

Reactive Metabolites and Adverse Drug Reactions

Clinical Considerations

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Abstract

Idiosyncratic reactions can affect many different organ systems, either as an isolated event (e.g., hepatitis) or as part of a syndrome (e.g., drug hypersensitivity syndrome). Formation of reactive metabolites of drugs in conjunction with a decreased ability for detoxification is believed to be the initiating step in many idiosyncratic reactions.

The drug hypersensitivity syndrome, defined by the presence of fever, rash and internal organ involvement, is estimated to occur in approx 1 in 1000 to 1 in 10,000 exposures with drugs such as anticonvulsants sulfonamide antibiotics, allopurinol, and dapsone. Symptoms usually start within 2–8 wk of drug initiation. Serum sicknesslike reaction, most frequently found after 7–14 d of drug exposure, is distinguished by a fever, cutaneous eruption and arthralgias. Medications such as cefaclor, minocycline and bupropion are most frequently implicated in this reaction. In contrast, drug-induced lupus can occur 1–2 yr after initiation of medication. Drug-induced lupus is characterized by musculoskeletal complaints and fever and weight loss. Drugs most commonly associated with drug-induced lupus include procainamide, hydralazine, chlorpromazine, isoniazid, and minocycline.

Management of patients who develop idiosyncratic reactions includes discontinuation of the implicated drug, initiation of corticosteroids (when appropriate), and symptomatic relief as required. Internal organ involvement, which may initially be asymptomatic, should be monitored. Confirmatory or diagnostic tests are not readily available in most areas, except for research purposes.

Index Entries:

Anticonvulsants; sulfonamide antibiotics; drug-induced lupus; serum sickness-like reaction; drug hypersensitivity syndrome; reactive metabolites.

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Table 1
Clinical Features of Drug-Hypersensitivity Syndrome, Drug-Induced Lupus, and Serum Sickness-Like Reaction

	Drug Hypersensitivity Syndrome	Serum Sickness-Like Reaction	Drug-Induced Lupus
Symptoms	Fever, cutaneous eruption, internal organ involvement	Fever, cutaneous eruption, arthralgias	Musculoskeletal complaints, fever, weight loss
Laboratory Abnormalities	Atypical lymphocytosis with prominent eosinophilia; laboratory abnormalities dependent on the organ involved	Milk leukocytosis with eosinophilia	Antinuclear (ANA) antibodies with homogeneous pattern
Onset of Symptoms	2–8 wk	7–14 d	Up to 2 yr
Implicated Drugs	Aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine), lamotrigine, allopurinol, dapsone, sulfonamide antimicrobials	Beta-lactam antibiotics (especially cefaclor), sulfonamide antimicrobials minocycline	Procainamide, hydralazine, chlorpromazine, isoniazid, methyldopa, penicillamine, minocycline

Introduction

Idiosyncratic reactions encompass many different types of adverse drug reactions, and can affect any organ system. Although the mechanisms of most idiosyncratic drug reactions are unknown, evidence suggests that a reactive metabolite plays a major role in the development of reactions such as the drug hyper-sensitivity syndrome, serum sickness-like reaction, and drug-induced lupus, hence the name “reactive metabolite syndromes” (1).

In order to understand the pathogenesis responsible for the reactive metabolite syndromes, this article focuses on the role of drug metabolism and the subsequent development of reactive metabolites.

Clinical Characteristics of Selected Reactive Metabolite Syndromes (Table 1)

Drug Hypersensitivity Syndrome

The drug hypersensitivity syndrome is defined by a triad of fever, skin eruption, and internal organ involvement, which may be

asymptomatic. The presenting symptoms in most patients include a fever and malaise, often accompanied by pharyngitis and cervical lymphadenopathy. A skin eruption, ranging from a simple red, flat, or slightly raised symmetrical rash (exathem-like) to a more serious blistering eruption such as Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN), often develops shortly after the presence of the fever (2). Atypical lymphocytosis with a subsequent prominent eosinophilia can occur during the initial phases of the reaction in a subset of patients (3). The liver is often targeted during the occurrence of drug hypersensitivity syndrome, although any organ can be involved. This includes bone marrow involvement (e.g., thrombocytopenia, agranulocytosis, aplastic anemia), kidney (interstitial nephritis, acute renal failure), central nervous system (encephalitis, aseptic meningitis), intestinal tract (colitis), and lungs (interstitial pneumonitis). In addition, a small subset of patients develop hypothyroidism as part of an autoimmune thyroiditis within 2 mo of onset of symptoms of drug hypersensitivity syndrome (4).

