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SEVERE IDIOSYNCRATIC DRUG REACTION (LYELLS SYNDROME) AFTER INGESTING DIHYDROARTEMISININ

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ABSTRACT
Lyells syndrome also called Toxic epidermal necrolysis is the extreme form of idiosyncratic drug reaction that is called Steven Johnsons Syndrome. The condition results in an extensive loss of the skin with mucous membrane involvement. Lyells syndrome has been induced by many agents. The commonest agent in the literature being sulphonamides. However, in our search of the medical literature there was no report of dihydroarthemisinin as a cause of Lyells syndrome.
We report three patients seen at two tertiary health institutions with Lyells syndrome after treatment for malaria with dihydroarthemisinin. This resulted from administration of dihydroarthemisinin with chloroquine in two patients and dihydroarthemisinin with Amodiaquine in one patient. The first patient was a seven year old child who developed 90% cutaneous involvement and died from hemorrhagic shock. The second was a 28 old female that developed a 76% body surface involvement and died from septicemia. The third patient was a pregnant 37year old woman that developed 52% body involvement and died from septic shock. In these patients the earliest symptoms were not recognized and there was considerable delay before referral.
In view of the recent WHO recommendation of Arthemisinin Combination Treatment (ACT) for malaria, we expect more cases of Steven Johnson Syndrome and Lyells syndrome from ACT treatment. The aim of this report is to raise the awareness of clinicians to this potentially fatal complication.

Key Words: Lyells syndrome; toxic epidermal necrolysis; artemisinine *(Accepted February 25 2008)*

INTRODUCTION
Toxic Epidermal Necrolysis (TEN) also known as Lyells Syndrome (LS) is a rare condition, causing a widespread life threatening muco-cutaneous disease resulting from idiosyncratic reaction to drugs. It is considered by many to be the severe form of Steven Johnson syndrome (SJS). Both LS and SJS present with muco-cutaneous involvement and are precipitated by similar agents. The classification separates these entities, based on extent of cutaneous skin loss[1]. It is classified as TEN when the involved area of skin is more than 30% and SJS when less than 10%. Steven Johnson syndrome-Toxic Epidermal necrolysis (SJS/TEN) is used to describe the cases between 10 and 30% surface involvement. Other problems of classification arise from the close association of TEN with erythema multiforme a condition which is strictly immunological and results from hypersensitivity reactions to various agents including infection. Staphylococcal Scalded Skin syndrome (SSSS) is another differential diagnosis that occurs in children under 1yr of age. Toxic Epidermal Necrolysis is characterized by high fever, rash, bullae and diffused exfoliation of skin surfaces which is like second degree burns Separation of the dermal epidermal junction causes Nikolsky sign and gives the skin the typical "wet dressing" appearance. Toxic Epidermal Necrolysis was first described in the medical literature by Alan Lyell in 1956 in the British Journal of Dematology[2]. It accounts for about 1% of all hospitalizations due to drug reactions. It can affect infants and adults but the incidence is higher in the adult population which is justified by the greater ingestion of drugs. It has two peaks: below 5yrs of age and after 64yrs[2]. The male female ratio is 3:2. No racial difference has been described. The incidence varies from 1 to 1.3 per million people per year and mortality is as high as 25% to 70%[2]. A recent review by Cabral[3] showed that Sulphonamides accounted for a third of the cases. Other drugs have also been implicated. These include Penicillin, non-steroidal anti-inflammatory drugs and anti-epileptics. However in our search of pubmed using the search words dihydroartemisin, Lyells syndrome and Steven-Johnson syndrome, we did not find any report of dihydroartemisinin or ACT as a cause of SJS or TEN.

Case Report 1
The patient was a seven year old male admitted to the pediatric ward through the children emergency ward of the Lagos University Teaching Hospital. The complaints were those of itching, rashes and desquamation of the skin. Six days prior to admission

