

Adverse drug reactions

Idiosyncratic drug reactions: the reactive metabolite syndromes

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Idiosyncratic drug reactions are unpredictable reactions that can result in significant morbidity and mortality. Severe idiosyncratic drug reactions are often characterised by fever and internal organ involvement. Despite progress in the identification of reactive metabolites believed to be the cause of idiosyncratic reactions, the basic mechanisms remain elusive. Furthermore, because of the lack of consensus regarding definition of these syndromes, reporting, and therefore epidemiological data, are often unreliable. Research is needed to explore further the pathophysiology of these reactions, so that better diagnostic tests and treatment methods can be developed.

Adverse drug reactions can be classified into type A, or predictable, reactions and type B, also known as unpredictable or idiosyncratic reactions. Type A reactions are dose-dependent and predictable based on the pharmacology of the drug; about 80% of all adverse drug reactions are type A. In contrast, idiosyncratic drug reactions cannot be explained on the basis of the pharmacology of the drug, and although they are dose-dependent in susceptible individuals, they do not occur at any dose in most patients. Idiosyncratic reactions can affect any organ system, and include IgE-mediated reactions such as anaphylaxis, teratogenicity, and carcinogenicity, as well as reactive metabolite syndromes such as hypersensitivity-syndrome reactions, serum-sickness-like reactions, and drug-induced lupus. The role of drug metabolism and reactive metabolites that cause these serious reactions have been investigated over the past 15 years and will be the focus of this paper. Clinical management is still empirical, but recognition of a drug-induced disease is important for future management of the patient.

Drug-hypersensitivity syndrome

Drug-hypersensitivity syndrome is a systemic disease that presents with fever and involves one or more internal organs. Because one organ is usually dominant (eg, liver, kidney, or skin) in the clinical presentation, drug hypersensitivity as a syndrome may not be recognised. This lack of recognition leads to problems in reporting, since many patients who seem to have single-organ dysfunction actually have drug-hypersensitivity syndrome.

Drug-hypersensitivity syndrome is usually defined by the triad of fever, skin eruption, and internal-organ involvement (table 1). It has been well described for anticonvulsants, sulphonamide antibiotics, dapsone, minocycline, and allopurinol.^{1,2} Drug-hypersensitivity syndrome associated with anticonvulsants (ie, phenytoin, phenobarbital, and carbamazepine) was originally called

the anticonvulsant hypersensitivity syndrome.³ There have been several reports of a similar syndrome associated with the anticonvulsant lamotrigine.⁴ There is cross-reactivity among the aromatic anticonvulsants, but no evidence to suggest that there is cross-reactivity between these drugs and lamotrigine.

The true incidence of drug-hypersensitivity syndrome is unknown because of the variable presentation and inaccurate reporting; however, this reaction has been estimated to occur in between one in 1000 and one in 10 000 exposures with drugs such as anticonvulsants and sulphonamides.^{5,6} Drugs with a higher frequency of this adverse reaction, such as sorbinil, have generally been discontinued during development.⁷ Drug-hypersensitivity syndrome generally occurs during first exposure to the drug, with initial symptoms starting 2–6 weeks later. In patients with a history of drug-hypersensitivity reaction, re-exposure after a previous reaction may cause symptoms within 1 day.

The presenting symptoms in most patients include a mild-grade to high-grade fever ranging from 38 to 40°C, and malaise, often accompanied by pharyngitis and cervical lymphadenopathy. About 85% of patients develop a skin eruption (such as a generalised exanthem) near the time of the fever or shortly after. Skin manifestations can range from an exanthematous eruption to more serious eruptions such as Stevens-Johnson syndrome and toxic epidermal necrolysis.³ Atypical lymphocytosis with a subsequent prominent eosinophilia can occur during the initial phases of the reaction in a subset of patients.¹ Bone-marrow involvement can result in isolated thrombocytopenia or agranulocytosis, but can

