Hematologic Side Effects of Drugs

MICHAEL M. LUBRAN, M.D., Ph.D.

Harbor-UCLA Medical Center,
Department of Pathology,
Torrance, CA 90509

ABSTRACT

Bone marrow and peripheral blood cells may be adversely affected by drugs. Although the risk from most drugs is very small, many cases are reported because of the millions of doses of drugs taken each year by the population. Neutropenia, thrombocytopenia, hemolytic anemia, aplastic anemia, and macrocytic anemia are the commonest effects, in that order. Aplastic anemia is rare, but very serious when it does occur. Adverse effects may be produced by a direct toxic action of the drug or its metabolites on the bone marrow or, less often, on circulating cells. Antineoplastic drugs and chloramphenicol are examples. Most drugs produce their adverse effects through an immunological mechanism. The drug may act as a hapten or may affect the immune system leading to the production of antidrug antibodies and sometimes autoantibodies. Hemolytic anemia may result. Penicillins may behave in this manner. Some drugs act on erythrocytes with enzyme defects, e.g. glucose-6-phosphate dehydrogenase (G-6-PD) abnormalities, to produce hemolysis. In many cases, the mechanism underlying the adverse effect is unknown. The paper lists the drugs reported to have caused some hematological adverse effect and describes the mechanisms in those cases where they are known.

Introduction

Many drugs may adversely affect the hematopoietic system and peripheral blood cells. The principal effects, in order of frequency, are neutropenia, thrombocytopenia, hemolytic anemia, aplastic anemia (and pancytopenia), and macrocytic (or megaloblastic) anemia. In addition, other types of anemia may occur and also methemoglobinemia and coagulation defects. A drug may cause more than one adverse reaction and may act by two or more different mechanisms. Often, the effect is dose and time related, and the affected cells return to normal after the drug is discontinued; however, in some cases the adverse effect is irreversible, and the patient may die. Serious adverse effects are uncommon, when viewed against the background of the millions of doses of drugs taken daily in the total population. Transient effects are commoner and pass unnoticed for the most part unless discovered during some clinical examination. The frequency of adverse reactions to drugs is thus difficult to determine. Much of our knowledge is derived from reports in the literature describing one...
or a small number of cases. Many of
these reports are anecdotal, and it is
sometimes difficult to be sure that the
effect described was caused by the drug
and not by the illness for which it was
given, or by some other drug. However,
a few large scale studies have been pub­
lished,5,8,16,17 and the modes of action of
some drugs on the blood system have
been studied. Many countries now col­
lect systematically adverse drug reac­
tions of all types reported to them by
physicians, and there are several books
detailing adverse reactions.9,11,15,22 This
paper will describe the adverse hemato­
logical reactions (excluding coagulation)
attributed to drugs, gleaned from the lit­
erature and, whenever possible, the
mechanisms underlying the reactions.
Only drugs used in the United States
will be considered.

Adverse Effects of Drugs

Drugs may produce their adverse
effects through toxicity, by an immuno­
logical process, by inhibiting the action
of important enzymes, by decreasing the
absorption of substances essential for
normal hematopoiesis, or by as yet
unknown mechanisms. A well-studied
drug, now not often used, is chloram­
phenicol.23 This drug binds to mito­
chondria, inhibiting the formation of
inner membrane enzymes by inhibiting
peptidyltransferase, necessary for the
formation of peptide bonds. The toxic
effects of chloramphenicol are caused by
its action on mitochondria. Bone marrow
aplasia occurs in about 1:19,000 to
1:200,000 courses of therapy. Most
patients develop a dose-related revers­
ible erythroid suppression, caused by
inhibition of ferrochelatase, an inner
membrane enzyme.