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the patient had developed cough and fever. He was diagnosed with malaria and dihydroartimesinin (Alaxin®) and chloroquine tablets was administered. The next day skin rashes and exfoliation were noted over the trunk, spread was rapid. The lesions coalesced, and by the third day the entire body surface skin exfoliated. The patient was consequently placed on Ampiclox 200mg per kg per day with paracetamol 250mg 8hourly before he was referred. On admission he was found to be severely ill looking, dehydrated and pale. Target lesions, blisters and skin exfoliation involved approximately 96% (Figure 1A) of the skin surface with positive Nikolsky sign. However, the feet, palms and scalp were spared (Figure 1B). There was extensive mucosal involvement with hyperemia of the conjunctiva and erosion of the oral mucosa. A tentative diagnosis of TEN was then made and skin biopsy confirmed the diagnosis. All medications were immediately withdrawn and fluid resuscitation commenced empirically using Parklands formula.The urinary output was monitored and maintained at 1.5 ml\kg\hr. Other medication given included: IV Ranitidine 14mg 8hourly; Anti-tetanus serum (ATS) 0.5ml sub cutis stat and IV pentazocine 15mg 6hrly. Surgical debridement of desquamated epithelium was carried out on the third day of admission and wound was temporarily covered with sofratulle gauze. Biologic dressing was not available. There was usually profuse bleeding during dressing changes for which the patient received three pints of blood Intravenous immunoglobulin therapy were ordered but was not procured due to financial constraints. Enteral feeding with custard and eggs through a naso-gatric tube. On admission he was found to be severely ill looking, dehydrated and pale. Target lesions, blisters and skin exfoliation involved approximately 96% (Figure 1A) of the skin surface with positive Nikolsky sign. However, the feet, palms and scalp were spared (Figure 1B). There was extensive mucosal involvement with hyperemia of the conjunctiva and erosion of the oral mucosa. A tentative diagnosis of TEN was then made and skin biopsy confirmed the diagnosis. All medications were immediately withdrawn and fluid resuscitation commenced empirically using Parklands formula.The urinary output was monitored and maintained at 1.5 ml\kg\hr. Other medication given included: IV Ranitidine 14mg 8hourly; Anti-tetanus serum (ATS) 0.5ml sub cutis stat and IV pentazocine 15mg 6hrly. Surgical debridement of desquamated epithelium was carried out on the third day of admission and wound was temporarily covered with sofratulle gauze. Biologic dressing was not available. There was usually profuse bleeding during dressing changes for which the patient received three pints of blood Intravenous immunoglobulin therapy were ordered but was not procured due to financial constraints. Enteral feeding with custard and eggs through a naso-gatric tube. On the fifth day of admission, patient was found to be febrile with a temperature of 30° Celsius tachycardia of 140 beats per minute, white blood cell count of 3200 per ul and ESR of 50mm per hour. Intravenous Ceftazidine 500mg 8hourly was administered as treatment for suspected septicemia. However, blood cultures did not grow any organism. The Ophthalmologist reviewed and commenced eye roding with 6hourly application of chloramphenicol ointment. On the ninth day of admission, active bleeding from the skin was observed during a dressing change which was uncontrolled by application of direct pressure and Adrenaline soaked dressings however, there was no bleeding from the mucosal surfaces or infusion sites. Transfusion of fresh blood was commenced. However, bleeding from the exfoliated surface was excessive resulting in severe cardiovascular instability and patient died shortly after from hemorrhagic shock.

Case Report 2

The patient was a 28 year old female who presented at the accident and emergency department with a two day history of blisters and exfoliation of the skin. Five days prior to presentation she was diagnosed to have malaria for which treatment with artemisinin and chloroquine therapy was administered at a private hospital. The symptoms of malaria subsided and she was then discharged after 3 days of admission. Subsequently, she developed pruritic maculo-papular rashes, which started from the extremities and then progressed to involve the trunk, face, buccal mucosa and the conjunctiva. A topical preparation of kerosene mixed with palm oil was used at home as dressing. The condition worsened and by the next day exfoliation of the cutaneous surface was observed on account of which she was then referred. There was no a history pulmonary complication, hematuria or gastrointestinal bleeding. On admission, she was found to be in painful distress and febrile with temperature of 38°C. Target lesions and desquamation of the skin involved 76% of the total body surface area. Nikolskys sign was found to be positive. There was ulceration of the buccal mucosa and purulent conjunctivitis. The patient was however hemodynamically stable. Fluid resuscitation was commenced empirically using the Parkland formula, which was regulated to achieve hourly urine output of 30ml. The wound was cleansed daily with 1% chlorhexidine and dressed with Vaseline gauze and gauze cotton wool. Dressing changes were usually associated with bleeding. However, this was not severe enough to require a transfusion. Other treatment received include: Tabs prednisolone 10mg daily; intravenous augmentin 1.2g stat, then 600mg 12 hourly; tetanus prophylaxis and analgesics. Ocular chloramphenicol eye drops and daily rodding of the eyes were commenced by the ophthalmologist.

On the 3rd day of admission, her condition deteriorated. Investigations done showed hyperglycaemic, with fasting blood sugar of 264mg/dl; Pack Cell Volume (PCV) of 21.3%; Urea of 19.2mg/dl; Sodium of 126 mEq/l; Potassium of 8.1 mEq/l and ESR of 138 mm/hr. She became increasingly dyspnoeic, attempts at resuscitation failed and patient subsequently died. The cause of death was Klebsilla aerogenes septicemia.

