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Artemether-lumefantrine: Pediatric formulations for the treatment of uncomplicated *Plasmodium falciparum*

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Abstract

Over a thousand deaths per day are exhibited due to malaria in infants and children under five years of age across the world. Despite this, there are no satisfactory World Health Organization (WHO)-endorsed pediatric anti-malarial formulations available including all age groups.
Artemisinin-based combination therapy is the current standard of care for patients with uncomplicated falciparum malaria in many African countries. Artemether/lumefantrine meets WHO prequalification criteria for efficacy, safety and quality. Coartem®, a fixed dose combination of artemether and lumefantrine, has consistently achieved cure rates of >95% in clinical trials. However, AL tablets are inconvenient for caregivers to administer as they need to be crushed and mixed with water or food for infants and young children. Besides, like other antimalarials, they have a bitter taste, which may result in children spitting the medicine out and not receiving the full therapeutic dose. There is a clear unmet medical need for a formulation of Artemether/lumefantrine specifically designed for infants and children in all age groups.

Keywords: Pediatric anti-malarial formulations, Artemisinin, Artemether/Luefantrine, Coartem, Antimalarials.

Introduction

Malaria is a major vector borne parasitic disease in the world, especially in Africa. It is responsible for 500 million new cases and about a million deaths every year, mostly among children under five years and pregnant women.[1] Children, particularly under-fives, are at risk of developing severe malaria due to their relatively less developed immunity to malaria and the decline of passively acquired immunity.[2]

Access to prompt and effective treatment of malaria is the main challenge in Africa, although dose accuracy and adherence to the treatment schedule are equally important to certify an adequate therapeutic response.[3] Reduction in malaria-associated morbidity and mortality largely depends on delivery of prompt, effective, safe and affordable antimalarial drugs.[4]

The World Health Organization recommends use of artemisinin-based combination treatments as first-line therapy. The artemisinin combination treatments combine fast-acting artemisinins with another structurally unrelated and more slowly eliminated compound which permits elimination of residual malarial parasites.[5] Of the 81 countries with endemic *P. falciparum*, 77 have now adopted the WHO recommendation.[6] Commonly used artemisinin-based combination treatments are artemether–lumefantrine, amodiaquine–artesunate, mefloquine–artesunate,

dihydroartemisin– piperaquine and napthoquine–Artemisinin.[7]

Despite the fact that infants and children bear the greatest burden of malaria, no antimalarial agent specifically formulated for this vulnerable group with respect to their age. The available oral paediatric formulations of artemisinin-based combination treatments are not optimal for this high-risk population; young children cannot swallow whole tablets and sometimes spit out the drug, because of the bitter taste of the crushed tablets. In addition, artemether–lumefantrine tablets are not recommended for patient's weight less of 5 kg.[8]

Epidemology of Malaria

World Health Organization report showed that malaria is widely disseminated in tropical and subtropical regions, including parts of America, Asia and Africa. The report also indicated that about 109 WHO countries are endemic to malaria and 45 of the countries belong to Africa.[6]

Malaria is seasonal in most part of the endemic countries and the transmission rate is unstable. The instability of the transmission is one of the reasons for the outbreak of epidemics. The transmission pattern and intensity widely vary across the country due to variation in altitude, rainfall and population movement.[9] High population growth and deforestation of the highland and midland areas like in Ethiopia is the reason for population movement to lowland areas conducive for agriculture, but rampant with communicable diseases like malaria, trypanosomiasis and other vector born diseases.[10, 11]

Life cycle and Pathophysiology of malaria

Members of the genus Plasmodium are eukaryotic microbes. Therefore, the cell and molecular biology of Plasmodium is similar to other eukaryotes. A unique feature of the malaria parasite is its intracellular lifestyle. Because of its intracellular location the parasite has an intimate relationship with its host cell which can be described at the cellular and molecular levels. Specifically, the parasite must enter the host cell, and once inside, it modifies the host cell.[12]

The malaria parasite shows a complex life cycle involving an insect vector (mosquito) and a vertebrate host (human). Four Plasmodium species infect humans: *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. All four species exhibit a similar life cycle with only minor variations. A female anopheline mosquito needs a blood meal for egg production (figure 1). It comprises the exoerythrocitic and erythrocytic stages in the vertebrate host and the sporogonic cycle in the mosquito. The humans and other vertebrates act as the intermediate host for the parasite, while the mosquito, in which the sexual reproduction takes place, is considered to be the final one.[13]

The exoerythrocytic sporogonic cycle

The infection is initiated in humans when sporozoites are injected with the saliva of a feeding mosquito. Sporozoites are carried by the circulatory system to the liver and invade hepatocytes. A single sporozoite is capable of initiating the infection in men. However,the greatest the sporozoite load, the shortest the incubation period and the most serious the symptoms. The sporozoites remain into the circulation for a short period, calculated as 60 minutes at maximum, before they actively enter the liver of the host.[13]

The asexual exo-erythrocitic schizogonic cycle starts in hepatocytes. The liver sporozoite initially appears as a mononucleated round body into the cytoplasm of the hepatocytes. Following, it begins to develop and multiply asexually, a mature schizont (the multinucleated stage of the parasite) is formed. The mature schizont is 30-70 μm large, has no pigment (there is no hemoglobin into the hepatocyte), and occupies the entire cell cytoplasm.[14]

