Clinical pharmacology

Primary drug-induced anaemia and the importance of adverse drug reaction (ADR) monitoring

Drug-induced blood dyscrasias, while uncommon compared with other reported ADRs, are associated with significant drug-related fatalities,[1] varying from mild thrombocytopenia through to life-threatening aplastic anaemia and thrombosis. An understanding of the mechanism is essential for effective management and identification of possible causal agents. Anaemia, together with neutropenia and thrombocytopenia, are common presentations of drug-induced dyscrasias. A basis for understanding the pathogenesis, clinical presentation, and differential diagnosis of primary drug-induced anaemias is the focus of this article.

Background

The primary function of red blood cells is to deliver oxygen from the lungs to the tissues. A normal red blood cell has a lifespan of about 120 days. Anaemia is the result of excessive blood loss (acutely, i.e. a haemorrhage, or chronically through low-volume loss), excessive blood cell destruction (haemolysis) or deficient red blood cell production (ineffective haemopoiesis). It can be classified in several ways; most commonly by morphology (hypochromic microcytic, normochromic normocytic and macrocytic) and aetiological mechanism (increased red cell loss, decreased red cell production and abnormal distribution). Anaemia can manifest in a wide variety of ways depending on the severity and duration of onset.

The incidence of drug-induced haematological dyscrasias also increases with age, more specifically with age-related declines in renal/hepatic function and haemopoietic stem cell potential.[2] This is especially true where the offending drug causes dose-related toxicity, and thus overall exposure depends on drug clearance.[3]

Several other factors contribute towards the frequency of ADR events. Genetic susceptibility has been identified as a possible contributor, especially where

Table I. Common drugs associated with blood dyscrasias

Aplasia	Agranulocytosis	Thrombo-cytopenia	Haemolytic anaemia
Gold	Anti-thyroid drugs	Gold	Beta-lactams
Choramphenicol	Phenylbutazone	Heparin	Quinine/quinidine
Penicillamine	Sulphonamide	Quinine/quinidine	Thiazides
NSAIDs	Clozapine	Sulphonamides	Sulphonamides
Sulphonamides	Phenothiazines	Anticonvulsants	NSAIDs
Anti-thyroid drugs	Mianserin	NSAIDs	Rifampicin
Sulphonylureas	NSAIDs	Diuretics	Isoniazid
Phenothiazides	Beta-lactams	Rifampicin	Phenothiazines
Allopurinol	Captopril	Sulphonylureas	Sulphonylureas
	H_2-antagonists	Cimetidine	Nomifensine

the capacity to cope with oxidative stress within the red blood cell is reduced (e.g G6PD deficiency, an inheritable X-linked recessive disorder affecting intracellular enzyme levels). Drugs that increase intracellular oxidative stress include antimalarials and the sulphonamide antibiotics.

Pathogenesis

Drug-induced haematological dyscrasias occur through two main mechanisms: (*i*) immune-mediated anti-drug antibodies cause cell haemolysis; and (*ii*) toxic effects of the drug or its metabolite suppress cell production in the bone marrow.

Immune mediated

Haemolytic anaemia occurs when the premature destruction of red blood cells outstrips any increase in the reproductive rate in the bone marrow and spleen. The active compound or its metabolites bind with the red blood cell membrane, causing the cell to become antigenic. This stimulates the formation and binding of antibodies, resulting in the premature destruction of the red blood cells. Clinical importance stems from its potentially life-threatening consequences. While, overall, it is the commonest form of drug-induced anaemia, the incidence is rare in children.

Three main mechanisms have been identified to cause drug-induced haemolysis: (*i*) hapten type – the drug binds to the red blood cell membrane directly, acting as a hapten, stimulating IgG antibody production (e.g. penicillin); (*ii*) innocent bystander type – circulating drug-immune complexes bind erythrocyte

membranes and initiate complement activation; (*iii*) autoantibody type – antibodies specific to the drug are formed (e.g. methyldopa). Drugs implicated in these type of reactions include the penicillins, cephalosporins, levodopa, methyldopa, mefenamic acid, salicylic acid, sulfonamides, thiazide diuretics, chlorpromazine, and isoniazid.