The drugs most frequently associated with the drug hypersensitivity syndrome include

Table 2
Differentiation Between Serum Sickness and Serum Sickness-Like Reaction

	Serum Sickness	Serum Sickness-Like Reaction
Signs/Symptoms	Fever, lymphadenopathy, arthralgias, cutaneous eruption, GI disturbances, malaise, proteinuria (without evidence of glomerulonephritis)	Fever, cutaneous eruption, arthralgias
Mechanism	Deposition of circulating immune complexes in tissues, activation of complement, ensuing inflammatory response	Formation of reactive metabolite
Causative Agents	Foreign antigens (e.g., tetanus antitoxin, antirabies serum, antithymocyte globulin, streptokinase)	Beta-lactam antibiotics, especially cefaclor, sulfonamides, minocycline
Onset	1–2 wk following antigen injection	1–3 wk after drug exposure
Treatment	Withdrawal of offending agent, systemic corticosteroids in patients with multisystem involvement, supportive measures (e.g., antihistamines, antiinflammatories)	Withdrawal of drug, supportive measures (e.g., oral and/or topical corticosteroids, antihistamines)

anticonvulsants (phenytoin, phenobarbital, carbamazepine, lamotrigine), sulfonamide antibiotics, dapson, minocycline, and allopurinol (3,5). Because of the variable presentation, the true incidence of the drug hypersensitivity syndrome is unknown. Estimates have indicated that this reaction occurs in between one in 1000 and one in 10,000 exposures with drugs such as anticonvulsants and sulfonamides.

Serum Sickness-Like Reactions

It is important to differentiate between true serum sickness and serum sickness-like reactions (Table 2). True serum sickness is characterized by fever, lymphadenopathy, arthralgias, cutaneous eruptions, and gastrointestinal (GI) disturbances and malaise, as well as proteinuria (6). In contrast, serum sickness-like reaction is defined by fever, rash (usually urticarial or erythema multiforme-like), and arthralgias occurring 1–3 wk after drug exposure. Lymphadenopathy and eosinophilia may also be present; however, immune complexes, hypocomplementemia, vasculitis, and renal lesions are usually absent in serum sickness-like reaction, but are features of true serum sickness.

Serum sickness-like reaction occurs more commonly with cefaclor than with other antibiotics, including other cephalosporins (7,8). The overall frequency of cefaclor-induced serum sickness-like reaction has been estimated at 0.024–0.2% per course of cefaclor prescribed. Evidence indicated that in genetically susceptible hosts, a reactive cefaclor metabolite is generated during its metabolism that may bind with tissue proteins and elicit an inflammatory response that manifests as serum sickness-like reaction (9). Other drugs that have been implicated in serum sickness-like reaction include minocycline (5) and bupropion (10).

Drug-Induced Lupus

There are important differences between drug-induced lupus and systemic lupus erythematosus (SLE). Drug-induced lupus is characterized frequently by musculoskeletal complaints, fever and weight loss, pleuropulmonary involvement, and rarely renal, neurological or vasculitic involvement (11). Cutaneous findings are rare in drug-induced lupus. Symptoms and serological changes generally appear more than 1 yr after starting therapy. Because of the time lag between drug

initiation and the onset of drug-induced lupus, physicians may overlook a drug as the cause of the symptoms.

The serological abnormality usually seen is positivity for antinuclear antibodies with a homogenous pattern; however, some patients with a serological abnormality do not develop clinical disease. Although up to 95% of patients with drug-induced lupus have antihistone antibodies, this finding is not specific for drug-induced lupus and is also observed in 50–80% of patients with SLE (12). In comparison to idiopathic lupus erythematosus, antibodies to double-stranded DNA are typically absent in drug-induced lupus (13). In patients with minocycline-induced lupus, positive anti-neutrophil cytoplasmic antibodies have been observed, which may be directed against anti-myeloperoxidase or elastase (14,15).

Drugs most commonly associated with drug-induced lupus include procainamide, hydralazine, chlorpromazine, isoniazid, methyldopa, penicillamine, acebutolol, and more recently, minocycline (16). Seroconversion from negativity to positivity for antinuclear antibodies, with no development of symptoms, is not a sufficient reason to discontinue treatment with a suspected drug. For example, with procainamide, positive serological tests are obtained in 50–74% of patients, and drug-induced lupus develops in only 5–10%. However, with the development of symptoms, the implicated drug should be discontinued. Symptoms are usually self-limiting and resolve within 4–6 wk of drug discontinuation, although antinuclear antibodies may remain positive for 6–12 mo.