The lenght of the schizogonic liver cycle (prepatent period) is constant for each Plasmodium species (5.5, 8, 9 and 15 days for *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* respectively). The number of merozoites produced at the end of the cycle is also species dependant and determines the severity of clinical symptoms: it is estimated as 2,000 for *P. malariae*, 10,000 for *P. vivax*/*P. ovale*, and up to 30,000 for *P. falciparum*. The liver cycle ends when the mature schizont ruptures and releases the merozoites into the sinusoids of the liver. Released merozoites disiminate into the circulatory syatem and can only invade red blood cells.[14]

The erythrocytic sporogonic cycle

The blood phase of the life-cycle is initiated when the merozoites from liver schizonts are discharged into the circulation. The time required to complete the erythrocytic cycle is a fixed characteristic of the parasite species: *P. falciparum*, and *P. vivax*, have a 48-hour development period, in *P. ovale* it lasts 50 hours, while *P. malariae* has a longer cycle of 72 hours. Theoretically the periodicity of the erythrocytic cycle would determine the classical

cyclical presentation of symptoms every other day in tertian malaria infections and every third day in quartan malaria. In practice, however, the typical periodicity of malaria paroxysm cannot be recognized in the initial periods, since most parasite populations are heterogeneous and continuous fever therefore results from the completion of a synchronized schizogonic cycle.[15]

The merozoite is 1 μm in diameter, consisting of a single nucleus and adjacent cytoplasm. It invades almost immediately an erythrocyte to enter its trophozoite stage. A vacuole is produce by the parasite which assumes the characteristic ring form (the young trophozoite). Whithin 12-24 hours, as the parasite grows, the cytoplasm expands, the vacuole slowly disappears and a characteristic parasitic pigment becomes visible within the cytoplasm. At the end of this phase the trophozoite has a single nucleus, a large cytoplasm, no vacuole, and a variable amount of pigment. The nucleus starts to divide approximately 30 hours after invasion in the case of *P. falciparum*, *P. vivax*, and *P. ovale*, while in *P. malariae* this requires approximately 40 hours. As nuclear division produces two or more nuclei the parasite enters the stage of a schizont. Nuclear division continues until an appropriate number of merozoites is produced: approximately 36 for *P. falciparum*, 24 for *P. vivax* and *P. ovale*, and 12 for *P. malariae*. At the end of this phase the schizogonic cycle is completed, the erythrocyte ruptures releasing the merozoites into the blood stream and determining the typical malaria paroxysm. The merozoites discharged into the circulation invade new erythrocytes to repeat the schizogonic cycle untill the process is inhibited by the specific immune response or by chemotherapy. In the course of a schizogonic cycle (whithin a red blood cell) some of the merozoites become differentiated into sexual forms (the gametocytes); the mechanisms at the basis of this differential development are unknown. Gametocytes appears early (approximately from the third generation) in infections caused by *P. vivax*, *P. ovale*, and *P. malariae*, while at least 10 generation are thought to be required before *P. falciparum* gametocytes appears in the blood, which probably reflects the slow maturation and the sequestration of the immature stages in this species.[16]

The saprogenic cycle in Anopheles Mosquito

It initiates when mature female and male gametocytes are ingested by a suitable species of Anopheles during a blood meal as a protein source for egg production. As soon as gametocyte reaches the midgut of the insect the female gametocyte shed the red blood cell and remains free in the extracellular space as a macrogamete. The male gametocyte nucleus divide into eight sperm like flagellated microgametes each of which also leaves the erythrocyte reaches the midgut and actively moves to fertilize a macrogamete. Exflagellation of the microgametocyte is triggered by factors present in the mosquito midgut and begins about ten minutes after the blood meal. The result of the fertilization process is the zygot, which develops into the elongated, slowly motile ookinete within 18 hours from the blood meal. The ookinete actively penetrates the peritrophic membrane and the epitelium of the midgut and settles beneath the basal lamina of the outer gut wall, where it develops into a non motile oocyst 24-72 hours after the blood meal. The initial oocyst is 6-8 μm in diameter, has a single nucleus and a thin cist wall; the oocyst nucleus divides repeatedly leading to the formation of as many as 10,000 new individual nuclei within a mature oocyst of 40-60 μm in diameter. The time required from the establishment of the initial oocyst to its maturation depends on the parasite species, the anopheline species and on the temperature: it varies from 7 to 30 days. The products of the mature oocyst are the sporozoites, narrow and curved in shape, actively motile, 10-15 μm in length. The sporozoites leave actively the cyst passing through small perforations without destroying the wall, at least till most of the parasites have been released, and move into the haemocelomic space of the insect. The sporozoite migrates and reaches the salivary glands (though most tissues may be invaded) where it penetrates the basal membrane, pass intracellularly through a secretory cell and settles into the salivary duct. Oocyst sporozoite are poorly motile and less infectious and immunogenic than salivary gland sporozoites, showing that significant changes occur during the transfer journey into the hemolimphl. When the mosquito feeds, the salivary fluid (which has anti-clotting properties) and its content of sporozoites are actively injected into the vertebrate host to start another asexual replicative cycle. Temperature has an important effect on the speed of the cycle in the mosquito, which is a poikilothermic host. Development slows down and ceases for temperature of about 16°C with *P. vivax*; at very high temperature (about 45°C) the cycle is interrupted because the parasite dies. In general, the length of the sporogonic cycle in the mosquito is an irregular variable which strongly depends on the temperature and other climatic factors.[17]

