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Full Length Research Paper

Efficacy and safety of artesunate in microspheres form in the treatment of uncomplicated *Plasmodium falciparum* malaria in adults in Abidjan

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The treatment of malaria with effective and well-tolerated antimalarial is an ongoing challenge in the fight against this disease. To contribute to the development of better drugs, this study was undertaken to evaluate the efficacy and safety of administration of artesunate 200 mg in microspheres form. It was conducted in Abidjan, Côte d'Ivoire, in 50 adult patients with an uncomplicated *Plasmodium falciparum* malaria. After inclusion in the study, the clinical and parasitological follow-up of patients was performed according to the WHO protocol for 28 days. Artesunate in microspheres form was administered at a dose of 400 mg taken twice daily on day 1 and 200 mg on day 2 to day 5 single dose. Biological tolerance was assessed by hematological and biochemical examinations on day 1, day 7 and day 28. Therapeutically, the cure rate at day 14 and day 28 were 100%. However, we noted 6% (3 cases) of reinfestation confirmed by a Polymerase Chain Reaction (PCR). The average clearance time for heat and parasite were 54.32 hours and 32.64 hours respectively. The overall tolerance (Clinical and biological) was estimated as very good or good in 96% of cases and moderate in 4% of patients. The most frequent side effects were nausea (12%), asthenia (12%) and vomiting (10%), but with no clear relationship with the drug under study. Artesunate 200 mg in microspheres thus is an effective and well-tolerated drug. It could thus be recommended in combination with another antimalarial drug in artemisinin combination therapy recommended for malaria treatment.

Keywords: Uncomplicated malaria, *Plasmodium falciparum,* Artesunate, microspheres.

INTRODUCTION

The World Health Organization estimates the number of reported malaria episodes in 2012, to 207 million approximately 80% in the African region. This condition has caused about 627,000 deaths, 90% in Africa (World Malaria Report, 2013). Combination therapies based on artemisinin derivatives (ACTs) are currently the best drugs and readily available recommended (World Health

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Organization, 2010) as the first line treatment of uncomplicated malaria caused by *P.falciparum.* They are known to improve cure rates, reduce the risk of relapse, reduce the development of chemo resistance of *P. falciparum* and thus reduces the spread of resistant parasites (Adjuik et al., 2004; Ibrahium et al., 2007).

Many studies have shown the effectiveness of some ACTs (Adjei et al., 2008; Faucher et al., 2009; Momoh et al., 2013) but, with some side effects and relapses. It is therefore necessary to improve the performance of some of these associations. This improvement could be achieved by optimizing the pharmacokinetic parameters using appropriate pharmaceutical formulations.

This option will thus enhance prompt and effective malaria treatment can significantly reduce morbidity and mortality caused by malaria.

In this context, the transportation of active ingredient through microsphere is an innovative method for improving the pharmacokinetic performance. In addition, artesunate in microspheres form facilitate its association in co-formulation with several active ingredients and could thus be used in the development of ACTs now recommended for the treatment of uncomplicated malaria (World Health Organization, 2010).

The aim of our study is to evaluate the efficacy and safety of Artesunate 200 mg transported in microspheres in the treatment of uncomplicated *Plasmodium falciparum* malaria in adults in Abidjan.

PATIENTS AND METHODS

Type and population study

It is an experimental study on the effectiveness and safety of Artesunate 200 mg in microsphere. It was conducted in Abidjan from 06 January 2005 to 11 May 2005 and involved 50 patients suffering from uncomplicated *P. falciparum* malaria. Patients were included based on the following criteria : 1) patients aged at least 15 , 2) having a parasitemia between 2,000 and 200,000 asexual forms / µl of blood, 3) presenting no danger signs or severe malaria, 4) not suffering from associated febrile conditions, 5) able to take medication *orally,* 6) patients not having received antimalarial treatment 7 days before the start of the study for the 4 - amino quinolines, halofantrine, mefloquine and sulfadoxine-pyrimethamine and 3 days for artemisinin derivatives and quinine, 6) and have given their informed consent or the consent of their legal guardian, 7) not pregnant or lactating and 8) with no antimalarial treatment in progress.

Study protocol and treatment procedure

Patients in the study were treated with 200 mg artesunate transported in microspheres provided by Pharmaceutical Laboratories of Côte d'Ivoire (PLCI). Treatment was administered at a dose of 400 mg on day $_1$ and 200 mg on days 2 to 5. All daily doses were taken with supervision by a member of the research project.

