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ESSAIS CLINIQUE

COMPARISON OF CLINICAL AND PARASITOLOGIC RESPONSES TO SULFALENE/ PYRIMETHAMINE PLUS AMODIAQUINE VERSUS AMODIAQUINE PLUS ARTESUNATE IN THE TREATMENT OF UNCOMPLICATED MALARIA IN ENDEMIC AERAS IN AFRICA

PENALI LK[1], OFFIANAN AT[1], SAMÉ-EKOBO A[2], NDIAYE JL[3], GAYE O, KUETÉ TH[2], BEUGRE GRAH E[1], FAYE O[3], FAYE B[3], BARRO KIKI P[4], KONÉ M[4]

RESUME

Malgré tous les efforts déployés dans le cadre de divers programmes internationaux, le paludisme représente encore un énorme problème de santé publique. Le traitement des patients a été compliquée par l'émergence et la propagation de Plasmodium falciparum résistant aux médicaments antipaludiques réguliers. Ainsi, la recherche s'est concentrée sur l'identification des plus efficaces, mais sûre des modalités de traitement, notamment des combinaisons de médicaments. Dans ce contexte, nous avons étudié l'efficacité et l'innocuité d'une combinaison inédite, à savoir sulfalène / pyriméthamine + amodiaquine, en le comparant à l'amodiaquine plus artésunate (une combinaison récemment adopté comme traitement de première intention dans de nombreux pays). Le randomisée, multicentrique, l'étude comparative a été menée simultanément au Cameroun et en Côte-d'Ivoire au cours des six premiers mois de 2005. Méthodes de l'OMS pour l'évaluation de l'efficacité des antipaludiques a été utilisé et un total de 461 patients ont été inclus. Les deux traitements ont été une efficacité comparable avec un taux de réponse clinique et parasitologique de 97% pour sulfalène / pyriméthamine + amodiaquine par rapport à 98,1% pour l'artésunate plus amodiaquine après correction PCR. La tolérance était également comparable dans les deux groupes.

Mots-clés: paludisme, le traitement, sulfalène/ pyriméthamine + amodiaquine, artesunate plus amodiaquine, efficacité, sécurité.

ABSTRACT

Despite all the effort expended in the context of diverse international programmes, malaria still represents a massive public health problem. The treatment of patients has been complicated by the emergence and spread of Plasmodium falciparum resistant to the regular antimalarial drugs. Thus research has focussed on the identification of more effective but safe treatment modalities, notably drug combinations. In this context, we have investigated the efficacy and safety of a novel combination, namely sulfalene/pyrimethamine plus amodiaquine, by comparing it to amodiaquine plus artesunate (a combination recently adopted as first-line treatment in many countries).

The randomised, multicentre, comparative study was conducted simultaneously in Cameroon and Ivory Coast in the first six months of 2005. WHO methods for the evaluation of the efficacy of antimalarial drugs was used and a total of 461 patients were included. The two regimens were comparably effective with a clinical and parasitologic response rate of 97% for sulfalene/ pyrimethamine plus amodiaquine compared with 98.1% for artesunate plus amodiaquine after PCR correction. Tolerance was also comparable in both groups.

KEYS WORDS: *malaria, treatment, sulfalene/pyrimethamine plus amodiaquine, artesunate plus amodiaquine, efficacy, safety.*

1- Malariology Department - Institut Pasteur, Abidjan (Côte d'Ivoire)
2-Laboratory of Parasitology - CHU and FMSB. Yaoundé. (Cameroon)
3- Laboratory of Parasitology - CHU Cheikh Anta Diop. Dakar. (Sénégal)
4- Laboratory of Parasitology - Faculty of Pharmacy Abidjan. (Côte d'Ivoire)
Corresponding author: Louis Penali, 01 BP 490 Abidjan 01 (Côte d'Ivoire)
Tél. (225) 07 34 07 076 ; fax : (225) 22 48 66 63 E-mail : lou.penali@gmail.com

INTRODUCTION

At the beginning of the third milennium, malaria continues to be a global scourge with more than 40% of the planet's population-2.5 billion people-exposed to the disease. Every year, malaria is responsible for 1-1.5 million deaths in the world, most of these being children under five. Somewhere in the world, a child dies of malaria every thirty minutes. Africa accounts for 90% of all infections[1,2,3,4,5].