The toxic effect of drugs may be deliber­
ately sought to suppress abnormal cell
activity, as in the use of chemotherapeu­
tic agents, or it may be an unwanted
side-effect of a drug. In the former case,
the toxic effect is dose and time depen­
dent; in the latter case, it is often not
dose dependent. Immunological mecha­
nisms require prior exposure to the
drug. Subsequent administration of the
drug results in antibody formation, lead­
ing to damage of blood cells. Enzyme
inhibition may be a property of the drug
and occur in all subjects receiving it (as,
for example, with many chemotherapeu­
tic agents), or the drug may act on cells
genetically deficient in an essential
enzyme (e.g., glucose-6-phosphate
dehydrogenase). A few drugs decrease
absorption of folate or B12, causing a
macrocytic anemia or megaloblastosis.
Although the adverse effect can be
explained in some cases, the cause is
unknown for the majority of drugs.
These idiosyncratic effects are unpredic­
table, cannot be deduced from the
known pharmacological properties of the
drug and may or may not be dose
related. They may be related to some
genetic feature of the patient, e.g., the
patient may be a slow acetylator, but in
most cases no cause can be found. Idio­
syncratic drug reactions affecting blood
cells are uncommon; nevertheless,
because of the enormous number of
doses of drugs given to the population,
they will occur almost inevitably, even
with the safest drugs. Most of the
reported adverse drug effects relate to
the idiosyncratic behavior of the drug in
one or a very few subjects. However,
there are some drugs which produce
adverse effects in an appreciable number
of subjects. The following sections will
describe the various adverse hematologi­
cal effects and the drugs causing them.

Aplastic Anemia

Aplastic anemia is an occasional com­
plication of the chemotherapy of cancer.
Antineoplastic drugs are usually used in
combination to treat cancers and hema-
ological malignancies by interfering with cell growth and division. In the doses used, rapidly dividing normal cells are also affected, including those in the bone marrow. A selective anemia, neutropenia, thrombocytopenia, or combination of these occur regularly depending on the dose, duration of treatment, and susceptibility of the patient. Less commonly, aplastic anemia or pancytopenia may develop.

Alkylating agents act on DNA, cross-linking its strands or breaking them. All phases of the cell cycle are affected and all bone marrow cells may be involved. Alkylating agents include busulfan, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, lomustine, mechlorethamine, melphalan, pipobroman, thiotapec, and uracil mustard.

Antimetabolites affect DNA synthesis by enzyme inhibition or by blocking the synthesis of purine or pyrimidine components. Azathioprine, mercaptopurine, thioguanine are purine antagonists; cytarabine, flouxuridine, fluorouracil are pyrimidine antagonists; methotrexate binds to dihydrofolate reductase and hydroxyurea inhibits ribonucleotide reductase. Antimetabolites may act during the entire cell cycle but are more effective in the S phase (DNA synthesis). Methotrexate inhibits folic acid synthesis and may cause megaloblastosis.

Antibiotic antineoplastic agents affect DNA and RNA synthesis. Dactinomycin and daunorubicin depress all cell types of the bone marrow; dexorubicin may cause agranulocytosis; mitramycin and mitomycin produce thrombocytopenia; bleomycin does not depress the bone marrow.

Other antineoplastic agents: Procarbazine inhibits DNA, RNA and protein synthesis and may cause leukopenia and anemia. Aminogluthethimide, which inhibits the synthesis of some steroid hormones, causes a transient leukopenia but may give a severe pancytopenia. Tamoxifen, an estrogen antagonist, may cause leukopenia or thrombocytopenia. Vinca alkaloids (vinblastine, vincristine, vindesine) and podophyllin derivatives (etoposide, teniposide) arrest mitosis in metaphase and stop cell division. The podophyllin drugs may severely depress the bone marrow; the vinca drugs are less toxic, causing usually a transient leukopenia and thrombocytopenia. Asparaginase may cause a leukopenia.

Aplastic anemia is an uncommon result of other drugs. Various estimates exist for the risk of developing it following use of certain classes of drugs. The incidence of aplastic anemia among subjects taking therapeutic drugs is about 2.2:1,000,000. More than half of these cases result from drugs and the mortality is high. For indomethacin the risk of aplastic anemia is about 1:100,000, for phenylbutazone about 1:300,000 and much lower for other analgesics. The risk is also very low for some antithyroid drugs.

Drugs with a relatively high risk for aplastic anemia include allopurinol, ampicillin, chloramphenicol, gold salts, indomethacin, meclofenamate, mefenamic acid, mephenytoin, oxyphenbutazone, paramethadione, phenobarbital, phenylbutazone, phentoin, quinacrine, trimethadione. Phenytoin toxicity may be related to a transient antibody formation and production of abnormal T-suppressor cells. Phenytin and carbamazepine give rise to toxic arene-oxide intermediate metabolites, which bind covalently to macromolecules of stem cells in the marrow and lymphocytes. About 70 percent of patients on long-term phenytin therapy have mild to severe abnormalities of the immune system.

