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CASE REPORT

Chinawa JM

Adverse Drug Event From Artemether/lumefantrine Ingestion: Case Series

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Chinawa JM (✉)
Department of Paediatrics
University of Nigeria, Enugu Campus,
& University of Nigeria Teaching Hospital ,Ituku - Ozalla, Enugu.
Email: josephat.chinawa@unn.edu.ng

Abstract We present rare cases of three adverse drug events from artemeter-Lumefantrine(AL) ingestion. This is an antimalaria combination therapy used in the management of malaria. Adverse reaction is rarely reported when using this drug.
We report these cases of our patients who developed urticaria and bullae. One had hypotension few hours after taking AL. We report these cases to show that though rare, adverse drug event can occur in AL.
Conclusion: Artemesinin combination therapy though safe in children, is not without adverse reaction.

Key Words: artemeter-Lumefantrine; Children; Adverse drug event.

Introduction

Malaria is one of the most significant causes of morbidity and mortality worldwide, causing approximately 881,000 deaths every year .[1] The current WHO guidelines for the treatment of malaria recommend the use of artemisinin-based combination therapy (ACT) owing to *Plasmodium falciparum* resistance to monotherapy .[2] Artemether/lumefantrine (AL) was the first fixed-dose combination of ACT to be approved by the European regulatory authorities according to the requirements of the International Committee on Harmonization (ICH). Artemether is derived from the Chinese herb sweet wormwood (Artemisua annua). The antimalarial properties of artemether stem from interference with parasite transport proteins, disruption of parasite mitochondrial function, inhibition of angiogenesis, and modulation of host immune function.[3] Artemether is absorbed very rapidly after oral administration reaching peak plasma concentrations within 2 hours after dose .[4,5] It has a half-life of 1–3 hours. It is metabolized quickly via CYP450 2B6, CYP450 3A4 and possibly CYP450 2A6 to the more potent antimalarial metabolite DHA, which in turn is converted to inactive metabolites primarily by glucuronidation via UGT1A1, 1A8/9 and 2B7.[6] Artemether induces CYP450 2C19 and 3A4. These metabolites may be a major trigger for adverse reaction.

Lumefantrine is an aryl-amino alcohol that prevents detoxification of heam, such that toxic heam and free radicals induce parasite death .[7] Lumefantrine absorption occurs 2 hours after oral intake reaching peak plasma concentration after 3-4 hours .[7] It has a half life of 3–6 days and is responsible for preventing recurrent malaria parasitemia. Lumefantrine is metabolized by N-debutylation mainly by CYP450 3A4 to desbutyl-lumefantrine with 5–8-fold higher antiparasitic effect than lumefantrine. Lumefantrine inhibits CYP450 2D6 .[8]

Adverse effects are rare.[3] There have been case reports of neurological problems (including ataxia, nystagmus, tremor and slurred speech) occurring after administration of herbal artemisinin or artesunate monotherapy .[9] However, it is questionable whether these neurological effects are related to artemisinin treatment.

Case series

Case 1

YI is a 7 year old female who presented with fever and cough of 2 days duration. Fever was low grade and intermittent while cough was unproductive with no difficulty in breathing. An empirical diagnosis of Malaria was made, following this, mother gave TM (*Ajanta pharma limited.MFD 07/2011.EXP 06/2013*) 2 tablets (*40mg lumafanthrine+240mgartesunate*), twice a day for 3 days(*This is appropriate for child's weight*). Few hours after the first dose of the drug, she was found to have developed urticarial rashes on the face and bullae on the lips. This rash was itchy and makes patient uncomfortable. There was slight wheeze and catarrh. Child had been treated with this drug before. There was no history of drug allergy.

Examination revealed pyrexia (38^{o}c), fast and rapid pulse (114 beats per minutes) and Blood pressure of 80/50mmHg. A diagnosis of adverse drug reaction was made. The drug was withdrawn and she was commenced on Intravenous promethazine and hydrocortisone for 3 days. The rash cleared, fever subsided and clinical signs were stable three days after therapy.

