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Case Report

Adverse Effects and Safety Issues with Use of α/β-Arteether for Treatment of Severe *Falciparum* Malaria: A Case Report on Drug-Induced Dermatitis

HATASO

Adverse Effects and Safety Issues with Use of α/β-Arteether for Treatment of Severe *Falciparum* Malaria: A Case Report on Drug-Induced Dermatitis

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Abstract
The use of artemisinin derivatives has become the mainstay in the treatment of both severe and uncomplicated *falciparum* malaria. The available report suggests that the derivatives are safe and well tolerated in most patients, with only a few cases of severe adverse drug reactions to some of these derivatives. In the present report, a 30-year-old breastfeeding mother and a resident of Ekpoma, Edo State, Nigeria, who on presentation was diagnosed with severe malaria, developed pruritus 4–6 h after receiving the first dose (150 mg) of intramuscular αβ-arteether. This condition became more intense with widespread pruritic rash and extensive erythematous eruptions and excoriating skin lesions following the second dose of the drug. However, the administration of the drug was discontinued on the third day with the eruptive lesions abating following the administration of antihistamines and steroids (loratadine and prednisolone) for 5 days. In conclusion, the clinical manifestation shows the case of an αβ-arteether-induced dermatitis secondary to an immediate hypersensitivity reaction, which is a rare occurrence with the drug. The adverse drug reaction to this agent also emphasizes the need for postmarketing surveillance and monitoring of most artemisinins, particularly in sub-Saharan Africa where they are being increasingly used for the treatment of malaria.

Keywords: Artemisinin derivatives; Malaria; Hypersensitivity reaction.

