this combination is that artemether rapidly reduces parasite biomass, and the long-acting lumefantrine eliminates residual parasites. Accumulating data suggest that, for optimum efficacy, it should be given as six doses and with food containing fat[6].

The fixed dose regimen ensures that malaria parasites always encounter artemether and metabolites in the presence of lumefantrine and provides protection against the emergence of resistance to both components, but absorption of the lipophilic lumefantrine is erratic, and the drug needs to be administered twice per day[7].The trial presented here was conducted to monitor the efficacy of the six-dose regimen of artemether-lumefantrine combination given over three days for the treatment of uncomplicated P.falciparum infections in children.

PATIENTS and METHODS

It is an open label in vivo drug study to determine the efficacy of oral combination of antimalarial tablets in terms of therapeutic efficacy, in uncomplicated plasmodium falciprum infection. The study included 75 patients during a period of six months from July 2009 to December, at children hospital larkana and children hospital Ghulam Muhammad Mahar medical college Sukkur.

Inclusion criteria:

1 Male or female, 1-12 year of age.
2 Weight > 10 kg.
3 Diagnosis of uncomplicated acute plasmodium Faciparum malaria parasitemia with history of fever and vegetative forms of falciparium malaria.

Exclusion criteria:

1 Has received antimalarial treatment in the past 7 days.
2 Severely ill (based on WHO criteria for severe malaria) or if patient is considered in the opinion of investigator or designee, to have moderately severe malaria (eg repeated vomiting, dehydrated).
3 Has received cotrimoxazole or chloramphenicol in the past 7 days.
4 Has a history of allergy to study drug (Artemether-Lumefantrine).

Patients with microscopically confirmed P.Falciparum malaria (vegetative forms) with fever were enrolled at hospitals. 75 children 1-12 years of both sexes, who gave voluntary consent was assigned to enter the study.

After obtaining the written consent from parents, medical history including presenting symptoms, current medications (single or combined) antimalarials were obtained. Case record form containing clinical history, examination and investigations were filled for each patient. Blood was collected for L.F.T. and Complete blood counts. Patients were given standard six doses of Artemether-Lumefantrine according to weight of patient as recommended by pharmaceutical company. Treatment was discontinued in patients who developed vomiting either due to disease or drug.

Follow-up

All the patients were followed-up on days 1, 2, and 3. On each day, in addition to physical examination, they were also enquired for adverse effects of drug.

RESULTS

Before treatment.

1 Age of patients

Ages of patients were between 1-12 years, majority were in age group of 1-8 yrears 48 (65.33%) and 26 (34.7%) were of age 9-12yrears, as shown in table: 1. All malaria patients clinically presented with fever 100%, chills 54 (72%), vomiting 52 (69.33%), malaise 38 (50.66%), anemia was found in 68 (90.66%), splenomegaly 50 (66.66%) and hepatomegaly 40 (53.33%) of cases as shown in table 2.

TABLE 1
SHOWS AGE OF PATIENTS.

Age group 1-4 years	25 patients 33.3%
5-8years	24 patients 32.0%
9-12 years	26 patients 34.7%

TABLE 2
CLINICAL PRESENTATION OF MALARIA PATIENTS

Clinical presentation	No of patients	Percentages
Fever	75	100%
Chills	54	72%
Vomiting	52	69.33%
Malaise	38	50.66%
Anemia	68	90.66%
Spenomegaly	50	66.66%
Hepatomegaly	40	53.33%

TABLE 3
SHOWS LEVEL OF HEMOGLOBIN AND PLATELETS

Normal hemoglobin level > 12g/dl	7 patients 9.3%
< 6g/dl	16 patients 21.3%
6-9 g/dl	40 patients 53.3%
10-12 g/dl	12 patients 16%
Normal platelets > 150,000/cmm	62 patients 82%
Thrombocytopenia <150,000/cm	13 patients 17%

TABLE 4
SHOWS REGRESSION OF CLINICAL FEATURES OF MALARIA PATIENTS AFTER TREATMENT.

