Cutaneous Reactions to Anticonvulsant Medications

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Skin eruptions are an important consideration for any clinician who prescribes anticonvulsant medications. The timely recognition and accurate diagnosis of cutaneous reactions can prevent potentially fatal reactions and affect subsequent anticonvulsant treatment options. This review addresses the most common and most serious cutaneous reactions to anticonvulsant medications. The anticonvulsant hypersensitivity syndrome and individual antiepileptic medications that cause severe skin reactions will be reviewed. These reactions include morbilliform and urticarial drug eruptions as well as the erythema multiforme spectrum. *(J Clin Psychiatry 2001;62[suppl 14]:22–26)*

Skin eruptions are an important consideration for any clinician who prescribes anticonvulsant medications. The timely recognition and accurate diagnosis of cutaneous reactions can prevent potentially fatal reactions and affect subsequent anticonvulsant treatment options.[1] This article addresses the most common and most serious cutaneous reactions to anticonvulsant medications.

DRUG-RELATED SKIN ERUPTIONS

Either prescription or over-the-counter drugs can cause cutaneous drug eruptions. A drug eruption may develop even if the patient takes the medication only once. A drug eruption also may occur in patients who have previously used the drug with no evidence of skin reaction. Synergistic and cumulative effects of polypharmacy may also provoke cutaneous adverse reactions.[2]

When evaluating a patient with skin eruptions, it is imperative to take a careful history and perform a thorough physical examination. The clinician must consider several questions:

Does the patient have any known allergies or hypersensitivities?
How long have the skin changes been present?
Are the skin changes compatible with a drug eruption?
What medications, including over-the-counter, is the patient using?
Which drug is most likely to be responsible?
Are further tests worthwhile?
Is treatment necessary?

If possible, the clinician should eliminate any medications that may complicate the ability to determine whether or not a particular drug is causing the reaction.

The most important laboratory parameters to consider when evaluating a patient with a drug rash include a complete blood count and skin biopsy. Eosinophils present in either the complete blood count or skin biopsy suggest the possibility of a drug eruption, although they are not absolute indicators.

TYPES OF DRUG ERUPTIONS

Drug eruptions can appear in a variety of ways, thus the expression, "For any rash, think drug!"[3] Manifestations can be both visual and symptomatic and may include pruritus, sore throat, fever, blisters, red eyes, and painful skin. The 3 most common types of drug eruptions include those that are morbilliform or urticarial or that fall within the erythema multiforme spectrum.

Morbilliform Drug Eruption

Morbilliform drug eruptions comprise the most common type of drug eruption. A morbilliform drug rash occurs as a generalized eruption of red- to salmon-colored erythematous macules and papules that start on the trunk and spread symmetrically to the extremities, usually becoming confluent in large areas.[3] Constitutional symptoms may or may not be present. The rash often clears rapidly after withdrawal of the implicated drug and may progress to a generalized exfoliative dermatitis if the drug is not discontinued.[2] Subsequent administration of the drug should be avoided if possible.[4]

Treatment is usually symptomatic after discontinuing the offending drug. Cool compresses and topical cortico-

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steroid creams and ointments can be helpful. With severe or extensive eruptions, systemic corticosteroids may be justified. Antihistamines are not helpful in reversing the eruption, as there is no evidence of histamine in maculopapular lesions, but may provide relief if the patient has pruritus.[4]

Urticarial Drug Eruptions

Urticarial drug eruptions are another common type of drug eruption. Urticaria, or hives, is characterized by transient wheals in the skin caused by acute dermal edema.[3] An individual hive lasts less than 24 hours, and new hives develop continuously. Hives often consist of scattered or generalized edematous plaques with pale centers and red borders that have geographic shapes and can be confluent. The lesions are migratory, usually changing in size or location over several hours. The epidermis is intact, and there is no scaling or vesiculation.[4]

The more sudden and explosive the appearance of the urticaria, the more likely a potentially life-threatening anaphylaxis may occur. Discontinuation of the offending drug is always important with urticaria. If the drug is continued, the patient may develop a more life-threatening reaction.[4]

Erythema Multiforme

Erythema, meaning "red," and multiforme, meaning "many forms," is actually an immunologic hypersensitivity reaction in the skin, possibly caused by circulating immune complexes and not a true allergy, as defined by Coombs and Gell.[5]