	Drug Hypersensitivity syndrome (multiorgan dysfunction)	Drug-induced lupus	Serum-sickness-like reaction
Type of rash	Exanthem Exfoliative dermatitis Pustular eruptions Erythema multiforme/ Stevens-Johnson syndrome/ toxic epidermal necrolysis	None (usually)	Urticaria Exanthem
Onset of symptoms	2–6 weeks	Up to 2 years	7–14 days
Fever	Present	Absent or present	Present
Internal organ involvement	Present	Absent (usually)	Absent
Arthralgia	Absent	Present	Present
Lymphadenopathy	Present	Absent	Present

Table 1: Clinical features of idiosyncratic drug reactions

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also cause "bi-penias" (ie, defects in two cell lines) and aplastic anaemia. Liver abnormalities, presenting as raised aminotransferase concentrations, alkaline phosphatase concentrations, prothrombin time, and bilirubin concentrations are present in about 50% of patients. Development of severe hepatitis with jaundice can occur.⁸ Other organs such as the kidney (interstitial nephritis, vasculitis), central nervous system (encephalitis, aseptic meningitis), intestinal tract (colitis), pancreas, or the lungs (interstitial pneumonitis, respiratory-distress syndrome, vasculitis) are less commonly involved. A small subgroup of patients may develop hypothyroidism as part of an autoimmune thyroiditis within 2 months of onset of symptoms of drug-hypersensitivity syndrome.⁹ These patients present with signs of hyperthyroidism at the time of the reaction, but because sore throat, fever, and tachycardia can be missed, biochemical evidence, such as low concentrations of thyrotropin are helpful in the diagnosis. Several months after the acute episode, this group of patients present with hypothyroidism with autoantibodies, including antimicrosomal antibodies.

The differential diagnosis of drug-hypersensitivity syndrome includes other cutaneous drug reactions, acute bacterial or viral infections (eg, with Epstein-Barr virus, hepatitis viruses, influenza viruses, and cytomegalovirus), lymphoma, and idiopathic hypereosinophilic syndrome.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions, which may represent variants of the same disease process, range from erythema multiforme major to toxic epidermal necrolysis. Erythema multiforme minor is usually not caused by drugs and does not have mucosal involvement. Differentiation among the patterns depends on the nature of the skin lesions and extent of body-surface-area involvement. The more severe forms are associated with epidermal detachment over a greater proportion of body-surface-area (table 2).¹⁰ Target lesions tend to change from the classical, raised three-ringed-iris lesion to a more purpuric or erythematous two-ringed lesion. Clinically, each of these reaction patterns is characterised by the triad of mucous-membrane erosions, atypical target lesions, and epidermal necrosis with skin detachment.¹⁰ The more severe the reaction, the more likely it is to be drug-induced. A large proportion of cases of erythema multiforme and Stevens-Johnson syndrome are not drug-related and may develop as a consequence of various other factors including infections, neoplasia, and autoimmune diseases. The most frequent drugs cited as causes of Stevens-Johnson syndrome or toxic epidermal necrolysis are the anticonvulsants, antibiotics (eg, sulphonamides), allopurinol, and non-steroidal anti-inflammatory drugs (eg, piroxicam).¹¹

Serum-sickness-like reactions

Serum sickness and serum-sickness-like reaction are two very different diseases. Serum sickness is a clinical syndrome characterised by fever, lymphadenopathy, arthralgias, cutaneous eruptions, gastrointestinal disturbances, and malaise, and is often associated with proteinuria without evidence of glomerulonephritis.¹² Serum sickness is mediated by deposition of circulating immune complexes in tissues, activation of complement, and the ensuing inflammatory response. Serum sickness is usually caused by the administration of foreign proteins, such as antithymocyte globulin.

In contrast, serum-sickness-like reaction is defined by fever, rash (usually urticaria), and arthralgias occurring 1–3 weeks after drug exposure (table 1). Lymphadenopathy and eosinophilia may also be present.