Monitoring of patients in the study was done in accordance with a schedule of 28 days. Visits took place on day 2, 3, 4, 5, 7, 14, 21 and 28 after the day of inclusion. Thick and thin blood smears were performed on each visit for the purpose of parasitological monitoring. Blood samples were taken on day 1, 7 and 28 for the hematological (hemoglobin, leukocytes, hematocrit) and biochemical assay (ALT, AST). Blood samples were collected on Whatman paper No. 3 at inclusion stage and from day 7 in case of traces of parasitaemia to search by PCR method for cases of recrudescence parasitaemia or reinfestation. Side effects have been reported and classified according to their severity (mild, moderate or severe). A side effect is defined as a symptom, a sign or unexpected and unfavorable condition for the patient's health. Therapeutic efficacy, clinical and biological tolerance were evaluated in this study.

Statistical Analyses

- **Evaluation of the effectiveness**

The cure rate at day 14, primary efficacy parameter, is defined as the proportion of patients for whom a clearance of parasitaemia is obtained in the first 7 days of the treatment without recrudescence within 14 days after the start of the study, the recrudescence is a new clinical manifestation of infection after initial clearance of parasites in the peripheral blood.

The cure rate at day 28 is defined as the proportion of patients for whom a clearance of parasitaemia is obtained within 7 days without recrudescence within 28 days of the start of the study.

The parasite clearance time (PCT) is the duration time between the first antimalarial administration and the first total and continuous loss of asexual parasite and persisting for at least 24 additional hours.

The Thermal clearance time (TCT) is the duration time from the first dose of drug and the time when the temperature drops below 37 ° .5C for at least additional 24 hours.

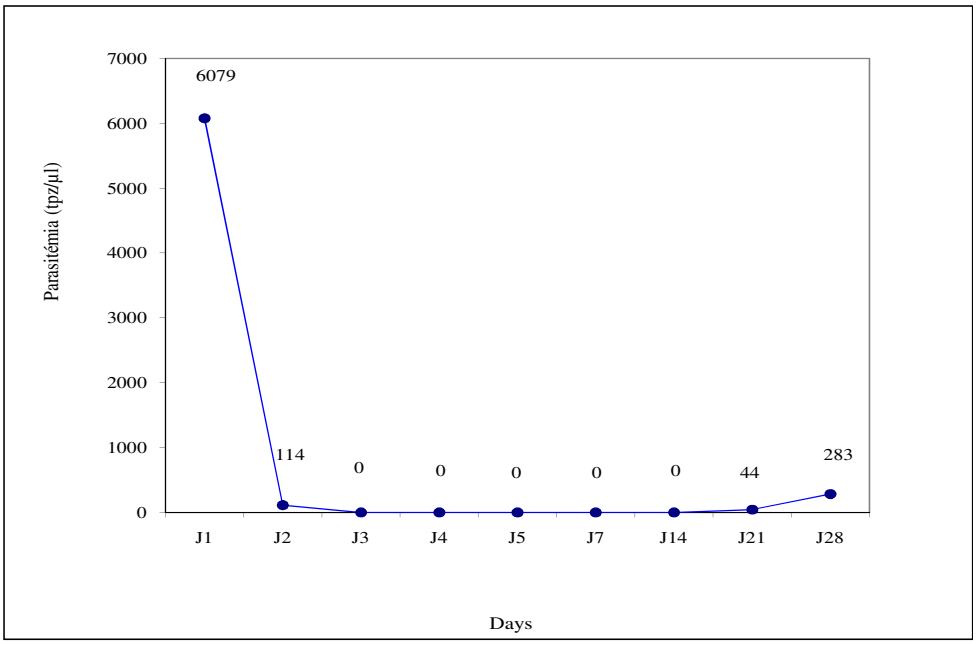

Figure 1. Evolution of the average parasitemia

- **Safety assessment**

It consisted of monitoring and recording all side effects (serious or not), regular laboratory monitoring and the assessment of the clinical status of the subject (vital signs, physical examinations).

- **Data management**

Data from each patient were collected and recorded in an observation notebook. Each patient was identified by a code consisting of the first two letters of the surname and the first letter of the first name followed by a registration number. Processing and data analysis were made using Epi dat software and Microsoft Office XP (Excel). We used the chi-2 test of independence for a risk α = 5%.