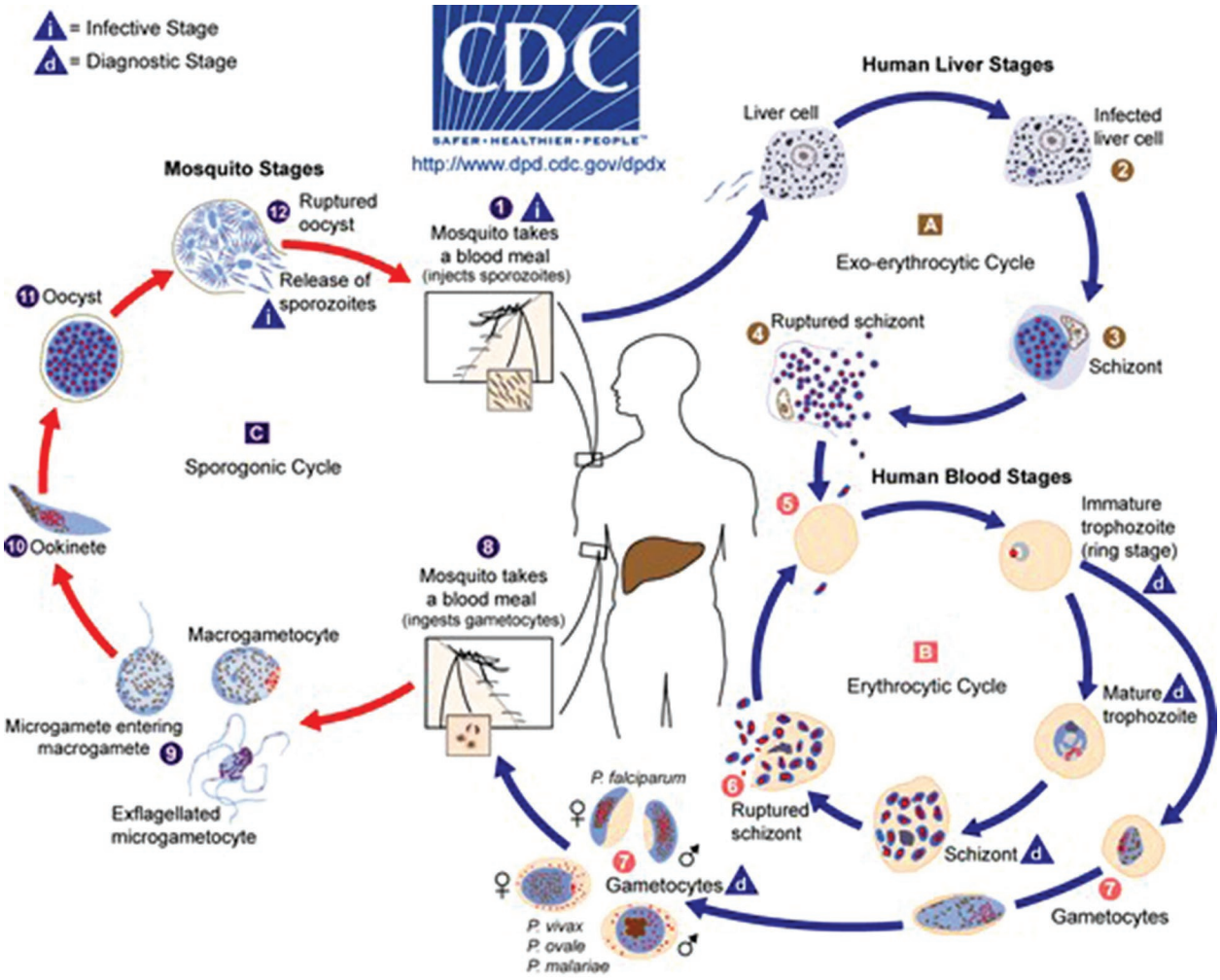
1. INTRODUCTION

Malaria is an agelong public health problem that is still ravaging Africa. It accounts for two-thirds morbidity and mortality among children resident in sub-Saharan Africa. A report from the World Health Organization (WHO) shows that the African region accounts for 92% of the global malaria burden compared to the Southeast Asian and Eastern Mediterranean regions, which contribute 5 and 2% to the global burden, respectively [1]. Malaria infection occurs following the bite of an infected female anopheles mosquito, which releases sporozoites into the blood of the human host. The sporozoites invade the hepatocytes and undergo asexual replication to develop into merozoites that are released into the bloodstream. The merozoites then invade the red blood cells (RBCs) and develop into schizonts with the eventual release of merozoites following the rupture of the parasitized RBCs [2]. The released merozoites reinvade RBCs to begin another replicative cycle (Figure 1).

Moreover, in individuals, the infection can progress from an asymptomatic stage to a stage of uncomplicated malaria and then to severe malaria resulting eventually in death if left untreated. Factors that influence the varied manifestations and progress of the disease include the parasite species, the host intrinsic or acquired immunity, and the timing and efficacy of the treatment given to patients [3]. Although *Plasmodium falciparum* has been implicated as the major cause of severe forms of the disease, other species such as *P. vivax* and *P. knowlesi* have also been implicated in severe or complicated malaria [1, 3].

Over the years, the quinolines have been the mainstay of treatment until the emergence of resistance to chloroquine, which was first reported in the Cambodia–Thailand border in the 1950s. This subsequently spread through Southeast Asia to other malaria-endemic regions of the world [4]. From that time until now, there has been an emergence of multidrug-resistant strains of *P. falciparum*, which has further constituted a challenge to malaria treatment [5]. Although research on the use of potent antimalarial vaccines is still ongoing, with the RTS,S being the first vaccine to demonstrate partial protection against malaria in children [6], the use of chemotherapeutic agents remains a vital tool in combating malaria. The artemisinin derivatives remain the most effective agents available and are being used in a combination regimen with antimalarials from other chemical groups and with different mechanisms of action with the advantage of ensuring rapid parasite clearance and delaying the emergence of drug-resistant strains in the population [5, 7, 8]. Several clinical and meta-analysis reports have suggested that

Figure 1: Life cycle of *Plasmodium* [2].



the artemisinins and their derivatives are generally safe and efficacious and have minimal adverse effects [8-13]; however, there is no known report of αβ-arteether-induced exfoliative dermatitis in sub-Saharan Africa. Additionally, clinical research evidence shows that the drug is generally safe; however, most large-scale trials cannot detect rare adverse effects. Also, reports are scanty about large-scale clinical trials with regard to the drug in sub-Saharan Africa; hence, the case report lays credence to the need to mobilize tools and resources for active pharmacovigilance and monitoring of the drug to improve the safety of its use in the population.