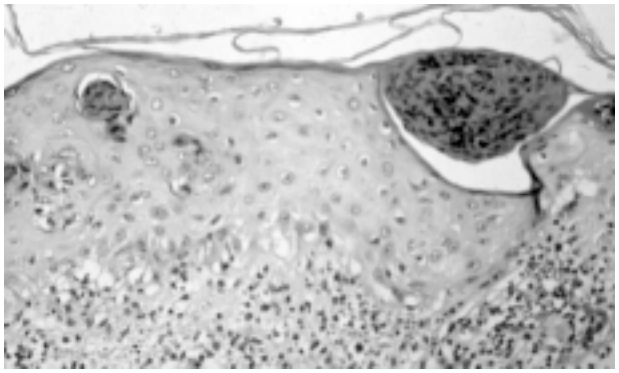
There are 2 types of erythema multiforme—a minor and a major form. The minor form consists of the typical "target" lesions. The major form includes Stevens-Johnson syndrome and toxic epidermal necrolysis, which are much more serious and life-threatening than the minor form.

Erythema multiforme minor. The minor form of erythema multiforme includes "target" lesions, erythematous plaques, and blisters. The distribution is typically symmetrical. Target lesions consist of 3 zones of color. Typically, a central dark area is surrounded by a pale edematous zone, which is surrounded by an annular peripheral margin of erythema. On histopathology, necrolytic keratinocytes can be seen. Subepidermal separation is often found in the center of target lesions (Figure 1).[6]

In erythema multiforme, the sites of cutaneous predilection include the palms and soles, although target lesions can occur anywhere.[2] Locations most often affected include the arms and legs, the hands and feet, the extensor surfaces, and sites of trauma.[4] Mucous membrane involvement is usually either not present or limited to the mouth.

Although drugs, especially anticonvulsants, are a common cause of erythema multiforme, herpes simplex and mycoplasma infections are also common etiologic agents. These infections are especially common causative agents in children.

Figure 1. Histopathology of Erythema Multiforme Showing Necrolytic Keratinocytes



The use of oral steroids to treat any form of erythema multiforme is controversial. No large studies have demonstrated the absolute efficacy of steroids, and inevitably, some patients will develop erythema multiforme while receiving steroids.

A technique known as "wet wrap therapy" may be used to treat patients with erythema multiforme. Wet wrap therapy consists of the following:

1. Apply triamcinolone 0.1% cream to trunk and extremities (avoid face, groin, and axillae).
2. Apply warm, moist towels over affected areas of skin.
3. Apply thermal blankets for 30 to 60 minutes over patient to prevent excessive cooling.
4. Remove towels and blankets.
5. Apply moisturizing cream to skin.

Wet wrap therapy can be done on an inpatient or outpatient basis.

Urticaria vs. erythema multiforme. Often, erythema multiforme is confused with urticaria. The 2 entities can be distinguished by the fact that urticarial lesions are pruritic and will "move." The lesions often move over 1 to 2 hours, so the clinician or the patient can circle the lesion and determine whether or not it is consistent with urticaria or erythema multiforme. Erythema multiforme lesions usually are not pruritic, are often painful, and typically last 1 to 4 weeks. Urticarial lesions are typically very pruritic.

Erythema multiforme major. Erythema multiforme major encompasses Stevens-Johnson syndrome and toxic epidermal necrolysis. These entities are actually components within a spectrum of a disease, with Stevens-Johnson syndrome less severe than toxic epidermal necrolysis. The diagnosis of erythema multiforme major consists of involvement of at least 2 mucosal surfaces as well as extensive denudation and erythema of the skin.

Stevens-Johnson syndrome typically has an abrupt onset of rash, with high fever, prostration, and a very extensive eruption, often with widespread bullae. The oral mucosa, lips, and conjunctivae are usually severely affected, to the point in which erosions can cause difficulty in eating and seeing. The mortality rate for Stevens-Johnson syndrome is 5% to 10%.

Treatment of Stevens-Johnson syndrome depends on the severity and extent of the disease. If extensive, therapy similar to that used to treat patients with toxic epidermal necrolysis is used. Milder forms may be treated with wet wrap therapy and analgesics.[4] Ophthalmologic consultation should be obtained.

Toxic epidermal necrolysis is a more serious form of erythema multiforme major. The mortality rate is as high as 45%, irrespective of therapies employed. Sheets of skin become denuded, and at least 20% of the body surface area is typically affected, resembling an extensive burn. Lesions are typically symmetrical, and intensely painful and often spare the scalp. Target lesions are not usually seen.[4] Death is typically caused by overwhelming sepsis originating in denuded skin or lungs.[7]

Toxic epidermal necrolysis must be treated as acute skin failure. Fluid loss, infection, heat regulation, immunocompromise, and energy expenditure are often best managed in a burn unit or intensive care unit. Oral or intravenous steroid use is very controversial, and steroids may mask signs of impending sepsis.[4]

SEVERE SKIN REACTIONS WITH ANTIEPILEPTIC DRUGS

The prescribing physician needs to be familiar with the antiepileptic drugs that are most frequently associated with severe skin reactions. Aromatic anticonvulsants such as carbamazepine, fosphenytoin, phenobarbital, and phenytoin and other anticonvulsants such as lamotrigine and valproic acid are often implicated in severe skin reactions.