Toxic type

Pluripotential haemopoietic stem cells (PHSCs) form the backbone of blood cell genesis and the impact of toxic damage depends on the scale and location in the differentiation processes where it occurs – if less differentiated cells are involved, more cell lines will be affected. Factors suggesting a toxic cause are: slowly falling red cell numbers, and a dose relationship and delayed response if the agent is re-introduced in a smaller dose. However, immune-mediated bone marrow suppression is described so biopsies are often necessary to identify the cause.

Drug-induced aplastic anaemia causes significant mortality and is therefore worth mentioning independently. The pathogenesis is through either a direct toxic effect on the bone marrow or a dose-independent idiosyncratic reaction resulting in the destruction of haematopoietic precursors in the bone marrow. It progresses slowly over weeks unless exacerbated by bleeding and haemolysis. Several drugs have been implicated (see Table I) and therefore, in cases of polypharmacy, the offending agent may be difficult to identify.

Other

Other mechanisms occur, but are uncommon and are not covered in this article. These include cisplatin therapy that reduces serum erythropoietin levels and other drugs that are thought to inhibit erythrocyte growth.

Management

Signs and symptoms

The signs and symptoms of anaemia depend on several factors: the aetiology and pathogenesis, how rapidly it develops, the severity, the age of the person and other co-morbidities. Anaemia is often undetected, especially where the onset is slow. Chronic forms of anaemia allow compensation through physiological adaptation (increased synthesis of 23-DPG intracellularly and redistribution of blood flow) and increased red blood cell production (through increased erythropoietin synthesis in the kidney) to occur. In acute-onset or decompensated chronic anaemia, patients present with more pronounced symptoms: dyspnoea, palpitations and dizziness. Pallor is more apparent in moderate or severe anaemia so 'eyeball diagnosis' is discouraged. Cheilosis, koilonychia, pica and behavioral disturbances in children may also be present.

Treatment

Grading the severity and identifying the cause are the key initial steps when treating anaemia. Due consideration of possible drug-induced causes is vital as early identification and immediate cessation of all associated drugs are necessary to improve outcomes.

Once the patient has stabilised, mild to moderate haemolytic anaemia can be treated with simple oral supplementation of ferrous sulfate or ferrous gluconate. Vitamin C, folic acid and vitamin B_{12} are commonly given to facilitate red blood cell replenishment. Recombinant erythropoietin may be used in anaemias related to chronic disease (e.g. renal disease) and chemotherapy.

Mortality from aplastic anaemia is high and demands immediate intervention. Complete recovery may be achieved if there is early and effective intervention. Once established, aplasia is mostly irreversible and early bone marrow transplantation required.

Avoidance

Idiosyncratic ADRs are by nature unpredictable, and therefore avoidance is often difficult. Active haematological monitoring may be useful for some agents to identify early signs. Restricting access to potentially toxic medicines is recommended where good alternatives are available and affordable. Finally, continued medical education should be encouraged for all health care professionals.

ADRs – reporting and importance

Haematological effects are rarely identified before marketing of new drugs. Therefore reporting ADRs provides early insight into the possible cause-effect relationships. The incidence can be estimated with this information, although concerns around reporting bias reduce the certainty – in one study only 10 - 15% of severe and 5% of mild-moderate ADRs were reported.[4] Large case-control studies have been conducted on limited therapies to overcome these limitations. All suspected ADRs should be reported to a safety monitoring centre.

In summary

Direct drug-induced dyscrasias are rare, but potentially serious. Early involvement of a haematologist and drug information pharmacists is necessary as early withdrawal of any likely offending agents is vital to improve outcomes. It is essential to report ADRs, as some haematological adverse effects are rare and are only discovered once the drug has been released on the market.

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Recommended reading

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