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Review Article (Pages: 7451-7465)

Clinical Pharmacology of the Antimalarial Quinine in Children

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Abstract

Quinine is the best studied drug for treating severe malaria in very young children. Quinine may be administered in pregnancy and, at therapeutic doses, malformations have not been reported. Some strains of quinine from Southeast Asia and South America have become resistant. Quinine is the treatment of choice for the drug-resistant severe Plasmodium falciparum. The antimalarial mechanism of quinine is the binding to heme preventing its detoxification. The dose of quinine is 10 mg/kg every 12 hours, and it may be administered orally, intramuscularly or intravenously. When it is administrated intravenously it must be infused slowly over 2 to 4 hours.

The treatment of severe/complicated childhood malaria appears to be evolving, and in 2005, the Indian Academy of Pediatrics Guideline recommended quinine, suggesting that artesunate/artemether was the less preferred alternative. In 2008, the Infectious Diseases Chapter, Indian Academy of Pediatrics recommended quinine with tetracycline/doxycycline/clindamycin in line with the World Health Organization (WHO) 2006 statement. In 2010, the WHO recommended aresunate for treating malaria infection, positioning quinine as an alternative. Malaria is caused by three parasites namely: Plasmodium falciparum, Plasmodium vivax, and Plasmodium ovale.

Plasmodium falciparum is the most common and virulent parasite. These parasites are present in different areas of the sub-Saharan African countries and Asia. In 2010, there were estimated 219 million cases of malaria resulting in 666,000 deaths and two-thirds were children. Children are more vulnerable than adults to malaria parasites. The aim of this study is to review the published data on the clinical pharmacology of quinine in children.

Key Words: Antimalarials, Children, Infants, Malaria, Quinine.

*Please cite this article as: Pacifici G.M. Clinical Pharmacology of the Antimalarial Quinine in Children. Int J Pediatr 2018; 6(4): 7451-65. DOI: **10.22038/ijp.2018.30206.2658**

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Received date: Jan.22, 2018; Accepted date: Feb.22, 2018

1-INTRODUCTION

Quinine remains the best studied drug for treating severe malaria in the very young child (1). The cinchona bark contains the alkaloid quinine, which kills malaria schizont when it enters the blood stream. Glucose-6-phosphate dehydrogenase deficiency is not a contraindication; haemolysis may occur in exposed fetuses with Glucose-6-phosphate dehydrogenase deficiency. Quinine crosses the placenta and the fetus to mother ratio is about 0.32. Congenital malformations have not been reported at therapeutic doses of quinine. The oxytocic effects of quinine have not been seen with the smaller doses used to treat malaria. Only small amounts of quinine are excreted into breast milk and with the exception of infants with glucose-6-phosphate dehydrogenase deficiency, no adverse effects have been seen. Malaria can be rapidly fatal, especially in children less than one year old (1). Quinine acts against asexual erythrocytic forms and has no significant effects on hepatic forms of malarial parasites. This drug is more toxic and less effective than chloroquine against malarial parasites susceptible to both drugs.

However, quinine, along with its stereoisomer quinidine, is especially valuable for the parenteral treatment of severe illness owing to drug-resistant strains of Plasmodium falciparum. However, some strains from Southeast Asia and South America have become resistant to quinine. Because of its toxicity and short half-life, quinine is generally not used for chemoprophylaxis. Quinine is the treatment of choice for drug-resistant severe Plasmodium malaria. In severe illness, the prompt use of an intravenous loading dose is imperative and can be lifesaving. Oral medication to maintain therapeutic concentrations is then given as soon as tolerated and is continued for 5 to 7 days. Especially for treatment of infections with multidrug-resistant strains of Plasmodium falciparum, slower-acting blood schizonticides such as tetracycline or clindamycin are given concurrently to enhance quinine efficacy (2). The antimalarial mechanism of quinine is thought to share similarities to chloroquine in being able to bind heme and prevent its detoxification. The basis of Plasmodium falciparum resistance to quinine, nonetheless, is complex. Patterns of Plasmodium falciparum to quinine, correlate in some strains with resistance to chloroquine yet in others correlate more closely with resistance to mefloquine and halofantrine. Gene amplification of pfmdr1 in Plasmodium falciparum, implicated in resistance to mefloquine and halofantrine, can contribute to reduce quinine susceptibility in-vitro. Similarly, pfmdr1 point mutations can also contribute to quinine resistance, in particular the N1042D mutation (3, 4). Despite their close chemical similarity, quinine and quinidine sensitivity can also diverge in some strains harboring novel PfCRT haplotypes (5).

Recent evidence suggests that other transporter genes participate in conferring resistance to quinine, potentially including the sodium-hydrogen exchanger gene Pfnhe-1 (6, 7). Quinine must be used with considerably caution, if at all, in patients who manifest hypersensitivity (balanced against risks primarily of not urgently treating severe malaria in the absence of other effective antimalarial drugs). Quinine should be discontinued immediately if evidence of haemolysis appears. This drug appears to be safe in pregnancy and is used commonly for the treatment of pregnancy-associated malaria. Quinine has been said to induce hypoglycemia during therapy. This has been attributed to an increase in insulin production and glucose must be administrated. Glucose levels must be monitored because of the increased risk of hypoglycemia (2).