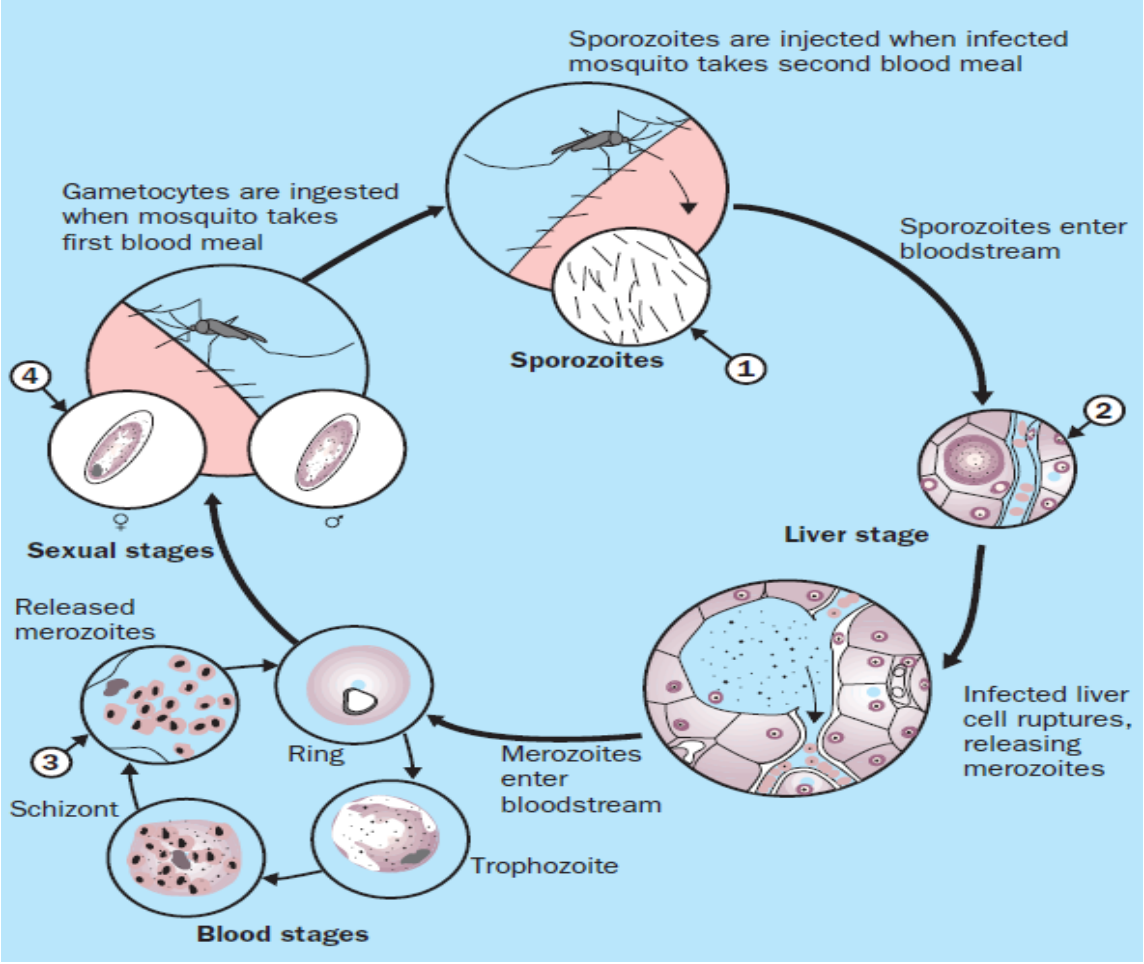

Figure 1: Life cycle of malaria

Biological basis of malaria relapse

Two species of human malaria determine a relapsing infection: *P. vivax* and *P. ovale*. In these two species some of the liver trophozoites immediately start the exo-erythrocytic schizogonic cycle which has been described above, while others remain into the liver in a latent (dormant) stage for varying periods of time and are termed hypnozoites.[18] The length of the period of dormancy varies with the subpopulations of *P. vivax* and *P. ovale*. A single inoculation of sporozoites of a relapsing species contains a mixture of genetically distinct parasites that give rise to discrete subpopulations of exo-erythrocitic trophozoites. The number of relapses, as their periodicity, seems to be a characteristic of the parasite strain. At one side of the spectrum of possibilities is the *P. vivax* hibernans strain who a homogeneus population of sporozoites has characterized by a latency of 250 days or more. At the other side is *P. vivax* chesson strain with a heterogeneous population of sporozoites, some programmed for immediate development, others to determine relapses at intervals of 2 to 3 months for a period of up to 2 years.[19]

