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Comparative study of the effectiveness of combination therapies based on atemisinine in Dassa Zounme and Parakou: case of *Artemether lumefantrine* and *Artesunate amodiaquine*

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Abstract

The National Malaria Control Program recommended in 1993, the use of Chloroquina (CQ) as first line drug for malaria treatment, and sulfadoxin pyrimethamin as second drug. After years, Benin knows resistance about these antimalarials. Quinina was to treat gravities. In 2004, the strategy of treatment changed. Treatment of malaria cases is based on use of arteminisinia therapeutic combination. The goal of this study is to be sure that these drugs are efficace before general use in the country and in some regions as Dassa Zounmè where the resistance is up (61. 3% for Chloroquina CQ and 45.9% for SP in 2002).The study is based on: comparison of therapeutic efficacy of artemether Lumefantrine and Artesunate Amodiaquine. Results show that all of the tested drugs have good therapeutic efficacy. Most important rate failure is in Dassa Zounmè (33, 86%) than Parakou (23, 44%). They are parasitologic failure and are probably due to the reinfestation of children. Two drugs have a good parasitological clearance and eliminate fever after 2 days of treatment.

Abbreviations

ACPR: Adequate Clinical and Parasitological Response
LPF: Late Parasitological Failure
ETF: Early Therapeutic Failure
LCF: Late Clinique Failure
NMCP: National Malaria Control Program

Scientific names

Plasmodium falciparum ; Plasmodium malariae ; Plasmodium vivax ; Plasmodium ovale ; Anopheles gambiae ; Artemether lumefantrine ; Artesunate Amodiaquine ; Sulfadoxine - Pyriméthamine

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Introduction

The intertropical zone is a region characterized by a varied Tropical Pathology, with a predominance of endemic-epidemic diseases and the most important is malaria. In Africa and in the countries in South of Sahara, as Benin, particularly malaria is the most important disease of all parasitic diseases. According to the most recent estimates, there are 300 to 500 million clinical cases each year with more than 90% in the countries in South of Sahara (Roll Back Malaria, 2005 Plan stratégique mondial Faire Reculer le Paludisme 2005-2015). Malaria is by far the most important tropical parasitic diseases in the world. Due to a parasite named *Plasmodium*, it is transmitted to humans by the bite of the infected female Anopheles. It is present in 100 countries.

Between 300 and 500 million clinical cases are recorded each year, causing more than a million deaths. 90% of death occurs in sub Saharan Africa where children are particularly affected. In Africa, a child dies every 30 seconds as a result of a malaria. In the WHO African region, where arise 80 to 90% of deaths, malaria is a major public health problem. He became a major obstacle to economic development and the improvement of the level of health of populations (OMS/CDS/RBM, 2000). It is estimated that, in many countries, spending on malaria can reach 40% of expenditures for the health sector and that 20 to 50% of hospital admissions are attributable (WHO and UNICEF, 2003).

Indeed, malaria maintains poverty. It costs Africa 12 billion dollars per year in GDP lost. It absorbs up to 25% of the household income and represents 40% of Government health spending. (Roll Back Malaria, PSM 2005-2015) Malaria is one of the leading causes of morbidity of children and teachers and truancy. The sick child cannot go to school or assimilate knowledge; In addition, neurological damage and lasting cognitive impairment are feared (Roll Back Malaria, PSM 2005-2015 Malaria) is a major cause of child mortality in Africa. It is responsible for 20% of all deaths of children aged less than 5 years. (Roll Back Malaria, PSM 2005-2015 Malaria) Currently antimalarial medicines are expensive and available in too small quantities. Public/private partnerships that are currently trying to improve access to affordable antimalarial drugs may be a starting point for the improvement of access to other essential medicines.

In Benin, this disease represents 39.7% of the causes of recourse to care in health units and is the major illness suffered by communities in 2006(Annuaire des statistiques sanitaires 2008). Malaria is the leading cause of hospitalization (24.7%) and death. It occurs in all regions of Benin. If today the disease makes many victims, it is due to resistance to antimalarial drugs. The resistance of the parasite to the drugs is the main obstacle to the control of malaria.

The challenge today is a permanent course against the ability of the parasite to resist treatments. The key axes of the strategy against malaria are to encourage the use of combination therapies (CTA), in countries where the disease is endemic, preferably containing a derivative of artemisinin (artesunate, artemether, etc.). The artemisinin derivatives (Qinghaosu), extracted from artemisia annua, a plant long used in Chinese medicine, allowed to make a new class of antimalarial drugs, for faster action on the disappearance of blood parasites. So far, no resistance of the parasite to the artemisinin derivatives was observed.

