Pharmacovigilance in kala-azar patients with severe thrombocytopenia caused by sodium antimony gluconate & miltefosine

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Sodium antimony gluconate (SAG) and miltefosine used in the treatment of kala-azar are known to cause several side effects but severe thrombocytopenia has not been reported. Four cases of severe thrombocytopenia, two caused by SAG and two by miltefosine were promptly detected and treated by immediate withdrawal of the offending drugs, platelet and blood transfusions and dexamethasone. After improvement Leishman-Donovan (LD) bodies were demonstrated in splenic aspirates of both patients of SAG group and one of miltefosine and they were treated with 1 mg/kg body wt of amphotericin B for 20 days and cured. One patient of miltefosine group treated outside only on the basis of rK-39 positivity did not show LD bodies in splenic aspirates and improved without any anti-kala-azar drug. None of the patients relapsed within 6 months of follow up. Prompt detection of side effects under the concept of pharmacovigilance can save life of such patients.

Key words Haemorrhages - miltefosine - pharmacovigilance - sodium antimony gluconate - thrombocytopenia

Sodium antimony gluconate (SAG) has been known to cause various adverse effects in kala-azar patients such as anorexia, nausea, vomiting, abdominal pain, metallic test in mouth, diarrhoea, pancreatitis, reversible elevation of liver enzyme activities, myalgia, arthralgia, proteinuria, ECG changes (T wave inversion, prolongation of QT interval, ST segment abnormalities), phlebitis, uveitis, optic atrophy, acute renal failure, hepatic necrosis and bone marrow hypoplasia1-3. Miltefosine, an anticancer drug used in the treatment of kala-azar, has undergone phase-II, III and IV trials in Bihar and no severe thrombocytopenia was reported4,5.

Thrombocytopenia can occur due to decreased marrow production of megakaryocytes as in marrow infiltration with tumour, fibrosis or due to marrow failure in aplastic anaemia; splenic sequestration of circulating platelets in enlarged spleen in portal hypertension, etc., or due to increased destruction of circulating platelets either due to non immune mechanism in vascular prosthesis or due to immune mechanism as happens in most of the drug induced perpura6.

Drugs induced immune destruction of platelets can be caused by two mechanisms: a drug dependent binding of Fab part of the pathological IgG with the platelets, causing their destruction, and in the second type Fab portion of the pathological IgG binds to platelet factor 4(PF4). When complexed with heparin or other drugs, the FC portion of the Ig G molecule is bound to the
platelet receptors of the reticuloendothelial cells causing platelet activation. Normal platelet count is 100, 000 to 450, 000 platelets/µl of blood. So long the count is above 100,000/µl, the patient is usually not symptomatic and bleeding time is normal.

Platelets counts between 50, 000 to 100,000 /µl cause mild prolongation of and bleeding time, and bleeding occurs after severe trauma. Patients with platelet counts <50, 000 /µl have easy bruising and patients with <20, 000/µl have an appreciable incidence of spontaneous bleeding.

We report here that under the practice of pharmacovigilance prompt identification of this severe complication and treatment helped saving lives of four such patients reported to Balaji Utthan Sansthan, Patna during July 2005.

The first patient, 28 yr old female of village Arap, District Patna, came with the chief complaints of nasal bleeding, with black stool, bleeding per vaginum and haemorrhagic spots on the body. She was diagnosed a case of kala-azar on the basis of 2+ Leishman-Donovon (LD) bodies in bone marrow aspirates. She was prescribed SAG which she took for 8 days, 4 ml morning and evening intramuscularly and then she developed this complication. She was febrile with mouth temperature of 100°F. Her previous WBC and platelet counts were 4200/µl and 120,000/µl, respectively and Hb 6.2 g/dl. Her liver was 4 cm below costal margin and spleen 8 cm. Total WBC count was 2500/µl neutrophil 32 per cent, lymphocyte 60 per cent, basophil 3 per cent, monocyte 5 per cent, eosinophil 0 per cent, Hb 4g/dl, platelet count 10,000/µl only on the day of admission (all determined on autoanalysed blood cell counter of MERCK, Germany). SAG treatment was discontinued and she was transfused with 300 ml of blood, and 2 units of platelets daily for 3 days. Dexamethasone was started 4 mg intravenously every 8 h. Bleeding completely stopped on day 3 but she was kept under observation for 8 days. On day 10 her platelet count was 1.5 lacs, and splenic aspiration showed grade 2 LD bodies. Amphotericin B (fungizone of Sarabhai Chemicals, India) was started at a dose of 1 mg/kg body wt. daily slow intravenous infusion for 20 days. The drug was diluted in 10 ml of sterile water and then with 500 ml of 5 per cent dextrose and given through a scalp vein canula in peripheral vein. On day 21 of treatment splenic aspiration was done and aspirates were negative for LD bodies. She was afebrile and her liver and spleen reduced to 2 and 3 cm respectively. She was discharged and followed up for 6 months. She remained normal during and at the end of follow up.