The appearance and spread of chloroquine-resistant *Plasmodium falciparum* have made it important to understand the sensitivity of different strains to the various 4-amino quinolines. Resistance to amodiaquine exists but to a lesser degree than resistance to chloroquine. Treatment failure rates are low, in Africa ranging from 0 to 5%[6,7]. Most of the countries of sub-Saharan Africa have had to confront resistance to 4-amino quinolines with, as a result, the need to use sulfadoxine/pyrimethamine for first-line treatment. The resultant selection pressure drove spread of the resistance of the parasite to this product especially in sub-Saharan Africa[8,9,10,11]. In the light of this situation, therapeutic combinations today constitute a choice option. Although combinations based on artemisinin are effective and safe in the treatment of malaria[12,13], they are expensive and sometimes difficult to get hold of. The scarcity of financial resources in most of sub-Saharan Africa has led us to believe that it may be possible to use compounds other than the artemisinin derivatives, with good results. Metakelfin™ (MF), a sulfalene/pyrimethamine has not been used for over three decades and, as a result, it is likely that today's plasmodia have not been subjected to selection pressure from this combination and have remained maximally sensitive (except for cases of spontaneous resistance, rare for folic and folinic acid antagonists). We set out to organise a trial to compare the combination of sulfalene/pyrimethamine *plus* amodiaquine (Dualkin™ from Pfizer) and artesunate *plus* amodiaquine (Arsucam™ from Sanofi-Aventis).

This prospective, multicentre, randomised comparative study was conducted in two parallel populations who were unaware of which treatment they were being given. The design was that of a non-inferiority trial comparing two therapeutic combinations, namely Sulfalene/Pyrimethamine+Amiodaquine (MK+AQ) and Artesunate+Amiodaquine (AS+AQ) in children and adults living in a zone where malaria is endemic.

PATIENTS AND METHODS

CENTRES

The study was conducted in health care institutions in two different countries, Ivory Coast and Cameroon. The Study Protocols were approved by Ethics Committees in both participating countries.

PATIENTS

The study population comprised people with the symptoms of uncomplicated malaria attending the participating health care institutions. All those, of all ages, in whom malaria was confirmed by the thick-drop test and who fulfilled the inclusion criteria (2003 WHO Protocol) were invited to take part.

– Inclusion criteria

. Male and female patients of at least two years of age;

. Patients who have given their informed consent to participate (or children whose parents have given consent) after having received explanations of the details of the study from the investigators;

. Outpatients;

. Patients with uncomplicated malaria (without gastrointestinal symptoms or any of the signs of severe disease) who could be diagnosed on the basis of clinical criteria (a fever of 37°5 C or above, with or without shivering, aching, generalised pain and headache) and in whose blood *P. falciparum*[2] has been detected;

. Patients who can take oral drugs;

. Patients who are not suffering from severe malnutrition (definition: children with a weight-to-height ratio lower than the

median, normalised NCHS/WHO reference figure by either a factor of over three standard deviations or more than 70%; or who have symmetrical œdema in both feet);

. No systemic signs of danger in under-five year-olds, or of severe or complicated *Plasmodium falciparum* malaria as stipulated in the current WHO definitions;

. An initial parasite density of between 2000 and 200000 per microlitre of blood;

. In women of child-bearing age (12 and over), a negative pregnancy test result ;

. No history of hypersensitivity to any of the drugs being studied.

RANDOMISATION AND REFERENCE TREATMENTS

After inclusion, the patients were weighed and randomised between two Treatment Groups. All daily doses of the Study Medication were administered at the health care institution under the supervision of the Investigator or one of the Co-Investigators. If the patient vomited within thirty minutes of taking the drugs, the same dose was re-administered.

CLINICAL EXAMINATION AND LABORATORY TESTS

Patients were given a full physical examination and their blood was tested for *Plasmodium* at inclusion and then again on d1, d2, d3, d4, d7, d14, d21 and d28. A PCR assay was carried out before the beginning of the study and for every patient with parasites in the blood between d7 and d28, in order to distinguish relapse from re-infection.

Haematological tests (blood count) and blood chemistry (transaminases, AST/ALT, Bilirubin, blood creatinine) were carried out on d0 and d7.

END POINTS

- The main efficacy end points were those stipulated in the WHO Classification of Response to Treatment, using the 28-day *in vivo* test (WHO/CDS/CSR/EPH/2002.17 WHO/CDS/RBM/2002.39).

- Secondary efficacy end points were time-to the disappearance of parasites from the blood, time-to temperature normalisation, and the blood gametocyte counts.

- Safety was evaluated by recording all Adverse Events and Serious Adverse Events.

STATISTICAL ANALYSIS

- Data were collected, recorded on a computer, and analysed using Epi-Info software. All analyses were carried out on both the Intention-to-Treat and Per Protocol populations.

