Suspected Allergy to Artemether–Lumefantrine Treatment of Malaria

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In the past two decades, several new antimalarial drugs, such as sulfadoxine–pyrimethamine, mefloquine and halofantrine, have been introduced in the treatment of chloroquine-resistant Plasmodium falciparum malaria. These antimalarials were considered safe until widespread use led to the discovery of rare but severe adverse effects, and more restricted use.

The Qinghaosu derivatives artemisinin, artesunate, artemether and arteether have become important additions to malaria treatment. Whereas these compounds have already been a mainstay of malaria treatment in Southeast Asia and China over the last 10 years, they are still relatively new in Africa.

Qinghaosu drugs appear to be well tolerated by patients, although early clinical studies have been regarded by some authors as not stringent enough to meet the requirements of many national or international drug-regulating agencies. In comparison to the wealth of knowledge about the adverse effects of classic antimalarials such as chloroquine and quinine, experience concerning the adverse effects of Qinghaosu derivatives is still somewhat limited. Although neuro- and cardiotoxic effects have been seen in animals at high dosages, few side effects have been reported in humans.

We would like to present a case of a suspected allergic reaction with angioedema to the combination of artemether and lumefantrine, which we recently experienced during the treatment of a patient with uncomplicated P. falciparum malaria in Yaoundé, Cameroon.

To our knowledge, this is the first such case to be reported.

Case Presentation

A 9-year-old American boy, resident in Yaoundé, Cameroon since birth, fell ill with malaise, general body ache, headache, fever up to 40.4°C, chills and vomiting. Although malaria tests were done within the first 24 h (thick film, Becton Dickinson QBCTM Malaria Test, Binax NowTM ICT Malaria P.f./Pv), P. falciparum malaria was not confirmed until 4 days after the onset of symptoms, by all three tests, with a low parasitemia (160 P. falciparum trophozoites/µL).

The boy was treated with oral artemether–lumefantrine (Beijing Novartis Pharma Ltd, Beijing, China). Following the manufacturer’s recommended treatment schedule (“treatment under the supervision of a doctor”) and according to his body weight of 37 kg (i.e., above 34 kg), the patient was given 4 tablets per dose, one tablet containing 20 mg of artemether and 120 mg of lumefantrine:

Day 1 of Malaria Treatment

11.30 a.m. 1st dose of 4 tablets of artemether–lumefantrine. Tolerated without problems.
7.30 p.m. 2nd dose of 4 tablets of artemether–lumefantrine.
12.00 a.m. Severe coughing episode, with nearly continuous coughing for one full hour. Vomiting due to the severity of the coughing. Lying down made the coughing worse. No wheezing, no skin rash. A “puffy left eye” was noted. 5 mL of a cough syrup containing guaifenesin and the antihistamine oxomemazine—a phenothiazine derivative—was given. The coughing subsided when the boy was drowsy enough to fall asleep.

Day 2 of Malaria Treatment

6.00 a.m. Another coughing episode, less severe than the night before. The swelling of the eyelids had disappeared. 5 mL of cough syrup were given.
11.30 a.m. 3rd dose of 4 tablets of artemether–lumefantrine.
Severe coughing episode, similar to the one the night before. Bilateral edematous swelling of eyelids. 7.5 mL of cough syrup were given. The coughing subsided after about 1 h.

Day 3 of Malaria Treatment

5.30 a.m. Loratadine was continued for 6 days. The edematous swelling of the face and eyelids disappeared over the next 2 days. Except for a slight cough on the evening of day 3, which was treated with a codeine-based cough syrup, the cough did not recur. The remainder of the illness was uneventful.

Discussion

The delayed malaria diagnosis appears to have been due to a slowly increasing parasitemia under chloroquine–proguanil prophylaxis, with a resistant parasite.

Our patient had no history of drug or other allergies. He had never suffered from angioedema. There is a family history of hay fever (grandmother), eczema (father) and asthma (sister), but not angioedema. In 1995, and twice in 1996, he was treated for malaria, the first and second episodes with quinine, and the third with artesunate, all without adverse effects. Prior to the artemether–lumefantrine treatment, he had received only one dose of 325 mg of paracetamol (acetaminophen) and another dose the same evening, but none afterwards. Although he had been suffering from a slight cough during the previous 3 weeks, he had not had a coughing episode like the ones described and had not required cough medication before malaria treatment.

In our patient, the severe coughing episodes and the edematous swellings appeared approximately 4.5 to 7 h after each intake of the antimalarial. In the package insert, included with the artemether–lumefantrine, the manufacturer mentions cough, among other common side effects that usually do not require treatment. One study, published by the manufacturer, reports cough in 2.1% of adults and 11.3% of children. In the discussion of the study, cough and other common events are considered more likely to be predominant symptoms that overlap with the underlying disease and concurrent illnesses. Neither severe coughing episodes nor angioedema are mentioned. The narrow time frame between our patient’s drug intake and his severe coughing episodes make an adverse effect of the antimalarial highly likely.

Price et al.,9 in a large study, found no evidence that artesunate and artemether caused allergic, neurologic or psychiatric reactions, or cardiovascular or dermatologic toxicity. However, single reports have been published regarding suspected neurotoxicity due to artesunate, and acute asymptomatic hepatitis after artesunate, in combination with amodiaquine. To our knowledge, no allergic reactions to the combined drug artemether–lumefantrine have been reported elsewhere to date. Leonardi et al.13 describe 2 cases of severe allergic reaction to oral artesunate and report an additional 4 patients with an urticarial rash. We found no reports of allergic reactions to lumefantrine (benflumetol) during an internet literature search.

The boy’s previous exposure (and possible sensitization) to artesunate in 1996, but not to lumefantrine, the recurring and increasing symptoms of severe cough and facial angioedema after the second and third artemether–lumefantrine doses, and the clinical improvement upon administration of an antihistamine, suggest that the reaction was due to hypersensitivity to the Qinghaosu metabolite dihydroartemisinin. Both artesunate and artemether are quickly metabolized to dihydroartemisinin, the biologically active compound.14

The use of Qinghaosu antimalarials appears to be surprisingly widespread in West and Central Africa. Artesunate has been readily available under different brand names in pharmacies in Cameroon for more than 6 years, and artemether–lumefantrine for about 3 years. We have found that, over the past few years, different brands of artesunate, artemether and dihydroartemisinin drugs, produced by Chinese, Korean, French, Belgian and Swiss companies (as tablets, syrup, and rectocaps, and in parenteral form), have been introduced extensively in West and Central Africa. The drugs may be purchased in pharmacies with a prescription, or, upon insistence, without one. They are frequently sold in marketplaces.

There seems to be a certain “drug pressure” introduced by the manufacturers, which is supported by the apparent lack of regulatory restrictions, for the use of Qinghaosu derivatives in the different countries, and they are readily prescribed for patients who can afford them. A treatment with artesunate or artemether–lumefantrine costs US$6 to US$7. It is our impression that the lack of significant side effects of Qinghaosu drugs has led to their increased use among expatriates, in cases of fever or simply fatigue, without laboratory testing for malaria being done. This practice has already been observed in
other parts of sub-Saharan Africa. With easier affordability and availability, the same can be expected for the indigenous population. This may therefore result in a higher frequency of adverse effects in this part of the world, although it is doubtful that they will be routinely reported.

References


Lake Nyos with carbon dioxide vent, Cameroon, Africa. Submitted by Julie Staples, RN.