An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

DRUG INDUCED HEMATOLOGICAL DISORDERS- A REVIEW

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ARTICLE INFO

Key Words
Drug-induced anaemia; aplastic anaemia; agranulocytosis; hemolytic anaemia; megaloblastic anaemia; thrombocytopenia; methemoglobinemia; sideroblastic anaemia; pureblood cell aplasia

ABSTRACT

Drugs can adversely affect both the bone marrow and peripheral blood cells. Hematological disorders arise through a variety of mechanisms and etiologies. Drugs can induce almost the entire spectrum of hematologic disorders, affecting white cells, red cells, platelets and coagulation system. Drug-induced anaemia and other blood disorders are potentially dangerous and have been a risk of modern pharmacotherapy for a long time. Some of the drug-induced syndromes include aplastic anaemia, agranulocytosis, hemolytic anaemia, megaloblastic anaemia, thrombocytopenia, methemoglobinemia, sideroblastic anaemia and pure blood cell aplasia. The mechanisms of these disorders can be explained either in terms of direct immune reaction or drug or metabolite toxicity. Early diagnosis and proper treatment of drug-induced anaemia are crucial because of the seriousness of these disorders. Some of the classic drugs known to cause hematologic abnormalities have been replaced by newer drugs, including biologics.

INTRODUCTION

Drugs can adversely affect both the bone marrow and peripheral blood cells.Many cases are reported because of the millions of doses of drugs taken each year by the population. Even though the risk from most drugs is very small but a drug can cause more than one adverse reaction. The effect is often related to dose and time which can be reversed by the withdrawal of the offending drugs. But in some cases, the adverse effect is irreversible and the patient may die. It is difficult to determine the frequency of adverse drug reaction of a drug. Some of the drug-induced syndromes include aplastic anaemia, agranulocytosis, hemolytic anaemia, megaloblastic anaemia and thrombocyto-penia. Drugs like anti-neoplastic and chloramphenicol or its metabolites produce direct toxic action on bone marrow. Hemolytic anaemia can be caused by immunological mechanisms. The drug may affect the immune system by acting as a hapten which leads to the production of autoantibodies or antidrug antibodies. Hemolysis may occur due to drugs act on erythrocytes with enzyme defects like glucose-6- phosphate dehydrogenase deficiency[1].

DRUG-INDUCED APLASTIC ANAEMIA

Aplastic anaemia is a syndrome of bone marrow failure characterized by peripheral pancytopenia and marrow hypoplasia[2]. It is a serious and rare disorder of unclear cause. Drug-induced aplastic anaemia is caused due to the damage of pluripotent stem cells. It leads to the reduction of normal levels of erythrocytes, neutrophils and platelets. About 2 cases per million population are the annual incidence of aplastic anaemia. Aplastic anaemia can be categorised into inherited and acquired[3].Inherited aplastic anaemia is an inherited disease that results in fatty infiltration, failure of bone marrow, loss of circulating blood cells. These include Fanconi's anaemia, Blackfan diamond anaemia and Dyskeratosis congenital. Acquired aplastic anaemia occurs due to drugs, radiation, viruses or by chemical exposure. Drugs that cause acquired aplastic anaemia include chloramphenicol, phenytoin, propylthiouracil[3-4]. Diagnosis can be made by the following criteria

i. WBC count 3500 cells/mm^3 or less
ii. Platelet count 55000 cells/mm^3 or less
iii. Hb value 10gm/dl or less[3]

Aplastic anaemia can be moderate if neutrophils are less than 1500 cells/mm^3, platelets less than 50,000cells/mm^3 and Hb less than 10 gm/dl. It is severe when neutrophils less than 500 cells/mm^3, platelets less than 20,000 cells/mm^3 and reticulocytes less than 1%. It is very severe when neutrophil count less than 200 cells/mm^3[3-5].Treatment of drug-induced aplastic anaemia involves the cessation of the causative drug. Blood transfusion is also recommended along with antibiotic therapy. Granulocyte colony-stimulating factor has been used even if the neutrophil count continues to fall. Purpura can be controlled using corticosteroids. Irreversible drug-induced aplastic anaemia can be treated using bone marrow transplantation[6].