Quinine may be administered orally, intramuscularly or intravenously. This drug is rapidly absorbed after intramuscular administration. The serum level of quinine is significantly higher at 2 hours than at 4 hours after intramuscular administration. Intramuscular administration is safe and is a reliable method to administer quinine to children with severe malaria. When quinine is administered intravenously it must be dissolved in 200 ml of saline and slowly infused over 2 to 4 hours, with this the toxicity is minimal (8). Quinine is quite effective against drug resistant Plasmodium falciparum malaria and in cerebral malaria and it should be given as an intravenous drip. The dose of quinine is 10 mg/kg repeated 12 hourly; 6 to 8 doses are usually sufficient. The total dose should not exceed 20 mg/kg in 24 hours. A rapid infusion can give rise to convulsion, delirium, confusion, coma, and hypotension. The advent of any of these side-effects necessitates the discontinuity of the drip. In the presence of renal failure or hepatic damage, the half-life of quinine is prolonged and the dose should be reduced to half (9).

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE via (PubMed), CINAHL, EMBASE, Google scholar as search engines; December 2017 was the cutoff point. Key references from extracted papers were also hand-searched.

2-2. Search Terms

The following key words "quinine neonates", "quinine effects neonates", "quinine pharmacokinetics neonates", and "quinine resistance neonates" were used. In addition the book Neonatal Formulary (1) was consulted.

3-RESULTS

Malaria is an infection caused by three parasites namely: Plasmodium falciparum, Plasmodium vivax, and Plasmodium ovale. Plasmodium falciparum is the most common and virulent parasite. These parasites are present in different sub-Saharan African countries and Asia. In 2010, there were an estimated 219 million cases of malaria resulting in 660,000 deaths and, approximately two-thirds were children. Children are more vulnerable than adults to malaria parasites. In sub-Saharan African countries, maternal malaria is associated with up to 200,000 estimated infant deaths yearly (1).

3-1. Recommendations of antimalarial-drugs for treating children with malaria in India and USA

The treatment of severe/complicated childhood malaria appears to be evolving, and in 2005, the Indian Academy of Pediatrics Guideline followed the National Malaria Infection Programme and recommended quinine, suggesting that artesunate/artemether is a less preferred alternative (10). In 2008, the Infectious Diseases Chapter, Indian Academy of Pediatrics modified the guideline for the treatment of malarial infection in children and recommended quinine with tetracycline/doxycycline/clindamycin (11) in line with the World Health Organization (WHO) 2006 statement. In 2009, the guideline for diagnosis and treatment of malaria infection, the Government of India, recommended artesunate, quinine, artemether, in that order, contraindicating arteether for plasmodium vivax and Plasmodium falciparum in 117 districts with documented chloroquine resistance (12). The WHO's 2010 guideline (13) strongly recommended artesunate in adults with severe malaria, positioning quinine as an alternative; however, it cites lack of evidence to frame a similar recommendation for children. Despite

appropriate therapy with parenteral quinine, the case fatality rate in severe malaria exceeds 20-30%. In addition, quinine administration requires hospital facilities for controlled infusion under close monitoring, owing to the risk of potentially serious side-effects. Therefore, alternate therapies are sought, to improve clinical outcomes and also simplify administration (14).

3-2. Antimalarial effects of quinine in children with malaria and comparison with other antimalarial-drugs

Studies were carried out in some areas of Nagaland, West Bengal and Mizoram where chloroquine resistant strains of Plasmodium falciparum were present during 1983 and 1984 (15). Sulfalene (1,000 mg) plus pyrimethamine (50 mg) is suitable for the treatment of Plasmodium falciparum cases not responding to chloroquine therapy in North West India. Treatment with sulfalene (1,500 mg) plus pyrimethamine (75 mg) pyrimethamine has no advantage over sulfalene 1,000 mg plus 50 mg pyrimethamine. Combination of quinine (1,000 mg per 3 days) plus sulfalene 1,000 mg and pyrimethamine 50 mg pyrimethamine is better than 1,000 mg sulfalene plus 50 mg pyrimethamine and 100% of patients were cured. Quinine is an effective drug to treat chloroquine resistant Plasmodium falciparum.

