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Hypersensitivity syndrome to antiepileptic drugs: A review including new anticonvulsants

ABSTRACT

Anticonvulsant hypersensitivity syndrome, a potentially fatal but rare reaction, manifests as rash, fever, tender lymphadenopathy, hepatitis, and eosinophilia. To manage hypersensitivity syndrome successfully, one must recognize the symptoms early, stop the offending drug immediately, and substitute a safe, alternative anticonvulsant medication. Hypersensitivity syndrome has not been described in patients taking benzodiazepines or the newer anticonvulsants gabapentin or topiramate, and these appear to be safe substitutes for drugs that cause the reaction.

KEY POINTS

Anticonvulsant hypersensitivity syndrome can occur with the use of phenytoin, carbamazepine, primidone, phenobarbital, lamotrigine, or felbamate. Cross-reactivity among these drugs may occur.

The clinical syndrome of hypersensitivity may fluctuate or even relapse, with fever and rash continuing for weeks after stopping the offending drug.

To control seizures in patients with anticonvulsant hypersensitivity syndrome, benzodiazepines have been used successfully in the short term, and valproic acid can be used after hepatitis has resolved.

Owing to its unique pharmacokinetics, gabapentin may become the anticonvulsant drug of choice in patients with anticonvulsant hypersensitivity syndrome, provided that the seizures are either partial or secondarily generalized.

OF THE MANY PATIENTS who take anticonvulsant drugs, one in a thousand or even fewer will experience hypersensitivity syndrome, a potentially fatal adverse reaction.

Although hypersensitivity syndrome is rare, early recognition of the clinical signs—rash, fever, tender lymphadenopathy, hepatitis, and eosinophilia—and immediate withdrawal of the offending drug are the first and most important steps. Once the offending drug is stopped, a safe substitute anticonvulsant must be selected; options include benzodiazepines, valproic acid, and newer agents such as gabapentin and topiramate.

This paper reviews the clinical and pathophysiologic characteristics of hypersensitivity syndrome, the drugs known to cause it, how it differs from toxic epidermal necrolysis and Stevens-Johnson syndrome, and how to choose safe alternative anticonvulsant drugs.

EARLY REPORTS

Phenytoin, whose anticonvulsant effect was described in 1938,¹ quickly became one of the most commonly used drugs to treat epilepsy. Almost as quickly, adverse effects were identified, particularly two cutaneous eruptions. The first, a mild morbilliform (measles-like) skin reaction, resolved when the drug was stopped and often did not recur when it was restarted.² The second reaction consisted of severe, exfoliative dermatitis with fever, lymphadenopathy, and eosinophilia, and it sometimes recurred after the drug was stopped. This was subsequently termed hypersensitivity syndrome.

Drugs linked to hypersensitivity syndrome

Since the systemic nature of hypersensitivity syndrome was first described in 1950,³ a limited number of anticonvulsants have been found to cause it⁴⁻⁷: phenytoin, carbamazepine, primidone, phenobarbital, lamotrigine, and felbamate.

Cross-reactivity among these drugs may occur: ie, a patient who experiences hypersensitivity syndrome in response to one of these drugs may have it with any of them. Other drugs linked to hypersensitivity syndrome include sulfonamide and allopurinol.^{4,5,8,9}

Although some clinicians believe valproic acid is less likely to produce cutaneous reactions,¹⁰ others report that the risk for developing hypersensitivity syndrome from valproic acid use is similar to that from aromatic anticonvulsants (phenytoin, carbamazepine, and phenobarbital).^{8,11} To the best of our knowledge, hypersensitivity syndrome has not yet been reported with use of benzodiazepines, gabapentin, vigabatrin, or topiramate.

WHO IS AT RISK?

In contrast to the mild morbilliform rash seen in 5% to 10% of patients taking the above-mentioned anticonvulsants,^{9,12,13} hypersensitivity syndrome occurs in one in every 1,000 to 10,000 patients. The risk is approximately equal with any of the above drugs.¹⁴ In a retrospective cohort study, Tennis and Stern¹⁰ reported that serious cutaneous reactions including Stevens-Johnson syndrome, toxic epidermal necrosis, and hypersensitivity syndrome occurred within 60 days after anticonvulsant prescription in 2.3 to 4.5 per 10,000 phenytoin users and 1.0 to 4.1 per 10,000 carbamazepine users.

