



Searching for Answers about Allergic Reactions and Antiseizure Medications

The medical literature is imprecise, complicating the assessment of medication reactions. Here's help in making the call.

Whenever a person starts a new medication, there's the possibility they might develop an allergic reaction. Cutaneous manifestations are the hallmark. When reviewing medical literature on this topic, there is a vast, confusing list of terms that are applied to the seemingly straightforward notion of "rash" (see Table 1). Some articles and book chapters refer to a "mild" cutaneous reaction, while others use terms such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) to refer to serious, potentially life-threatening allergic reactions. In the literature regarding allergic reactions to antiepileptic drugs, one theme consistently reappears: AEDs cause idiosyncratic reactions, including rash. How often this occurs in the use of specific medications is less well defined: in this article, we will try to better define what we know (or don't know) about this potentially life-threatening problem.

Background

Allergic reactions, which commonly cause dermatologic manifestations, occur within the first one to four weeks of treatment,¹ or at the most within the first few months.² In reviewing AED trials with newer medications such as lamotrigine, the appearance of a rash was within the first four weeks of therapy.³ In US and European trials, 85 percent of rashes associated with zonisamide occurred less than 16 weeks after initiation of treatment. In Japanese trials, 90 percent of rash appeared within two weeks of therapy (see package insert, Zonegran). A more recent

study, which looked at the rates of serious cutaneous reactions to several AEDs, observed that 90 percent of the cases of Stevens-Johnson syndrome and toxic epidermal necrolysis occurred within 63 days of initiating therapy.⁴

The tenet that rash occurs "early on in treatment" seems accurate. It also seems true that the rate of allergic reactions appears to correlate with the speed of titration of the AED.¹ An example of this has been documented with lamotrigine. When the drug was first studied, the titration schedule was more aggressive. This prompted a reduction in the initial doses and a more gradual increase. When the rates of rash between the two titration schedules were compared, there was a much reduced incidence of rash and more serious skin reactions.⁴ This observation has led to the mantra of "start low, and go slow" when initiating therapy with any antiseizure drug. In other words, when it is possible to gradually introduce an AED, this is the preferred method.

The group at Columbia University performed a retrospective review of the rates of rash in 1,286 patients who were treated at the Columbia Comprehensive Epilepsy Center.⁵ The agents used were: carbamazepine, clobazam, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproate and zonisamide. In the study, 15.2 percent of epilepsy patients reported having had a rash at some time in their lives and 3.6 percent experienced a rash on monotherapy. No single agent caused a rash in more than 10 percent of patients. However, carbamazepine, lamotrigine and phenytoin were associated with

Table 1. Terms to Describe a "Rash"

"Mild" Rash

Photosensitivity; Maculopapular rash; Morbilliform rash; Pruritic rash; Urticaria, Scarletiform rash

"Serious" Rash

Lupus-like skin eruptions; Exfoliative dermatitis; Erythema multiforme; Purpura; Stevens-Johnson Syndrome; Lyell Syndrome (Toxic Epidermal Necrolysis)

higher rates of rash. Oxcarbazepine and phenobarbital had similar rates, but the number of patients receiving these agents was less, slightly eroding the confidence in these numbers. Clobazam, felbamate, gabapentin, levetiracetam, topiramate and valproate were the agents that seemed to cause rash less often. Mockenhaupt's results confirm these observations, at least as they pertain to valproate (see Table 2).⁴

But how often does rash occur? How concerned should a physician be when starting an AED? These questions are more difficult to answer. The rates of rash are often derived from early trials. Although some medications are studied in monotherapy, most are used as add-on therapy. When a rash occurs during combination therapy, it can be difficult to know if this is the same that would occur if the medicine were used by itself. In addition, trials may use different titration schedules. Lamotrigine is again a good example. In trials in adults with epilepsy, serious rash (*i.e.*, Stevens-Johnson syndrome) occurred 0.3 percent of the time. In trials in adults with bipolar disorder, where a lower dose and slower titration

was used, serious rash occurred 0.08 percent percent of the time (see Table 2).

What's the Difference Between a Mild and a Serious Rash?

Most serious reactions begin as mild ones. There is a spectrum to the severity: in fact, there is an overlap between SJS and TEN, with TEN being the more severe. As a greater percentage of the skin surface area is affected by the bullous necrolysis, the seriousness of the illness increases. For instance, SJS is associated with a mortality of 5 to 15 percent. In TEN, the mortality is more than 30 percent.

