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Severe Allergic Reaction to Oral Artesunate-Amodiaquine Combination Treatment for Malaria: Case Report in the Democratic Republic of Congo

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Abstract

Background: In 2012-2013, a pilot study on implementation of community-based case malaria management by trained community health workers was implemented in southern Katanga Province in the Democratic Republic of Congo (DRC). We report one case of severe adverse reaction that was linked to artesunate-amodiaquine (ASAQ). **Case summary**: An apparent healthy, 15-year-old Congolese female with a positive rapid diagnostic test for *Plasmodium falciparum* without any sign of complications was prescribed a fixed dose combination of ASAQ. Under direct observation, she took two tablets of ASAQ (200 mg AS/540mg AQ total) with water. Approximately 30 minutes later, she developed a generalized pruritus and widespread urticarial rash, with marked periorbital and forearm swelling. She was immediately referred to the nearest clinic. She did not present with fever or any respiratory distress and was fully conscious. She received dexamethasone 8 mg IV, followed 20 min later by 4 mg of chlorphenamine orally. Approximately 40 minutes after, the rash and swellings had mostly resolved. She received oral quinine as a second line treatment. **Conclusion**: This single presentation was the only such occurrence from 1354 malaria-infected patients. As ASAQ is the most widely used first-line treatment in the DRC, increased awareness and close monitoring of the use of this drug are advised. Health care professionals should document, report and provide immediate medical assistance.

Subject Areas

Allergy & Clinical Immunology, Infectious Diseases

Keywords

Artesunate-Amodiaquine, Malaria, Adverse Event, Allergy, Case Report, Democratic Republic of Congo

1. Introduction

Oral artemisinin derivatives in combination with one or more other anti-malarial ingredients are recommended for the treatment of uncomplicated *Plasmodium falciparum* malaria in clinical and community settings by trained, supervised Community Health Workers (CHWs) [1] [2]. They are generally safe, well tolerated, and highly effective in rapidly clearing parasitemia and ultimately infection, and the preferred alternative for the treatment of multidrug-resistant Falciparum malaria [1] [3] [4] [5]. Herein we report one case of severe acute allergic reaction that was attributed to the combination of oral artesunate and amodiaquine.

In 2012, a pilot study investigating the deployment and feasibility of a community malaria case management strategy was carried out in a group of high malaria prevalence villages in southern Katanga Province (now Lualaba Province) in the Democratic Republic of Congo (DRC) [6]. The objective was to assess the feasibility and impact of prompt diagnosis using rapid malaria diagnostic tests (RDTs) and immediate effective treatment with an approved artemisinin combination therapy (ACT) administered by trained volunteer CHWs.

The ACT used in the study was a fixed dose combination of artesunate-amodiaquine (ASAQ) [Winthrop®] manufactured by Maphar (Morocco) under license by Sanofi Aventis, France (Batch 5489, MFG 04/2012, EXP 04/2015). The study took place over a continuous 10-month period from November 2012 to August 2013 targeting 3343 people residing in 14 rural villages. During this period, a total of 1354 persons of all ages found infected with malaria using the RDT (SD BIOLINE Malaria Ag P.f/Pan test, ref 05FK60, lot number 090158 from Standard Diagnostics Inc., Korea) received oral ASAQ.

2. Case Presentation

An apparently healthy 15-year-old native Congolese female, approximately 38 kg body weight, presented to the CHW in her village for an RDT and provided a small amount of blood by finger prick. She had a reactive RDT for *P. falciparum* with no signs of complicated malaria infection as judged by set case presentation criteria provided to the CHW [6] and was immediately prescribed oral ASAQ. Under direct observation, she took two tablets of ASAQ (total initial dose 200mg AS + 540 mg AQ) with water as part of a normal 3-day therapy based on age (≥14 years old) of patient at time of treatment. Treatment administration also met body weight (≥36 kg) criteria for the specific ACT product use. Approximately 30 minutes later, she developed a generalized pruritus and widespread urticarial rash, with periorbital and forearm swelling (**Figure 1** & **Figure 2**). The