Groups at higher risk include:

- Africans, African-Caribbeans, and African Americans^{15,16}
- Patients who had prior reactions to anticonvulsants and were re-exposed
- Siblings of patients who experienced hypersensitivity syndrome (suggesting an autosomal codominant inheritance of reactivity)^{4,14}
- Alcohol abusers¹⁷
- Patients receiving both phenytoin and brain radiation therapy (possibly)¹⁸

The risk of hypersensitivity syndrome does not vary by sex or age, although children under age 12^{13,19} and adults over age 64 are more likely to develop severe cutaneous reactions than are middle-aged adults.¹¹

DIAGNOSIS

Typically, hypersensitivity syndrome appears 1 week to 3 months after starting an anticonvulsant drug,¹⁷ most often within 2 to 4 weeks.^{20,21} However, in patients previously sensitized to the drug, severe hypersensitivity syndrome may occur within 1 day after rechallenge.²² Hypersensitivity syndrome has even been reported in patients who took anticonvulsants for up to 40 years.²³

Clinical features

Hypersensitivity syndrome is a clinical diagnosis. Fever and rash are the most common signs and may be the only signs, although tender lymphadenopathy, eosinophilia, hepatitis, and other features are also frequently seen (TABLE 1). Variability in the presentation may delay diagnosis.^{4,6,16,21,24-31}

Fever may precede the rash by days or may occur simultaneously. The temperature is usually between 38°C and 40°C (100.4–104°F), with “spikes.” Cultures of blood, urine, and cerebrospinal fluid are negative.

Rash. The skin reaction of hypersensitivity syndrome initially consists of patchy erythema, which evolves into a flesh-colored maculopapular rash that is usually pruritic and may generalize into a severe exfoliative dermatitis with sterile follicular-centered pustules.⁶ Involvement of mucous membranes is rare.¹⁰ These features help distinguish hypersensitivity syndrome from other cutaneous side effects, such as acneiform or morbilliform rash, hypopigmentation, hyperpigmentation, and other noncutaneous adverse reactions to anticonvulsant medications.⁶

Lymphadenopathy is marked, tender, and often generalized. Biopsy specimens of lymph nodes typically show benign lymphoid hyperplasia but can occasionally show pseudolymphoma, as described below.³²

Hepatitis. Most patients with hypersensitivity syndrome have significantly elevated liver function tests, and many have

Cross-reactivity is likely between anticonvulsant drugs

hepatosplenomegaly. Most are anicteric, although jaundice has been described.^{23,33} If jaundice is present, hypersensitivity syndrome tends to have a poorer prognosis.^{3,34} Liver biopsy may show a fatty or cellular infiltration with variable amounts of mononuclear cells, segmented leukocytes, and eosinophils in the portal and lobular areas.³⁴ The resulting hepatitis may be more severe if the patient continues to take the offending drug.³⁵

Prominent periorbital or facial edema is a characteristic feature that helps differentiate hypersensitivity syndrome from the typical "common" erythematous drug-induced skin reaction, which involves the body but spares the face.

Biopsy findings. Skin biopsy usually reveals a superficial perivascular infiltrate consisting of lymphocytes, histiocytes, and eosinophils, and a spongiotic or lichenoid dermatitis.^{7,15} Resolution is associated with marked desquamation.

Leukocytosis with eosinophilia of various degrees (up to 50%) is seen in most cases of hypersensitivity syndrome.^{6,28} Atypical lymphocytes are common.

Pseudolymphoma, with or without mycosis fungoides-like lesions of the skin, may also be present,^{7,25,28,29} and may be difficult to distinguish histologically from malignant lymphoma.²⁷ Pseudolymphomas usually disappear when the offending drug is stopped,^{25,27,32} although cases have been reported in which persistent pseudolymphoma was considered a premalignant state, and in which true lymphomas developed after long-term treatment with anticonvulsant drugs.^{36,37}

Leukocytopenia with anemia, thrombocytopenia, and positive antinuclear antibodies has been reported in rare cases.^{4,38}

Interstitial nephritis with proteinuria, hematuria, polyuria that is sometimes fatal, and pneumonitis has been reported in a small number of patients.^{24,31,39,40}

Lymphocytic thyroiditis may occur, in which case reversible hypothyroidism can develop with a delay of weeks to months after recovering from the acute reaction. This delay is presumably because of significant thyroid reserve.³⁰ The return to a euthyroid state may take up to 2 years.