Low risk drugs, reported in the literature once or a few times include acetaminophen, acetazolamide, acetohexamide, aspirin, bendroflumethiazide, benthiazide, captopril, carbamazepine,
HEMATOLOGIC SIDE EFFECTS OF DRUGS

Agranulocytosis and Neutropenia

Agranulocytosis may arise through the toxic action of the drug on bone marrow precursors or by destruction of cells by circulating neutrophil antibodies. Some drugs depress suppressor T-cells and allow the production of autoimmune antibodies by the B-cells. Antithyroid drugs may behave in this way. In most cases, the mechanism is unknown and presumed to be idiosyncratic.

Neutropenia and agranulocytosis may be produced by the drugs listed previously causing aplastic anemia. Antineoplastic drugs are responsible for many of the cases of neutropenia; in fact, a selective neutropenia is much commoner than aplastic anemia or agranulocytosis. Thrombocytopenia may or may not occur as well. Other drugs producing neutropenia, which may progress to agranulocytosis, include acetophenazine, amitriptyline, amoxapine, brompheniramine, carphenzine, chlorprothixene, clemastine, dapsone, desipramine, doxepin, ethacrylate, fluphenazine, furazolidone, griseofulvin, ibuprofen, imipramine, levamisole, maprotiline, mercaptopemer, mesoridazine, methotrimeprazine, methysergide, metronidazole, nifedipine, nortriptyline, novobiocin, para-aminosalicylic acid, penicillamine, perphenazine, piperacetazine, procainamide, protriptyline, quindine, quinine, thioethylperazine, thioridazine, thiothixene, tocinide, trifluoperazine, triflupromazine, trimeprazine, trimipramine, tybamate. Drugs usually producing a selective neutropenia include amoxicillin, ampicillin, bacampicillin, capreomycin, carbenicillin, cefaclor, cefadroxil, cefamandole, cefazolin, cefotaxime, cefoxitin, cephalin, cephalotaxine, cephalin, cephaloglycin, cephaloridine, cephalothin, cephalotaxine, cephapirin, cephradine, chlorpheniramine, clindamycin, clofibrate, cyclacillin, dantrolene, demeclocycline, diazepam, dexamethasone, doxycycline, flucytosine, haloperidol, ketacillin, levodopa, lincomycin,ioxapine, methacycline, methyl dopa, mezlocillin, molindone, moxa lac tam, nafcillin, oxacinil, oxytetracycline, penicillin G, penicillin V, pyrimethamine, rifampin, tetracycline, ticarcillin, trimethoprim, valproate, vidarabine.

Hemolytic Anemia

Drug-induced hemolytic anemia may occur as a result of a direct toxic effect on normal circulating erythrocytes, on cells with certain enzyme defects, on cells with some unstable hemoglobins, or through an immune mechanism.

Direct toxic effects are dose related, have a slow onset, and occur in all subjects. Few drugs are known to cause hemolytic anemia in this way. The best known are phenacetin (which also acts on enzyme-defective cells) and the sulfones used in the treatment of leprosy, especially dapsone. This drug causes hemolysis in all subjects, methemoglobinemia
in many and hemolytic anemia in a few on prolonged treatment. Drugs which may be toxic to erythrocytes, but may also act by other mechanisms, include cephalothin, chlorpromazine, clemastine, ethoxzolamide, hydrochlorothiazide, indomethacin, mefanamic acid, metaxalone, methazolamide, methyl-dopa, oxyphenbutazone, phenazopyridine, phenylbutazone, streptomycin, sulfamethazine.

Enzyme defects: The principal enzyme involved in hemolytic anemia is glucose-6-phosphate dehydrogenase (G-6-PD). These drugs give rise to acute episodes of hemolytic anemia which may be dose related, when administered to G-6-PD deficient patients. In some cases, the condition is self-limiting and disappears in about seven days, even though drug administration is continued. This occurs when existing G-6-PD deficient cells have been destroyed and the newly formed cells have become resistant to the drug. The erythrocytes in drug-induced hemolytic anemia caused by enzyme deficiency usually show basophilic stippling and may contain Heinz bodies. Drugs include chloramphenicol, chloroquine, dapsone, dimercaprol, furazolidone, isoniazid, nalidixic acid, nitrofurantoin, phenacetin, phytonadione, primaquine, probenecid, quinidine, quinine, sulfapyridine, sulfisoxazole, sulfoxone.