Two signs of a more serious allergic reaction are malaise (flu-like symptoms) and fever. These symptoms can precede the appearance of the dermatologic reaction for up to several days. However, these

symptoms are non-specific: if a person recently started an AED and developed fever and malaise, instead of allergy, it is quite possible that he or she simply contracted a viral illness. If these symptoms precede (or occur simultaneous to) cutaneous manifestations, halt the instigating agent. In fact, immediate withdrawal of the offending agent has been shown to reduce the mortality associated with this condition. In cases of TEN, when the agent was removed on the first day of signs of this syndrome, the mortality was reduced from 26 percent to five percent.⁶

Once TEN has been diagnosed, the patient should immediately be referred to a specialty center; specifically, TEN should be treated like a severe burn, and the person should be sent as soon as possible to a burn center. This patient will require spe-

cific supportive care, including treatment of the extensive skin wounds. In one study, the survival rate was higher in those who were referred early to a burn unit.⁷

Conclusions

An allergic reaction to AED can occur at any age. It usually manifests shortly after initiation of treatment, typically within two months of starting the new therapy. Most reactions are mild, causing a skin eruption that is unassociated with signs of systemic involvement. However, when a person develops malaise, fever and lymphadenopathy, the physician's concern must increase. Involvement of the oral mucosa is a sign of SJS. As the reaction continues, a greater proportion of the skin may become involved, making the transition to TEN. In either case, the offending agent must be immediately stopped, and the patient transferred to a medical center with expertise in treating these types of serious reactions. **PN**

Table 2. Rates of Rash and More Serious Dermatologic Reactions

<p>Carbamazepine <i>Package Insert:</i></p> <ul style="list-style-type: none"> Rash: Rate not given SJS/TEN: Listed under Warnings; Rate/incidence not given <p><i>Other Sources:</i></p> <ul style="list-style-type: none"> Rash: 2-17% (GL Holmes 1995) SJS/TEN: 1.4/10,000 (Mockenhaupt 2005) 	<p>adults, 4.4-14% in pediatric cases; Bipolar Trials: Adults =7-11%</p> <ul style="list-style-type: none"> SJS/TEN: Listed under Warnings; 0.3% adults with epilepsy; 0.8% kids with epilepsy; 0.08% adults with bipolar disorder (using current titration schedules) <p><i>Other Sources:</i></p> <ul style="list-style-type: none"> 2.5/10,000 (Mockenhaupt 2005) 	<ul style="list-style-type: none"> SJS/TEN: "Rare" <p>Phenobarbital <i>Other Sources:</i></p> <ul style="list-style-type: none"> 1-3%, up to 9% (Cramer 1995) 8.1/10,000 (Mockenhaupt 2005) 	<p>2-4% in migraine; Peds = 2% add-on in epilepsy</p> <p>Valproate <i>Package Insert:</i></p> <ul style="list-style-type: none"> Rash: >1% but less than 5% in both epilepsy and migraine trials <p>SJS/TEN: "Rare," "Reported" (Gogtay 2005)</p> <p><i>Other Sources:</i></p> <ul style="list-style-type: none"> 0% (0/1505 patients) (Tennis 1997) 0.5/10,000 (Mockenhaupt 2005)
<p>Gabapentin <i>Package Insert:</i></p> <ul style="list-style-type: none"> Rash: 1.2-1.3% in adults in treatment of PHN and as add-on in epilepsy SJS/TEN: "Rare" 	<p>Levetiracetam <i>Package Insert:</i></p> <ul style="list-style-type: none"> Rash: Adults: 0%; add-on trial in epilepsy 	<p>Phenytoin <i>Package Insert:</i></p> <ul style="list-style-type: none"> Rash: Rate not given SJS/TEN: Rate not given; Listed under Warnings and Precautions 	<p>Zonisamide <i>Package Insert:</i></p> <ul style="list-style-type: none"> Rash: Adults = 1.4-2.2% SJS/TEN: 46:1,000,000
<p>Lamotrigine <i>Package Insert:</i></p> <ul style="list-style-type: none"> Rash: Epilepsy Trials = 4.5-10% in 	<p>Oxcarbazepine <i>Package Insert:</i></p> <ul style="list-style-type: none"> Rash: Adults = 1.4-4%; Peds = 1.3-5.3% 	<p>Topiramate <i>Package Insert:</i></p> <ul style="list-style-type: none"> Rash: Adults = 1% add-on in epilepsy; 	

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