Alao et al. (16) investigated the disease burden, clinical features, treatment and outcomes of Plasmodium falciparum malaria infection in neonates and infants weighing less than 5 kg body weight in eight hospitals located in the following sub-Saharan African countries: Bénin, Burkina Faso, DRC (The Democratic Republic of the Congo, also known as DRC), Nigeria, and Togo. The annual number of Plasmodium falciparum malaria cases ranged from 12 to 120 cases across hospital and calendar years. The proportion of cases varied extensively by age-group among the countries studied. The most frequent reason for seeking care was fever, which was present in all children with malaria. Other common reasons included dyspnea, vomiting, cough, refusal to breast-feed, and diarrhea (**Table.1**) parasite loads were generally low (<5,000 parasites/μl). In all countries other than Togo, quinine was the most commonly antimalarial drug administered. In Togo, intramuscular artemether (AM) was the most the commonly used drug (55.0%), followed by oral quinine (43.9%). The second most common treatment type overall was an artemisinin-based combination in 22.3% of all cases. The clinical outcome was favorable in the vast majority of cases in all countries (range, 85.9% to 100%). Quinine was the most common treatment, followed by artemisinin-based combination therapy. The majority of patients recovered from their illness following treatment were cured. Plasmodium falciparum malaria exists in these populations. Further epidemiological data are needed to estimate malaria morbidity and mortality in young infants.

Moreover, clinical evidence on the efficacy and safety of artemisinin-based combination therapy in this population is warranted. Table 1 shows the patient demographic data and the case for confirmed Plasmodium falciparum malaria between 2006 and 2011 in eight hospitals located in the following sub-Saharan African countries: Bénin, Burkina Faso, DRC, Nigeria and Togo. The WHO recommended the use of an artemisinin-based combination therapy as first-line treatment for uncomplicated Plasmodium falciparum malaria in infants weighing less than 8 kg body weight, with the exception of artemisinin-based combination therapy for ≥ 5 kg body weight. No artemisinin-based combination therapy is currently registered for use in infants weighing < 5 kg, with the exception of artesunate-

amodiaquine, which is registered for use in those weighing ≥ 4.5 kg (17). A total of 138 children were included in the study, 69 in artemether and 69 in the quinine groups (18). The age distribution between the groups of artemether and quinine are shown in **Table.**2. In the quinine group there were 46 (66.66%) and in the artemether group 44 (63.76%) boys whereas 23 (33.33%) and 25 (36.23%) were girls in the quinine and artemether groups, respectively. The patients in this study came with the chief complaints of fever, coma, convulsions, pallor, jaundice, and oliguria. The most common presenting complain was fever, which was present in all patients, and the second most common presenting complaint was coma which was present in 50 (72.46%) and 48 (69.56%) in the quinine and artemether groups, respectively (**Table.3**).

Only 10 (14.49%) patients in the quinine group presented with convulsions while convulsions were observed in 12 (17.39%) patients in the artemether group. Patients with severe anemia (hemoglobin < 6 grams/dl) were transfused. After the commencement of treatment the fever clearance time was noted. On the third day of treatment 62 (89.8%) patients under the quinine treatment experienced decline of temperature to norm and 61 (88.40%) resolved fever in the artemether group. By the 5th day, 69 (100%), and 66 (95.62%) ($p < 0.05$) patients had no fever in the quinine and artemether groups, respectively (**Table.4**).

Table.5 shows the fever clearance time in the quinine and artemether treated groups (17), and **Table.6** shows the comparison of coma resolution in the quinine and artemether groups (17). Unlike the fever clearance, artemether had very rapid parasitaemia clearance time in comparison to quinine. Parasitaemia clearance time was seen in 68 (98.55%) in artemether group but was only 64 (92.75%) with quinine therapy. Coma was one of the prominent presenting complaints which resolved more rapidly with quinine than artemether therapy. Forty three (86%) out of 50 patients recovered from coma in less than 24 hours after the initiation of quinine therapy but only 39 out of 48 (81.25%) comatose patients recovered with the artemether during the same time period. Between 25 and 72 hours after initiation of therapy 49 (98.0%) and 41 (85.41%) were out from coma with quinine and artemether, respectively, ($p = 0.029$). After 72 hours of treatment quinine therapy gave rise to 49 (98.0%) patients while artemether therapy yielded only 42 (87.5%) patients, $p = 0.0568$ (**Table.5**). There is no statistically difference between intravenous quinine and intramuscular artemether therapy in the treatment of severe pediatric malaria infection except for the more rapid coma resolution with quinine therapy after 24 hours of treatment. An eighteen day old neonate presented with features of early neonatal sepsis. The mother had a travelled from non-endemic malaria area, and on the 7th gestational month age the mother was detected as having malaria. She was treated with quinine and cured (19).