2. ETHICS AND PATIENT CONSENT

Ethical approval is not required for such a study in the authors' institution. However, in presenting this report, a written informed consent was obtained from the patient both for the presentation of the report and the display of the images on drug-induced eruptive skin lesion.

3. CASE REPORT

A 30-year-old breastfeeding mother with a body mass index of 24 kg/m^2 and a temperature of 39°C at presentation complained of fever, abdominal discomfort, and diarrhea, all of 1-day duration. Symptoms were of sudden onset and were associated with weakness and generalized body pain. On examination, she was found to be acutely ill-looking, markedly febrile, and anicteric. There was evidence of tachycardia and associated postural hypotension. An initial assessment of gastroenteritis was made, and the patient was rehydrated with 2.5 L of normal saline and was placed on observation pending the outcome of laboratory

Table 1: Results of laboratory investigation.

FBC		Urinalysis		E/U/CR		LFT	
Pcv 37.7%		Specific gravity	1.025	Bicarbonate	23 mmol/L	Total Bilirubin mg/dL	0.9
Hb 12.8 g/dL				Chloride	104 mmol/L		
RBC 4.18×10^9/L		pH 6.0		Potassium	4.2 mmol/L	Conj. Bilirubin mg/dL	0.5
MCV 89.5 fL		Bilirubin	-	Sodium	140 mmol/L		
MCH 30.6 pg		Urobilinogen	-	Urea	11 mg/dL	AST IU/L	17
MCHC 34.2 g/dL		Leucocyte	-	Creatinine	0.7 mg/dL		
RDW 13.8% W		Protein	-			ALT IU/L	8
Platelet 294,000/mm^3		Ascorbic acid	-				
MPV 8.4 fL		Ketones	-			ALP IU/L	34
PDW 12.2		Nitrites	-				
ESR 60 mm/h		Glucose	-				
TBW 9800/mm^3							
Neutrophil = 85.5%							
Lymphocyte = 9.2%							
Monocyte = 4.5%							
Eosinophil = 0.7%							

NB: FBC = Full Blood Count; E/U/CR = Electrolyte, Urea, and Creatinine; LFT = Liver Function Test.

investigation. The laboratory result ruled out viral hemorrhagic fever, which is endemic in the community, but confirmed the presence of *P. falciparum* malaria (*P. falciparum* count 9,000/μL). Full blood count, urinalysis, and electrolyte, urea, and creatinine were within the normal range (Table 1). The patient was subsequently administered with intramuscular αβ-arteether at a dose of 150 mg daily for 3 days. She later developed generalized pruritus 4–6 h after the first dose. The pruritus became more intense with subsequent administration of the drug, and by the third day when the drug was discontinued, a generalized eruptive, erythematous, and scaling skin lesion (Figures 2a and 2b) was observed in the patient, which culminated in the administration of loratadine and prednisolone for 5 days. The medical history suggests that the patient was being placed on αβ-arteether for the first time and has been exposed to other artemisinin drugs without any prior adverse reaction. Apart from chloroquine, which elicited a similar response in the patient in the past, there was no history of an adverse drug reaction to any other antimalarial drug.

4. DISCUSSION

Alpha/beta-arteether is an artemisinin derivative used in the treatment of uncomplicated and severe forms of *P. falciparum* malaria resistant to chloroquine, mefloquine, halofantrine, quinine, pyrimethamine, cycloguanil, and amodiaquine. It is a lipid-soluble ethyl ether with a heterocyclic ring structure (Figure 3) and a molecular formula of $C_{34}H_{56}O_{10}$ [14]. It is usually compounded in an oil-based vehicle. Additionally, it is made up of a racemic mixture of the α- and β-diastereomers of the drug in a ratio of 30:70, and it is available in injectable formulations containing 150 mg of the active agent dissolved in 2 mL of *Arachis* oil or 80 mg dissolved in 1 mL of *Arachis* oil [15]. The drug is chemically more stable than other artemisinins and is administered intramuscularly at a dose of 150 mg daily for 3 consecutive days achieving a total dose of 480 mg or at a dose of 3 mg/kg/day in children and adults weighing up to 50 kg [15, 16]. However, novel oral preparations are still being investigated [16, 17]. The drug is an effective and rapidly acting schizonticidal agent with gametocytocidal action against *P. falciparum*, with a high cure rate and low recrudescence reported for most patients treated with the drug [9, 10].