This study compared the effectiveness of therapeutic combinations of artemisinin in Dassa Zounme and Parakou to support on two acts recommended by the National Control Program against malaria named Artemether Lumefantrine and Artesunate Amodiaquine for uncomplicated malaria in Benin.

Materials and Methods

Presentation of the study site

The study took place in the municipalities of Dassa-Zoumé and Parakou. The choice of the site of Dassa-Zoumé is justified by the rate especially high therapeutic failures (61.3% to CQ, 45% for MS) studies in 2002 and due to their epidemiological facies. Investigations covered two by commune health centres (Paouignan and Dassa centre; Parakou and Kpebie).

Study population

Participants are children aged 6-59 months. Patients who present an axillary ≥ temperature 37.5 ° C are recruited after consent of parents or guardians in the service of external consultations and then headed the investigation team.

The selection criteria

Age between 6 and 59 months in Republic of Benin.

Absence of systemic signs of danger or severe malaria.

Absence of other pathologies febrile obvious (IRA, Infections ORL)

Absence of severe malnutrition

Mono Infection to *P. falciparum* parasite between 2000/µl and 200,000 density-specific parasites/µl of blood;

Informed consent of the parent or guardian;

Ease to meet appointments

Axillary Temperature greater than or equal to 37.5oC

Absence of allergy or history of allergy to any of the tested drugs,

Conservation of blades

The blades are stored in a box of blades during the study

At the end of follow-up, each patient blade should be packed and stored to free boxes.

Conservation of filter paper

Blood samples on filter papers are dried at room temperature, away from light and transferred to a plastic bag containing silica gel for conservation.

Treatment

Treatment for malaria was randomized, until the inclusion of 50 patients per treatment group. It is also recommended to keep below 10% of the total sample size errors in classification of patients. Discrepancies of more than 10% during quality control would require proofreading of all blades and the reclassification of all subjects in the study. Make sure that the patient swallows all drugs tested on day 0, 1 and 2 in your presence and observe the patient for 30 minutes at least. If the patient vomits during this period, repeat the treatment. If the repeated dose is spewed out, remove the patient from the study and refer them to specialized services for adequate support. The recommended dosage and doses are treatment guidelines provided by the National Malaria Control Program**.** The participants received systematically paracetamol on days 0, 1 and 2 depending on weight.

Study methodology

The Determination of the size of the sample is made with SCHWARZ formula. For this study, the chosen size is 120 children by region (sixty by drug) or 240 children who fulfil the conditions laid down for inclusion.

Difficulties encountered

This study was very restrictive on several fronts: some parents or guardians of children are not honoring meeting; some roads to the homes of children are very difficult. The study was approved by ethical committee of the Faculty of Health Science (University of Abomey-Calavi) in Benin. Written informed consent was given by all women for their children participating in this study.

Characteristics of the study population according

to age

Sex ratio (male on female) is 1.46

Children aged 6 months to 3 years are almost 75% of the sample Dassa Zoume.

The distribution is balanced by age group. Contraire of the case of Dassa Zoume, no age category will not affect the results.

Apyrexy

The above table indicates that all children included in the study had a J0 temperature which varies between 37 ° 5 c and 41° C. After 2 days of treatment with Artemether lumefantrine or Artesunate amodiaquine, more than 96% of febrile children had their temperature below 37°5° C. . There is no statistically significant difference between Lumefanrine Artemether and Artesunate Amodiaquine in relation to the apyrexie (P > 0.05).

Parasitic clearance

82% to 98% of treated children have a density parasitic zero on the second day of treatment regardless of the drug. Regardless of the site and the drug,no treated children had parasite density to J3 greater than or equal to 25% of that of J0. There is no statistically significant difference between Lumefanrine Artemether and Artesunate Amodiaquine regards (P > 0.05).

Rate of treatment failures and clinical and parasitological response adequate

Dassa Zoume

- Artemether Lumefantrine and Artesunate Amodiaquine have respectively a late parasitological failure (EFA) from 33.86% rate and 23.44%.
- Artemether Lumefantrine and Artesunate Amodiaquine have a rate of early therapeutic failure no (FTE) of 0%.
- Artemether Lumefantrine and Artesunate Amodiaquine have a clinical response rate and parasitological adequate (APCR) respective 66.13% and 76,56%.

Parakou

- Artemether Lumefantrine and Artesunate Amodiaquine have a failure rate therapeutic early (FTE) of 0%.
- Artemether Lumefantrine and Artesunate Amodiaquine have a clinical response rate and parasitological adequate (APCR) 98.55% and 100%.