The neonate was also evaluated for congenital malaria in the first few neonatal days and discharged. The neonate on evaluation showed anemia, hepatosplenomegaly and was diagnosed with Plasmodium vivax infection on peripheral smear. The quinine failed to prevent transplacental transmission. Prolonged interval between birth and onset of symptoms may be explained by transmission late in pregnancy or during delivery or by presence of transplacentally acquired maternal antibody (Immunoglobulin G). The mother acquired malarial infection after travel to an endemic malarial area and transmitted the parasite to the neonate. The efficacy of intravenous quinine, which is the mainstay for treating severe malaria in children, is

decreasing in South East Asia and Africa. Artemisinin derivates are potential alternatives to quinine. However, their efficacy compared to quinine in treating severe malaria in children is not clearly understood. Praygod et al. (20) assessed the efficacy of parental artemisinin derivatives versus parenteral quinine in children with severe malaria. Twelve trials were included (1,524 subjects). There was no difference in the mortality rate between artemisinin derivatives and quinine groups. The artemisinin derivatives resolved coma faster than quinine, but when trials with adequate concealment only were considered this difference disappeared.

There was no statistically difference between artemisinin derivatives and quinine in parasite clearance time, fever clearance time, incidence of neurological sequelae and 28th day cure rate. One trial reported significantly more local reactions at the injection site with intramuscular quinine compared to artemether. None of the trials was adequately powered to demonstrate equivalence. There was no evidence that treatment of children with severe malaria with parenteral artemisinin derivatives was associated with a lower mortality rate or long-term morbidity compared to parenteral quinine. Future studies require an adequately powered equivalence trial design to decide whether both drugs are equally effective.

One hundred and two children aged between 0 to 10 years with cerebral malaria (Blantyre coma score of 2 or less) were randomly treated either with intramuscular artemether (3.2 mg/kg on day 0, followed by 1.6 mg/kg on days 1 to 4) or intravenous quinine dihydrochloride (20 mg of the salt/kg every 8 hours up to day 6) (21). Treatment with oral quinine sulfate (10 mg/kg every 8 hours) was substituted for intravenous quinine when the patient was able to take oral medicine. All patients were followed-up in the hospital for 7 days; thereafter, they were treated as outpatients on days 14, 21, and 28. Mortality rate, the main efficacy parameter, was lower in the artemether treatment group than in the quinine group (15.7% versus 27.4%, respectively); however the difference was not significant ($p = 0.25$). Means for fever clearance time, coma resolution time, and parasite clearance time were similar in the 2 treatment groups (42.2 ± 34.9 hours; 34.8 ± 18.8 hours, and 46.3 ± 28.5 hours, respectively, for artemether, versus 45.0 ± 26.7 hours; 30.3 ± 18.9 hours, and 40.7 ± 18.9 hours, respectively, for quinine). At 28 days, the cure rates were 73.2% and 64.9% ($p < 0.05$) for the artemether and quinine treatment groups, respectively. Artemether is safe and therapeutically as effective as quinine for the treatment of cerebral malaria in children in Cameroon. Because of its ease of administration, artemether appears to be suited for use in the rural zones where monitoring facilities do not exist.

Each year more than 10 million African children suffer from severe Plasmodium falciparum malaria, and more than 1 million die, the children are more vulnerable than adults to malarial parasites. The vast majority of these children received parenteral quinine therapy. However, the usually recommended 7-day regimen causes compliance problems if the children leave the hospital before treatment is finished (22). Short-term quinine regimens were not sufficient to cure Gabonese school-children of even uncomplicated Plasmodium falciparum malaria (23).

In South East of Asia tetracyclines are commonly combined with quinine for treating Plasmodium falciparum malaria (22). However, because of the side-effects of these antibiotics, this combination cannot be used for children and pregnant women, the two groups most vulnerable to severe malaria. Clindamycin is a lincosamide antibiotic with antiplasmodial

properties which can be given to children (24). The use of clindamycin in combination with quinine for treating human volunteers with chloroquine-resistant malaria was first described two decades ago (25). In comparative trials, clindamycin combined with quinine improved the cure rate of South America (26-28). Children with severe Plasmodium falciparum malaria were enrolled in the hospital, and had to fulfill at least one of the following criteria: Hyperparasitemia (≥ 250,000 parasites/µl), severe anemia (hemoglobin score of < 50 g/l or hematocrit score of < 15%), hypoglycemia (glucose, < 2.2 nmol/l), or cerebral malaria (unarousable coma not attributed to other cause). In a randomized trial, a 4-day quinine-clindamycin regimen was compared with the standard 7-day quinine regimen for 100 Gabonese children (50 in each group) with severe Plasmodium falciparum malaria (29).

Only four patients in the quinine group and two in the quinine-clindamycin group showed parasite recrudescence by day 28 of the following-up. One patient died in the quinine and quinine-clindamycin groups. However, parasite clearance and fever clearance times were significantly shorter for the quinine-clindamycin group than for the quinine group (p-value were 0.03 and 0.01, respectively). Moreover, significantly more patients in the quinine group than in the quinine-clindamycin group showed a recurrent lower fever clearance and parasite clearance times ($p < 0.001$). This study indicates that the addition of clindamycin to standard quinine treatment substantially improves and shortens the chemotherapy of African children with severe malaria.