Additionally, the drug has an endoperoxide bridge that interacts with heme ingested by the *Plasmodium* parasite. This leads to a feton-induced cleavage of the peroxide bridge with the release of hydroxylated reactive molecules that cause peroxidative damage to the parasite membrane and other molecules within the parasite, resulting in the inhibition of protein synthesis and death of the parasite [11, 13, 15]. The other proposed mechanism of action of the drug includes the carbon-centered destruction of the *P. falciparum* sarcoplasmic endoplasmic reticulum ATPase (*SERCA*) gene, which is essential for parasite survival [18].

This report has shown that the drug is well tolerated in most patients [5, 8]; however, there have been few reports of hypersensitivity reactions, which may be due to the active compound or the oil-based vehicle [8, 19]. Although adverse effects, such as headaches and gastrointestinal disturbances, have been reported [8], the observation of an immediate hypersensitivity response characterized by generalized pruritus and erythematous eruptive lesions with a scaly surface is a rare occurrence with the drug in this environment. The underlying pathophysiological process of the response is mediated by immunoglobulin E (IgE) antibodies that bind to mast cells and basophils in the skin following sensitization by an allergen [20]. The medical history suggests earlier predisposition with chloroquine since the patient experienced a similar reaction following exposure to the drug in the past. The administration of αβ-arteether may have elicited IgE-mediated degranulation of mast cells and basophils resulting in the release of histamine and other pro-inflammatory cytokines.

Figure 2a: Eruptive skin lesion involving the lateral surface of the thigh.

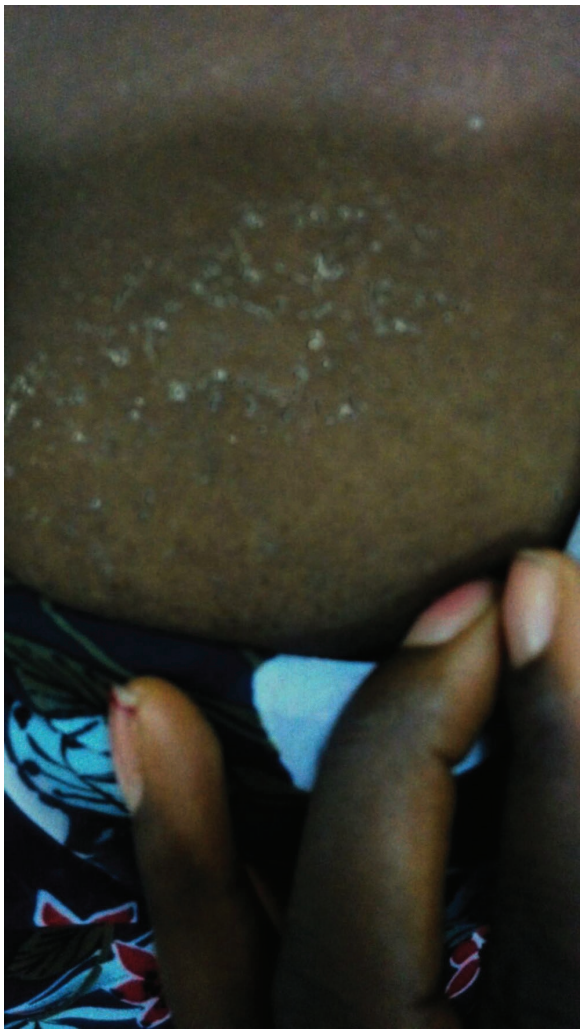


Figure 2b: Eruptive skin lesion of the ventral surface of the thigh bilaterally.