Hemolytic anemia is seldom caused by drugs in the case of other red cell enzyme deficiencies, but existing anemia may be exacerbated. Sulfoxone may cause hemolytic anemia in glutathione reductase deficiency.

Unstable hemoglobins: Exacerbation of existing hemolytic anemia may occur in subjects with some unstable hemoglobins, e.g., Hb-Zurich, when given the drugs causing hemolysis in G-6-PD deficiency.

Drug-induced immune hemolytic anemia: Antibodies which react with red cells to activate complement and produce lysis may be formed by two different mechanisms. In the hapten-cell mechanism, certain drugs given in large doses bind to proteins of the red cell membrane and act as haptens. Cephaplorins and penicillins may produce these antibodies. Penicillin is present on the surface of red cells of all patients receiving the drug. About three percent of patients on high doses of penicillin have IgG antibodies, and a small number of these patients go on to develop hemolytic anemia.

In the immune complex mechanism, the drugs bind to a serum protein and combine with the resulting antibody to form an immune complex. This adsorbs to the surface of the red cell and to other cells, e.g., thrombocytes and leukocytes, binds complement and causes cell destruction. The antibody is usually IgM in type. Quinidine and rifampin produce immune complexes.

An auto-immune hemolytic anemia may be drug-induced. It is believed that the drug binds to one of the blood group antigens on the red cell surface, usually an Rh antigen. The resulting antibody is directed against the blood group antigen; occasionally, an anti-drug antibody coexists. About 15 percent of patients on methyldopa and about nine percent on levodopa have demonstrable autoimmune antibodies in their sera after treatment for three months to a year; about one in ten thousand develop hemolytic anemia. An alternative to the hapten mechanism is the suppression of T-cell function through an increase of c-AMP in lymphocytes, leading to an unregulated production of autoantibodies by B-cells. The autoantibodies are usually of the Rh system. The drug does not act as a hapten, but produces its effects via the immune system. The immune system plays an important role in regulating normal hematopoiesis.

Drugs giving rise to antibodies include cefamandole, cefotaxine, cefoxitine, cephalothin, co-trimoxazole, isoniazid,
levodopa, mefanamic acid, methicillin, methyldopa, moxalactam, nalidixic acid, oxacillin, para-aminosalicylic acid, penicillin G, penicillin V, quinidine, quinine, rifampin, sulfacytine, sulfadiazine, sulfamerazine, sulfamethizole, sulfapyridine, sulfasalazine, ticarcillin, tolmetin. Autoantibodies are found with levodopa, methyldopa and mefanamic acid.

**Thrombocytopenia**

This may result from a direct toxic effect of the drug on platelet precursors in the bone marrow or on the circulating platelets. Drugs associated with aplastic anemia also cause thrombocytopenia, through action on megakaryocyte precursors in the marrow. Low risk drugs may cause a selective thrombocytopenia, which is often the only indication of suppression of marrow activity. Ristocetin acts directly on circulating platelets. Lithium carbonate given for one or more years lowers the platelet count, but rarely causes purpura.²

Thrombocytopenia may also result from an immune mechanism. Drug and platelet combine and produce an antibody against the drug. An immune complex is formed which is adsorbed non-specifically on to platelets and other cells. This is referred to as “the innocent bystander” hypothesis. As an example, valproate depresses the platelet count in about one third of the cases.³,²⁴ However, the immune complex may combine specifically with platelets. The antibody to quinidine combines with the major glycoprotein complex on the platelet surface and the antibody to ticarcillin combines with a polymorphic platelet antigen.¹⁴ Drugs acting by an immune mechanism include antimony potassium tartrate, azatadine, brompheniramine, capreomycin, captopril, chlorothiazide, chlorpromazine, chlorpropamide, clofazimine, clindamycin, clonazepam, deferoxamine, diazoxide, digitoxin, ethacrylate, ethchlorvynol, ethinamate, ethionamide, flucytosine, fluphenazine, furosemide, isoniazid, lincomycin, mephabarbital, meprobamate, metharbital, methimazole, para-aminosalicylic acid, penicillamine, penicillins, phenacetin, phenobarbitone, phenylbutazone, phenothiazine, phentoin, procainamide, propylthiouracil, quinidine, quinine, rifampin, salicylates, streptomycin, sulfonamides, ticarcillin, tocainide, trimelormethiazide, trimethoprim, valproate, vidarabine.