Table.7 summarizes the children demographic data and the treatment efficacy of quinine and quinine-clindamycin combination in 50 children for each group. Significantly more recurring fever episodes occurred in the quinine group than in the quinine-clindamycin group shortly after initial fever clearance ($p < 0.001$). Newborn infants whose erythrocytes contain decreased concentrations of glucose-6-phosphate dehydrogenase may be especially prone to hyperbilirubinemia upon exposure to a variety of chemical agents and to hypoxia and acidosis (30). Quinine has been reported as a hemolytic agent in glucose-6-phosphate dehydrogenase deficient white male adults (31). Its hemolytic effect depends upon both individual sensitivity and total exposure. To our knowledge, this drug has never been shown to be responsible for a hemolytic crisis in a newborn.

Glass et al. (32) have observed a glucose-6-phosphate dehydrogenase deficient full-term black male infant born to a heroin-addicted mother who consumed 10 to 20 "bags" (each containing about 30 to 50 mg of quinine in addition to the heroin) per day by intravenous route. The infant developed significant jaundice in the absence of a blood group incompatibility. At birth, the infant weighed 2,650 grams, and physical examination was unremarkable. There was no clinical evidence of jaundice and the capillary hematocrit was 64 per cent. Both the mother's and infant's blood types were O, Rh positive, and the infant's direct Coombs test was negative.

At age 40 hours, jaundice was first noted. The total serum bilirubin was 12.0 mg per 100 ml, with 11.4 mg per 100 ml of unconjugated bilirubin. A screening test for erythrocyte glucose-6-phosphate dehydrogenase was performed. After three hours of incubation, no discoloration of dye was noted, indicating a marked deficiency of erythrocyte glucose-6-phosphate dehydrogenase. Morphine and quinine were present in neonatal urine during the first 24 hours of life. On the third day of life, the total serum bilirubin concentration rose to 16.0 mg per 100 ml

(unconjugated bilirubin was 15.7 mg per 100 ml), and phototherapy was begun; there was a subsequent decline in the bilirubin concentration. Although the etiology role of quinine in the production of jaundice in this glucose-6-phosphate dehydrogenase deficient infant has not been conclusively proved a causal relationship appears extremely likely. In literature, there are no data on the pharmacokinetics of quinine and Plasmodium parasites resistance to quinine in neonates, infants, and children. There is the need to carry out an international survey to establish the most effective antimalarial-drugs to administer to children living in areas where malaria is endemic.

Table-1: Patient demographic data for confirmed cases of Plasmodium falciparum malaria between 2006 and 2011 at eight hospital located in Bénin, Burkina Faso, DRC, Nigeria, and Togo, by Alao et al. (16).

Variables	Bènin 2010-2011	Burkina Faso 2009-2011	DRC 2006-2010	Nigeria 2009-2010	Togo 2009-2010
Number of cases	60	241	292	143	171
Age	Number of patients (%)				
≤ 1 month	5 (8.3)	135 (56.0)	38 (13.0)	9.1 (63.6)	129 (75.4)
> 1 month	55 (91.7)	106 (44.0)	254 (87.0)	52 (36.4)	42 (24.6)
Reasons for seeking care	Number of events (% of patients)				
Fever (> 37.5 ^{0}C)	46 (76.7)	157 (65.1)	----------	143 (100)	108 (63.2)
Dyspnea		40 (16.6)	----------	----------	35 (20.5)
Vomiting	6 (10.0)	20 (8.3)	----------	----------	13 (7.6)
Cough	1 (1.7)	37 (15.4)	----------	----------	----------
Refusal to breast-feed	----------	14 (5.8)	----------	----------	----------
Diarrhea	1 (1.7)	13 (5.4)	----------	----------	23 (13.5)
Crying	3 (5.0)	5 (2.1)	----------	----------	20 (11.7)
Icterus	----------		----------	----------	13 (7.6)
Conjunctival paleness	----------	13.4 (5.4)	----------	----------	----------
Prematurity	----------	13 (5.4)	----------	----------	----------
Other	3 (5.0)	48 (19.9)	----------	----------	74 (43.3)

DRC: Congo country.

Table-2: Age group frequency distribution table among artemether and quinine treated groups, by Rehman et al. (18).

Age group (year)	Artemether	Quinine
	Number (%)	Number (%)
0 - 2	13 (18.84)	10 (14.5)
3 - 5	19 (27.54)	20 (29.0)
6 - 8	20 (28.99)	11 (15.9)
9 - 11	12 (17.39)	14 (20.3)
12 - 14	3 (4.35)	11 (15.9)
15 -17	2 (2.90)	3 (4.3)
Total	69	69

Table-3: Clinical features among the study groups, by Rehman et al. (18).

Clinical features	Quinine Number (%)	Artemether Number (%)
Fever	69 (100%)	69 (100%)
Coma	50 (72.46)	48 (69.56)
Convulsions	10 (14.49)	12 (17.39)
Severe anemia	5 (7.25)	6 (8.7)
Jaundice	1 (1.45)	2 (2.9)
Oliguria	1 (1.45)	1 (1.45)

Table-4: Comparison of fever clearance in quinine and artemether treated groups, by Rehman et al. (18).