Clinical feature regressed	Clinical feature persistent
Fever 62 (92%)	6 (8%)
Chills 50 (92.5%)	4 (7.5%)
Vomiting 47 (90.3%)	5 (9.7%)
Malaise 34 (89.5%)	4 (10.5%)
Spleen 48 (96%)	2 (04%)
Liver 34 (85%)	6 (15%)

The complete blood count revealed normal hemoglobin in7 (9.3%) of cases and severe anemia (Hb < 6g/dl) in 16 (21.3%) of cases and moderate anemia (Hb< 12g/dl) in52 (69.33%) of cases, thrombocytopenia (platelets less than 150,000/cmm) in 13 (17.33%) of cases and 62 (82.67%) had normal platelets as shwn in table 3.

Serum bilirubin was elevated in 8 (10.67%) patients and normal in 67 (89.33%) patients. SGPT was normal in all patients.

After treatment

The key criterion used to assess the efficacy of antimalarial drug was clinical response by 3rd day in all patients such as fever disappearance. Fever clearance, after taking 6 doses of Artemether-lumefantrine, fever subsided (defined as a temperature of < 37.5c) on day 1 was found in 15 (20%) patients, fever disappeared on day 2 in 42 (56%) patients, on day 3 in 12 (16%) patients.

Regression of clinical features

After start of treatment fever relieved in 69 (92%) patients, while fever persisted in 6 (8%) patients and drug was changed. Chills disappeared in 50 (92.5%) patients, but remained in 4 (7.5%) patients. Forty seven (90%) patients out of 52 got relief from vomiting after completion of therapy. Thirty four (89%) patient out of 38 got relief from malaise after completion of treatment. Spleen size regressed in 48 (96%) patients out of 50 patients. Liver size regressed in 34 (85%) patients out of 40 patients as shown in table 4.

Adverse effects

No adverse effect was seen except vomiting which can be either due to drug or disease.

DISCUSSION

The loss of affordable effective amtimalarial drugs to resistance represents a major threat to the people of malaria endemic countries[8]. Using ineffective drugs with high failure rates kills many patients and is unacceptable. The rising threat of plasmodium falciparum resistance to monotherapies prompted the world health organization 2006 guidelines for the treatment of malaria to recommended that combinations of antimalarials be used to treat malaria caused by P.falciparum[3].The combinations of artemether (an artemisinin derivative) and lumefantrine in a 1: 6 ratio was the first fixed dose ACT to meet the WHO's prequalification criteria for efficacy, safety and quality[9]. Artemisinin derivatives have the most potent and rapid onset of anti-parasitic activity of anti-malarial drug available today and are active against all plasmodium species that infect humans. Importantly, they allow more parasite clearance than any other antimalarial drug (parasite numbers can be reduced by a factor of 10^5 per asexual cycle, compared with 10^2-10^3 with other antimalarial drugs)[7] When combined with efficacious antimalarials with slower elimination rates, such as lumefantrine, shorter courses of treatment (three days) become effective[7].

Our results showed a high cure rates for artemether –lumefantrine and are consistent with efficacy reported from several sub-Saharan African countries [10, 11,] indicating a high overall cure rate with these regimens in the short (28-days) term. Hutagalung R[12] et all reported that combination therapy (artemether-lumefantrine) had rapid initial clinical and parasitological response and highly effective 98.8% in uncomplicated cases, and same clinical response was reported in south African study[13] .Valecha N et all results are comparable with present study and reported one resistance case in uncomplicated malaria on 7th day of treatment.

A recent study from Karachi, reported resistance to artemether alone 50% (7 out of 14) cases while combination 16% (one out of 6 patients) in severe or complicated malaria cases.

Fever clearance in our study in 69 (92%) of patient in 3 days is similar as reported by Hutagalung R[12, 16]. The age of our patient ranges from 1-12 years which is comparable with many different studies as reported by Abdulla S et all,[17,16.] The drug is safe and effective in in paediatric population as reported in many different studies as young as 2 months to 12 years [17, 16.]

CONCLUSION

Current study proved the excellent therapeutic efficacy of Artemether-lumefantrine, which is 92% associated with rapid fever and parasite clearance in all patients by day 3.

RECOMMENDATION

Malaria in children should be treated according to standard guidelines i,e with Artimisinin combination P Falciparum malaria dominate area rather than alone to avoid the development of resistance.

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