Pathogenesis

Constitutional factors that influence the risk of development of idiosyncratic reactions include pharmacogenetic variation in drug-metabolizing enzymes and Human Leukocyte Antigen (HLA) associations. Acetylator phenotype has been shown to alter the risk of developing drug-induced lupus caused by hydralazine (17). In this study, hydralazine-

induced lupus occurred only in slow acetylators. As well, fast acetylator status appears to partially protect against the risk of developing toxic epidermal necrolysis (TEN) and drug hypersensitivity syndrome caused by sulfonamide antibiotics (18,19).

Individual HLA characteristics are also associated with an altered risk of many idiosyncratic drug reactions. HLA-DR4 is significantly more common in hydralazine-related drug-induced lupus than in people with idiopathic SLE (20). HLA DR2 and DR4 are also significantly more common in minocycline-induced lupus (21).

Many drugs associated with severe idiosyncratic drug reactions are metabolized by the body to form reactive, or toxic, drug products (22), such as an epoxide, quinone, nitroso derivative, or acyl halide (23) (Table 3). These reactive products only comprise a small proportion of a drug's metabolites, but may be very important in the development of severe reactions. The major enzymes involved in drug bioactivation are the cytochrome P450 enzymes (23). The role of enzymes in white blood cells that generate active oxygen species that can activate drugs, such as propylthiouracil or clozapine, to radicals or electrophilic metabolites—particularly with respect to immunotoxicological reactions—may also be important for certain idiosyncratic reactions (24). In most individuals, these reactive products are usually rapidly detoxified. However, lymphocytes from patients who are suffering from drug hypersensitivity syndrome and severe skin eruptions to sulfonamide antibiotics and the aromatic anticonvulsants show increased *in vitro* sensitivity to the oxidative, reactive drug metabolites of these drugs compared to cells from controls. These observations suggest that patients who develop these adverse reactions have an impaired ability to detoxify these minor drug metabolites.

The hapten hypothesis is used to explain the association between the formation of reactive metabolites and the induction of idiosyn-

Table 3
Reactive Intermediaries for Selected Drugs

Drug	Bioactivation	Reactive Metabolite	Clinical Outcome
Halothane	CYP2E1	Reactive acyl intermediate	Hepatitis
Carbamazepine	CYP2C9 CYP3A4	Unknown	DHS, serious skin reactions (e.g., SJS/TEN)
Sulfonamide antibiotics	CYP2C9	Hydroxylamine ↓ Reactive nitroso	DHS, serious skin reactions (e.g., SJS/TEN)

DHS: drug hypersensitivity syndrome. SJS: Stevens-Johnson syndrome. TEN: toxic epidermal necrolysis.

cratic drug reactions. Since most drugs are too small to form complete immunogens on their own, these drugs are presented to the immune system in association with tissue macromolecules (25). The immunogen may involve the binding of native drug or drug metabolites to these tissue haptens. Certain drugs, such as the beta-lactam antibiotics, may form drug-protein conjugates directly. Some intermediate drug metabolites are highly reactive chemical species that have the ability to covalently bind and damage tissue macromolecules. Such haptens are likely to occur to at least some degree in most people who are taking prescribed medications; however, only a minority develop clinical disease. One theory to explain the occurrence of disease in these patients is Matzinger’s danger hypothesis (26). The danger hypothesis suggests that the immune response is triggered by signs of danger or cellular injury. Concurrent disease or impaired defenses against reactive intermediary drug metabolites may cause tissue damage and the generation of a “danger” signal leading to activation of effector immune response and clinical disease. A reactive metabolite may be required to modify protein and cause injury or stress cells in order to induce an immune response. However, some drugs may cause direct cell toxicity that could act as a danger signal and increase the risk of development of an idiosyncratic reaction.