- The comparability of the two treatment groups was evaluated on all included patients, using Student's Test for continuous variables, and the Chi^2 test for discrete variables.

- Secondary end points (safety, compliance) were evaluated using the Chi^2 test and Fisher's Exact Test.

2 – RESULTS

Baseline data

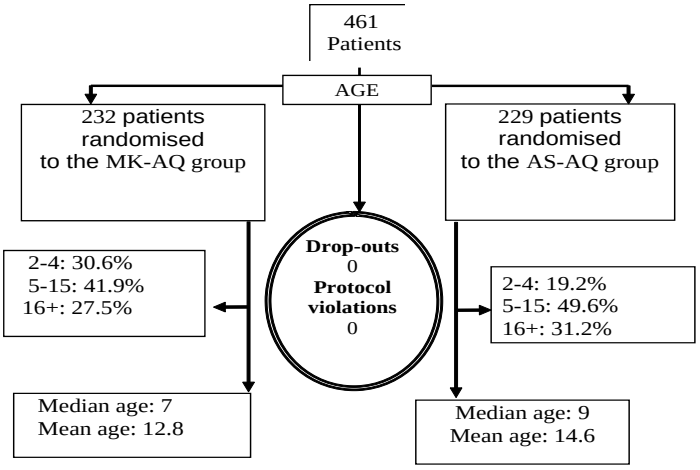

Figure 1. Age distribution in the two Treatment Groups

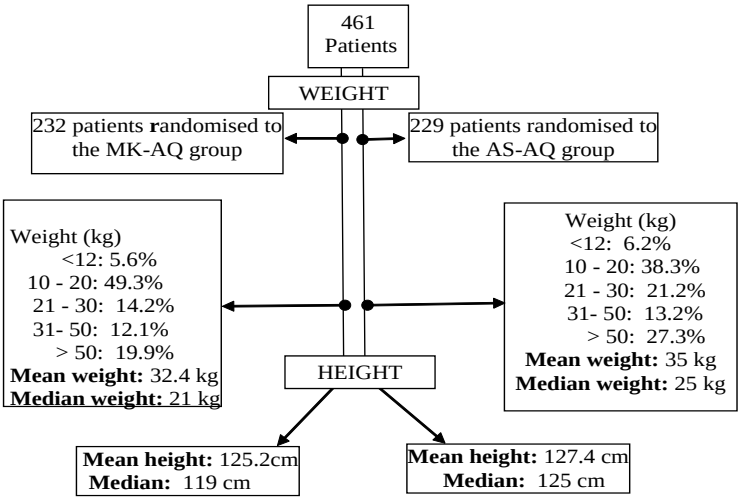

Figure 2. Weight and height distribution in the two Treatment Groups

A total of 461 patients were recruited between 15 February and 23 April 2005. After randomisation, there were 232 patients in the Sulfalene/Pyrimethamine+Amiodaquine arm and 229 in the Artesunate+Amiodaquine arm. In the first group, the median age was 7 and the mean 12.8; in the second group the corresponding figures were 9 and 14.6. Median and mean weights were respectively 21 and 32.4 kg in the first arm, and 25 and 35 kg in the second arm.

No patient dropped out and no protocol violation was recorded.

Table I. Therapeutic efficacy: MK+AQ *versus* AS+AQ

EFFICACY PARAMETER	DRUG	
	MK+AQ	AS+AQ
ETF	4	2
LCF	2	0
LPF	5	2
CPR on d14	97.3%	99% P=0.30
CPR on d28	95.1%	98.1% P=0.07
CPR after PCR correction on d28	97.0%	98.1% P=0.17

Clinical and parasitologic response rates were over 95% in both arms.