RESULTS

Epidemiological data

We received during our study 400 patients of which 220 showed a positive thick smear, a parasite rate of 55%. *P. falciparum* was the only species found, that is a value of 100% infestation.

Of these patients, 53 met the differents inclusion criteria. However, during follow-up, 3 of them have been withdrawn, 2 for protocol violation (one in the evening day 1and the other on day 2) and the third for voluntary withdrawal of consent to participate in $D_{3.}$ There have not been lost in sight of any patients in the course of follow up.

So we followed until day $_{28,}$ 50 patients aged between 15 and 64 years, with a mean age of 24.8 years (SD = 8.01). The average weight was 62.9 kg (SD = 10.31). This population consisted of 32 males and 18 females, a sex ratio of 1.8.

At inclusion, the mean parasitaemia was 6079 tpz / /µl (sd= 6411). with an average temperature = 38.7 ° C (SD = 1.18) among the patients, 41 (82%) had an axillary temperature of ≥ 37.5 ° C.

Parasitic and thermal clearances

The average Parasite Clearance Time (PCT) was 32.64 hours.

After 24th hours of treatment we noted a drop in parasite density of 98% (Figure 1). An appearance of parasitaemia was observed at day $_{21}$ in 2 patients and at day 28 in 1 patient, the PCR enable us to confirm a reinfestation.

The apyrexia was obtained from the 24th hour of treatment and was maintained through day 28 (Figure2). The average thermal clearance time (TCT) was 54.32 hours.

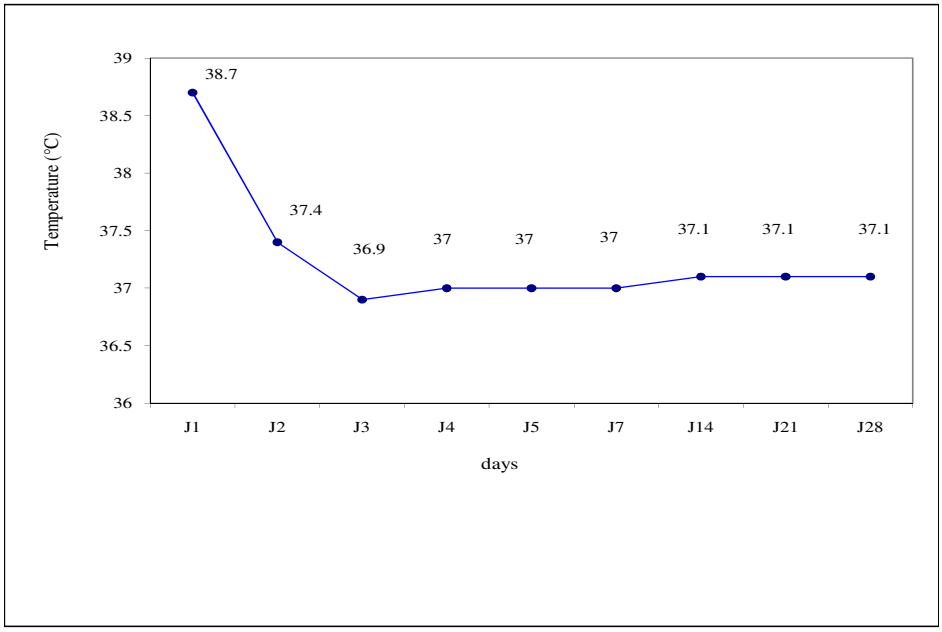

Figure 2. Evolution of the average temperature.