Fever clearance	Quinine (n=69) (%)	Artemether (n=69) (%)	P-value	Risk ratio	95% CI
Day 3	62 (89.85)	61 (88.40)	0.791	1.0164	0.9046-1.1421
Day 5	69 (100)	66 (95.65)	0.244	1.0455	0.9942-1.0994

CI: confidence interval.

Table-5: Comparison of parasitaemia clearance between quinine and artemether treated groups, by Rehman et al. (18).

Parasitaemia clearance	Quinine (n=69) Number (%)	Artemether (n=69) Number (%)	P-value	Risk ratio	95% CI
Day 3	64 (92.75)	68 (98.55)	0.2084	0.9412	0.8759-1.0113
Day 5	67 (97.10)	69 (100)	0.2446	0.9571	0.9109-1.0058

CI: confidence interval.

Table-6: Comparison of coma resolution between the quinine and artemether treated groups, by Rehman et al. (18).

Coma resolution (hour)	Quinine (n=50) N (%)	Artemether (n=48) N (%)	P-value	Risk ratio	95% CI
< 24	43 (86)	39 (81.25)	0.5271	1.0585	0.8876-1.2622
25-72	49 (98)	41 (85.41)	0.0292	1.1473	1.0141-1.298
> 72	49 (98)	42 (87.50)	0.0568	1.1200	0.9993-1.2553

CI: confidence interval.

Table-7: Demographic data and treatment efficacy parameters of quinine and quinine-clindamycin combination in African children with severe malaria, by Kremsner et al. (29).

Patient parameters	Quinine (n = 50)	Quinine-clindamycin (n = 50)
Age (year)	3.0±2.2	3.1±1.9
Weight (kg)	13±5	13±5
Parasitaemia (parasites/µl)	265,000 (3,500-1,600,000)	250,000 (500-1,200,000)
Duration of symptoms before admission (days)	4.0±4.0	3.9±2.7
Parasite clearance time (hour)*	73±14	65±16
Fever clearance time (hour)*	59±29	43±26
Number of patients with recurrent fever episodes*	21	7
Number of patients cured by 28 days	43	43
Number of patients with parasites recrudescence	4	2
Died	1	1

*P-value = 0.03, 0.01, and <0.001 for differences between groups in parasite clearance, fever clearance, and the number of patients with recurrent fever episodes, respectively; for parasitaemia the data are median and ranges.

4- DISCUSSION

Quinine remains the best studied drug for treating severe malaria in the very young child. Quinine crosses the placenta and the fetus to mother ratio is about 0.32. At therapeutic doses, congenital malformations have not been reported (1). Quinine acts against asexual erythrocyte forms and has no significant effect on hepatic forms of malarial parasites. This drug is more toxic and less effective than chloroquine against malarial parasites susceptible to both drugs. Quinine is especially valuable for the parenteral treatment of severe illness owing to drug-resistant strains of Plasmodium falciparum. The antimalarial mechanism of quinine is thought to bind heme and prevent its detoxification. Gene amplification of pfmdr1 in Plasmodium falciparum, implicated reduced quinine susceptibility in-vitro (2). Quinine has historically been the treatment of choice for drug-resistant severe Plasmodium falciparum malaria. In severe illness, the prompt use of the loading doses of intravenous quinine is imperative and can be lifesaving. Oral quinine to maintain therapeutic concentrations is given as soon as tolerated and is continued for 5 to 7 days. Especially for treatment of infections with multidrug-resistant strains of Plasmodium falciparum, slower-acting blood schizonticides such as tetracyclines or clindamycin are given concurrently to enhance quinine efficacy. Quinine is associated with a triad of dose-related toxicity when given at full therapeutic or excessive doses; the side-effects are hypoglycemia, tinnitus, high-tone deafness, visual disturbances, headache, dysphoria, nausea, vomiting, and postural hypotension. Hypoglycemia is common, mostly in the treatment of severe malaria, and can be life threatening if not treated promptly with intravenous glucose. Glucose levels must be monitored because of the increased risk of hypoglycemia. Quinine should be discontinued immediately if evidence of hemolysis appears. Quinine is safe in pregnancy and is used commonly for the treatment of pregnancy-associated malaria (2).

Quinine is quite effective against drug-resistant Plasmodium falciparum malaria. The dose of quinine is 10 mg/kg repeated 12 hourly, 6 to 8 doses are usually sufficient. Quinine may be administered orally, intramuscularly or intravenously. This drug is rapidly absorbed after intramuscular injection and the serum concentrations are higher at 2 hours than at 4 hours after the administration. When this drug is administered intravenously, quinine should be dissolved in 200 ml of saline and slowly infused over 2 to 4 hours (8). Malaria is an infection sustained by 3 parasites namely: Plasmodium falciparum, Plasmodium vivax, and Plasmodium ovale. Plasmodium falciparum is the most common and virulent parasite.