Aromatic Anticonvulsants

Carbamazepine. Cutaneous reactions are major side effects that lead to the discontinuation of carbamazepine. Cutaneous side effects include oral ulceration, unusual bruising, urticaria, Stevens-Johnson syndrome, and photosensitivity. Evidence shows that a low initial dose and slow titration can significantly reduce the occurrence of rash.[8] Additionally, patients who develop cutaneous reactions to carbamazepine should avoid amitriptyline, because carbamazepine is a metabolite of amitriptyline.

Fosphenytoin. Fosphenytoin is a water-soluble prodrug of phenytoin. Adverse cutaneous reactions include bullous rash, exfoliative dermatitis, gingival hyperplasia, lupuslike syndrome, pruritus, and erythema multiforme. In 1 major clinical trial, 49% of patients had pruritus.[9] Pruritus with fosphenytoin is a dose-related reaction and develops more often if the drug is given intravenously. The groin is most often affected; the pruritus may last for hours.

Phenobarbital. Patients taking phenobarbital can have many skin reactions, including the 3 previously mentioned: morbilliform, urticaria, or erythema multiforme. Additional skin reactions include photosensitivity, acneiform rash, and purpura. Discontinuation of the drug may be sufficient to reverse the cutaneous reactions due to the slow metabolism and excretion of phenobarbital.[10]

Phenytoin. Phenytoin is the most common cause of the anticonvulsant hypersensitivity syndrome. Five percent to 10% of patients using phenytoin have a cutaneous reaction. Patients may have fever, erythroderma, tibial and facial edema, facial pustules, hyperpigmentation, hypertrichosis, abnormal liver function tests, or lupuslike symptoms.[11] Additionally, phenytoin may exacerbate preexisting lupus. Hypertrichosis may be irreversible and is located most often on the extremities, but may affect the face and trunk. Erythema multiforme is more likely if the patient is receiving concomitant x-ray therapy. Transient maculopapular rash occurs in 5% of children treated with this medication, most often within 3 weeks of drug initiation, and is more likely if high loading doses are given initially.

Other Anticonvulsants

Lamotrigine. Lamotrigine is a new anticonvulsant that belongs to the triazine family.[6] Life-threatening skin eruptions occur with lamotrigine as often as 1 in 100 pediatric patients and 1 in 1000 adult patients.[12] A skin eruption is significantly more likely if lamotrigine is given with valproic acid, especially if the recommended dose is exceeded.[13] As many as 1% of patients taking lamotrigine may develop Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, or pruritus.[10] Approximately 10% of patients taking lamotrigine may develop both erythema and a maculopapular rash. Females have a greater risk of developing rash.[14] The rash typically develops within the first 2 to 8 weeks of therapy, but it may occur later. Early manifestations of hypersensitivity to lamotrigine include fever and lymphadenopathy, consistent with the anticonvulsant hypersensitivity syndrome. Some of the hypersensitivity reactions have been fatal, with multiple organ dysfunction including hepatic abnormalities and disseminated intravascular coagulation.

Serious eruptions are 3 times more likely to occur in children than adults treated with lamotrigine.[15] To minimize the risk of rash, the prescribing physician should initiate therapy at the lowest possible dose and increase slowly.[14] Lamotrigine is not currently approved by the U.S. Food and Drug Administration for children under 16 years of age, unless they have seizures associated with the Lennox-Gastaut syndrome.[10,15]

Valproic acid. The most common dermatologic reaction with intravenous valproic acid is diaphoresis.[10]

Patients taking valproic acid may experience erythema multiforme, transient alopecia, petechiae, and photosensitivity, as well as pruritus. Valproic acid is almost completely metabolized by the liver. This drug interacts with other antiepileptics, such as carbamazepine and phenobarbital, which decrease its half-life by approximately 50%.[16] Valproic acid may triple the half-life of lamotrigine, giving it special implications for cutaneous reactions.[17]