Halothane

Halothane adversely affects the liver to various degrees. Asymptomatic increases in transaminases occur in approx 20% of patients who receive halothane. The mechanism is unknown, although it is believed to involve direct toxicity. Halothane hepatitis is much more severe, and is characterized by massive liver-cell necrosis. This reaction is much more rare, and occurs in 1 in 35,000 patients on first exposure. Halothane is metabolized by the cytochrome P450 CYP2E1 with concomitant release of bromide to produce the reactive intermediate trifluoroacetyl chloride. This intermediate binds covalently to lysine residues in proteins, forming trifluoroacetylated proteins. In patients who develop halothane-induced hepatitis, antibodies of the IgG class have been detected that are directed against the trifluoroacetyl antigen and against natural antigens on microsomal proteins (27).

Anticonvulsants

The aromatic anticonvulsants—namely phenytoin, carbamazepine, and phenobarbital—are often implicated in the development of drug hypersensitivity syndrome, as well as severe cutaneous reactions such as Stevens-Johnson syndrome and TEN. Early studies suggested that the reactive metabolite responsible for these reactions was an epoxide; the

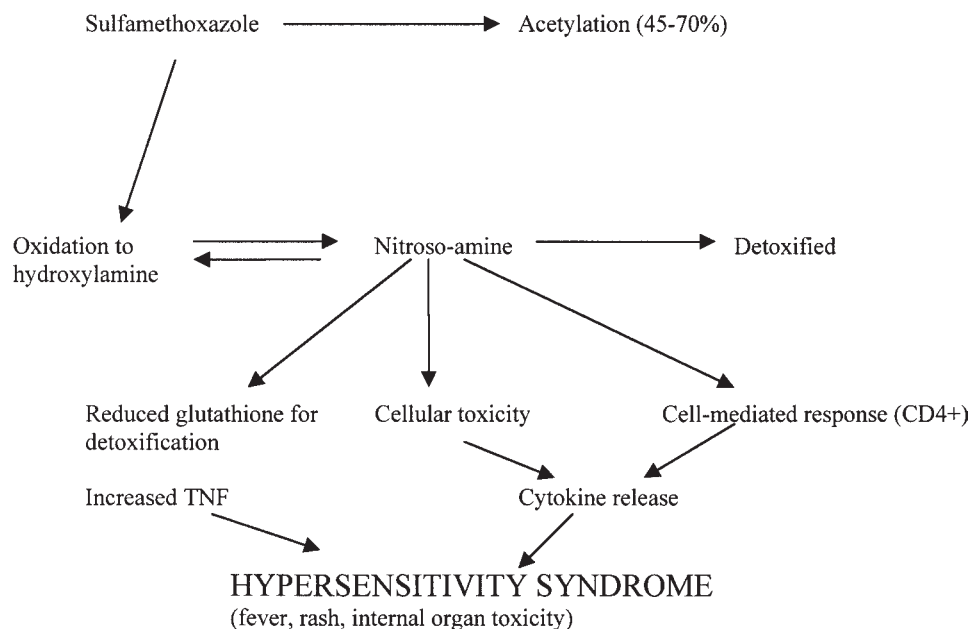


Fig. 1. Proposed mechanism of reactive metabolite syndrome due to sulfonamide antimicrobials.

basis for increased susceptibility in individuals and crossreactivity among these agents was hypothesized to be caused by a deficiency of epoxide hydrolase (28). However, more recent evidence indicates that no difference exists in the frequency of the gene associated with low epoxide hydrolase activity in patients with a history of anticonvulsant hypersensitivity (29,30); this suggests that the epoxide hypothesis is not the explanation. As well, phenytoin has been shown to form a reactive free radical (31) and an orthoquinone (32), whereas carbamazepine forms a reactive iminoquinone that also undergoes redox cycling (33).

Further studies have shown that circulating immunoglobulin G antibodies in nine patients with anticonvulsant hypersensitivity syndrome are manifested by a variety of clinical patterns (34). Theoretically, covalent adduct formation with the cytochrome P450 generating the reactive species could lead to neoantigen formation, and to an immune response that includes antibody formation. Multi-organ involvement in the anticonvulsant hypersensitivity syndrome could then be a function of the expression of the antigen in different tissues.

The pathophysiology of lamotrigine-induced anticonvulsant hypersensitivity syndrome is unknown. Higher starting doses of lamotrigine and/or faster escalation of dose increase the risk of serious hypersensitivity reactions. Concurrently administered drugs also alter the incidence of serious hypersensitivity reactions associated with lamotrigine (35). Coadministration of valproate increases the risk of serious reactions associated with lamotrigine. Although lamotrigine is extensively metabolized, the main metabolic pathways are conjugation reactions, predominantly N-glucuronidation (36). Only minor fractions of lamotrigine undergo phase I metabolism, resulting in the 2-N-oxide and the 2-N-methylated metabolites. Whether one of the phase I biotransformation products may act as a toxic metabolite is unknown.