Artemisinin-based combination for treatment of uncomplicated malaria

Artemesinin from which artemether is derived is obtained from the Chinese herb sweet worm wood (*Artemisua annua*). Artemisinins have the most potent and rapid onsets of antiparasitic activity against all Plasmodium species that infect humans.[4] The combinations are artemisinin and its derivatives (artesunate, artemether, dihydroartemisinin). The artemisinins produce rapid clearance of parasitaemia and rapid resolution of symptoms, by reducing parasite numbers 100 to 1000 fold per asexual cycle of the parasite (a factor of approximately 10,000 in each 48 h asexual cycle), which is more than the other currently available antimalarials activity. The other advantage from a public health perspective is the ability of the artemisinins to reduce gametocyte carriage and transmission blocking of malaria. This contributes to malaria control, particularly in areas of low-to-moderate endemicity.[7]

Since artemisinin and its derivatives are eliminated rapidly, a 7-day course of treatment with an artemisinin compound

is required. However, combination of artimisinins with slowly eliminated animalarials has reduced the 7 day regimen to 3 days. With the 3-day course, the complete clearance of all parasites is dependent on the slowly eliminated compound being effective and staying at antimalarial concentrations until all the infecting parasites have been removed. Thus, the partner compounds need to be relatively slowly eliminated. This also results in protection of resistance development by defending each other.[7]

To eliminate at least 90% of the parasitaemia, a 3-day course of the artemisinin is required to cover up to three post-treatment asexual cycles of the parasite. This ensures that only about 10% of the parasitamia is present for clearance by the combined medicine, thus enhancing efficacy and reducing the potential for development of resistance. Shorter courses of 1–2 days of the artemisinin component of the ACTs would lead to a larger proportion of parasitaemia for clearance by the combined medicine; this is not recommended for the following additional reasons: they are less efficacious (except when the combined drug is highly effective), they have less of an effect on gametocyte carriage, and they provide less protection of the slowly eliminated combined antimalarial from resistance development.[7]

Pharmacology of artemether–lumefantrine

The fixed-dose combination of artemether-lumefantrine (AL), called co-artemether, encompasses 20 mg of artemether and 120 mg of lumefantrine (previously called benflumetol). It was initially developed by scientists at the Academy of Military Medical Sciences in China before the pharmaceutical company Novartis (Switzerland) became a partner and was licensed to market it as Coartem® or Riamet®. This oral preparation has been designed for use against chloroquine-resistant *P. falciparum* malaria.[20]

Artemether and lumefantrine have different modes of action and act at different points in the parasite life cycle.[21] Artemether interferes with parasite transport proteins, disrupts parasite mitochondrial function, inhibits angiogenesis and modulates host immune function.[22] Lumefantrine is an aryl-amino alcohol that prevents detoxification of heme, such that toxic heme and free radicals causes parasite death.[21]

Artemether acts rapidly with half-life of 1 to 3 hours, whereas lumefantrine has a half-life of 3 to 6 days and is responsible for preventing recurrent parasitaemia.[23] Oral formulations of Artemether - lumefantrine are available as tablet and dispersible formulations which have similar pharmacokinetic properties.[24] Artemether and lumefantrine differ in rates of absorption and elimination. Artemether is rapidly absorbed reaching peak plasma concentrations within 2 hours post dose.[25] It is metabolized rapidly by cytochrome P450 (CYP) 2B6, CYP3A4 and possibly CYP2A610 to dihydroartemisinin (DHA) which is active metabolite and converted to inactive metabolites primarily by glucoronidation via UGT1A1, 1A8/9 and 2B7. The metabolite DHA reaches peak plasma concentration within 2 to 3 hours post dosing.[26] Both artemether and DHA offer potent antimalarial properties causing significant reduction in asexual parasite mass of approximately 10,000 fold per reproductive cycle, with prompt resolution of symptoms.[27]

Lumefantrine is absorbed and cleared more slowly, acting to eliminate residual parasites that may remain after artemether and DHA have been cleared from the body and thus prevent recrudescence.[21] Lumefantrine is highly lipophilic, thus absorption is enhanced with a fatty meal; its absorption occurs 2 hours after intake reaching peak plasma concentration after 3 to 4 hours with an elimination half life of 4 to 10 days.[28]

Food enhances absorption of both artemether and lumefantrine although this effect is more significant for lumefantrine. Administration of artemether and lumefantrine with high-fat meal increased bioavailability of both artemether and lumefantrine by 2-fold and 16-fold respectively.[29]

Efficacy and effectiveness of Artemether-lumefantrine

Efficacy of the 6 dose regimen of artemether-lumefantrine judged by elimination of malaria parasites using the 28-day polymerase chain reaction (PCR)-corrected cure rates and resolution of symptoms, has been demonstrated in semi-immune and non-immune populations in Asia and Africa to be consistently greater than 95%, with rapid parasite and symptom clearance and significant gametocidal effect.[30] Many studies in Africa and Asia have demonstrated Arthemether-Lumefantrine to be as efficacious as other artemisinin-based combination therapy when used in pediatric and adult populations with differing immunity. PCR-corrected day 28 and day 42 cure rates range between 91% and 100% using evaluable patient analysis.[31] Correction by PCR enables differentiation between recurrence and recrudescence of the initial infection from re-infection. A few cases of treatment failure were recorded after artemether-lumefantrine AL treatment, but these were mostly re-infections.[32] This is of particular

importance in areas with very intense malaria transmission where antimalarial drugs with longer half-life may offer the advantage of preventing re-infection. Lumefantrine with an estimated elimination half-life of 4 to 10 days offers post-treatment antimalarial prophylaxis of up to 4 weeks.[33] In addition to excellent efficacy and effectiveness, artemether-lumefantrine has demonstrated significant gametocidal effects.[34] A meta-analysis of randomized trials showed artemether-lumefantrine to be one of the most effective artemisinin-based combination therapies with 28-day parasitological cure rates of 97.4%.[35]