Discussions

Results of clinical and biological examinations

Follow-up of children during the 28 days of treatment helped to obtain interesting results to the clinical and biological perspectives. Indeed, all the children treated with either of the drugs had a systematic reduction of fever. Biological diagnosis also shows a good reduction in parasite load.

The rate of treatment failures

According to the rates, of treatment failures, the results show that early treatment failure rate is 0% regardless of the medication and the site. The LPF vary between 23.44 and 33.88% at Dassa Zoume. On the other hand, in Parakou, these rates are zero. The high rate of EPT can be explained by several parameters:

-children do not sleep under bednets at home as recommended in the study.

-The strains of parasites are resistant. But this analysis was rejected by the rate zero of early treatment failure. Parasites has been cleaned, it is not probably these strains remain until J28.

-Clearly, hypothesis of reinfestation is more logical. Indeed, if the children are not sleeping under nets, it may be infected the last weeks of their follow-up. It is therefore necessary to make confetti of filter paper for these cases of late treatment failures are subject of a genotyping. Therefore, the molecular weights of the parasites can make difference between reinfestation and recrudescence. If these cases were classified as reinfestation, it would reduce the overall failure

rate. Cases of clinical and parasitological responses adequate confirm although other authors and researchers believe the drug. Indeed, the therapeutic combination of drugs has for interest to exploit their synergistic and additive properties. It induces the rapid and sensitive parasitic biomass reduction, rapid elimination of the parasite, rapid disappearance of clinical symptoms.

Table 1. Drop in temperature (Apyrexy) in patients.

	T° à J0 > 37°5				T° J2 < 37°5			
	Dassa Zoumè		Parakou		Dassa Zoumè		Parakou	
	n	%	n	%	n	%	n	%
ATM LUM	62	100%	69	100%	61	98,4	68	98,6
ASAQ	64	100%	64	100%	62	96,9	63	98,4

Parasite clearance and the decrease of fever.

After 48 h of treatment, parasitic biomass was strongly reduced. It becomes zero for 82.3 to 98.4% of treated patients. On the other hand, there is that fever falls in most of the children at the end of the same period. This efficiency observed in the drug presents a worrying aspect related to the behavior of populations. Indeed, the disappearance of clinical signs may be a factor which will influence further processing. If we know that a patient who feels better is struggling has continue his treatment, he must recognize therefore that awareness must be made to avoid resistance to these drugs. These results are trend to those obtained by J.B. Oke *et al* who also found that these drugs reduce the parasitic biomass and caused the disappearance of clinical signs.

Table 2. Parasite clearance after 48 h treatment.

	2000< DP< 200000				DP J2 = 0			
	Dassa Zoumè		Parakou		Dassa Zoumè		Parakou	
	n	%	n	%	n	%	n	%
ATM LUM	62	100%	69	100%	51	82,3	67	97,1
ASAQ	64	100%	64	100%	54	84,4	63	98,4

Furthermore there is no significant difference between the results obtained with Artemether Lumefantrine and Artesunate Amodiaquine. The high rate of EPT parasitological failure late obtained at Dassa Zoume with both drugs should be linked to the behaviour of the population in individual protection against malaria. It has been evaluated on the number of people cured to J3. The graphics showed that more than 80% of children were cured at J3.

Table 3. Rate of treatment failures and clinical and parasitological responses adequate for children aged 6-59 months.

Sites	n	ACPR	ETF	LPF	LCF	TE
		Arteméther Luméfantrine				
Dassa Zoumè	62	66,13%	0%	32,25%	1,61%	33,86%
Parakou	69	98,55%	0%	0%	1,45%	1,45%
		Artésunate Amodiaquine				
Dassa Zoumè	64	76,56%	0%	23,44%	0%	23,44%
Parakou	64	100%	0%	0%	0%	0%
TOTAL	259					

Analysis of sociological parameters that can influence the effectiveness of antimalarial drugs

In 2004, the study of the socio-cultural determinants of treatment failures of antimalarial drugs in the management of uncomplicated malaria Plasmodium falciparum in the municipalities of Dassa Zoume and Lokossa revealed that 73% of people believe that chloroquine is still effective in the treatment of malaria (therefore 27% think that chloroquine is not effective). This response compared with that obtained by the NMCP, shows that the difference between 27 and 35% is not significant (P > 0.05). One can therefore estimate that the results obtained by the scientists are in line with the populations. Furthermore, molecular biology tests had been made on samples, it would certainly have failure rate slightly lower than those that led to the change in policy, so closer to the results obtained in the community.