Sulfonamide Antimicrobials

All sulfonamide antimicrobials are aromatic amines (37). Using sulfamethoxazole as a representative sulfonamide antimicrobial, in normal hosts, 45–70% of sulfamethoxazole is acetylated at the N4 position to form N4-acetyl

sulfamethoxazole, which is excreted renally as a nontoxic metabolite (Fig. 1). However, in patients who are slow acetylators, the cytochrome P450 (CYP) mixed-function oxidase system plays an important role. Sulfamethoxazole is oxidized to sulfamethoxazole hydroxylamine by the CYP2C9 system (38). The hydroxylamine circulates in blood, and is excreted unchanged in the urine. The hydroxylamine auto-oxidizes to a more reactive nitroso metabolite, with redox cycling between the two (37). The redox cycling can lead to oxidative stress, and the nitroso derivatives also react covalently with proteins (23). In most individuals, this nitroso metabolite is subsequently detoxified. However, in susceptible individuals, a combination of cytotoxic and immunological events are likely to be involved in the development of the drug hypersensitivity syndrome reaction and other reactive metabolite syndromes. For example, the hydroxylamine metabolites of sulfa-methoxazole have been shown to inhibit the ability of natural killer (NK) cells to act, suppress the production of the cytokine tumor necrosis factor (TNF), and inhibit the ability of T-lymphocytes to respond to mitogenic stimulation (39,40). Reactive N4-metabolites bind to proteins and cause apoptosis, leading to severe drug reactions (41). One study reported that 17 of 21 patients with histories consistent with sulfonamide hypersensitivity syndrome and none of 11 controls had antibodies against at least one of three rat liver microsomal proteins of 95 kDa, 80 kDa, or 96 kDa. These were found to be endoplasmic reticulum (ER) luminal proteins (42).

Management

Patients who develop an idiosyncratic drug reaction require immediate treatment of the reaction as well as follow-up. This can include diagnostic testing, if available, and counseling to educate the patient about which drugs to avoid and which drugs can be safely taken.

Treatment

Immediate discontinuation of the drug is recommended when a patient develops a suspected idiosyncratic drug reaction that has systemic features, such as fever. Corticosteroids are often recommended (prednisone 1–2 mg/kg/d) for the treatment of drug hypersensitivity syndrome and serum sickness-like reaction, if symptoms are severe. Corticosteroids may not be required in many cases, and it may be difficult to wean patients off of the steroid because of exacerbations. Symptomatic relief can be obtained with the use of antihistamines and topical corticosteroids. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used for the relief of musculoskeletal complaints in patients with drug-induced lupus.

The treatment of more severe skin reactions such as Stevens-Johnson syndrome and TEN is more controversial. Corticosteroids were initially believed to be beneficial when given early in the disease and at a fairly high dose. However, corticosteroids may not shorten the recovery time, and may actually increase the risk of complications, including secondary infections and GI bleeding (43,44). Thalidomide was shown to be detrimental in the treatment of TEN, possibly because of paradoxical enhancement of TNF- α production (45). Intravenous immunoglobulin (IVIG), which contains naturally occurring FasL-blocking antibodies, has been shown to halt progression of TEN in 10 patients, and produced a favorable outcome in all patients within 48 h of administration (46). The dose of IVIG that has been used is 0.75 g/kg/d for four consecutive days.

Patients who develop the drug hypersensitivity syndrome should be evaluated for internal organ involvement, which may initially be asymptomatic. Measurement of liver aminotransferase concentrations, complete blood count, urinalysis, and measurement of serum creatinine concentrations should be done in the initial assessment. In addition, additional laboratory tests may be ordered as dictated by the patient's symptoms. Thyroid function tests

should be done and repeated in 2–3 mo (4). A skin biopsy may be helpful if the patient has a blistering or pustular eruption.