Effectiveness of artemether-lumefantrine may be influenced by poor adherence to the 3-day, 6-dose regimen and the food requirements for artemether-lumefantrine absorption.[36]

Safety of Artemether-lumefantrine

Safety and tolerability of artemether-lumefantrine has been assessed in clinical trials in Asia and Africa. Most adverse events are mild or moderate, mostly affecting gastrointestinal and nervous systems; however, most are typical of the symptomatology of malaria or concomitant infections. Studies show that serious adverse events were unlikely and were unrelated or most unlikely to be related to study medication.[37] Two meta-analysis concluded that artemether-lumefantrine is well tolerated, with mild or moderate adverse events mostly affecting gastrointestinal and nervous systems. Ototoxicity associated with AL has been reported recently in a few cases.[38] Lumefantrine possesses a similar chemical structure to halofantrine which is known to cause cardiac arrhythmia; however, safety studies have not shown lumefantrine to be cardio toxic or to prolong QTc interval.[39]

Safety assessment has been conducted during treatment of single episodes of malaria. Safety concerns become more important when artemether-lumefantrine is administered over the counter, which commonly results in over diagnosis and overtreatment of malaria, and when patients get recurrent infections requiring repeated treatment. Over diagnosis of malaria is common in malaria-endemic areas.[40]

Artemether-lumefantrine use in children

Drug intake especially in children may be influenced by vomiting, which may be due to disease-related nausea or taste of the medication. A more palatable dispersible formulation of artemether-lumefantrine is now available and has been shown to be as efficacious as the currently used crushed tablet in infants and children, and with similar safety and pharmacokinetic profile.[24]

Pediatric dosing of artemether-lumefantrine is deduced from adult-based regimens adjusted for body weight, with little consideration for maturational effects on drug absorption and metabolism. Although diet and nutritional status are important determinants of pharmacokinetic processes, drug responses and toxicity, there are few relevant data for artemether-lumefantrine in this patient group. In resource-constrained areas, children may not be weighed at each clinic visit and dosing in such settings is usually based on age as a proxy measure for weight. Besides research on therapeutic dose levels based on body weight, there is urgent need for evidence-based translation of weight based dosing regimens to regimens that can be based on age, as the majority of fevers in malaria endemic areas are treated with over-the-counter antimalarial drugs without involvement of the formal health sector. Age-based dose regimens are more practical than weight-based regimens, but will inevitably result in a greater proportion of children receiving either too much or too little drug. This is a particular concern with lumefantrine, which has a narrow therapeutic margin between effective and toxic concentrations. This dosing consideration is especially important in malnourished, pre-school children and during onset of puberty when physiological variations in body weight by age are greatest.[41]

Different age-based regimens are already being used in countries that have recently switched to artemisinin-based combination therapies. These concerns apply also to young infants <6 months old or of <5 kg body weight. Most artemisinin-based combination therapies are contra-indicated in this group because of lack of safety data, even though these children are at considerable risk. In western Kenya, 50% of infants not protected by insecticide-treated mosquito nets had their first infection by 3 months.[42] In southern Mozambique, an estimated 9% of out-patient visits for uncomplicated malaria are children aged <6 months. Infants in endemic areas have the highest burden of severe malarial anemia, blood transfusions and death.[43]

Artemether-lumefantrine use in pregnancy

Pregnant women with malaria, symptomatic and asymptomatic alike should be treated without delay with effective and safe antimalarial drugs in order to reduce risks for adverse outcomes for both mother and fetus. Artemether-lumefantrine is a very attractive alternative because it is highly effective, acts rapidly and is well

tolerated. However, there is insufficient information on safety and efficacy of artemisinin-based combination therapies in pregnancy, including exposure in the first trimester. Early data indicated that artemisinins were embryo toxic and potentially teratogenic in several animal species without maternal toxic effects or impaired fertility, and more recent studies have confirmed this findings.[44]

Artemisinin derivatives have shown embryo-toxic effects in animal reproductive toxicology studies. The mechanism of embryo-toxicity is thought to occur through depletion of embryonic erythroblasts causing severe anemia and cell damage and death due to hypoxia.[45] The most sensitive time window for embryo-toxicity in humans is between weeks 4 to 10. From these data artemisinin-based combination therapies are not indicated for malaria treatment in the first trimester of pregnancy unless no alternatives exist. There is increasing experience with artemisinin derivatives in second and third trimesters with no evidence of adverse outcomes in more than 1000 prospectively followed pregnancies.[46]

WHO Malaria Treatment Guidelines of 2006 recommend use of artemisinin-based combination therapies in pregnant women in the second and third trimester of gestation. None of the studies on artemether-lumefantrine use in pregnancy have reported increased risk of serious maternal adverse events, adverse birth outcomes or neuro-developmental deficits. However, all these studies were underpowered to detect rare adverse outcomes.[47] Data from Sudan from a cohort of women who reported use of artemisinins in first trimester and were followed up until delivery and their babies followed up till 1 year of age showed that most delivered apparently healthy babies at full term with no congenital malformations and no maternal deaths, and none of the babies died during their first year of life.[48]

Pediatric formulations of Artemether-lumefantrine

Artemether-lumefantrine is an Artemisinin-based combination therapy that meets WHO prequalification criteria for efficacy, safety and quality.[39] Coartem®, a fixed dose combination of artemether and lumefantrine, has consistently achieved cure rates of >95% in clinical trials of children with malaria and was shown to be safe and well tolerated.[49].