In 2010, there were an estimated 219 million cases of malaria resulting in 660,000 deaths. Most cases (approximately two-thirds) occurred in children. Children are more vulnerable than adults to malaria parasites. Malarial parasites are present in sub-Saharan African countries and Asia. In sub-Saharan African countries, maternal malaria is associated with up to 200,000 estimated infant deaths yearly. Residents in endemic areas develop considerable immunity over time, but pregnancy makes women more vulnerable, and infection during pregnancy increases the risk of anemia, miscarriage, stillbirth and prematurity (1). Patterns of Plasmodium falciparum to quinine, correlate in some strains with resistance to chloroquine yet in others correlate more closely with resistance to mefloquine and halofantrine. Gene amplification of pfmdr1 in Plasmodium falciparum is implicated in resistance to mefloquine and halofantrine, and can contribute to reduced quinine susceptibility in-vitro. Similarly, pfmdr1 point mutations can also contribute to quinine resistance, in particular the N1042D mutation (3, 4). Recent evidence suggests that other transporter genes participate in conferring resistance to quinine, potentially including the sodium-hydrogen exchanger (Pfnhe-1) gene (6, 7). In India and in the USA there are different recommendations about the antimalarial-drugs to administer to children affected by severe malaria. In 2005, the Indian Academy of Pediatrics recommended quinine for treating children with malaria (10). In 2008, the Indian Academy of Pediatrics modified the guideline for the treatment of malarial infection and recommended quinine with tetracycline/doxycycline/clindamycin (11) in line with the WHO 2006 statement. In 2010, the WHO's guideline strongly recommended aresunate in adults with severe malaria infection, positioning quinine as an alternative (13).

Some hospitals located in the following sub-Saharan African countries: Bénin, Burkina Faso, DRC, and Nigeria, recommended quinine as the first-choice drug for treating infections caused by Plasmodium falciparum. In Togo, intramuscular artemether was most common (55.0%), followed by oral quinine (43.9%) (16). The clinical outcome was favorable in most cases in all countries (range, 85.9% to 100%). Quinine administration requires hospital facilities for controlled infusion under close monitoring, owing to the risk of potentially serious side-effects (14).

Chloroquine resistant strains of Plasmodium falciparum were present in Nagaland, West Bengal and Mizoram in 1983 and 1984. The addition of quinine (1,000 mg per 3 days) to sulfalene (1,000 mg) plus pyrimethamine (50 mg) was more effective than sulfalene (1,500 mg) plus pyrimethamine (75 mg) to cure patients affected by Plasmodium falciparum and 100% patients were cured (15). Alao et al. (16) investigated the disease burden, clinical features, treatment and outcomes of Plasmodium falciparum malaria in neonates and infants weighing less than 5 kg body weight in five sub-

Saharan African countries. The most frequent reasons for seeking cure was fever, which was present in all neonates and infants. Other common reasons were dyspnea, vomiting, cough, refusal to breast-feed, and diarrhea. The WHO recommended the use of an artemisinin-based combination therapy as first-line treatment for uncomplicated Plasmodium falciparum malaria in infants with a body weight less than 8 kg. No artemisinin-based combination therapy is currently registered for use in infants weighing < 5 kg body weight, with the exception of artesunate-amodiaquine, which is registered for use in the infants weighing ≥ 4.5 kg (17).

A total of 138 children were enrolled, 69 children received quinine and 69 children received artemether (18). The patients in this study were afflicted by fever, coma, convulsions, pallor, jaundice, and oliguria. The most common presenting complaint was fever, which was present in all children with malaria, and the second most common presenting complaint was coma which was present in 72.46% and 69.56% in the children receiving quinine and artemether, respectively. Convulsions were present in 14.49% and 17.39% in children receiving quinine and artemether, respectively.

The declaim of temperature to norm was present in 89.8% and 88.40% in children under quinine and artemether, respectively, on the third day of treatment. By the 5th day of treatment, no fever was observed in 100% and 95.62% in children treated with quinine and artemether, respectively. Patients in the artemether group had more rapid parasitaemia clearance time (98.55%) than the children treated with quinine (92.75%) ($p < 0.05$). Coma resolved more rapidly with quinine (86.0%) than with artemether (81.25%) 24 hours after treatment ($p = 0.029$). Praygod et al. (20) assessed the efficacy of parental artemisinin derivatives versus parenteral quinine in treating children with severe malaria. There was no statistical difference between the two groups in parasite clearance time, fever clearance time, incidence of neurological sequelae, and 28 day cure rate. One hundred and two children aged between 0 and 10 years with cerebral malaria (Blantyre coma score of 2 or less) were randomly treated with intramuscular artemether (3.2 mg/kg on day 0, followed by 1.6 mg/kg on days 1 to 4) or intravenous quinine dihydrochloride (20 mg/kg every 8 hours up to day 6). All patients were followed-up in the hospital for 7 days. Mortality rate was lower in the artemether than in the quinine group, however the difference was not statistically significant. Fever clearance time, coma resolution time, and parasite clearance time were similar in the 2 groups (21). Artemether is safe and therapeutically as effective as quinine. A short-term quinine regimen was not sufficient to cure Gabonese school-children of even uncomplicated Plasmodium falciparum malaria (23).