DRUG-INDUCED AGRANULOCYTOSIS

Agranulocytosis is a rare condition in which there is a severe reduction in the number of WBC (granulocytes and immature granulocytes) in the circulating blood[6]. Drug-induced agranulocytosis is more susceptible in elderly women. The incident rate of agranulocytosis in Europe is 1.6 to 9.2 cases per million when compared to the US, where it is slightly higher ranging from 2.4 to 15.4 cases per million population[7]. Various mechanism of actions have been proposed for the development of this type of agranulocytosis, some of them are

i. Destruction of neutrophils by drug antibodies
   Eg: Chlorpromazine, procainamide, clozapine, dapsone, sulphonamides, carbamazepine, phenytoin, indomethacin, etc
ii. The development of a lupus-like syndrome
   Eg: Penicillin, quinidine, levamisole
iii. The toxic depression of bone marrow
   Eg: phenothiazine, chlorpromazine, tricyclic antidepressants[7]

The withdrawal of the offending drug is the primary treatment which is followed by restoration of adequate neutrophils count. Corticosteroid therapy can promote the recovery but antibiotics should adjuvantly given for the treatment of infection. Sargramostim and filgrastim, are drugs that are most effective in reducing the duration of neutropenia[6].

DRUG-INDUCED HAEMOLYTIC ANAEMIA

Haemolytic anaemia is defined as the destruction of RBC with lysis of cell membrane and the removal of blood cell by phagocytosis[6]. The severity and morbidity of haemolytic anaemia will

depend on the mechanism of induction. The two basic mechanisms are

i. Direct effect on the metabolic process of the red blood cells (G6PD deficiency)
   Eg: Dapsone, nalidixic acid, vitamin C, aspirin, etc
ii. An immune mechanism involving both the drug and red blood cells.
   Eg: Cimetidine, insulin, penicillin, sulphonamides, etc

According to the study conducted by George Garratty[8], it is estimated that one in one million of the population have immune haemolytic anaemia when compared it with autoimmune haemolytic anaemia, which is found to be one in eighty thousands of the population[7].Haemolytic anaemia can be acute or chronic. Acute symptoms are of fatigue, weakness, breathlessness, chills, fever and back pain. The increased destruction of RBC level may lead to jaundice, haemoglobinuria and renal failure.In patients with known G6PD deficiency, all reported drugs that cause haemolytic anaemia should be withdrawn that may recover the haemoglobin levels. As well as in immune haemolytic anaemia, the offending drug should be withdrawn along with supportive measures like dialysis. This type of anaemia responds well to corticosteroids [6].

DRUG-INDUCED MEGALOBLASTIC ANAEMIA

Megaloblastic anaemia occurs when DNA synthesis in the bone marrow is inhibited but RNA synthesis continues causing the formation of defective macrocytic red blood cells [8]. The mechanism involves interference with vitamin B_{12} or folate metabolisms [9]. Drugs can induce megaloblastic anaemia in two ways by inhibiting the absorption or utilization of B_{12} or folic acid and by directly inhibiting DNA synthesis without depleting folate or vitamin B_{12}.Antimetabolites are mostly associated with drug-induced megaloblastic anaemia. 3 to 9 % of patients were diagnosed with megaloblastic anaemia when treated with methotrexate, which may inhibit the DNA synthesis by the irreversible inhibition of dihydrofolate reductase enzyme [11]. Patients having vitamin B_{12} deficiency are more prone to megaloblastic anaemia if cotrimoxazole is taking in low or high dose [11-12].If drug-induced megaloblastic anaemia is caused by chemotherapy, it is considered as its side effect. Methotrexate induces megaloblastic anaemia in a dose-related manner and when large intravenous doses are used, rescue with calcium leucovorin must be employed. If it is induced by cotrimoxazole, a trial dose of folic acid 5 to 10 mg four times a day is administered. Anticonvulsant drugs induced megaloblastic anaemia are corrected with folate supplements [6].

DRUG-INDUCED THROMBOCYTOPENIA

Thrombocytopenia is a reduction in the platelet count to below 150 x 10^9/L although symptoms of haemorrhage are unlikely to occur unless the count falls below 100 x 10^9/L[13]. The incidence rate of drug-induced thrombocytopenia is 10-18 cases per million [14]. Drug-induced thrombocytopenia may occur by any one of the following two mechanisms

i. Selective bone marrow suppression
ii. An immune mechanism where antibody production causes platelet agglutination [15-16].

Drugs like thiazide diuretics can cause thrombocytopenia within 7 to 10 days after drug administration. Since platelet precursors are more vulnerable to cytotoxic agents than other stem cells.

An IgG mediated response is seen in immune mediated thrombocytopenia. Various mechanisms have been proposed for the development of this type of thrombocytopenia, some of them are

i. Hapten mediated immune thrombocytopenia
   Eg: Penicillin, cephalosporin
ii. Drug depended antibody mechanism
   Eg: Quinine, anticonvulsants, NSAIDs

The offending drugs should be withdrawn followed by the restoration of adequate platelet counts within several days. When the drug is excreted rapidly, the recovery is quick. Particularly with immune type the drug is no longer available to participate in drug antibody reaction and excreted rapidly. Platelet transfusion is done when the platelet count comes very low. Corticosteroids can be used when a drug allergy is found. As the effectiveness of platelet is decreased by aspirin and NSAIDs, it should be avoided. Quinine and heparin are worth highlighting. Quinine is found in OTC preparations, tonic water and soft drinks. An alternative to heparin such as snake venom and prostacyclin should be administered when the anticoagulants are unavoidable. Low molecular weight heparin may be safe for some patients but cross sensitivity tests should be carried out [7].