Artemether and lumefantrine tablets are available in pediatric doses; however, they must be crushed for infants and small children as whole tablets may present a choking hazard. The crushed tablets, in common with many anti-malarial, have a bitter taste that may cause children to spit them out, and may result in a sub-therapeutic dose being taken. Further, crushing of the tablets by caregivers at home may result in loss of active ingredients and thus under dosing. Together, these factors could result in an opportunity for parasite resistance to develop.[50]

Recognizing that few medicines have been successfully created to address the needs of children with malaria, Novartis and Medicines for Malaria Venture (MMV) formed a public-private partnership with the aim of developing a pediatric formulation of artemether-lumefantrine. MMV is a global, non-profit organization created to discover, develop and deliver safe, effective and affordable antimalarials for vulnerable populations, while Novartis is a global pharmaceutical company with a wealth of experience in drug development and a team of investigators in endemic countries. The partners were ideally placed to develop a formulation of AL specifically designed for infants and young children.[50]

The biggest challenge in developing a new formulation is to ensure that it is acceptable to all stakeholders. For patients, it must be palatable and easy to take. For caregivers, accessibility and ease of administration to a sick child is a prime concern. For regulatory authorities, there must be sufficient data to support the use of the new formulation in the target population in terms of quality, efficacy and safety. Purchasers are most concerned about cost and availability.[50]

Clinical trials have shown pediatric formulations needs careful considerations. Currently available dosage forms like syrups and powder for reconstitution has many limitations: they are bulky to supply and store, and once opened/reconstituted, the stability and hygiene of the products is deteriorating. Besides precise volume measurement of syrups and powders for reconstitution is difficult for those formulated in multi–dose preparations.[50]

Ahead of a call from WHO for child-friendly medicines, Novartis, working in partnership with Medicines for Malaria Venture (MMV), developed a new formulation of artemether-lumefantrine for infants and young children: Coartem® Dispersible. The development of a dispersible tablet of artemether-lumefantrine allowed an accurate dose of the active ingredient to be contained in a tablet form, and for the dosing schedule to match that of existing artemether-lumefantrine tablets. The dispersible tablets are simpler for caregivers to prepare and administer than crushed bitter tablets and easier for sick children and

infants to take. They require only a small amount of water for dispersion.[51]

A pharmacokinetic comparison in children with malaria was undertaken as part of a randomized, multicentre, investigator blinded study in African children.[52] Similar pharmacokinetic profiles were reported for artemether, DHA and lumefantrine in the dispersible and the crushed tablet formulations.[50]

Artemether-lumefantrine tablets have achieved cure rates of >95% in children with falciparum malaria. The efficacy of the new dispersible artemether-lumefantrine tablets was compared with that of crushed artemether-lumefantrine tablets in a study of 899 African children with uncomplicated falciparum malaria.[52]

Artemether-lumefantrine tablets have demonstrated an excellent safety profile in children with falciparum malaria. The safety and tolerability of dispersible AL tablets was examined in the same randomized study of 899 African children (5 ≤ 35 kg body weight) and showed a similar pattern and incidence of adverse events as crushed artemether-lumefantrine tablets.[52]

Dispersible artemether-lumefantrine tablets rapidly disperse (<1 min) in water to form a sweet-tasting medicine. They require only a small amount of water to disperse in a spoon or a beaker and have no need for any special equipment. They can be administered with food or milk. Dispersible tablets are simpler for caregivers to prepare and administer than bitter crushed tablets. Dispersible artemether-lumefantrine was approved by Swiss medic in December 2008 and received WHO prequalification in February 2009. It has been approved in 24 African countries to date.[51]

Conclusion

Different dosage forms of artemether-lumefantrine are supposed to promote ease of administration of antimalarial medications in utmost vulnerable groups to malaria such as infants and children. It is also known that ease of administration of artemether-lumefantrine dosage forms like dispersible tablets greatly contribute adherence to the 3 day regimens and as a result reduce morbidity and mortality in infants and young children. This is also important to minimize the opportunity for emergence of resistance. However, various studies have been conducted about the safety, efficacy and pharmacokinetic profiles of artemether-lumefantrine dosage forms in young children (weight based), still there is no sufficient data to use artemether-lumefantrine in infants < 5 kg and pregnant woman. Appropriate studies evaluating carcinogenicity, mutagenicity and fertility impairment by artemether-lumefantrine also needs serious consideration. Importantly, the safety, efficacy and pharmacokinetic must be studied on all pediatric age groups since age of human patient indicates the maturity of vital organs, which determine the pharmacokinetic performance of antimalarial medications.

References

1. WHO, World Malaria Report, 2010. Geneva, Switzerland.

2. Gebre B., Negash Y. Severe malaria among children in Gambella, western Ethiopia. Ethiop. J. Health Dev., 2002; 16 (1):61-70.