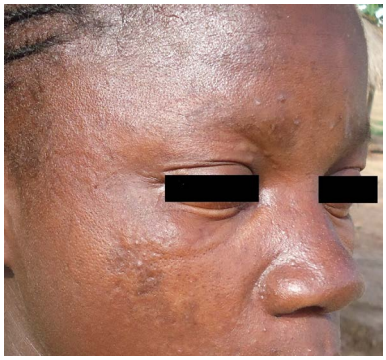

Figure 1. Urticarial rash on face and periorbital area with swelling 30 minutes after taking a fixed dose combination of artesunate-amodiaquine in a 15-y.o. female.

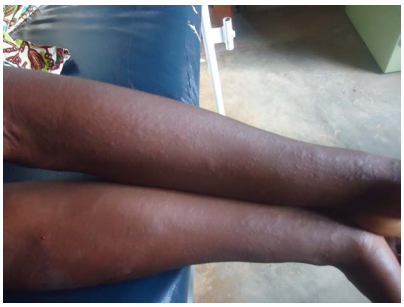

Figure 2. Generalized pruritus and urticarial rash with forearm swelling.

reaction was deemed 'severe' and she was immediately referred to the nearest public medical clinic where she arrived less than 10 minutes after referral. She did not present with high fever despite having malaria or any evidence of respiratory distress and was fully conscious and lucid throughout. At initial presentation, her blood pressure was 90/60 mmHg with a pulse of 110/min. Given the limited capacity of the health care facility, no other clinical measurements were made. She was immediately provided dexamethasone 8 mg IV, followed 20 min thereafter by 4 mg of chlorphenamine orally. Approximately 40 minutes after the first medication was given, the rash and swellings had mostly resolved. She recovered fully from the adverse reaction with no obvious post-event sequel. Medication was based on standard dosing prescribed for adults in response to severe allergic reactions: dexamethasone 6 - 8 mg IV as a single dose and to be repeated, if necessary. In our case, there was no need to repeat dexamethasone, and oral chlorphenamine was provided in the follow up. For malaria, the patient was provided oral quinine (500 mg every 8 hours for 7 days) as a second line treatment and was advised not to take ASAQ again unless under direct medical supervision.

3. Discussion

Adverse reactions attributed to ASAQ are infrequently reported, as it may be a rare event. However, health care professionals and community health workers should be aware that adverse reactions can occur and are advised to quickly refer the patient to a health care facility for appropriate case management.

This case report was an independent observation in the context of a larger pilot study looking at the feasibility of implementing a community-based diagnosis & treatment program in the DRC [6]. The described adverse reaction was not a specific component or intent of the study design. During the 10-month pilot study, a total of 6619 contact cases, including 1803 children below 5 years of age with fever and other malaria-like symptoms were seen by the CHWs. Of these, 1354 (20.4%) had a positive test for malaria-infection and were duly treated with ASAQ. One malaria case (0.07%) presented an acute allergic reaction immediately following standard antimalarial treatment as described herein.

Upon interview, the patient did not recall having received ASAQ previously for malaria infection. The patient's mother reported that the case had had malaria several times when younger but she could not recall the medication provided or if she had received an artemisinin derivative as a monotherapy, with another drug, or in a fixed-dose ACT. However, the lack of strict application to DRC Ministry of Health guidelines that prohibit administration of artemisinin monotherapy and the fact that various forms of artemisinin synthetic derivatives could be easily obtained in the open market pharmacies that are ubiquitous in the country presumes that she could have been exposed previously to either artesunate or amodiaquine, alone or in combination.