Diagnostic Testing

Confirmatory or diagnostic tests are not readily available in most centers. An *in vitro* test with a mouse hepatic microsomal system has been used for the evaluation of patients who develop drug hypersensitivity syndrome (2,47). This assay has been used for anticonvulsant and sulfonamide hypersensitivity syndrome reactions and serious skin reactions, as well as serum sickness-like reaction to cefaclor (9). The Lymphocyte Transformation Test (LTT) attempts to provide evidence of cell proliferation or blastogenesis *in vitro* after antigen exposure. A retrospective study using this test system found a sensitivity of approx 75%, and specificity of 85% (48). Patch testing has limited application in patients who have developed anticonvulsant hypersensitivity syndrome (49). Oral challenges are not recommended for patients who develop idiosyncratic drug reactions, because of the potential severity of the reaction.

Patient Counseling

Patients who develop serious idiosyncratic reactions must be counseled regarding the safe future use of drugs. Because of the potential for crossreactivity with other aromatic anticonvulsants, patients with anticonvulsant hypersensitivity syndrome should avoid phenytoin, phenobarbital, and carbamazepine. In one study, 40 of 50 patients with an anticonvulsant hypersensitivity syndrome to one aromatic anticonvulsant showed *in vitro* crossreactivity to the other two (2). Seven of 10 patients who had received all three anti-convulsants (e.g., phenytoin, carbamazepine, and phenobarbital) had adverse reactions to each. Another report described four children who manifested symptoms of anticonvulsant hypersensitivity syndrome with carbamazepine. In three patients, the syndrome was exacerbated after treatment

with another aromatic anticonvulsant. Discontinuation of the aromatic anticonvulsant resulted in resolution of symptoms; valproic acid was well-tolerated in three patients who required continued anticonvulsant therapy (50). Since *pri-midone* is metabolized to phenobarbital, it would be expected to have a high rate of cross-reactivity. Although some reports have indicated that oxcarbazepine may be an alternative to carbamazepine (51), the reports are conflicting (52), and therefore oxcarbazepine should be considered to potentially crossreact with carbamazepine. Benzodiazepines, valproic acid (not in the acute phase because of the risk of hepatitis), or one of the newer anticonvulsants (gabapentin, topiramate, vigabatrin, or zonisamide) can be used for seizure control. There is no evidence that lamotrigine crossreacts with the aromatic anticonvulsants, but it can cause hypersensitivity reactions including Stevens Johnson syndrome/TEN on its own.

For patients who develop sulfonamide-induced drug hypersensitivity syndrome, other aromatic amines such as procainamide, dapsone, and acebutolol should probably be avoided because they form similar reactive metabolites; however, there is little clinical data to confirm that this is necessary (53). There is little evidence to suggest crossreactivity between sulfonamide antimicrobials and drugs containing the sulfonamide (SO_2NH_2) moiety (e.g., sulfonylureas, thiazide diuretics, furosemide, and acetazolamide).

For patients who develop a cefaclor-induced serum sickness-like reaction, cefaclor must be avoided in the future, although other cephalosporins are generally well-tolerated (9,54). Nevertheless, some clinicians recommend that all beta-lactam drugs should be avoided in patients who have serum sickness-like reaction from cefaclor (55). There is no information regarding crossreactivity among the tetracycline antibiotics in patients who develop minocycline serum sickness-like reaction (56).

In vitro testing has shown that there is a familial occurrence of hypersensitivity to anti-

convulsants, with an autosomal pattern of inheritance (2,57). This suggests that among the patients' siblings, the risk of a reaction to an aromatic anticonvulsants may be as high as 1 in 4. In one study, three siblings from a family of 12 siblings, of which 8 were available for study, developed hypersensitivity reactions to phenytoin characterized by fever, rash, lymphadenopathy, and hepatitis. Using the lymphocyte toxicity assay, cells from each of the patients who had experienced an anticonvulsant hypersensitivity syndrome exhibited increased toxicity from metabolites of phenytoin and carbamazepine, yet the response to phenobarbital was within normal limits. Of the other five siblings, four showed an abnormal response to phenytoin metabolites, and one sibling detoxified phenytoin metabolites normally (57).

Conclusion

The production of reactive oxidative metabolites of some drugs coupled with a decreased capacity for detoxification may be the initiating step for some idiosyncratic reactions. The defects that cause the drug hypersensitivity syndrome, severe skin reactions, serum sickness-like reaction, and drug-induced lupus may be genetically inherited. Although the pathogenesis of these reactions is not completely understood, it is important to recognize a reaction in order to decrease morbidity and mortality. The safe use of drugs by a patient in the future will depend on the chemical nature of the drug in question and the expected metabolism of the drug. The immunopathogenesis is even more poorly understood, and is an important area for research.

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