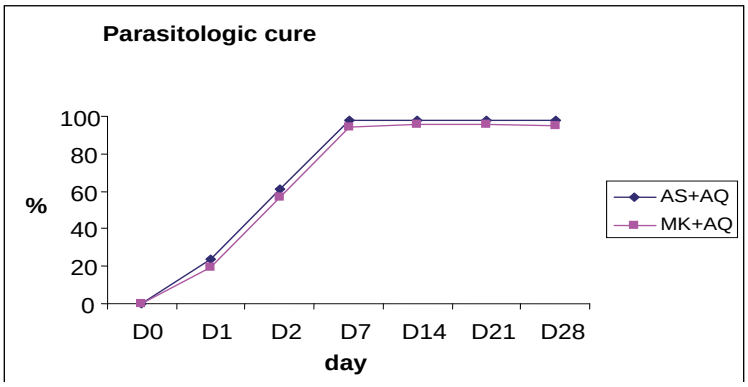

Figure 1. Parasitologic cure rates : MK+AQ versus AS+AQ

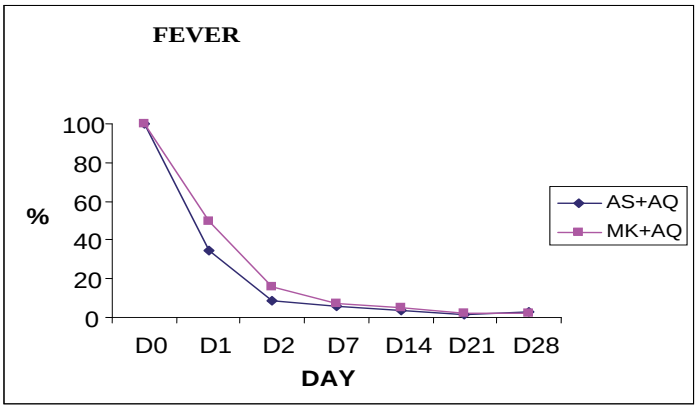

Figure 2. Clinical efficacy

Table II. Safety : MK+AQ *versus* AS+AQ

SIDE EFFECTS	DRUG	
	MK+AQ	**AS+AQ**
Abdominal pain	2	2
Pruritus	7	8
Vomiting	4	1
Dizziness	2	1
Diarrhœa	0	4
Asthænia	4	1
Itching	0	1
Insomnia	2	0

The most common problems were:
pruritus, asthænia and vomiting. No serious problem was reported (Table II).

Table III. Laboratory test results: MF+AQ *versus* AS+AQ

TEST RESULT	DRUG			
	MF+AQ		AS+AQ	
	d0	d7	d0	d7
% Blood creatinine >14 mg/L	0.9	1.3	0.4	0.4
% AST >100 IU/ml	1.7	0	1.3	0.4
% ALT >100 IU/ml	0	0	0.4	0.4
% Patients with Hb <11 g/dL	42.8	33.2	36.6	27.9

No notable abnormalities in key laboratory parameters (blood creatinine, transaminases and hæmoglobin) were reported in either Group (Table III).

DISCUSSION

Sulfalene and sulfadoxine are folic acid antagonists which inhibit a *Plasmodium*-specific enzyme, dihydropteroate-synthase (DHPS). These drugs bind protein strongly and have relatively long half-lives (65 and 180 hours respectively)[14].

Sulfalene/pyrimethamine has not been used for over three decades and, as a result, it is likely that today's plasmodia have not been subjected to selection pressure from this combination and have remained maximally sensitive. Since amodiaquine remains effective (15), we organised a study to compare the combinations sulfalene/pyrimethamine+amodiaquine and artesunate+amodiaquine.

The chemical structure of sulfalene is close to that of sulfadoxine and it therefore seems reasonable to combine sulfalene/pyrimethamine with amodiaquine since it has been shown that a combination of sulfadoxine/pyrimethamine + amodiaquine is more effective than either product on its own, and that its safety profile is identical to that of chloroquine and sulfadoxine/pyrimethamine. In 2002 (before PCR) in Uganda, Talisuna et al. (10) recorded a parasitologic efficacy rate of 85.7%, and in Rwanda in 2001, Rwagacondo et al.[16] obtained an efficacy rate of 97.7% with sulfadoxine/pyrimethamine+amodiaquine.

In our study, clinical and parasitologic responses were comparable with the two combinations (MK+AQ and AS+AQ) on d14: 97. 3% versus 99%. By d28, outcomes were still comparable : 97% for MK+AQ versus 98.1% for AS+AQ after PCR. The most common adverse events were pruritus, asthænia and vomiting with incidences being comparable on both regimens. A similar picture was seen for the laboratory test results probing organ function: no significant change in liver or kidney function was observed. These findings are consistent with the published results[17,18] and pinpoint the potential of a combination of sulafalene/ pyrimethamine and amodiaquine in the treatment of simple *Plasmodium falciparum* malaria.

CONCLUSION

The efficacy of the combination Sulfalene/ Pyrimethamine+Amiodaquine is comparable to that of Artesunate+Amodiaquine. Similarly, fever control and parasite clearance are comparable. A reduction in gametocyte load was observed in both groups.

Both regimens were well tolerated, and neither induced significant changes in functional test results.