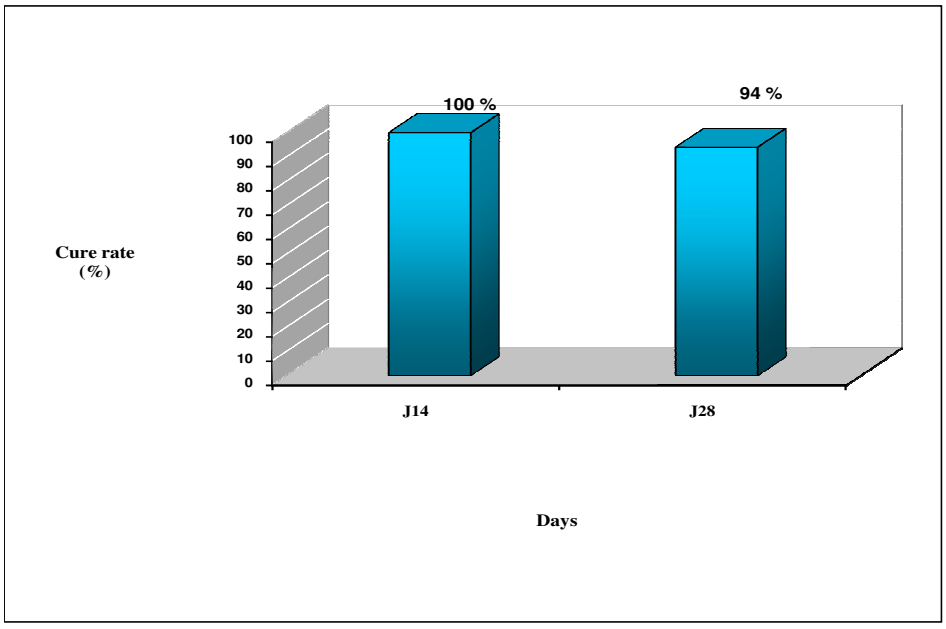

Figure 3. Cure rate of patients at day 14 and day 28 before PCR correction.

Cure rate at day 14 and day 28

The cure rate at day 14 and day 28 were 100% and 94% respectively (Figure 3). After PCR correction, the rates were 100% and the three cases of relapses at d21 were reinfections (Figure 4).

Biological and clinical tolerance

No significant disturbance in hematological parameters after the administration of 200 mg artesunate in microsphere was observed ($p > 0.05$).

We noted a significant decrease in total bilirubin,

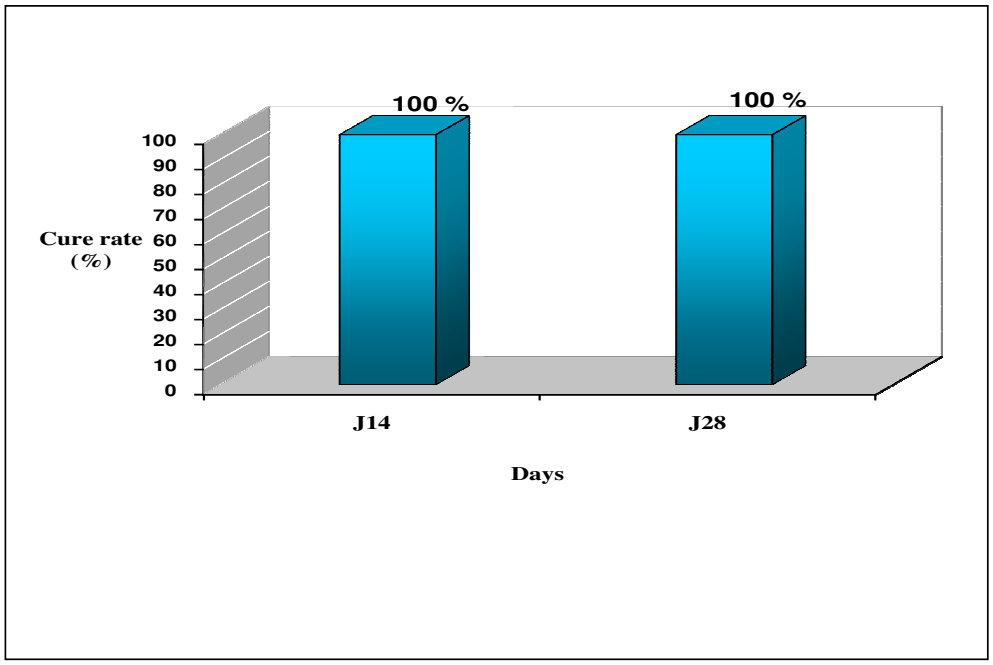

Figure 4. Cure rate of patients at day 14 and day 28 after PCR correction.

abnormally high at the beginning of the study to normal values (p = 0.0 00 1). Also, we noted a significant increase in rates of AST (p = 0.005) and ALT (p = 0.0001) on day 7 wich thereafter decreases to normal value by day 28.

66% of patients showed no adverse effects. In those who experienced side effects, these effects were dominated by nausea (12%), asthenia (12%) and vomiting (10%).

In 90% of cases, the overall tolerability was rated as good and very good in 6% of patients.

Mean values of systolic blood pressure and pulse rate went through a significant decrease from 112.9 mmHg (SD = 15.3) and 88.9 (SD = 18.0) respectively in day 1 to 107.0 mmHg (SD = 10.2) (P = 0.0001) and 79.2 (SD = 12.1) (P = 0.0001) respectively in day 28.

