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Artemether-Lumefantrine for the Treatment of Malaria in Infants and Children

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Malaria remains a significant medical burden in many parts of the world. It is responsible for approximately 1 million deaths per year, mostly in infants and children. The availability of artemisinin-based compounds, derived from the Chinese plant *Artemisia annua*, during the past decade has introduced a new era in the treatment of this disease. Effective and well tolerated, these drugs appear to offer substantial benefits over traditional agents such as chloroquine or sulfadoxine-pyrimethamine. Artemisinin-based combination therapies (ACT) are recommended as first-line therapy for malaria by the World Health Organization (WHO) and have been accepted as a mainstay of treatment in more than 70 countries.¹⁻³

A combination of artemether and lumefantrine recently became the first ACT to be made available in the United States. Initially introduced in 1999, it was approved by the Food and Drug Administration on April 7, 2009 for the treatment of infants, children, and adults with acute *Plasmodium falciparum* infections.^{4,5} This issue of *Pediatric Pharmacotherapy* will review the pharmacology of the artemether-lumefantrine combination and describe recent studies of its use in infants and children.

Mechanism of Action

The combination product contains artemether and lumefantrine in a fixed 1:6 ratio. Artemether is a semisynthetic chiral acetal derivative of artemisinin. It interferes with parasite transport proteins, produces disruption of mitochondrial function, inhibits angiogenesis, and modulates host immune function. Artemether and its active metabolite have been estimated to reduce parasite biomass by approximately 10,000-fold per reproductive cycle (every 2 days). Lumefantrine is a racemic mixture of a synthetic fluorine derivative and is structurally related to quinine, mefloquine, and halofantrine. It interferes with the conversion of heme, the toxic intermediate step produced during hemoglobin

break-down, to non-toxic hemozoin. Accumulation of heme and free radicals results in parasite death.¹⁻⁵

Artemether, like other artemisinin-derived compounds, acts quickly to rapidly reduce the parasite burden, while lumefantrine serves as a longer-acting agent to eliminate remaining parasites. The combination is effective in strains known to be resistant to traditional antimalarials such as chloroquine, and can be used for infections acquired in areas known to have parasites that are multidrug-resistant.¹⁻⁵

Pharmacokinetics

Both artemether and lumefantrine are well absorbed after oral administration. Peak plasma artemether concentrations typically occur within 2 hours after administration and peak lumefantrine concentrations occur in 6-8 hours. Administration with fat-containing foods, including milk, improves bioavailability by more than two-fold for artemether and up to 16-fold for lumefantrine in adults. In a study of 899 children, administration with food increased the mean observed plasma concentrations of lumefantrine by 55-100%, while milk increased concentrations by 57-65% compared to administration without food.^{4,6}

Artemether is rapidly and extensively metabolized, primarily by cytochrome P450 (CYP) 3A4/5 but also by CYP2B6, CYP2C9, and CYP2C19. Metabolism through CYP3A4 produces an active metabolite, dihydroartemisinin (DHA) that contributes substantially to its antimalarial activity. Lumefantrine is metabolized primarily by CYP3A4 and then undergoes glucuronidation. Artemether has an estimated oral clearance of 2.6 L/hr/kg in children and an elimination half-life of approximately 1-3 hours. Its DHA metabolite has a half-life in children of 1-1.7 hours. The clearance of lumefantrine is much slower, 77

mL/hr/kg, with a half-life in clinical trials of approximately 3-6 days.^{3-5,7}

Clinical Trials in Infants and Children

Numerous clinical trials have demonstrated the safety and efficacy of artemether-lumefantrine in pediatric patients. Most studies report 28-day cure rates greater than 90% and a mild adverse effect profile. In 2005, Falade and colleagues at the University of Ibadan in Nigeria studied the response to artemether-lumefantrine in 310 children with acute, uncomplicated *P. falciparum* malaria.⁸ Patients were treated with a weight-adjusted six-dose regimen given over 3 days, with the first two doses given at diagnosis, another dose 8 hours later, and the remaining doses given twice daily for 2 days. Cure rates at 7 and 14 days were greater than 97%. The overall cure rate at 28 days (corrected to exclude cases of re-infection as detected by PCR analysis) was 93.9%. There was no difference in response between those children who had been treated for malaria in the past and those who had not (93.3% versus 95%). Adverse effects were reported to be mild.