**Megaloblastic Anemia**

This may result from administration of drugs interfering with the absorption of folic acid or vitamin B₁₂ or the metabolic functions in which they are involved. Frank megaloblastic anemia is uncommon. The usual effect is macrocytosis, unless the patient is severely ill or undernourished and deficient in folic acid or vitamin B₁₂. In many cases, there is no clinical evidence of folate or B₁₂ deficiency, but their concentrations in the blood are low.

**Folic acid:** Low serum folate concentrations caused by poor absorption of folate may result from administration of cycloserine, ethotoin, mephabarbital, metharbital, nitrofurantoin, phensuximide, phentoin, primidone. Megaloblastic anemia may occur in a few cases. About 50 percent of patients on phentoin have low serum folate concentrations and about 30 percent have red cell macrocytosis and early megaloblastic changes in the bone marrow. About one percent develop frank megaloblastic anemia.⁴ It may take many years of drug administration for this to occur. It is not clear why some patients should develop this condition, but dietary intake of folate may be a contributory factor.

Dihydrofolate reductase is inhibited by methotrexate, triamterene, pyrimethamine, trimethoprim. This is a key
enzyme in folate metabolism and DNA synthesis. Megaloblastic anemia will occur if the drug is given for a sufficient length of time, in high enough doses, but in practice it is unusual.

Cytarabine, floxuridine, fluorouracil (antimetabolite antineoplastic agents) inhibit pyrimidine synthesis; hydroxyurea inhibits ribonucleotide reductase; azathioprene, mercaptopurine, thioguanine inhibit purine synthesis; (antimetabolite antineoplastic agents) block the synthesis of folic acid, which impair absorption of vitamin B₁₂.

Vitamin B₁₂: Low serum concentrations may result from administration of colchicine, neomycin, para-aminosalicylic acid, slow release potassium chloride, ampicillin, ampicillin, bacampicillin, cefadroxil, cefazolin, cephalaxin, cephaloglycin, cephaloridine, cepapirin, novobiocin, oleovitamin A, vidarabine.

Drug-induced Methemoglobinemia

The commonest cause is self-medication with pain-relieving drug combinations containing phenacetin. Other drugs are amyl nitrite, dapsone, prilocaine, primaquine, sulfoxone, trimethoprim. Primaquine acts on red cells deficient in NADH methemoglobin reductase. Methemoglobinemia is produced by drugs which are redox compounds or form a complex with heme. Hydrogen peroxide or peroxide radicals are formed, leading to the formation of methemoglobin. In some cases, the reaction proceeds further, resulting in Heinz bodies and hemolytic anemia. Most drugs producing hemolytic anemia by direct toxic action on the red cells will also produce methemoglobin in the early stages. Some drugs act by producing toxic metabolites in the liver.

Anemia

Drugs which may cause aplastic anemia may also have lesser effects, of which anemia is one. Other drugs, not associated with aplastic anemia, may produce anemia by depression of the bone marrow or by other means. Isoniazid increases the severity of the anemia in patients suffering from pyridine-responsive hypochromic anemia. Rarely, it may produce a pure red cell hypoplasia. This condition may also be produced by chlorpropamide, co-trimoxazole, penicillin, phenylbutazone, phenytoin, tolbutamide. Indomethacin produces an iron-deficiency anemia and amphotericin B a normochromic, normocytic anemia. Other drugs which may produce anemia, usually hypochromic, include amoxicillin, ampicillin, bacampicillin, cycloclavulin, cycloxepin, cefadroxil, cefazolin, cephalaxin, cephaloglycin, cephaloridine, cepahapirin, novobiocin, oleovitamin A, vidarabine.

References