Case 2

EK is a 3- year old male who presented in a clinic with a two days history of fever, vomiting, diarrhea and weakness of 3 days duration. On examination, he was found to be lethargic but in no obvious respiratory distress. Other findings were normal. He was diagnosed as acute uncomplicated malaria and then placed on Intravenous fluids and Intravenous Artesunate. Just few minutes later, we noted generalized urticarial rash and maculopapular rash. Vital signs were within normal ranges.
A diagnosis of adverse drug reaction was made, and patient was placed on Intravenous hydrocortisone and promethazine. The rash cleared thereafter.

Case 3

B is a 3 month old male who presented with fever and poor sucks at breast of three days duration. Systemic examination revealed no obvious abnormality. A tentative diagnosis of malaria was made. He was given intramuscular Artemerter, after which fever subsided. The parenteral drug was then changed to syrup P-alaxin 8mls daily for three days. On the third day of commencement of this drug, baby was brought back to the hospital with an urticarial and maculopapular rash. Pulse rate then was 142 beat per minute and respiratory rate was 68 cycles per minute (tachypnoea). The patient was managed with antihistamine and low dose steroid; he is doing well as at the time of writing this report

Discussion

Adverse drug reaction is an unpleasant reaction, which results from an intervention related to the use of a medicinal product which predicts hazard from future administration, and warrants prevention or a specific treatment or alteration of the dosage regimen or withdrawal of product.[9]
Adverse drug reactions caused by immune and nonimmune mechanisms are a major cause of morbidity and mortality worldwide. They are the most common iatrogenic illness, complicating 5 to 15 percent of therapeutic drug courses.[10] Three to six percent of all hospital admissions are because of adverse drug reactions, and 6 to 15 percent of hospitalized patients (2.2 million persons in the United States in 1994) experience a serious adverse drug reaction.[10]

The body's response can affect many organ systems but the skin is the organ most frequently involved as seen in our patients.[11] Symptoms of Artemeter -Lumafanthrine vary and could present as urticarial rash, itching, swelling of the lips, wheezing, hives and systemic features as hypotension, fainting, palpitations etc. Our patients presented with uticarial rash, itching and swelling of the lips and hives but only one presented with hypotension. [12] At times it can make the skin blister and peel: A phenomenom called Toxic epidermal necrolysis(TEN).[11] None of our series presented with palpitations nor TEN. Combisunate is an artemether-lumefantrine derivative which side effects were mild, did not lead to artemether-lumefantrine discontinuation, and can resolve. Hartz et al noted that artemether-lumefantrine 6-dose regimen was discontinued in 0.2% of adult patients due to side effects. He also noted few adverse effects in his series.[12] Urticaria was reported in less than 3% of his patients. Serious skin reactions (bullous eruption) have been reported rarely during postmarketing experience.[13] Neurological deficits and ototoxicity have been reported in some cases of artemerter –Lumenfantrin ingestion.[13] our series had urticaria and a bullous eruption on their lips but no neurological deficits or hearing problems. The relationship between the drug intake and the onset of clinical symptoms is critical. Unless the patient has been previously sensitized to a drug, the interval between initiation of therapy and the onset of reaction is rarely less than one week or more than one month.[11] Our first and second cases occurred few hours after initiation of therapy while the third occurred after two days.

The most important measure in managing drug hypersensitivity reactions is the discontinuation of the offending medication.[14] Alternative medications with unrelated chemical structures should be substituted when available. In the majority of patients, symptoms will resolve within two weeks if the diagnosis of drug hypersensitivity is correct.[14] All the signs and symptoms resolved in one of our patients within minutes while the other two happened in just three days after treatment. Additional therapy for drug hypersensitivity reactions is largely supportive and symptomatic.[11] Systemic corticosteroids may speed recovery (as in our patient) in some cases of drug hypersensitivity. [11] Topical corticosteroids and oral antihistamines may improve dermatologic symptoms. Antihistamines were used in all our cases and we had good response.

Conclusion

Artemether-lumefantrine combination can lead to minor skin related adverse events.

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