In South East of Asia tetracyclines are commonly combined with quinine for treating Plasmodium falciparum malaria (22). However, because of the side-effects of these antibiotics, this combination cannot be used in children and pregnant women, the two groups most vulnerable to severe malaria. Clindamycin is a lincosamide antibiotic with antiplasmodial properties which can be given to children (24). The use of clindamycin in combination with quinine for treating human volunteers with chloroquine-resistant malaria was first described two decades ago (25). Clindamycin combined with quinine improved the cure rate of malaria in South America (26-28). On the basis of this rationale, Kremsner et al. (29) compared the 7-day quinine regimen with 4-day quinine-clindamycin regimen for treating 100 Gabonese children with severe malaria; 50 children received the

standard 7-day quinine regimen and 50 children received a 4-day quinine-clindamycin regimen. The parasite clearance and the fever clearance times were significantly shorter in the quinine-clindamycin group than in the quinine standard regimen (p-value were 0.03 and 0.01, respectively). Significantly more patients in the quinine group than in the quinine-clindamycin group showed a recurrent fever clearance time and the parasite clearance time ($p < 0.001$). These findings are consistent with the view that the addition of clindamycin to quinine improves and shortens the chemotherapy of African children with severe malarial infection. In literature, there are no data on quinine pharmacokinetics and on the resistance of malarial parasites to quinine in neonates, infants, and children. There is the need to carry out an international survey to establish the most effective antimalarial-drugs to administer to children living in areas where malaria is endemic.

5- CONCLUSION

In conclusion, quinine remains the best studied drug for treating severe malaria in the very young child. Quinine crosses the placenta and the fetus to mother ratio is 0.32. Congenital malformations have not been reported at therapeutic doses of quinine. Malaria is an infection caused by three parasites namely: Plasmodium falciparum, Plasmodium vivax, and Plasmodium ovale. Plasmodium falciparum is the most common and virulent malaria parasite. These parasites are present in different sub-Saharan African countries and Asia. In 2010, there were an estimated 219 million cases of malaria resulting in 660,000 deaths and, approximately, two-thirds were children. Children are more vulnerable than adults to malaria infection. In sub-Saharan African countries, maternal malaria is associated with up to 200,000 estimated infant deaths yearly. Malaria contributes to maternal illness and anemia in pregnancy, and chemoprevention reduces the risk of antenatal parasitaemia. The Indian Academy of Pediatrics and the WHO recommended different antimalarial-drugs to administer to children affected by malaria. In 2005, the Indian Academy of Pediatrics recommended quinine as the first-choice drug for treating children with malaria. In 2008, it was modified, and the Indian Academy of Pediatrics recommended quinine with tetracycline/doxycycline/clindamycin for treating children with malaria, in line with the WHO 2006 statement; in 2010, the WHO recommended aresunate in adults with severe malaria, positioning quinine as an alternative; however, it cites lack of evidence to frame a similar recommendation in children. Some hospitals located in the following sub-Saharan African countries: Bénin, Burkina Faso, DRC and Nigeria recommended quinine as the first-choice drug to treat children with malaria.

In Togo, intramuscular artemether was more common (55.0%), followed by oral quinine (43.9%). The clinical outcome was favorable in the vast majority of cases in all countries (range, 85.9% to 100%). The most frequent reasons for seeking care were fever, which was present in all children with malaria, and the second common presenting complaint was coma. Other common reasons include dyspnea, vomiting, cough, refusal to breast-feed, and diarrhea. Unlike the fever clearance time, artemether has a more rapid parasitaemia clearance time (98.55%) in comparison to quinine (92.75%) ($p <0.05$). The efficacy of intravenous quinine, which is the mainstay for treating severe malaria in children, is decreasing in South East Asia and Africa. Artemisinin derivatives and quinine have similar efficacy in parasite clearance and fever clearance times in children with malaria. Intramuscular artemether and intravenous

quinine have similar fever clearance time, coma resolution time and parasite clearance time. The combination of quinine with clindamycin yielded parasite clearance and fever clearance times significantly shorter than quinine. In literature, there are no data on the pharmacokinetics of quinine and Plasmodium parasites resistance to quinine in neonates, infants, and children. There is the need to carry out an international survey to establish the most effective antimalarial-drugs to administer to children living in areas where malaria is endemic.

6- CONFLICT OF INTERESTS

The author declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

7- ACKNOWLEDGMENTS

The author thanks Dr. Patrizia Ciucci and Dr. Francesco Varricchio, of the Medical Library of the University of Pisa, for retrieving the scientific literature.

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