TABLE 1

Signs and symptoms of hypersensitivity syndrome ranked by frequency

FREQUENT FINDINGS	INCIDENCE (%)
Fever	90–100
Rash	90
Lymphadenopathy (with or without systemic or cutaneous pseudolymphoma)	70
Multiorgan involvement	60
Hepatitis (with or without hepatosplenomegaly)	50–60
Hematologic abnormalities (eg, eosinophilia, anemia, thrombocytopenia)	50
Periorbital or facial edema	25
Myalgia, arthralgia	20
Interstitial nephritis	10
Pharyngitis	10
INFREQUENT FINDINGS	
Anorexia	Encephalitis
Carditis	Myositis and rhabdomyolysis
Conjunctivitis	Pneumonitis
Diarrhea	Thyroiditis

Differential diagnosis

Toxic epidermal necrolysis (also known as Lyell syndrome) can also occur in patients receiving anticonvulsant drugs, but it is far less common than hypersensitivity syndrome.⁴¹ The incidence of toxic epidermal necrolysis is estimated at 0.4 to 1.2 cases per million person-years.^{8,42}

Although hypersensitivity syndrome and toxic epidermal necrolysis share certain characteristics, such as onset with fever and similar histology, several features help distinguish the two (TABLE 2).^{43,44}

Stevens-Johnson syndrome is considered a milder variant of toxic epidermal necrolysis. Many experts differentiate the two on the basis of the percentage of skin detachment.^{8,43}

Other diagnoses to consider include cytomegalovirus infection, human immunodeficiency virus infection, Epstein-Barr virus infection, staphylococcal scalded skin syndrome, *Staphylococcus aureus*-induced toxic shock syndrome, collagen vascular diseases, Kawasaki syndrome, lymphoma, viral hepatitis, porphyria, and syphilis.

When doubt remains, patch testing or in

**TABLE 2****Clinical features of hypersensitivity syndrome vs toxic epidermal necrolysis**

FEATURE	HYPERSENSITIVITY SYNDROME	TOXIC EPIDERMAL NECROLYSIS
Rash	Maculopapular rash with pinpoint pustulation and facial swelling	Generalized urticarial plaques with epidermal sloughing
Healing	By desquamation	By reepithelialization
Hepatitis	Elevated liver function tests with or without hepatitis	Elevated liver function tests only
Hematologic	Often leukocytosis with eosinophilia	Often leukopenia

vitro lymphocyte transformation tests^{4,45} can confirm the diagnosis of hypersensitivity syndrome. Patch testing, however, should be cautiously interpreted when the skin eruption is still present because of possible false-positive results due to increased skin reactivity or false-negative reactions due to a refractory state of the skin.⁷

■ PATHOPHYSIOLOGY IS UNCLEAR

Hypersensitivity syndrome is idiosyncratic,^{21,22} and its exact pathogenesis is unknown. Horneff et al⁴⁶ postulate that hypersensitivity syndrome is a reaction to circulating antibodies to antiepileptic drugs. Others link it to an acute graft-vs-host reaction, since both share certain clinical features.⁴⁷

A third theory focuses on toxic metabolites of these drugs and raises hope for predicting which patients are at risk.⁴ The molecular structure of phenytoin, carbamazepine, and phenobarbital contains an aromatic ring compound that is metabolized to reactive arene oxides by the cytochrome P450 system. These arene oxide metabolites are usually detoxified by epoxide hydrolases.⁴ Under certain circumstances, such as a genetically determined structural alteration of these enzymes, hydroxylation may be inefficient, and these intermediates may accumulate. They may bind to tissue macromolecules, causing cell damage or acting as haptens stimulating CD4⁺ and CD8⁺ T cells and triggering a systemic autoimmune response, in which T cells have a changed recognition of "self."^{4,7,48}

Clinical cross-reactivity between phenytoin, carbamazepine, phenobarbital, and

oxcarbazepine has been reported.⁴⁹⁻⁵¹ Although the exact incidence in vivo is unknown, in vitro analysis using lymphocyte toxicity assays suggests that up to 80% of patients who are sensitive to one of these drugs are also sensitive to the others.⁴ Pirmohamed et al,⁵² however, could not replicate this high percentage of biochemical cross-reactivity in a group of patients with carbamazepine hypersensitivity, suggesting that a variation in enzymatic structures on the basis of genetic heterogeneity could cause different degrees in cross-reactivity.