Based on the success of this trial, the following year the authors conducted a pooled analysis of individual patient data from all manufacturer-sponsored trials conducted up to that time to compare the safety and efficacy of the six-dose regimen in children to a reduced four-dose regimen being used in some countries.⁹ Data from eight trials were included, with a total of 201 children receiving the four-dose regimen and 343 receiving the six-dose regimen. Parasitological cure rates were significantly higher in the six-dose group, with a 28-day corrected cure rate of 96% compared to 76% in the four-dose group. Median parasite clearance time was 24.2 hours in the six-dose group, significantly shorter than that of the four-dose group (45 hours). The authors also found a significantly greater rate of patient discontinuation in the four-dose group (30.3% versus 4.1%), primarily resulting from lack of efficacy. There were no differences in the rates of discontinuation because of adverse effects (1% in the four-dose group versus 0.3% in the six-dose group). Based on their findings, the authors concluded that the six-dose regimen was more efficacious than the four-dose regimen, without increasing the risk for adverse effects. These data support the current use of a six-dose regimen for all patients, with dosing adjusted by patient weight and age.

In 2009, Achan and colleagues from Makerere University compared artemether-lumefantrine to quinine for the treatment of uncomplicated falciparum malaria in 175 Ugandan children.¹⁰

The patients, between 6 and 59 months of age, were randomized to receive either a six-dose regimen of the combination product or a week of quinine 10 mg/kg/dose given three times daily. The first dose was given by the study nurse, with subsequent doses given at home. Eighty-six patients received quinine and 89 were treated with artemether-lumefantrine. The 28-day cure rate was significantly higher in the artemether-lumefantrine group, 96% compared to only 64% in the quinine group ($p = 0.001$). Adherence rates were also different, 94.5% for the combination group and 85.4% for the quinine group ($p = 0.06$). Adverse effects were similar between the groups. This study, along with others demonstrating similar results, led the WHO to adopt ACT-based regimens as first-line therapy for the treatment of malaria.

Another recent trial compared sulfadoxine-pyrimethamine, another standard treatment for malaria in children, with two ACT regimens: artemether-lumefantrine and artesunate-amodiaquine.¹¹ A total of 240 children (ages 6-60 months) were enrolled in this open-label trial. Patients were treated at home, to provide results that would more accurately represent cure rates in actual clinical practice. The per-protocol analysis revealed 28-day corrected cure rates of 94% for the artemether-lumefantrine group and 93.2% for the artesunate-amodiaquine, but only 28.3% for the sulfadoxine-pyrimethamine group. The results lend further support to the replacement of traditional therapies with ACT regimens for initial treatment.

With the availability of newer ACT combinations, artemether-lumefantrine has become a “gold standard” for non-inferiority studies. Earlier this year, Tshefu and colleagues compared pyronaridine-artesunate with a standard treatment course of artemether-lumefantrine.¹² A total of 1,272 patients ranging in age from 3 to 60 years were randomized into this parallel-group, double-blind multicenter trial. The primary outcome, the adequate clinical and parasitological cure rate, was no different between the groups (99.5% in the pyronaridine-artesunate group versus 99.2% in the artemether-lumefantrine group, $p = 0.578$). Sixty percent of the patients in the comparator group developed an adverse event, versus 57% in the standard treatment group, however most were mild and did not require discontinuation of therapy. With multiple similar trials published or underway, it appears that there will be many ACT products available for use in the future.

Contraindications and Precautions

Artemether-lumefantrine is contraindicated in patients with cerebral or severe malaria,

according to the World Health Organization definition. It should not be used in patients with a previous history of hypersensitivity reactions to either component or who are in the first trimester of pregnancy, unless no other treatment options are available. Because of the potential for prolongation of the QTc interval associated with the combination, it is contraindicated in patients with a history of congenital QTc prolongation or those with a family history of symptomatic cardiac arrhythmias or sudden death. It should be used with caution in patients with electrolyte imbalances that may predispose them to arrhythmias. The combination has not been evaluated as prophylaxis or in the treatment of patients with malaria caused by *P. vivax*, *P. malariae*, or *P. ovale*.^{4,5}

Adverse Effects

The artemether-lumefantrine combination is generally well tolerated. The most frequently reported adverse effects in pediatric clinical trials have been fever (29%), cough (23%), vomiting (18%), headache (13%), and anorexia (13%). Dizziness, nausea, abdominal pain, diarrhea, rash, arthralgias and myalgias, asthenia, fatigue, and elevations in serum transaminases have been reported in 1-10% of children. Prolongation of the QTc interval on ECG has not been a common occurrence, but was reported in 0.1-1% of children treated during clinical trials. There have been no reports of clinical adverse events attributable to QTc prolongation caused by use of the combination.^{4,5}

Drug Interactions

Due to a lack of safety data, it is recommended that artemether-lumefantrine not be administered concurrently with other antimalarials. If it is given before or after a course of quinine, ECG monitoring is advised to identify additive effects on the QTc interval. In patients who have previously taken halofantrine, the combination should not be started any earlier than one month after the last halofantrine dose. Mefloquine administration may reduce bile production, resulting in a reduction in the absorption of lumefantrine by 30 to 40%.