Classification	Erythema multiforme major	Stevens-Johnson syndrome	Toxic epidermal necrolysis
Epidermal detachment (% of body-surface area)	<10	<10	>30
Typical targets	No	No	No
Atypical targets	Flat	Flat	Flat
Macules	No	Yes	Yes
Mucous membrane involvement	Yes	Yes	Yes
Severity	Low	Medium	High
Likelihood of drug-induced aetiology	Low	Medium	High

Table 2: Classification and characteristics of severe cutaneous adverse reactions

Immune complexes, hypocomplementaemia, vasculitis, and renal lesions are absent in serum-sickness-like reactions.

Epidemiological studies in children suggest that the risk of serum-sickness-like reaction is greater with cefaclor than with other antibiotics, including other cephalosporins.^{13,14} The overall frequency of cefaclor-induced serum-sickness-like reactions has been estimated at 0.024–0.2% per course of cefaclor prescribed. Other drugs implicated in the causation of these reactions include cefprozil¹⁵ and minocycline.² The incidence rates for these drugs are unknown.

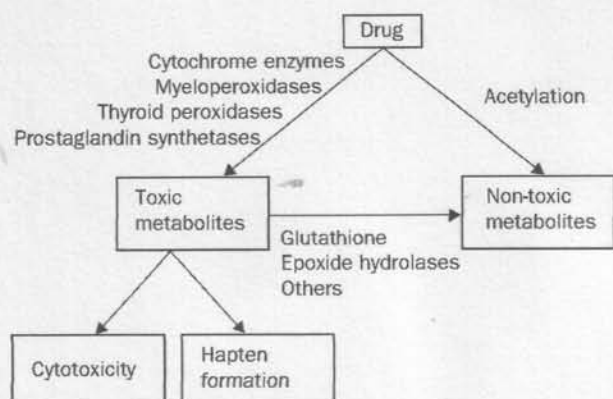
Drug-induced lupus

Drug-induced lupus is not the same disease as systemic lupus erythematosus, but the disorders have some features in common. Drug-induced lupus is characterised by frequent musculoskeletal complaints, fever and weight loss, pleuropulmonary involvement in more than half of patients, and rarely, renal, neurological, or vasculitic involvement (table 1). Most patients have no cutaneous findings of lupus erythematosus. Positivity for antinuclear antibodies with a homogenous pattern is the most common serological abnormality. Importantly, few patients who develop positivity for antinuclear antibodies related to drug ingestion develop clinical disease compatible with drug-induced lupus. This disorder should be suspected in patients who do not have a history of idiopathic systemic lupus erythematosus, who develop antinuclear antibodies and at least one clinical feature of systemic lupus erythematosus after an appropriate duration of drug treatment, and whose symptoms resolve after discontinuation of the drug.¹⁶ In general, symptoms and serological changes appear more than 1 year after starting therapy.

Some drugs, including procainamide, hydralazine, chlorpromazine, isoniazid, methyldopa, and penicillamine, have been implicated in drug-induced lupus; minocycline's association with the disorder is well described.^{2,17}

Although antihistone antibodies are seen in up to 95% of cases of drug-induced lupus, they are not specific for the syndrome and are also found in 50–80% of patients with idiopathic lupus erythematosus.¹⁸ Unlike in idiopathic lupus erythematosus, antibodies against double-stranded DNA are typically absent in drug-induced lupus.¹⁹ Several patients with drug-induced lupus attributed to minocycline have had positive antineutrophil cytoplasmic antibodies, which may be directed against antimyeloperoxidase or elastase.^{20,21}

In general, seroconversion from negativity to positivity for antinuclear antibodies alone is not a sufficient reason to discontinue treatment with a drug. However, once drug-induced lupus is suspected, treatment with the drug believed to be responsible should be stopped immediately.



Formation and detoxification of reactive metabolites

Symptoms of drug-induced lupus are usually self-limiting once treatment with the offending drug has been discontinued, and generally resolve in 4–6 weeks; however, positivity for antinuclear antibodies may remain for 6–12 months.