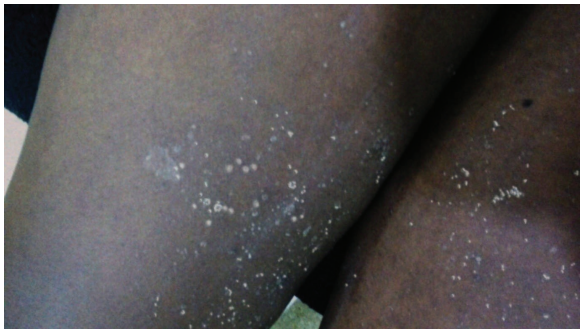
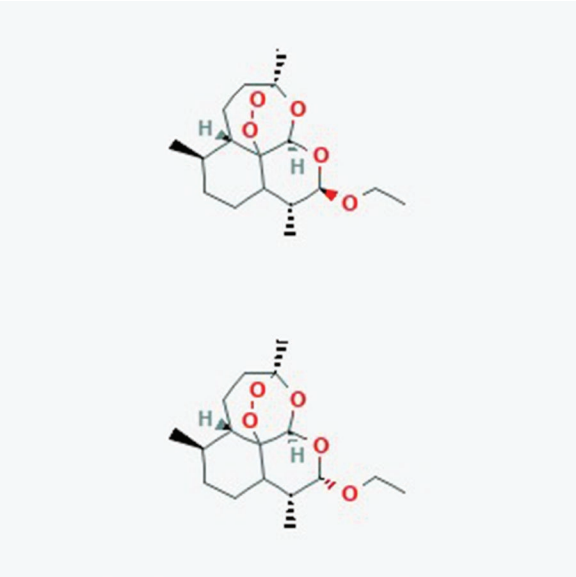


Figure 3: Chemical structure of α- and β-arteether (first and second images) [14].



However, studies have shown that the adverse effect profile of most artemisinin derivatives is determined by the particular agent [8]. Moreover, the possibility of a drug–drug interaction as the predisposing factor to the hypersensitivity response cannot be overemphasized. The gene primarily involved in the metabolism of arteether is the *CYP3A4* gene with a secondary contribution from the *CYP3A5* gene [18]. These genes can be inhibited when the drug is coadministered with protease inhibitors or antifungal agents, such as ketoconazole, or stimulated with drugs, such as carbamazepine and phenobarbital [18, 21]. Although the underlying drug history of the patient suggests chloroquine-induced predisposition, studies have shown that drugs, such as ketoconazole, can potentiate the antimalarial activity of αβ-arteether and thus also predispose to toxicity [21, 22].

Additionally, apart from hypersensitivity reactions to the drug, other reports from preclinical studies have shown that arteether has neurotoxic potential based on the finding of neurotoxic degenerative events observed in rats and dogs. These neurotoxic events mainly involve the vestibular, motor, and auditory functions of the experimental animal [23–25]. Although this was not reported in clinical trials, there is a report of αβ-arteether-induced neuropsychiatric manifestations in an adolescent with a family history of chloroquine-induced psychosis [26, 27]. Moreover, in preclinical studies, arteether demonstrated a significant prolongation of QTc interval with none of such changes observed in clinical studies [7]. Similarly, the finding of embryotoxic changes in animal studies [7, 27, 28] informed the decision of WHO to recommend the use of the drug only in the second and third trimesters of pregnancy despite lack of clinical evidence of embryotoxicity [6].

5. CONCLUSION

Most clinical studies showing the toxicity profile of αβ-arteether were done in a sample population that represents a tip-of-the-iceberg of the actual population exposed to the regular use of the drug. Also, very few such studies were conducted in sub-Saharan Africa, where malaria is endemic; hence, the possibility of underreporting of adverse reactions in this setting. There is, therefore, the need to strengthen postmarketing surveillance systems in the sub-Saharan African regions.

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Conflict of Interest
None.

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