The combination sulfalene/ pyrimethamine+amodiaquine is a very promising option for the first-line treatment of uncomplicated malaria in Africa although a pharmacovigilance system should be set up, as for all combinations currently being prescribed.

REFERENCES

1- Winstanley P, Ward S, Snow R et al. Therapy of *falciparum malaria* in sub-saharan Africa : From molecule to policy. Clin Microbiol Rev. 2004. 17: 612-637

2 - Snow R, Trape Jand Marsh K. the past, present and future of childhood malaria mortality in Africa. 2001 Trends parasitol. 17: 593-597.

3 - Snow R, Trape JF and Marsh K. the past, present and future of childhood malaria mortality in Africa. 2001 Trends parasitol. 17: 593-597.

4 - Snow R, Craig M, Deichmann U et al. Estimating mortality, morbidity and disability due to malaria among Africa's non- pregnant population. Bull. W.H.O. 1999. 77: 624-640

5 - Nabbarro D and Tayler E. The "Roll Back Malaria" campaign. Science 1998. 280: 2067-2068. World Health Organization. Roll Back Malaria 2002.

6- Penali l. k. . ; Coulibaly a. l. ; Kaptue b. ; Konan d. ; Ehouman a.Réponses parasitologique et clinique de l'amodiaquine versus chloroquine dans le traitement de l'accès palustre simple à *Plasmodium falciparum* chez l'enfant en zone d'endémie. Bull. Soc. Path. Exot. ; 1994 ; vol 87 ; N° 4 ; 244 – 247.

7- Raccurt c.p. ; Arouko h. , Djossou f. ; Macaigne f., Massougbodji a. ; Zohoun t. ; Sadeler b.c. ; Ripert c.Sensibilité in vivo de *Plasmodium falciparum* à l'amodiaquine dans la ville de Cotonou et ses environs (Bénin). Med. Trop. ; 1990 ; 50 ; 21 – 26 health and control. J Med. Microbiol. 2000. 49: 1053-1055.

8 - White, N. Antimalarial Drug Resistance. J Clin Invest. 2004. 113: 1084-1092.

9- Djaman JA, Kauffy PC, Yavo W, BASCO LK & KONE M Evaluation in vivo de l'efficacité thérapeutique de l'association sulfadoxine/ pyrimethamine au cours du paludisme non compliqué chez les enfants de Yopougon (Abidjan, Côte d'Ivoire).Bull. Soc. Pathol. Exot., 2004, 97, 3, 180-182

10 - Talisuma A, Nalunkuma-kazibwe A, Bakyaita Net al. Efficacy of sulphadoxine-pyrimethamine alone or combined with amodiaquine or chloroquine for the treatment of uncomplicated falciparum malaria in Ugandan children. Tropical Medicine Int Health. 2004. 9: 222-229.

11 – Ronn A., M, Msangeni H., A, Mhina J., Werndorfer., W. H., Bygbjerg I.C. High level of resistance of *Plasmodium falciparum* to sulfadoxine pyrimetamine in children in Tanzania. Trans. Roy. Soc. of Trop. Med. and Hygiene, 1996, 90: 179-181

12 - OMS., «Progrès en chimiothérapie du paludisme.», Série Rapports Techniques, O.M.S. édit., Genève, 1984, n° 711.

13 - WHO technical consultation on the antimalarial drug combination therapy. Geneva, World Health Organization, 2001.

14- White N.J., «Clinical pharmacokinetics of the antimalarial drugs.», Clin. Pharmacokinet., 1985, 10, 187-215.

15 - Bray P, Hawley S, Mungthin M et al. Physicochemical properties correlated with drug resistance and the reversal of drug resistance in Plasmodium falciparum. Mol Pharmacol. 1996. 50: 1559-1556.

16 - Rwagacondo C, karema C, Mugisha V et al.Is amodiaquine failing in Rwanda ? Efficacy of amodiaquine alone and combined with artesunate in children with uncomplicated malaria. Trop Med Int Health. 2004. 9: 1091-1098.

17- Agnamey P, Brasseur R, Sarrassat S, Cisse M, Gaye O, Sokhna C, Trape JF & Olliaro P.Impact de l'utilisation de l'association Artesunate+Amiodaquine pour le traitement du paludisme non compliqué en Casamance. Méd. Trop. 2003, 63(3), 315

18 - Abacassamo F., Enosse S., Aponte J., et al. Efficacy of chloroquine, amodiaquine, sulfadoxine-pyrimethamine and combination therapy with artesunate in Mozambican children with non-complicated malaria. Trop Med Int Health. 2004. 9: 200-208.