3. Teklehaimanot A, Teklehaimanot HD. Alternative form of artemether-lumefantrine for infants. Lancet, 2008; 372:1786-1787.

4. Kibwika PB, Lamorde M, Kizza HM, Merry C, Colebunders B, Geertruyden JPV. Update on the efficacy, effectiveness and safety of artemether–lumefantrine combination therapy for treatment of uncomplicated malaria. Therapeutics and Clinical Risk Management, 2010; 6:11–20.

5. Ajayi IO, Browne EN, Bateganya F. Effectiveness of artemisinin based combination therapy used in the context of home management of malaria: a report from three study sites in sub-Saharan Africa. Malar J.2008; 27(7):190.

6. WHO, World Malaria Report, 2008. Geneva: Switzerland.

7. WHO, Guidelines for the treatment of malaria,2010. 2nd ed., Geneva, Switzerland.

8. Juma EA, Obonyo CO, Akhwale WS, Ogutu BR. A randomized, open-label, comparative efficacy trial of artemether-lumefantrine suspension versus artemether-lumefantrine tablets for treatment of uncomplicated *Plasmodium falciparum* malaria in children in western Kenya. Malar J.2008; 7:262.

9. Sachs, J.,and Malaney, P. The economic and social burden of malaria. Nature, 2002; 415: 680-685.

10. Roundy R.W. Altitudinal mobility and disease hazards for Ethiopian population. Economic Geography, 1976; 52:103-115.

11. Deressa W., Ali A., Berhane Y. Review of the interplay between population dynamics and malaria transmission in Ethiopia. Ethiop.J.Health Dev.2006; 20(3).

12. Gratzer WB, Dluzewski AR. The red blood cell and malaria parasite invasion. Semin Hematol, 1993; 30: 232-247.

13. Lopez-Antunano FJ, 1980. Shmunis G. (Eds). Diagnosis of malaria. Scientific Publication, 1980; 512: Pan American Health Organization.

14. Garnham PCC. Malaria parasites and other Haemosporidia, 1966. Oxford Blackwell Scientific Publication.

15. Garham PCC. Malaria parasites of man: life-cycles and morphology (excluding ultrastructure). In Malaria - Principles and practice of malariology, Wernsdorfer WH and McGregor I eds. vol I pp., 1988; 65-96 Churchill Livingstone.

16. Carter R, Gwadz RW. Infectiousness and gamete immunization in malaria. In Kreser JP (ed), Malaria Vol. 3 pp.,1980; 263-297, New York Academic Press.

17. Bruce-Chwatt LJ, Black RH, Canfield CJ, Clyde DF, Peters W, Wernsdorfer WH.Chemotherapy of malaria,1981; 2nd edition. World Health Organization.

18. Krotoski WA. Discovery of the hypnozoite and a new theory of malarial relapse. Trans R Soc Trop Med Hyg,1985; 79: 1-11.

19. Coatney GR, Cooper WC, Young MD. Studies in human malaria. XXX. A summary of 304 sporozoite-induced infections with the Chesson strain of Plasmodium vivax. J Natl Malar Soc, 1950; 9: 381-396.

20. Omari A, Gamble C, Garner P. Artemether-lumefantrine (six-dose regimen) for treating uncomplicated falciparum malaria. Cochrane Database of Systematic Reviews,2009; Issue 4. Art. No.: CD005564. DOI: 10.1002/14651858.CD005564.

21. Kokwaro G, Mwai L, Nzila A. Artemether/lumefantrine in the treatment of uncomplicated falciparum malaria. Expert Opin Pharmacother, 2007; 8:75–94.

22. Golenser J, Waknine JH, Krugliak M. Current perspectives on the mechanisms of action of artemisinins. Int J Parasitol.2006;36:1427–1441.

23. Travassos, Mark A, Laufer. Resistance to antimalarial drugs: molecular, pharmacologic, and clinical considerations. Pediatr Res.2009; 65(5):64R–70R.

24. Abdulla S, Borrmann S, D'Alessandro U, et al., 2008. Efficacy and safety of artemetherlumefantrine dispersible tablets compared with crushed commercial tablets in African infants and children with uncomplicated malaria: a randomised, single-blind, multicentre trial. Lancet. 372:1819–1827.

25. Ezzet F, Mull R, Karbwang J. Population pharmacokinetics and therapeutic response of CGP 56697 (artemether + benflumetol) in malaria parasites. Br J Clin Pharmacol.1998; 46:553–561.

26. Aweeka FT, German PI. Clinical pharmacology of artemisinin-based combination therapies. Clin Pharmacokinet., 2008; 47(2):91–102.

27. Djimdé A, Lefèvre G. Understanding the pharmacokinetics of Coartem®. Malar J. 2009; 8(1):1186/475-2875-8-S1–S4.

28. Ezzet F, Van Vugt M, Nosten F. Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria. Antimicrob Agents Chemother. 2000;44:697–704.

29. White NJ, Van Vugt M, Ezzet F, Ezzet F. Clinical Pharmacokinetics and pharmacodynamics of artemetherlumefantrine. Clin Pharmacokinet., 1999; 37:105–125.

30. Hatz C, Soto J, Nothdurft HD. Treatment of acute uncomplicated falciparum malaria with artemether/lumefantrine in nonimmune populations: a safety, efficacy and PK study. Am J Trop Med Hyg.2008;78:241–247.