Another patient, a 29 yr male residing in village Birpur, Nepal, came to our hospital with the major complain of pain abdomen and epistaxis for the last three days and fever for the last three months. He was also diagnosed a case of kala-azar and was given initially 2 capsules of miltefosine daily for 6 days, but fever did not come down and he was put on SAG 4 ml morning and evening for 4 days. He developed pain abdomen, and bleeding from nose and gums. He was pale with axillary temperature of 100°F, pulse rate was 116/min. His liver was 3 cm below costal margin and spleen 4 cm. His body wt. was 51 kg. His total leucocyte count was 2500/µl, neutrophil 46 per cent, lymphocyte 48 per cent, basophil 1 per cent, monocyte 5 per cent, eosinophil 0 per cent, Hb 4g/dl, platelet count 15,000/µl, his previous platelet count not available. He was transfused 1 unit of blood and 1 unit of platelet daily for 4 days and dexamethasone 4 mg/iv 8 hourly for 4 days. His bleeding stopped and he became better. On day 10, his splenic aspiration was done which showed LD body 1+. He was treated with amphotericin B. On day 21 of treatment splenic aspiration was done and aspirates did not show any LD body. He was followed up for 6 months and he was absolutely normal.

The third patient, a 15 yr old female residing in Sultanganj, Mahendru, Patna came to our hospital with complaint of epigastric pain with melaena for the last five days with history of fever for one month. She was diagnosed kala-azar outside and was advised miltefosine 100 mg daily for 28 days. After taking 30 capsules of miltefosine she developed melaena. She had axillary temperature of 99°F, pulse 110/min, and was pale. Her liver was 6 cm below costal margin and spleen 8 cm. Her leucocyte count was 3200/µl, neutrophil 34 per cent, lymphocyte 62 per cent, basophil 1 per cent, monocyte 3 per cent, eosinophil 0 per cent, Hb 6 g/dl, platelet count 12,500/µl; body wt. was 45 kg. Her previous WBC count was 3800, platelet count 110,000/µl. Her splenic aspiration done outside showed 2+ LD bodies. She was given 300 ml of blood transfusion and 2 units of platelet transfusion daily for 3 days, dexamethasone was given 6 hourly, bleeding stopped after 2 days. On day 8 her platelet count was 1.6 lacs and splenic aspirates showed 3+ LD body. She was put on amphotericin B for 20 days and her splenic aspirates were negative for LD body on day 21. She was followed up for 6 months and was in normal health.

A male aged 38 yr came with severe epistaxis and bleeding gums. He gave history of treatment of kala-azar with miltefosine for the last 12 days, his pathological report done outside revealed rk39 positivity and platelet count was not available. His bone marrow
or splenic aspiration were not done and treatment with miltefosine was started on the basis of rk39 positive test. He had bleeding from nose and gums and spleen was enlarged with 4 cm and liver 2 cm. His blood count showed leucocyte count of 3400/µl, platelet count 12000/µl, and Hb 5.6 g/dl. The treatment with miltefosine was stopped and he was given 1 unit of blood and 2 units of platelets daily for 4 days and dexamethasone 4 mg 8 hourly for 4 days. He recovered completely. Splenic aspiration done on day 8 did not show any parasite. He was not put on anti kala-azar drug. He remained afebrile for 6 months and spleen regressed.

Kala-azar drugs SAG and miltefosine produced severe thrombocytopenia and haemorrhages in all the four cases. Offending drugs were withdrawn immediately and whole blood and platelet transfusions were started and dexamethasone was given intravenously. All patients improved. The response of treatment was quick in all these cases and haemorrhage stopped. This indicates that the mechanism of thrombocytopenia was more like immunogenic destruction of platelets caused by offending drugs. Chunge et al reported epistaxis in 19 patients in Kenya who received parental antimonial therapy. In three cases it was associated with pancytopenia but they were not clear about thrombocytopenia. The mechanism of toxicity of antimony compound is unclear but may involve disruption of thiol proteins binding to sulphydryl groups. Thrombocytopenia has not been reported clearly during antimonial treatment in India.

Miltefosine is comparatively a new drug which is being used for treatment of kala-azar. We could not come across a single report in literature on this toxicity of miltefosin therapy. Its use is still in the period of post marketing studies of safety of the drug. The fourth case in our study was treated by miltefosine on the basis of rk39 positive result only and recovered after stopping the drug without any other anti-kala-azar drug. The practice of pharmacovigilance needs to be more extensively propagated in India as done in USA, UK and other European countries and Nigeria.

In USA, pharmacovigilance programme is not mandatory but elaborate and exhaustive programme has been developed. This is based on the recommendations of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) held in 2005 and also on the inputs provided by local experts. In India, though the concept of pharmacovigilance has been recognized, in 2004 but has not been much used in practice.

In conclusion, pharmacovigilance should be widely published and propagated in India and a national body should be formed to monitor side effects of old and new drugs which can save lives of many patients developing severe complications such as thrombocytopenia.

References