Pathogenesis

Little is known with certainty about the mechanisms of most idiosyncratic drug reactions. A large amount of circumstantial evidence suggests that reactive metabolites of a drug, rather than the parent drug, are responsible for most idiosyncratic drug reactions (figure 1). In the case of the anticonvulsants—phenytoin, carbamazepine, and phenobarbital—the reactive metabolite responsible for idiosyncratic reactions is thought to be an epoxide, and the basis for increased susceptibility in specific individuals and cross-reactivity between these agents is thought to be due to a deficiency of epoxide hydrolase.²² However, two studies have found no difference in the frequency of the gene associated with low epoxide hydrolase activity in patients with a history of anticonvulsant hypersensitivity,^{23,24} and this finding has placed the epoxide hypothesis in doubt. Furthermore, there is no direct evidence that these drugs form an epoxide in humans. More recently, phenytoin has been shown to form a reactive free radical²⁵ and an orthoquinone,²⁶ whereas carbamazepine forms a reactive iminoquinone that also undergoes redox cycling.²⁷ These metabolites are alternative candidates for the agents responsible for idiosyncratic reactions.

The metabolic pathway leading to reactive metabolites of sulphonamide antibiotics, such as sulphamethoxazole, is less controversial. These drugs are aromatic amines that are oxidised, first to hydroxylamines and then to nitroso derivatives, with redox cycling between the two.²⁸ The redox cycling can lead to oxidative stress and the nitroso derivatives also react covalently with proteins. Other aromatic amines, such as dapsone and procainamide, form similar hydroxylamine and nitroso metabolites and so there could be some degree of cross-reactivity between aromatic amines and sulphonamide antibiotics; however, there are few clinical data available, so this mechanism must be regarded as theoretical. Several other drugs are sulphonamides but not aromatic amines—eg, sulphonylureas, thiazide diuretics, furosemide, acetazolamide, and celecoxib. These drugs are not recommended for patients with a history of an adverse reaction to a sulphonamide antibiotic. However, since these drugs are unlikely to form similar reactive metabolites and there is little clinical evidence for cross-reactivity with sulphonamide antibiotics, this precaution may be unwarranted.

The working hypothesis that most investigators use to explain the association between the formation of reactive metabolites and the induction of idiosyncratic drug reactions is the hapten hypothesis—ie, that the reactive metabolite covalently binds to proteins and the altered proteins are seen as foreign by the immune system and induce an immune response.²⁹ In some cases, this immune response can lead to substantial damage resulting in an idiosyncratic drug reaction. Although this hypothesis may be partly correct, it does not explain many aspects of idiosyncratic reactions, and the complete mechanisms involved are likely to be much more complex. For example, many drugs that form reactive metabolites, such as paracetamol, are not associated with a high incidence of idiosyncratic reactions. With notable exceptions, such as penicillin-induced IgE-mediated allergic reactions, many idiosyncratic reactions are not associated with evidence of an immune response against drug-modified proteins. The most important characteristic of idiosyncratic drug reactions is their idiosyncratic nature, and the hapten hypothesis does not explain why most individuals do not have a clinically evident immune response against drug-altered proteins.

The involvement of the immune system in most idiosyncratic drug reactions has not been proven; however, such proof can be difficult to acquire for several reasons. For example, the pathology of toxic epidermal necrolysis suggests the involvement of cytotoxic T cells, but showing the presence of specific cytotoxic T cells is much more difficult than showing the presence of drug-dependent antibodies. In addition, idiosyncratic reactions are often autoimmune in nature—ie, the response is against native protein rather than drug-modified protein. Furthermore, some reactions may be mediated by the innate immune system and, therefore, may not involve specific antibodies or cytotoxic T cells.³⁰