Case Report 3

This patient was a 37 year old gravida 5 para 3, who was seen at the medical emergency department of the Lagos State University Teaching Hospital. She presented with generalized itching, skin exfoliation, bilateral eye discharge and ulceration of the mouth of 10 days duration. She had been prescribed a standard course of Artesunate and Amodiaquine for malaria. Four days later, she developed extensive skin exfoliations which progressed over 5 days to affect the entire body. On examination, the patient was found to have generalized macular and exfoliation rashes with a positive Nikolsky sign of over 52% body surface area. The patient presented in shock. She was admitted into ICU. All previous medication was discontinued. The patient was prescribed IV fluids with the Modified Brooke Army Formula. Dressing was commenced using gauze and sofratulle. She was also commenced on prophylactic intravenous Rocephin Ig 12 hourly. However, the patient died 15 hours after admission. Autopsy findings confirmed death from septicemia and presence of 8 week pregnancy.

Legend to Figure 1a and Figure 1b

Picture of patient showing 90% of body involvement sparing scalp, palms and soles.

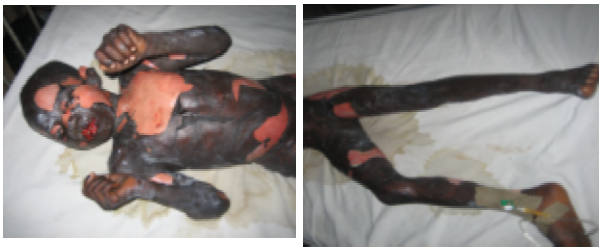

Figure 2

Twenty eight year old woman with Lyells syndrome scalp, palms and sole are also spared

DISCUSSION

Toxic Epidermal Necrolysis is an idiosyncratic drug eruption which is life threatening. Some researchers have accepted a few cases to be idiopathic but this may be due to difficulties in obtaining history of causal agent, as the latent period have been reported to range from 1-45 days. More than 100 drugs have been associated with development of SJS/TEN and in the review by Roujeau et al[4] sulphanamide group of drugs was the most implicated in TEN. Other antibiotics in order of descending frequency are: cephalosporins, quinolones, aminopenicillins, tetracyclines, and macrolides. Sulphonamides accounts for over 65% in most literatures while antiepileptics especially phenetoin, carbamazipine and Phenobarbital account for the majority of cases in children[3]. Incidence of TEN is also quite common with the use of Allupurinol and non steroidal anti-inflammatory drugs. The less common agents are other antibiotics, anti-tuberculostatic agent, antifungal agents and cytostotoxic agents. Our literature search did not reveal dihydroartemesinin or other similar agent as a causal agent for SJS or TEN. TEN has also been found to be closely associated with various disease conditions, such as autoimmune disorders e. g systemic lupus erythromatosis and Sjorgen syndrome. Other associations are lymphomas, leukaemias and graft host disease[5]. Immunosuppression and certain viral infection may facilitate development of TEN following exposure to known causal agents.

Management of this condition requires urgent admission into a specialized burn unit and withdrawal of all medication containing sulphonamides and other potential initiating agents[6]. Fluid resuscitation should be commenced based on any burn resuscitation formula bearing in mind the fundamental differences between this condition and thermal burns[3]: It usually requires less volume of fluid as compared with thermal burns of same surface area. It should also be considered as a systemic illness with mucosal involvement, pulmonary complications and visceral manifestations renal, hepatic gastrointestinal and pancreatic. This occurs as a direct consequence of the disease process. Fluid therapy should therefore proceed with caution requiring close monitoring. Catheterization is indicated only in severe cases and should be used for short durations. Urinary output of 30-50 ml/hr in adult is required. Another significant difference is that TENS is self limiting[3], because separation of the skin occurs at the dermal-epidermal junction representing an epidermal skin loss which is expected to heal spontaneously within two to three weeks in the absence of complications. For this reason local wound care has assumed a central role in management of these patients. Biological membrane

dressings are recommended for provision of temporary wound coverage[7]. They minimize fluid loss, prevent wound infection, reduce pain, and provide a moist, clean wound environment that would encourage re-epithelisation. The only drawback is the risk of transmission of infection. They are commercially available as amniotic membrane, porcine xenograft, cadaveric allograft and cultured epidermal allograft. There are also synthetic skin substitute which can be used with the same effectiveness but do not carry the potential risk of transmission of infection Conventional dressing materials were used in our patient due to lack of skin substitute in this environment. Conventional gauze dressing that debrides the raw surface was the cause of bleeding and mortality of first patient and bleeding in the second patient. They also promote infection and could have responsible for infection and septicemia in the second patient and third patient.

CONCLUSION

The world health organization (WHO) in Washington, released a guideline for the treatment of malaria using artemisinin combination therapy (ACT)[8], this was adopted by the Federal ministry of Health Nigeria since 2005[9]. Ever since then, it has been observed that ACT is widely used in the treatment of malaria in Nigeria. The search of the literature has not revealed artemisinin as a causal agent for TENS. However this was observed in three our patients who were treated with ACT. The purpose of this report therefore, is to raise the index of suspicion amongst clinicians of this fatal complication which could result from Arthemisinin. Furthermore it should be emphasized that immediate transfer of such patient to burn unit is paramount. The use of conventional gauze dressings could result in severe hemorrhage which could be fatal.

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