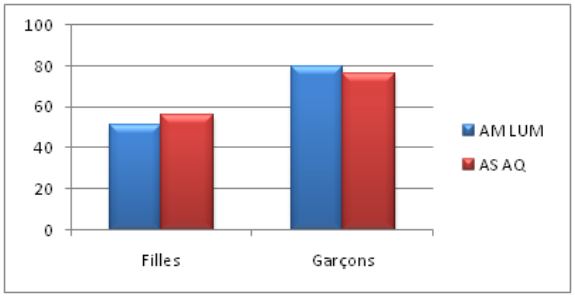

Fig. 1. Distribution of children according to the sex and drug.

For populations, chloroquine is effective for the management of malaria cases. Therefore, one might think that the change in policy of support for malaria by the Ministry of health (MS/NMCP) is not appropriate. However, the change in the national policy of support for malaria cases is governed by the principles of public health taking into account the problems of health in macro terms. Indeed, although the majority (73%) think that the drug is effective, do not change would mean that on 1261000 children of less than five years that will make malaria each year, 27% or 340470 will have therapeutic failures and therefore will move to severe malaria with approximately 234924 death. Furthermore, WHO recommends that as soon as the failure rate reached 10-15%, must begin the process of policy change.

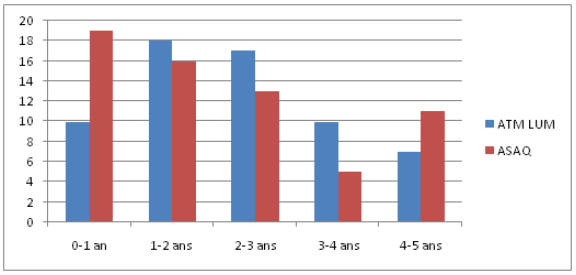

Fig. 2. Numbers of children by age according to the drug to Dassa.

Note, however, that people adopt behaviors that do not promote:

-the protection of the molecules

-the decline or rates of parasite resistance to antimalarials.

In fact, 76% of respondents use chloroquine to prevent malaria on a frequency ranging from daily to weekly (66%).These behaviours that are contrary to the requirements of the national malaria policy makes them used parasites in insufficient doses of molecules, thus to induce resistance. Following all this, and in order to protect its populations, Benin has opted for the revision of its policy of anti-malarial drugs, now oriented therapeutic combinations based on artemisinin (CTA) and more particularly the Artemether-Lumefantrine association instead of CQ.

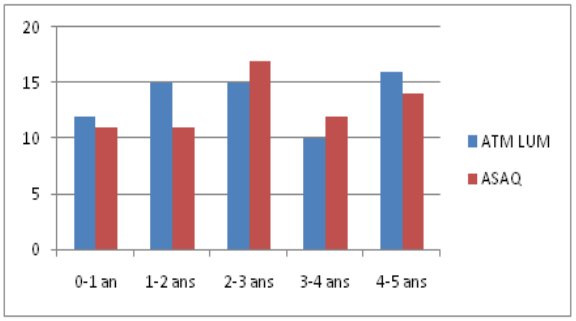

Fig. 3. Number of children by age according to the drug in Parakou.

Currently, combination therapies are available in the health centres. Their use is preceded by a consultation and a laboratory diagnosis of malaria

rapid diagnostic tests or by microscopy. These attitudes adopt populations should be reviewed in order to safeguard the effectiveness of these new drugs. It is important in this connection that the National Malaria Control Program increases the awareness of the populations on the use of drugs exclusively in confirmed cases of malaria and that prevention should essentially be to avoid contact vector man by the use of insecticide-treated nets.

Conclusion

The comparative study of the therapeutic efficacy of Artemether lumefantrine and Artesunate amodiaquine with children aged 6-59 months doing simple malaria Plasmodium *falciparum* has revealed that the two drugs are very effective Plasmodium over than 90%.

The ETP early treatment failure rate is zero regardless of the site. The drugs reduce to zero the parasitic biomass and caused the disappearance of clinical signs.

Under the preliminary results and discussion, the topic deserves to be deepened by the following axes:

-Organize a study on the therapeutic efficacy of Artemether lumefantrine and Artesunate lmodiaquine at Dassa Zoume and other sites in the Republic of Benin.

-Do the genotyping of molecular biology confetti made in cases of ETT late treatment failures

-Identify the probable causes of EPT late parasitological failures obtained during this study.

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