■ THERAPEUTIC CONSIDERATIONS**Stopping the offending drug**

Immediate withdrawal of the drug is the first and most important step in treatment. If symptoms promptly disappear, the diagnosis is even more probable.

Systemic corticosteroids and antihistamines are given in severe cases,^{7,24,44} although this treatment has not been formally studied in randomized placebo-controlled trials. Its main beneficial effect may be on the cutaneous manifestations rather than on the systemic ones.^{16,53} Usually, the rash also responds well to topical steroids, antihistamines, and wet wraps. Most experts do not use systemic corticosteroids in toxic epidermal necrolysis with a skin detachment of more than 20% of the body surface, because of the increased risk of infection and gastrointestinal bleeding, as well as impairment of reepithelialization.⁴³ Hepatic, hematological, and renal function should be closely monitored with special attention to hydration and electrolytes.

Fever and rash may be the only signs

Substituting anticonvulsants

Once hypersensitivity syndrome develops with one antiepileptic drug, other potentially cross-reacting drugs (phenytoin, phenobarbital, primidone, carbamazepine, or oxcarbazepine) can blur or even worsen the clinical course and should not be used. Felbamate and lamotrigine may also cause hypersensitivity syndrome and other idiosyncratic reactions; they need to be started at low dosages and increased slowly.^{5,9,13} Therefore, they may not be the anticonvulsant drugs of choice in patients with hypersensitivity syndrome. The utility of topiramate as a first-choice medication may be limited by a relatively high frequency of cognitive side effects. Vigabatrin is not yet approved in the United States, and the experience with this drug in Europe is still limited,⁵ so its possible indication in hypersensitivity syndrome is unclear.

Benzodiazepines can be substituted for acute seizure control.^{14,54}

Valproic acid has also been used successfully in hypersensitivity syndrome,^{7,14,53} but should not be given during the acute or convalescent phase because of its hepatic metabolism.^{16,50}

Gabapentin may be given in the acute phase of hypersensitivity syndrome.⁵⁵ It can be quickly loaded and is not metabolized by the liver, but rather excreted unchanged by the kidney. Its elimination half-life is directly proportional to creatinine clearance.^{56,57} Gabapentin is not protein-bound and has few if any interactions with other drugs.^{56,58} It has not been associated with hypersensitivity syndrome or other severe idiosyncratic reactions and has a low potential for other serious adverse effects.^{5,56,58} Gabapentin is approved as an adjunct in the treatment of partial seizures and secondarily generalized tonic-clonic seizures, but has also been shown to be effective as monotherapy.^{59,60} Therefore,

gabapentin appears to be a good alternative drug for seizure control in patients with hypersensitivity syndrome due to other anticonvulsant drugs.

CLINICAL COURSE

Most patients recover from hypersensitivity syndrome without sequelae within days or a few weeks. However, the syndrome may fluctuate or even relapse with fever and rash for weeks after stopping the offending drug. The interval should not detract from the diagnosis of hypersensitivity syndrome.^{4,54} Full resolution of the hepatitis may take months to a year.¹⁶

Deaths due to hypersensitivity syndrome have been infrequent. In contrast to toxic epidermal necrolysis, in which sepsis is the leading cause of death, liver failure is the most common cause of death in hypersensitivity syndrome, but nephritis and carditis have also been associated with death.²¹ The overall mortality rate in hypersensitivity syndrome has been estimated at about 10%.²¹ However, if liver involvement is significant, mortality is 20% to 38%.^{20,34,61,62} Continued use of the offending anticonvulsant drug or re-exposure to a drug in a sensitized patient greatly increases the risk for a severe course of hypersensitivity syndrome and for a fatal outcome.^{39,63,64}

Most experts agree that hypersensitivity syndrome is not dose-related.^{20,22} However, Chadwick et al¹² and Wilson et al¹⁹ found that high initial serum concentrations of phenytoin or carbamazepine appeared to increase the occurrence of different types of skin eruptions. They recommend starting treatment with low doses and increasing the dose slowly. The same is true for lamotrigine, showing a clear relationship between the starting dose, the rate of dose increase, and the incidence of rash.^{9,65} ■

Susceptible patients may have altered drug metabolism

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