

Oral Chloroquine Induced Toxic Epidermal Necrolysis: A Rare Case Report

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Abstract: Toxic Epidermal Necrolysis (TEN) is an uncommon but acute life-threatening idiosyncratic mucocutaneous syndrome characterized by widespread epidermal necrosis followed by epidermal detachment. The average annual incidence of Toxic Epidermal Necrolysis is about 0.4-1.3 cases per million population and the mortality rate is about 25-30%. Drugs are considered to be the most common causative agents for 80-95% cases of drug induced TEN. Here, we report a case of a 35 years old female diagnosed for Malaria presented with the picture of adverse drug reaction of Toxic Epidermal Necrolysis due to oral Chloroquine given by the local physician. The patient was managed with Antibiotics, Corticosteroids and Intravenous fluids and recovered well within 25 days of admission from this fatal drug reaction. Since such cases have been rarely reported, we are intended to notify about this potentially dangerous drug reaction due to Chloroquine which is used extensively in the treatment of Malaria

Keywords: Toxic Epidermal Necrolysis (TEN), adverse drug reaction, Chloroquine.

INTRODUCTION

Toxic Epidermal Necrolysis (TEN) is a rare and severe adverse cutaneous drug reaction, characterized by mucocutaneous hemorrhagic ulcers and erosions, severe epidermal detachment presenting as blisters initially then areas of denuded skin closely resembling that of scalding of the skin. It was first described by Alan Lyell in 1956, and is now recognized as Toxic Epidermal Necrolysis also called as "Lyell's syndrome. TEN affecting approximately 0.4-1.3 cases per million population annually and are considered as medical emergencies which are potentially fatal. The average mortality rate of TEN is 25-35%. So, rapid diagnosis and prompt treatment is must so as to save patient from this fatal drug reaction. Diagnosis mostly relies on clinical signs and histopathology of skin lesions [1].

Chloroquine phosphate is a 7-chloro, 4-aminoquinoline most potent blood schizonticidal anti-malarial drug. It is highly effective against the erythrocytic forms of all four plasmodial species. It is a weak base and it buffers intracellular pH, thereby inhibiting cellular invasion by parasitic organisms. It also inhibits haem polymerase; the enzyme that polymerizes haem to haemozoin. Intracellular

accumulation of haem is toxic to the parasite. Chloroquine is completely absorbed orally, extensively distributed and has a large volume of distribution. It is usually given orally and can also be given by I.M., S.C., or as slow I.V. infusion. It has a half-life of ~ 50 h. It is the mainstay for the treatment and chemoprophylaxis of malaria. Adverse reactions commonly associated with chloroquine include severe gastritis, headache, urticaria, confusion, convulsions, toxic psychosis, widening of QRS interval, T wave abnormalities, blurring of vision, corneal opacity, photosensitive dermatoses and even retinal damage on prolonged use, rare instances of hemolysis and blood dyscrasias have been reported [2].

However, the toxic epidermal necrolysis with chloroquine have been rarely noted. Hence, we report a case of TEN which was induced by Chloroquine phosphate (rarely concerned in the causation of TEN).

CASE REPORT

We report a case of a 35 years old female who was brought to the Emergency department of a tertiary care hospital with the chief complaints of extensive peeling of skin all over the body, severe orogenital ulcerations with bilateral edema feet started two days prior to admission. She was conscious, but with obvious

distress and dehydrated, tachypneic pulse rate 130/min, BP- 140/100 mm Hg and afebrile. A detailed past history revealed that she was suffering from high grade fever since last ten days and was diagnosed for malaria and started oral Chloroquine phosphate as per schedule for the treatment of Chloroquine sensitive malaria (Tab. Lariago DS 500 mg, 2 tablets stat, 1 tablet after 6 h on 1st day then 1 tablet daily on 2nd and 3rd day) as empirical treatment of Malaria by a local physician

along with other supportives like antihistaminic (levocetizine), inj. Febrinil, antibiotic (T. Cefixime).

Towards end of this Chloroquine treatment within 48 h, she started developing red erythematous patches with peeling of skin all over the body which progressed to give rise to present picture (as shown in Figure 1).



Fig-1: Photo showing Toxic epidermal necrolysis

On Clinical examination, she had erythematous, burning patches all over body which developed into multiple vesicular, large bullous eruptions over neck, chest, shoulders, intermammillary areas, axillas, abdomen, back, thighs, face progressed to almost whole body skin peeling (greater than 60% cutaneous detachment). She had difficulty in swallowing due to painful ulcers of mouth, palate, and crusting necrotizing lesions over lips. Crusting was present in bilateral nasal cavities. On Ophthalmic examination, crusted plaques were present over both eyelids without conjunctivitis and without visual impairment. On Gynecological examination, bullous lesions over thighs, suprapubic region, ulcers over vulva, majora and perineal region were found.