Artemether-lumefantrine should not be used concurrently with other drugs known to prolong the QTc interval (see www.qt drugs.org for a current list). It should be used with caution in patients taking drugs metabolized by CYP2D6 or drugs that act as a substrate, inhibitor, or inducer of CYP3A4. The clinical impact of these metabolic drug-interactions has not been extensively studied. In a trial conducted in healthy adults, ketoconazole, a strong inhibitor of CYP3A4 function, produced only a modest (less than 2-fold) increase in artemether and

lumefantrine concentrations. Lumefantrine inhibits CYP2D6 and has the potential to produce significant inhibition of drugs metabolized via this pathway. Although no formal drug interaction studies have yet been performed, it is recommended that artemether-lumefantrine be used with caution in patients receiving concurrent antiretroviral therapy or hormonal contraception due to concerns for reduced efficacy.^{4,5}

Availability and Dosing Recommendations

The combination product (Coartem[®]; Novartis) is available in tablets containing 20 mg artemether and 120 mg lumefantrine. The tablets may be crushed and mixed with 5-10 mL of water for younger children.^{4,5} A dispersible tablet for infants and young children was introduced in 2008, developed through a collaboration of Novartis and the Medicines for Malaria Venture (MMV). Once dissolved in water, the tablet produces a sweet-tasting solution better accepted by children than the bitter-tasting crushed tablets. The two preparations have been shown in clinical studies to produce equivalent results, with cure rates greater than 96%.^{13,14} Dispersible tablets are not yet available in the United States.

Treatment with artemether-lumefantrine consists of a six-dose regimen given over 3 days, with doses based on patient age and weight (described below). No dosage adjustment is needed for mild to moderate renal or hepatic impairment, but the combination should be used with caution in patients with severe impairment.^{4,5}

Adults and children > 35 kg or 12 years

Four tablets are given as a single dose at the time of diagnosis, followed by four tablets 8 hours later, and then four tablets twice daily for 2 days (a total of 24 tablets over 3 days).

Infants and Children < 35 kg or 12 years

5-14 kg

One tablet is given at diagnosis, another tablet 8 hours later, and then 1 tablet twice daily for 2 days (a total of 6 tablets over 3 days).

15-24 kg

Two tablets are given at diagnosis, another two tablets 8 hours later, and then two tablets twice daily for 2 days (a total of 12 tablets over 3 days).

25-34 kg

Three tablets are given at diagnosis, another three tablets 8 hours later, and then three tablets twice daily for 2 days (a total of 18 tablets over 3 days).

Artemether-lumefantrine should be taken with food or milk. Children receiving crushed or dispersible tablets breastfeeding, should be fed immediately after a dose. Patients unable to eat during treatment should be monitored for possible treatment failure resulting from lower drug levels. If the patient vomits within 1-2 hours of taking a dose, it should be repeated.⁴⁻⁶

Cost

Novartis entered into an agreement with the WHO in 2001 to provide Coartem[®] without profit to malaria-endemic countries. Over 250 million treatment courses have been provided through this arrangement, with a current cost of \$0.80 for an adult treatment pack and \$0.37 for a child pack.^{1,5} In the United States, the average cost for bottle of 24 tablets is approximately \$70.00.

Summary

The combination of artemether and lumefantrine, the first ACT to be made available in the United States, has been shown to be a safe and effective option for the treatment of malaria in infants, children, and adults. It is especially useful for patients with multidrug-resistant strains. Close adherence to dosing instructions, including the need to take the tablets with food, is necessary to optimize results.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 9/24/10:

1. Denosumab (Prolia[™]) was added to the Formulary with restriction to the treatment of osteoporosis in outpatients who cannot receive other agents or who have failed to adequately respond to other agents.
2. Ustekinumab (Stelara[™]) was added for the treatment of moderate to severe plaque type psoriasis for outpatients not responding to other immunologic agents.
3. The restriction on enoxaparin was removed, making it the low molecular weight heparin of choice for venous thromboembolism prophylaxis.
4. A number of practice guidelines and reference documents were approved, including the Anticoagulation Reference for Infants and Children. This document will be available to UVA faculty and staff through the anticoagulation website on the Clinical Portal.

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