DISCUSSION

The results obtained in our study showed excellent efficiency of artesunate 200 mg transported in microspheres in the treatment of uncomplicated *Plasmodium faliciparum* malaria in adults in Abidjan.

Previous studies on artesunate in tablet form as monotherapy reported cure rates significantly lower (94% at day 14 and 72% at day 28) (Borrmann et al., 2003) This new formulation of the artesunate seems to be more effective. Indeed, microspheres form constitutes the stabilization and protection of the active ingredients (Benita et al., 1996). This formulation provides a increased blood concentrations of the active ingredient s whose distribution is not based on its owners' é s physicochemical miq wheels, but those of the vector (Benita et al., 1996).

The microspheres were also used by Momoh et al (Momoh et al., 2013) as an alternative for a secure utilization of diclofenac, thus avoiding its ulcerogenic effects.

The therapeutic efficacy of artesunate transported in microspheres is superior to that observed in some ACTs, including combination artesunate + amodiaquine (AS + AQ) and artemether + lumfantrine (AL) who presented respective cure rates of 98.7% and 96.9% in a multicenter study in children using syrup form (AS + AQ) and tablet forms dissolve in water before administration (AL) in 3 countries (Senegal, Côte d'Ivoire and Cameroon) (Faye et al., 2012). The single formulation in the form of microspheres provide similar result to that of ACTs.These ACTs have indeed proved effective in various studies (Adjei et al., 2008; Ibrahium et al., 2007; Van den Broek et al., 2006).

This new formulation was also administered under supervision. This must have contributed to the very good efficacy observed. This observation was also made by Faye et al. (2012) in their study comparing associations AS + AQ and AL. Many studies have also demonstrated

a lower efficiency when taken under no supervision (Faucher et al., 2009, Oyakhirome et al., 2007) .This lack of supervision impede good adherence to treatment which would cause lower efficiency and would eventually be responsible for the selection of resistant (Faucher et al., 2009).

TCT obtained with these microspheres artesunate was 54.32 hours. Faye et al. (2012) have shown that with the associations AS + AQ and AL, fever disappeared on the third day (72 hours) clearance time assessed to be fast enough, as confirmed by previous data (Van den Broek et al., 2006).

The parasite clearance time (PCT) 32.64 hours obtained with artesunate microspheres is comparable to that obtained by Borrmann et al. (2003) with artesunate monotherapy (34 hours). Faster parasite clearance is very advantageous because the processing prevent the transformation of merozoites into gametocytes and thus the transmission of the latter by the female Anopheles mosquito to healthy subjects (Price et al., 1999; Price et al., 1996).

The overall tolerability of artesunate microspheres was good or very good in 96% of cases. The decrease in total bilirubin may reflect the stopping of the destruction of red blood cells by malaria parasites after initiation of treatment. Krudsood S. et al. (2010) also noted in their study a High total bilirubin on day 0, which is normalized at D7 and stabilized until day 28.

Increased rates of AST and ALT on day 7 might suggest the site of metabolism of artesunate microspheres. This rate is normalized by day 28. This increase in hepatic factor was also observed by Faye et al. (2012) in day 7 in both associations AS + AQ and AL, as well as Krudsood S. et al. (2010) Artesunate + Mefloquine association (AS + MQ) and artesunate / mefloquine (AS / MQ). The values were normalized on day 28. Indeed, in 2001, studies by Haynes RK et al. showed that the artemisinin derivatives were metabolized by cytochrome P450 and other liver enzymes.

Overall, the use of artesunate 200 mg transported in microspheres for 5 days did not result in significant disruption of biological parameters. Clinically, no significant changes were noted in vital signs (pulse, blood pressure).

Side effects were dominated by nausea, asthenia and vomiting, effects that have not yet motivated stopping treatment. Note also that no deaths occurred during this study. Faye et al (2012) and Sowunmi et al. (2009) have also reported cases of anemia for the association AS + AQ.

CONCLUSION

This study showed that artesunate 200 mg transported in microspheres is an effective and well-tolerated antimalarial. However, relapses can be observed in areas of intense malaria transmission due to the relatively short artemisinin derivatives (Batty et al., 1998; Ilett et al., 2002) half-life. In this context, this medication may be a good choice for artemisinin base derivatives combination therapy (ACTs).

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