On rare occasions, amodiaquine is associated with causing a pruritus as an allergic, drug-induced reaction [7] [8]. But generalized pruritus and widespread urticarial rash, with patent periorbital and forearm swelling as was witnessed with this particular case has not been reported in connection with the use of amodiaquine alone. Serious and life-threatening adverse reactions due to amodiaquine have been described during its use as routine anti-malarial chemoprophylaxis [9]. The risk of developing agranulocytosis appears to be between 1 in 2000 to 2200 with a risk of death in such cases as 1 in 31,300 and 1 in 15,650 for serious hepatic reactions [9].

Overall, artemisinin and its various synthetic derivatives are overwhelming safe and remarkably well tolerated in the vast majority of people [3] [4] [5]. For example, Leonardi *et al*. [10] reported only two cases of severe adverse reaction of type 1 hypersensitivity due to oral artesunate in approximately 1 in 3000 patients treated.

More recently, Ndounga *et al*. [11] reported pruritus in four children and rashes in one child in the Republic of Congo based on a cohort of 129 children under 10 years of age treated with ASAQ. Skin manifestations (rash, pruritus) were mostly observed in children under-five years of age. However, pruritus was not observed until the third and final day of treatment (2 cases), on day 4 (1 case) and day 7 (1 case). The single case of rash was not noted until day 8 following initial treatment. The allergic reactions seen in our case were immediate (within 30 minutes) and closely associated with the first dose of ASAQ. Onyamboko *et al*. [12], based on analyzed on cohort of 221 children aged from 3 to 59 months in the Democratic Republic of Congo did not observe any adverse skin manifestations in a ASAQ-treatment group. Clinical tolerability of a fixed-

dose combination of ASAQ has been recommended and deployed for the management of uncomplicated malaria in several malaria-endemic countries in recent years [13] [14] [15]. Gastro-intestinal disorders and physical weakness are the most common reported adverse reactions but classified as minor or mild together with transient pruritus, rash and other minor events [13] [14] [15].

Our observations cannot definitively determine which drug component was responsible for the allergic outcome or if it might have been a synergistic effect from both drugs. Due to ethical concerns for this patient, we were unable to perform a provocation test with each drug to determine probable causative agent. In our observations, only one allergic reaction was reported from 1354 treated patients who received observed ASAQ therapy. This ratio is lower compared to what has been published elsewhere [10]. The lower number of people under direct observation in our study may be one explanation for this observation.

4. Conclusion

ASAQ is the current and most widely used first-line ACT treatment for uncomplicated falciparum malaria approved by the DRC National Malaria Control Program and provides free-of-charge at clinics and in the community. Although severe adverse reactions with ASAQ are relatively rare events, given its reported profile compared to other treatment combinations, an increased awareness and close monitoring of this drug combination are advised. In accordance with the DRC national malaria policy, ASAQ treatment failures or complications should be treated with artemether-lumefantrine (AL), or alternatively with quinine as a second-line therapy. This and other cases of documented adverse reactions following administration of ASAQ suggest that an alternative first-line drug like AL should be readily available to treat patients who are reluctant to take ASAQ due to side effects or past history of allergic reactions. Health care professionals providing ASAQ should document, report and be prepared to provide immediate medical assistance to patients who might experience adverse allergic reactions to this treatment combination.

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The case report was an independent observation made during the pilot study on community-based malaria diagnosis and treatment. The noted adverse reaction was not a specific part or a component of the study design.

Conflict of Interest

The authors declare that they have no competing interests.

Consent

Written informed consent was obtained from the patient's legal guardian for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Authors' Contributions

EKS was the principal investigator, CK as field Supervisor and OLN as public health advisor. EKS, OLN and MJB wrote the manuscript. All authors have read and approved the final manuscript.

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List of Abbreviations

ACT: Artemisinin combination therapy;

AL: Artemether-lumefantrine;

ASAQ: Artesunate-amodiaquine;

CCMm: Community case management of malaria;

CHWs: Community health workers;

DRC: Democratic Republic of the Congo;

RDT: Rapid diagnostic test.