

Anaphylactic Reaction to Intravenous Artesunate

Sir,

Artemisinin derivatives alone or in combination have been recommended as first or second line treatment in severe and uncomplicated falciparum malaria. Artesunate, a water soluble hemisuccinate derivative of artemisinin has been recommended for the treatment of severe falciparum malaria for its rapid antimalarial effect, convenient dosage regimen, easy administration, and safety.¹ Despite of its widespread and frequent use, adverse reactions to this drug are very infrequent except severe allergic reactions to oral artesunate.^{2,3} Here, we report a case with anaphylactic reaction after single intravenous injection of artesunate in view of its rarity.

SM, a 20 years male was admitted to 2nd unit Medicine Ward of V.S.S. Medical College, Burla, Sambalpur, Orissa with chief complaints of fever for 2 days and decreased urination for 1 day. The fever was associated with chill and rigor. On the 2nd day of fever he developed oliguria and admitted to the hospital. On examination, he was conscious, febrile with axillary temperature of 101°F, pulse rate: 110/minute, blood pressure (BP): 110/70 mm of Hg. There was pallor, no icterus, no pedal edema. The amount of urination in 24 hours was 800 ml. Abdominal examination revealed that liver was enlarged 2 cm. below costal margin, soft and non-tender, spleen was palpable 2 cm. below costal margin and firm in consistency. Investigations showed, Hb.- 8.0 gm/dl, total leukocyte count - 12,000/cmm, total platelet count - 1,80,000 /cmm, fasting blood glucose-80.0 gm/dl, blood urea-40.0 mg/dl, s.creatinine-3.6mg/dl, s.bilirubin-1.8mg/dl, AST-40 IU/l, ALT-60 IU/l, s.sodium-138.0 mmol/l, s. potassium-3.9 mmol/l. Giemsa stained peripheral smear showed asexual forms of *P.falciparum* with a count of 8200/cmm.

With the above clinical and investigation findings, the diagnosis of severe falciparum malaria with renal failure and anemia has been made and he was treated with artesunate injection 120 mg IV as per WHO recommendation.¹ Just after the administration of artesunate, the patient complained of difficulty in breathing, generalized itching, and bluish discoloration of hands and legs. On examination, patient had peripheral cyanosis, cold and clammy skin. Pulse was feeble and rate could not be counted, BP was low with a systolic BP of 70 mm of Hg. and the diastolic BP could not be recorded. The diagnosis of artesunate induced anaphylaxis had been made and he was treated with inj. Epinephrine (1:1000) at a dose of 0.01 ml/kg SC at 15 minute interval for 2 doses and inj. Hydrocortisone, 5mg/kg IV. As the blood

pressure did not improve dopamine had been administered through normal saline at a dose of 2-5mcg/kg/min IV and the dose had been increased by 1-4 mcg/kg/min every 10 minute till the optimal response obtained after 2 hours. In addition hypotension was treated with normal saline. The patient recovered from shock and treated with inj. Quinine dihydrochloride (10mg salt/kg infused over 4 hr. at 8 hour interval.) and Doxycycline (3mg/kg/day for 7 days)³. The patient recovered and discharged after full recovery on 8th day. Intradermal skin sensitivity test prior to discharge had been done with 0.1 ml of artesunate at 1:100 dilutions which produced a localized pruritic wheal and flare that was maximal at 15 minutes (12×16 mm).

Anaphylaxis is an IgE mediated Type I hypersensitivity reaction in which within minutes after exposure, the antigen links to IgE molecules that activates and degranulates mast cells and other cells (basophil, monocyte etc.) with antigen specific IgE. As a result, various mediators that cause vasodilatation, contraction of visceral smooth muscles, and increase in vascular permeability and tissue inflammation are released causing cardiovascular compromise.⁴ Early recognition is of importance, since death occurs within minutes to hours after the first symptom. Various drugs, insect stings cause systemic anaphylaxis. But anaphylaxis due to administration of artesunate has not been reported in spite of its extensive use.^{1,3,4} The present case has developed anaphylaxis after injection artesunate without history of prior exposure to the same drug. As falciparum malaria is prevalent and artesunate has been used as the first line antimalarial drug in this part, prior exposure to this drug cannot be ruled out. A skin sensitivity test prior to discharge had been done to show whether the patient was sensitive to artesunate or not. In this patient a positive skin test with artesunate goes in favor of anaphylaxis. In vivo skin testing is preferred to in vitro radioallergosorbent testing for anaphylaxis because the former detects the presence of IgE antibody in tissue and shows biological activity. It is also more sensitive, more specific, more rapid, and less expensive than in vitro test. However, there is a remote risk of inducing a systemic reaction. To avoid this, epicutaneous (prick) test may be performed. Positive skin test differentiates anaphylaxis from 'anaphylactoid' reactions that resemble immediate hypersensitivity reactions but are not mediated by allergen-IgE interaction. In 'anaphylactoid' reaction mediators are released by direct mast cell activation and the symptoms are confined to urticaria without cardiovascular compromise.⁴

The present report warns for the possibility of anaphylaxis reactions to artesunate and one should be vigilant for such an uncommon but life threatening adverse reaction.

Fig. 1 : Showing bilateral breast hematoma

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