Investigations revealed Widal test negative, Dengue NS1 test negative, Hb 8.4gm%, WBC- 5500 cells/cu.mm, N-82%, L-12%, E-2%, ESR-30mm/hour,

RBS-110mg/dl. Renal function and liver function tests were within normal limits. Chest Xray, 2D Echo revealed no abnormality. She was kept admitted in medicine ICU, and started measured fluid administration, Inj. Pheniramine maleate 1 amp i.m BD and Inj. Hydrocortisone 100mg i.v BD for 7 days, Inj. Metronidazole 100ml TDS for 10 days. Oral care with metronidazole gel to be applied locally, chlorhexidine mouth wash was given. Skin care done with potassium permanganate soaks, Tess gel, Fusibet cream, Moyzen lotion, Vaseline lotion. Other antibiotics used were Inj. Widimix 4.5mg QID (Piperacillin sod. and Tazobactam sod.) for 14 days, Inj. Ceftriaxone 1 gm BD for 7 days along with multivitamin supplements during her hospital stay.

Patient showed steady improvement (Figure 2) and complete recovery (Figure 3) and was discharged after 25 days from the hospital.



Fig-2: Photo during hospital stay



Fig-3: Photos after complete recovery

DISCUSSION

Cutaneous adverse drug reactions are common, affecting about 2-3 percent of the hospitalized patients. There is a wide spectrum of cutaneous adverse drug reactions ranging from transitory rash to the potentially fatal Toxic epidermal necrolysis [3]. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but severe cutaneous drug reactions endangering patient's life. SJS and TEN comprise <10% and >30% of the body surface area respectively. Due to the fact that SJS and TEN can sometimes hardly be separated from each other, an overlap group of SJS/TEN has been defined with blisters and erosions between 10% and 30% of body surface area called as SJS-TEN Syndrome [4]. Many etiological factors have been proposed, but Drug-induced TEN is the commonest and cause nearly 80-95% of TEN cases. TEN have been observed with more than 100 drugs [1].

Several drugs including Allopurinol, Aminopenicillins, Cephalosporins, NSAIDs (oxicam type mainly), Quinolones, Carbamazepine, Phenytoin etc. are the most commonly implicated agents. An increased incidence of TEN has been observed in patients with brain tumors, systemic lupus erythematosus, acquired immune deficiency syndrome and high dose steroid therapy. Other precipitating causes include viruses, bacteria, fungi, immunization,

neoplasms, graft versus host disease, radiotherapy, beverages fumigants and idiopathic.

The exact mechanism of pathogenesis of TEN is still indefinite but is believed to be immune-mediated, as re-challenging an individual with the same drug can result in rapid recurrence of TEN. In spite of few case reports of TEN occurring due to Chloroquine, this drug has not yet been added to the list of most common drugs capable of causing TEN [5]. In present case, there were signs and symptoms of TEN after oral administration of Chloroquine. The patient had not taken Chloroquine in the past and there was no history of any other drug allergy. No other causative drugs like NSAIDs, anticonvulsants etc. were taken. No history of burning sensation on exposure to sunlight was present. Other skin diseases like pemphigus vulgaris and bullous pemphigoid etc. were also excluded on clinical grounds.

As other probable causes like upper respiratory tract infection, viral infection or malignancy were not present in the female and this reaction started to appear within 48 hrs. of the consumption of Chloroquine, there is a chronological relationship to Chloroquine consumption. Hence, it was diagnosed as a case of Chloroquine induced Toxic Epidermal Necrolysis by the dermatologist as case showed more than 30% i.e. around 60% cutaneous detachment. According to World Health Organization causality assessment criteria,

causality was determined as 'possible' due to Chloroquine [6]. Using Naranjo's ADR probability scale, the causality assessment score of 4 was calculated, which again indicates that this reaction is 'possible' due to Chloroquine [7]. However, for ethical constrains, we did not perform Chloroquine re-challenge. This adverse reaction is bizarre, unpredictable and can be labelled as Type 'B' class of adverse reaction. To the best of our literature search, we came across only two previously reported cases of TEN due to Chloroquine [8, 9]. But in spite of previous two reporting, Chloroquine is ignored as an offending drug causing TEN. So we are aimed to bring this into notice of physicians to prevent occurrence of drug reactions.

CONCLUSION

The female was diagnosed as a case of Toxic Epidermal Necrolysis and the culprit was traced as drug Chloroquine. We thereby would like to conclude that Chloroquine is also a possible drug to cause TEN as its adverse drug reaction. So, it is advisable that the physicians should prescribe Chloroquine judiciously and monitor its adverse reactions meticulously to prevent such fatal reactions. Toxic Epidermal Necrolysis should be included in the ADR profile of Chloroquine and a caution comment should be mentioned on the drug label. Patients should be instructed to consult a healthcare professional promptly if they develop any type of skin reaction while being treated with Chloroquine.

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