

SciAnews

Assessment of Drug Related AE's and ADR's

Introduction

As the range of therapeutic products available has expanded, regulatory agency requirements for safety documentation have also grown. Hence, all individuals involved in the process of risk-benefit assessment of investigational and approved drug products need to be familiar with the most frequently encountered drug reactions. This includes investigational site clinical staff as well as clinical research monitors, project managers and safety officers of sponsoring pharmaceutical companies and CRO's working as partners with the pharmaceutical industry.

At SciAn Clinical, adverse event tracking and reporting is an important part of the management of both clinical trials and clinical data. Clinical trial monitors must be attentive in their source data validation, and in second (in-house) review of CRF's to ensure that important drug related events are appropriately reported.

Assessment of Adverse Events

The following discussion outlines the three major groups of adverse events typically related to therapeutic agents, and some keys to their assessment. These are:

- liver function impairment
- cutaneous reactions
- hematologic cytopenias.

The diagnosis of AE's involve two diagnostic steps, specifically:

- 1) *Differential diagnosis*, describing and defining the nature of the abnormality.
- 2) *Etiologic diagnosis*, where drug and non-drug causes are considered, in concert with the patient's medical condition and risk factors.

Assessment of Causality

Consider the following parameters for causality assessment:

1. Chronology

- time to onset of reaction
- initial or secondary exposure
- rate of metabolism of the drug in question, the course of the reaction
- continuance or cessation of drug administration.

2. Risk factors for drug reaction

- age
- ethanol consumption
- pregnancy
- previous history

3. Concomitant Medications

- evaluate known toxicity
- review published and/or labeled reactions
- include assessment of chronology as related to the medication concerned.

4. Non-Drug Related Causes

- recent infections, particularly of viral etiology
- the medical condition under treatment
- concurrent medical conditions

5. Previous Information

- toxicity of the drug class
- toxicity of the drug in question
- labeled reactions
- published but not labeled reactions

6. Response to Readministration

Key Organ Systems for The Expression of Drug Toxicity:

I. Drug Induced Liver Injuries

Three main types of liver injury may be classified by evaluating liver function assays, primarily alanine aminotransferase (ALT), aspartate aminotransferase (AST), AP (alkaline phosphatase), conjugated bilirubin (CB) and total bilirubin (TB). Enzymes should be considered with reference to the normal ranges (N) of the laboratory. A ratio (R) of ALT/AP (in multiples of N) is useful.

Hepatocellular Injury

Increases of $> 2N$ in ALT alone or an R value ≥ 5 is diagnostic.

Cholestatic Injury

An increase in AP $> 2N$, and an R value between 2 - 5 is diagnostic.

Mixed Hepatocellular/Cholestatic Injury involves increases of both ALT and AP $> 2N$, and an R value between 2 -5.

Changes in liver function enzyme levels over time, after drug withdrawal, play a key role in evaluating causality.

Non-drug causes to be considered include recent viral infections (Hepatitis A, B or C, CMV, EBV or Herpes), biliary obstruction, alcoholism, recent acute hypotension and/or underlying heart disease. A history of simple hepatic injury (e.g. viral hepatitis) increases the risk of developing acute drug induced liver injury with alcohol consumption.

II. Drug Induced Cutaneous Reactions

Skin disorders are the most prevalent adverse reactions causally associated with drugs. *The most commonly seen milder forms, representing 80% of all drug related skin reactions, include:*

Urticaria: usually appears within minutes to hours of drug administration. This extremely common disorder is linked to drugs in only 5-10% of all cases, more frequently being associated with food allergens and viral or parasitic infections.

Diffuse maculopapular erythematous eruptions account for most cutaneous drug reactions, usually appearing 5-10 days after the beginning of treatment, or 2-7 days after the cessation of drug therapy in cases of short treatment or prolonged drug half life.

Drug Induced Photosensitivity appears as a 'sunburn' resulting from direct UVA absorption. A *phototoxic response* is characterized by early onset, and is limited to areas directly exposed to sunlight. A *photoallergic reaction* is characterized by onset > 5 days after exposure to sunlight and first time exposure to the drug, often extending beyond the light exposed areas, and

represents an immunologic response to UVA conjugated proteins. With prior sensitization, a photoallergic response can occur within 3-72h of the start of drug administration.

Fixed drug eruptions, appear as 1-5 large, painful, inflammatory, erythematous and pruritic peripheral lesions, always localized to the same sites for each occasion of drug administration. These are *always* causally related to drugs, usually appearing within hours of first dose of a secondary administration of the drug. A large number of drug classes have been implicated.

Severe forms of cutaneous drug reactions include:

Vascular purpura, involving inflammation of the blood vessels. Typical onset time 1 - 3 weeks after first exposure, and < 3 days after subsequent exposure. May also be associated with bacterial infections and immunologic disorders. Less than 10% of cases are attributable to drugs (commonly antibiotics); up to 50% of cases are of idiopathic etiology.