ANTICONVULSANT HYPERSENSITIVITY SYNDROME

The anticonvulsant hypersensitivity syndrome is a rare, potentially life-threatening complication that occurs with antiepileptic medications. The aromatic anticonvulsants such as phenytoin, phenobarbital, and carbamazepine most often cause the anticonvulsant hypersensitivity syndrome.[18] This condition also occurs with non-aromatic anticonvulsants such as lamotrigine or other drugs, including sulfonamides, dapsone, minocycline, azathioprine, allopurinol, terbinafine, and others.[12]

The rate of occurrence is 1 in 1000 to 1 in 10,000 exposures of the above-mentioned drugs.[18] The anticonvulsant hypersensitivity syndrome is most likely to occur within 2 to 6 weeks after the antiepileptic drug therapy is initiated, but can occur at any time. The tendency to develop the anticonvulsant hypersensitivity syndrome is familial,[19] but a single genetic defect has not been identified.[20]

The anticonvulsant hypersensitivity syndrome is recognized by the following triad: fever, rash, and lymphadenopathy, usually accompanied by internal organ involvement.[1,12,21] Prior to initiation of therapy with an aromatic anticonvulsant or lamotrigine, the patient should be instructed to immediately report if this triad occurs. The prescribing physician's office staff should be trained to recognize this triad, so if a patient or physician calls with concern over these issues, the patient will be seen promptly. The patient should discontinue use of the drug at the first sign of rash.

The first signs of the anticonvulsant hypersensitivity syndrome include fever, malaise, and pharyngitis,[18] which is important to remember because if patients report these symptoms, they may be thought to have the flu. However, they will have a second sign—the rash. The rash may be a simple maculopapular exanthem, but the patient may develop a more serious form of erythema multiforme known as toxic epidermal necrolysis. The third sign, internal organ involvement, is a grave concern. The liver, kidneys, central nervous system, and lungs may become affected. Fatal outcomes are most often associated with liver failure.[1] The syndrome may mimic infectious, neoplastic, or collagen vascular disorders. Manifestations may include agranulocytosis, hepatitis, nephritis, or myositis.[12]

The organ involvement of anticonvulsant hypersensitivity syndrome is often symptomatic. The liver is usually involved, but the hematologic, renal, and pulmonary systems may be affected. The most prominent manifestations include hepatitis, nephritis, eosinophilia, and blood dyscrasias. Hypothyroidism may be a complication approximately 2 months after the onset of symptoms.[18]

Management of the anticonvulsant hypersensitivity syndrome consists of discontinuation of the drug, checking the liver function tests consecutively over time, complete blood count with differential, creatinine, and urinalysis. If the reaction is severe, corticosteroids are indicated, especially if the liver function tests are elevated over time.[18] For seizure control in patients with the anticonvulsant hypersensitivity syndrome, benzodiazepines have been used acutely, and after the resolution of hepatitis, valproic acid, gabapentin, or clobazam have been used.[22,23] Family counseling is an important component of patient management.[18]

A patient who develops the anticonvulsant hypersensitivity syndrome should avoid all aromatic anticonvulsant drugs, because the anticonvulsant hypersensitivity syndrome is associated with a relative excess of reactive oxide metabolites of the aromatic antiepileptic drugs.[19] Insufficient detoxification may lead to cell death or contribute to the formation of antigen that triggers an immune reaction.[12] Patients' cells become sensitized, and they develop the cutaneous reactions.

CROSS-SENSITIVITY WITH ANTIEPILEPTIC DRUGS

There is evidence of cross-sensitivity of antiepileptic drugs in causing skin eruptions.[19] Cross-sensitivity is of concern when phenytoin then carbamazepine are used. In 1 study, 58% of patients developed rashes when the sequence was prescribed. In patients who were given carbamazepine then phenytoin, 40% developed a skin reaction.[23] Lamotrigine has shown no evidence of cross-reacting with the aromatic anticonvulsants.[18]

CONCLUSION

This review summarizes some of the most common drug eruptions associated with antiepileptic medications. Physicians prescribing these medications should become familiar with the spectrum of cutaneous reactions that may develop as a consequence of these medications. Prompt recognition of an anticonvulsant-induced rash should prompt discontinuation of that drug regimen. When concerned about a cutaneous eruption, the prescribing physician should consider consultation with a dermatologist who can correlate the biopsy findings with the cutaneous picture and help direct the skin care.

Drug names: amitriptyline (Elavil and others), azathioprine (Imuran and others), carbamazepine (Tegretol and others), fosphenytoin (Cerebyx), gabapentin (Neurontin), lamotrigine (Lamictal), minocycline (Minocin,

Dynacin), phenobarbital (Donnatal and others), phenytoin (Dilantin and others), terbinafine (Lamisil), triamcinolone (Aristocort and others), valproic acid (Depakene).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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