31. Rojanawatsirivej C,Vijaykadga S,Amklad I. Monitoring the therapeutic efficacy of antimalarials against uncomplicated falciparum malaria in Thailand. Southeast Asian J Trop Med Public Health.2003; 34:536–541.

32. Yeka A, Dorsey G, Kamya MR. Artemether/lumefantrine versus dihydroartemisinin-piperaquine for treating uncomplicated malaria: a randomized trial to guide policy in Uganda. PLoS ONE.2008;(3):e2390.

33. Zongo I, Dorsey G, Rouamba N. Randomized comparison of amodiaquine plus sulfadoxine-pyrimethamine, artemether/lumefantrine, and dihydroartemisinin-piperaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Burkina Faso. Clin Infect Dis.2007; 45:1453–1461.

34. Fanello CI, Karema C, van Doren W. A randomised trial to assess the safety and efficacy of artemether/lumefantrine (Coartem®) for the treatment of uncomplicated *Plasmodium falciparum* malaria in Rwanda. Trans R Soc Trop Med Hyg., 2007; 101:344–350.

35. Jansen FH, Lesaffre E, Penali LK. Assessment of the relative advantage of various artesunate-based combination therapies by a multi-treatment Bayesian random-effects meta-analysis. Am J Trop Med Hyg.2007; (77):1005–1009.

36. Piola P, Fogg C, Bajunirwe F. Supervised versus unsupervised intake of six-dose artemether-lumefantrine for treatment of acute, uncomplicated *Plasmodium falciparum* malaria in Mbarara, Uganda: a randomised trial. Lancet, 2005; 365(9469):1467–1473.

37. Falade C, Manyando C. Safety profile of Coartem®: the evidence base. Malar J.2009; 8 Suppl 1:S6.

38. Miller LG, Panosian CB. Ataxia and slurred speech after artesunate treatment for falciparum malaria. N Engl J Med.1997; 336:1328.

39. Cousin M, Kummerer S, Lefèvre G, Marrast AC, Stein D, Weaver M. Anti-infective Drugs Advisory Committee Meeting. Coartem® (artemether-lumefantrine) Tablets for the treatment of malaria in patients with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*. NDA 22-268 October, 2008, 28[http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4388b1-02-Novartis.pdf].

40. Nankabirwa Zurovac D, Njogu JN. Malaria misdiagnosis in Uganda—implications for policy change. Malar J.2009; 16(8):66.

41. Barnes KI, Little F, Smith PJ. Sulfadoxine-pyrimethamine PKs in malaria: pediatric dosing implications. Clin Pharmacol Ther. 2006; 80:582–596.

42. Ter Kuile FO, Terlouw DJ, Kariuki SK. Impact of permethrin-treated bed nets on malaria, anemia, and growth in infants in an area of intense perennial malaria transmission in western Kenya. Am J Trop Med Hyg.2003; 68:68–77.

43. Schellenberg D, Menendez C, Kahigwa E. African children with malaria in an area of intense *Plasmodium falciparum* transmission:features on admission to the hospital and risk factors for death. Am J Trop Med Hyg.1999; 61:431–438.

44. Nosten F, White NJ. Artemisinin-based combination treatment of Falciparum malaria. Am J Trop Med Hyg. 2007; 77(6):181–192.

45. Dellicour S, O ter Kuile F, Stergachis A., 2008. Pregnancy exposure registries for assessing antimalarial drug safety in pregnancy in malaria-endemic countries. PLoS Med. 2008; 5(9):187.

46. Nosten F, McGready R, Mutabingwa T., 2007. Case management of malaria in pregnancy. Lancet Infect Dis., 7(2):118–125.

47. Dellicour S, Hall S, Chandramohan D. The safety of artemisinins during pregnancy: a pressing question. Malar J.2007; 14(6):15.

48. Adam I, Elhassan EM, Omer EM, Abdulla MA.. Safety of artemisinins during early pregnancy, assessed in 62 Sudanese women. Ann Trop Med Parasitol.2009; 03(3):205–210.

49. Piola P, Fogg C, Bajunirwe F, Biraro S, Grandesso F, Ruzagira E, Babigumira J, Kigozi I, Kiguli J, Kyomuhendo J, Ferradini L, Taylor W, Checchi F, Guthmann JP.,2005. Supervised versus unsupervised intake of six-dose artemether-lumefantrine for treatment of acute, uncomplicated *Plasmodium falciparum* malaria in Mbarara, Uganda: a randomised trial. Lancet, 365:1467-1473.

50. Abdulla and Sagara. Dispersible formulation of artemether/lumefantrine: specifically developed for infants and young children. Malaria Journal 2009, 8(Suppl 1):S7

51. Novartis Drug Regulatory Affairs. Coartem®/Riamet® Dispersible (artemether/lumefantrine) Basic Prescribing Information, 2009.

52. Abdulla S, Sagara I, Borrmann S, et al. Efficacy and safety of artemetherlumefantrine dispersible tablets compared with crushed commercial tablets in African infants and children with uncomplicated malaria: a randomised, single-blind, multicentre trial. Lancet 2008, 372:1819-1827. Malaria Journal 2009, 8(Suppl 1):S7 http://www.malariajournal.com/content/8/S1/S7Page.