Acute Generalized Exanthematic Pustulosis (AGEP) is frequently associated with drug administration (80% of all cases), typically appearing within 1-3 days of start of therapy. This reaction consists of an acute febrile eruption of numerous tiny amicrobial pustules on a burning, edematous erythema, and elevated neutrophil counts.

Stevens-Johnson syndrome (SJS) is characterized by severe mucosal lesions of an atypical concentric "target" form. SJS is drug induced in 60-90% of cases, and is fatal in about 5% of cases.

Toxic Epidermal Necrolysis (TEN) is one of the most severe cutaneous reactions, involving widespread loss of the full epidermal thickness, with onset between 1-3 weeks of first time drug exposure. TEN is always attributable to drug. The mortality rate is 20-30%; advanced age and wide lesion extent are poor prognostic indicators.

III. Drug Induced Blood Cytopenias

This discussion excludes the expected drug induced reactions involving cytotoxic and antiviral therapies.

Neutropenia: Polymorphonuclear neutrophil counts < 1.5 x 10⁹/L are considered abnormally low; < 0.5 x 10⁹/L constitutes severe neutropenia. When no other hematologic parameters are affected, first rule out infectious causes, systemic diseases (e.g. autoimmune), blood disorders, and exposure to toxic agents. Drug related etiology is likely when onset is recent, bone marrow shows regenerating forms, existing literature documents drug induced neutropenia, and neutropenia reverses upon drug withdrawal. Drug induced neutropenias have been documented in most therapeutic classes. Proposed mechanisms are either antibody mediated, or involve direct PMN toxicity.

Thrombocytopenia is defined as platelet counts < 100,000 μ L⁻¹, with or without accompanying bleeding disorders. This is rarely attributable to drug administration; more commonly it is caused by idiopathic thrombocytopenic purpura (ITP). Drug related etiology should be considered when :

- bone marrow is normal and rich in megakaryocytes
- TP develops within 1 month of first administration, or after 1 week of subsequent treatment
- the event resolves completely within 6 weeks after discontinuation of the medication, without corticosteroid treatment.

Proposed mechanisms for drug induced TP include direct toxicity and antibody mediated cell lysis.

Agranulocytosis: The abrupt onset of absence or scarcity of granulocytes (including neutrophils and banded forms) is a serious and potentially fatal side effect associated with a wide range of therapeutic agents. Patients may present with only fever and a sore throat, despite absolute neutropenia. The event is more prevalent in populations > 60 years of age, and is twice as likely to occur in females as males. The overall incidence is 3 - 7 cases per million. About 65% of cases are directly attributable to drug reactions. Drugs implicated include analgesics (including NSAIDs), antibiotics (including sulfa compounds), antithyroid agents, cardiovascular drugs (including ACE inhibitors, antiarrhythmics), antihistamines, antidepressants, antipsychotics, sedatives, quinolones and heavy metals. Such drugs may act by immunologic mechanisms, or by direct toxicity, including toxicity to myeloid precursors. Diagnosis requires bone marrow examination and assays of antibody binding.

Specific risk factors have been identified in some cases. For example, the incidence with the immunomodulator levamisole is higher in patients of Jewish origin, suggesting a genetic component, and the incidence with the ACE inhibitor captopril is increased in patients with renal failure or underlying autoimmune diseases, e.g. rheumatoid arthritis.

Before modern therapies and frequent laboratory monitoring, agranulocytosis was associated with mortality rates >90%. Early IV broad spectrum antibiotics in combination with hematopoietic growth factors have reduced mortality rates to about 10%.

Hemolytic Anemia is characterized by hemoglobin levels below the normal range, combined with normal MCV, reticulocytosis, low haptoglobin levels, hyperbilirubinemia, increased serum LDH and increased serum iron. Drug induced hemolytic anemia originates by four distinct mechanisms:

1. *Autoimmune hemolytic anemia* produces autoantibodies to RBC's. Drug etiology is rare (<10% of cases).
2. *Immune hemolytic anemia* produces antidrug antibodies which bind to RBC's, causing complement activated lysis. All cases are drug related; hemolysis usually appears within 24 h of secondary administration. No rechallenge testing should ever be attempted due to increasingly serious reactions.
3. *Abnormalities of hemoglobin or RBC enzymes* are often associated with a genetic defect (e.g. G6PD deficiency is common in Mediterranean ancestry).
Microangiopathic hemolytic anemia produces RBC fragmentation, and intravascular microthrombi which may result in neurologic manifestations as with cerebral ischemia, and renal failure. Oral contraceptives and some anticancer therapies have been implicated.

Reference: *Adverse Drug Reactions: A Practical Guide to Diagnosis and Management*, (1994) C. Bénichou ed., J. Wiley & Sons.