One concept that may help to explain why not all drugs that form reactive metabolites are associated with a high incidence of idiosyncratic reactions is the “danger hypothesis”.³⁰ The basis for this hypothesis is that the immune system does not directly differentiate self and non-self, and it only responds to a foreign antigen if the antigen is associated with a danger signal. The exact nature of what can constitute a danger signal is unknown, but necrotic cell death and cell stress are likely to be two such signals. Thus, a reactive metabolite may not only have to modify protein, it may also have to injure or stress cells in order to induce an immune response and an idiosyncratic drug reaction. This may explain why drugs such as paracetamol, which form reactive metabolites but only cause cell toxicity at concentrations above the therapeutic range, do not usually cause idiosyncratic reactions. As mentioned earlier, some drugs, such as isoniazid and halothane, cause an increase in aminotransferase concentrations in a high percentage of patients, and this effect probably reflects direct cell toxicity that could act as a danger signal and increase the probability of an idiosyncratic reaction.

Cell injury caused by other factors such as surgery or viral infections, especially HIV infections, also seems to increase the risk of an idiosyncratic drug reaction.³⁰ Furthermore, despite what is commonly stated, idiosyncratic drug reactions are dose dependent, and we have not been able to find any drug that is given at a dose of 10 mg/day or less that is associated with a high incidence of an idiosyncratic drug reaction.³⁰ Thus, even when a large fraction of the drug is metabolised to a reactive metabolite, only a small amount of reactive metabolite is required to induce an immune response.

Management of patients with drug-hypersensitivity syndrome

- Discontinue offending drug
- Obtain the following laboratory data.
Complete blood count and differential
Liver function
Urinalysis (routine and microscopy)
Serum creatinine concentrations
Other tests, depending on symptom presentation (eg, chest radiograph for respiratory symptoms)
Baseline thyroid function tests (eg, thyroxine). Repeat at 3 months
- Do skin biopsy if blistering or pustular eruption
- Use antihistamines or topical corticosteroids to treat symptoms
- Assess need for systemic corticosteroid therapy or other therapy (eg, intravenous immunoglobulin for toxic epidermal necrolysis)
- Review warnings about cross-reacting drugs and risk to family members

The probable reason for the apparent dose independence is that the range of therapeutic doses for a specific drug is usually narrow and most patients will not have an idiosyncratic reaction to a specific drug at any dose. In fact, with several drugs, if a patient starts at a low dose and then gradually increases the dose, the risk of an idiosyncratic reaction is decreased. This risk reduction is presumably due to the low dose being insufficient to induce an idiosyncratic reaction and instead induces immune tolerance.³¹ Even in a sensitised patient, tolerance can often be induced by starting with a very low dose and then increasing to a therapeutic dose.³²

Even in the face of a strong danger signal such as surgery, the usual response of most patients to a drug that forms a reactive metabolite seems to be tolerance. In fact, idiosyncratic reactions will often resolve despite continued treatment with the causative drug, probably because of the induction of tolerance.^{33,34} Tolerance could also explain why idiosyncratic reactions, with the exception of drug-induced lupus, almost always occur early in the course of treatment, and why if they do not occur then, the patient develops tolerance to the drug. Thus, a better understanding of the mechanisms of immune tolerance could contribute to our ability to predict which drugs are likely to cause a high incidence of idiosyncratic reactions and which patients are likely to have an idiosyncratic reaction to a specific drug.

Management

Management of patients who develop an idiosyncratic drug reaction involves the treatment of the reaction, and follow-up of the patient, including diagnostic testing, if applicable, and counselling.

In patients who develop an idiosyncratic drug reaction, immediate discontinuation of the culprit drug is essential (panel). Although the role of corticosteroids is controversial in the treatment of drug-hypersensitivity syndrome and serum-sickness-like reactions, most clinicians elect to start prednisone at a dose of 1–2 mg/kg per day if symptoms are severe. Antihistamines or topical corticosteroids can also be used to alleviate symptoms. For patients who develop drug-induced lupus, non-steroidal anti-inflammatory drugs can be used for symptomatic treatment of musculoskeletal complaints. Short courses of prednisone may be necessary in severe cases.³⁵ Treatment of erythema major, Stevens-Johnson syndrome, and toxic epidermal necrolysis includes discontinuation of a suspected drug and supportive measures, such as careful wound care, hydration, and