DRUG-INDUCED METHEMOGLOBINEMIA

Methemoglobinemia is a blood disorder, which is defined as abnormal formation of methemoglobin (MetHb), thus unable to release oxygen effectively to body tissues. The formation of MetHb is by deoxygenation of haemoglobin or reactive oxygen species (ROS). The superoxide or peroxides oxidized iron in haem group from ferrous state (Fe_2+) to ferric state. The normal levels of MetHb in adult should be < 0.14 -0.175 gm/dl and 0.12 – 0.153 gm/dl [12-13]. In methemoglobinemia, the level of MetHb is > 1% of Hb level in blood [14-16].Methemoglobinemia is caused by rare genetic gene mutation or acquired through certain foods or drugs. The acquired methemoglobinemia is caused by oxidizing drugs or a metabolically activated to oxidizing species such as nitroglycerin, dapsone, sulphonamides, primacine, phenytoin, phenacetin and prilocaine. Commonly it occurs in individuals who consume untreated water containing a high amount of nitrate and nitrite [17-18]. Acquired methemoglobinemia is acute in nature can lead to other complications such as haemolytic anaemia, which can be life threatening also.Methemoglobinemia is commonly treated with methylene blue solution with supplemental oxygen. It can be used to treat methemoglobinemia because of its rapid action. Methylene blue is not advisable for the treatment of individual having G_6PD deficiency because it induces methemoglobinemia and promotes haemolysis [19]. The offending drugs to be withdrawn and administered with 1 to 2mg/kg of 1% methylene blue solution in i.v for > 20 minutes. Asymptomatic patients are treated with supplemental oxygen [20].

DRUG-INDUCED SIDEROBLASTIC ANAEMIA

Sideroblastic anaemia is a group of disorder which is characterized by ring sideroblast in the bone marrow and impaired haem biosynthesis. Erythroblasts contain iron positive granule surrounding the nucleus. Sideroblast anaemia can be inherited or acquired.The inherited forms are X linked, autosomal dominant or autosomal recessive modes of transmission. The acquired sideroblastic anaemia is more common when compared to the inherited types. Alcohol abuse can cause sideroblastic anaemia in some people [20]. Linezolid which is used to treat respiratory tract disorder and skin infection can cause mitochondrial toxicity. It binds with mitochondrial ribosomes when inhibits the formation of mitochondrial proteins [21]. Various drugs are inducing reversible sideroblastic anaemia such as isoniazid, chloramphenicol, penicillamine, busulfan, etc., [22-23].

The reversible drug-induced sideroblastic anaemia due to isoniazid and penicillamine can be treated with pyridoxine [24]. The withdrawal of the offending drugs shows a sudden response to this anaemia[25].

DRUG-INDUCED PURE RED CELL APLASIA

Pure red cell aplasia is characterized by the absence of reticulocytes and erythroblastopenia in the bone marrow. It can be congenital or acquired [26]. The mechanism of the drug can include,

i. Interference of drug in the metabolism of nucleated red cells
ii. Immune-mediated reactions, with antibody formation against red cell precursors
iii. Inhibitory effect of DNA synthesis [27].

Mainly acquired pure red cell aplasia is caused by malnutrition, autoimmune disease, drugs such as α interferon, lamivudine, INH, diphenylhydantoin, sodium valproate and infection like mononucleosis, viral hepatitis, parvovirus B_{19} and tuberculosis [28]. Pure red cell aplasia is an acute self-limiting and can be idiopathic or secondary. Pure red cell aplasia can mainly occur in renal failure patients with subcutaneous administration [28]. Life threatening adverse reaction are found in pure red cell aplasia and cholestatic liver injury associated with dapsone therapy. It is treated in a case by stopping the offending drug40mg by stopping the offending drug40mg prednisolone per day can be given and also 4 units of red blood cells can be transfused in severe cases [29].

CONCLUSION

The most common drug induced anaemia are aplastic anaemia, megaloblastic anaemia and haemolytic anaemia. The mechanism of drug induced anaemia can be either direct immune reaction (or) drug (or) metabolite toxicity. The first step in the treatment of drug-induced anaemia is removal (or) withdrawal of the causative agents. As medicines advances, older drugs are no longer used and replaced by the newer formulation of drugs, such as penicillin, quinidine, gold and chloramphenicol are becoming absolute. However, clopidogrel, linezolid, ribavirin and GPIIP/IIIA inhibitors are newer drugs found to be associated with own potential haematological toxicities.

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