nutritional support.^{36,37} The use of corticosteroids in Stevens-Johnson syndrome and toxic epidermal necrolysis is controversial. Some clinicians believe corticosteroids may be beneficial when given early in the disease and at a relatively high dose.³⁸ However, others suggest that corticosteroids do not shorten the recovery time and may increase the risk of complications including secondary infections (potentially leading to sepsis) and gastrointestinal bleeding.^{36,39} In addition, thalidomide has been shown to be detrimental in toxic epidermal necrolysis, possibly because of paradoxical enhancement of tumour necrosis factor α production.⁴⁰

Apoptosis (programmed cell death) is a normal process in healthy skin. It can be triggered by the interaction between the cell-surface death receptor (Fas antigen; CD95) and its respective ligand (FasL).^{41,42} Serum from patients with toxic epidermal necrolysis has high concentrations of soluble FasL.⁴³ Intravenous immunoglobulin contains naturally occurring FasL-blocking antibodies, and has been shown to block Fas-mediated cell death *in vitro*.⁴³ In a pilot study, ten patients with toxic epidermal necrolysis were treated with intravenous immunoglobulin at a dose of 0.75 g/kg for 4 consecutive days. In all cases, progression of the skin disease was interrupted and a favourable outcome was achieved.⁴³

After multiorgan drug-hypersensitivity syndrome has been recognised by the symptom complex of fever, rash, and lymphadenopathy, a few laboratory tests will help to assess internal organ involvement, which may be asymptomatic. In patients who develop single-organ drug-hypersensitivity syndrome, the full gamut of laboratory tests should be done to rule out multiorgan dysfunction. Measurement of liver aminotransferase concentrations, complete blood count, urinalysis, and measurement of serum creatinine concentrations should be done in the first assessment. In addition, clinicians should be guided by the presence of symptoms (eg, respiratory symptoms), which may suggest specific internal organ involvement. Thyroid-function tests should be done and repeated in 2–3 months. A skin biopsy may be helpful if the patient has a blistering or pustular eruption.

Unfortunately, diagnostic or confirmatory tests to establish drug causation are not readily available. An *in vitro* test with a mouse hepatic microsomal system is used for research purposes to assess patients who develop drug-hypersensitivity syndromes.^{3,44} Patch testing has been used in the diagnosis of anticonvulsant drug-hypersensitivity syndrome with inconsistent results.⁴⁵ Oral rechallenges are not recommended for patients who develop an idiosyncratic drug reaction, especially if associated with fever, because of the severity of the reaction.

A familial occurrence of hypersensitivity to anticonvulsants has been shown, with an autosomal pattern of inheritance. This heredity suggests that a patient's siblings' risk of having a reaction to an aromatic anticonvulsant may be as high as one in four; therefore counselling of family members is a crucial part of the assessment of this syndrome.³ For patients who develop sulphonamide-induced drug-hypersensitivity syndrome, other aryl amines, such as procainamide, dapsone, and acebutolol should probably be avoided because they form similar reactive metabolites; however, there are few clinical data to confirm that this precaution is necessary. Although it is often stated that there is likely to be cross-reactivity between sulphonamides and drugs such as sulphonylureas, thiazide diuretics, furosemide, and acetazolamide, the rationale for this statement is obscure and there are few data to support such cross-reactivity.

A patient who has experienced a serum-sickness-like reaction should avoid the implicated drug in the future. For cefaclor and cefprozil, the risk of cross-reaction between β -lactam antibiotics is small, and the further administration of another cephalosporin is usually well tolerated.⁴⁶ Despite this information, some clinicians recommend that all β -lactam drugs should be avoided in patients who experience serum-sickness-like reaction from cefaclor.⁴⁷ No information is available regarding cross-reactivity among the tetracycline antibiotics in patients with a minocycline-induced serum-sickness-like reaction.

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