

# AEDs Linked to Rare but Lethal Dermatoses

*Severe anticonvulsant-induced skin reactions might result from reactivation of human herpesvirus 6.*

BY DIANA MAHONEY  
New England Bureau

STOWE, VT. — Initiating use of anticonvulsant therapy or switching antiepileptic drugs used may trigger life-threatening dermatoses, Dirk M. Elston, M.D., said at a dermatology conference sponsored by the University of Vermont.

The dermatoses associated with antiepileptic drugs (AEDs) typically involve blistering or are exfoliative. Patients at greatest risk are those with the triad of fever, swelling, and point tenderness who have recently initiated or altered seizure medications, Dr. Elston said.

Although these conditions are rare, it is critical that neurologists be aware of their possible occurrence as well as the signs and symptoms of the potentially fatal, acute syndromes when prescribing the implicated agents, epileptologist Jacqueline French, M.D., told CLINICAL NEUROLOGY NEWS.

Neurologists can reduce the risk of these events by commencing all new medications at a low dose, avoiding rapid dose increases, steering clear of known or presumed cross-reactive agents in patients with a history of sensitivity to a particular agent, and directing patients to report all adverse events, according to Dr. French of the University of Pennsylvania in Philadelphia.

Patients may not link their rash to their epilepsy medication, and instead of reporting it to their neurologists, they may seek care from their primary care doctor or dermatologist.

During his presentation, Dr. Elston noted that the differential diagnoses for such patients should include anticonvulsant hypersensitivity syndrome, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN)—all of which can be fa-

tal if not properly addressed. Time is critical for these patients, as their survival often depends on prompt recognition and appropriate multidisciplinary treatment, stressed Dr. Elston of Geisinger Medical Center, Danville, Pa.

The severe cutaneous manifestations noted are most commonly associated with the first-generation aromatic-ring antiepileptic agents (carbamazepine, phenobarbital, and phenytoin).

However, SJS and TEN have also been reported with the second-generation agent lamotrigine, particularly when used in combination with valproic acid.

Valproic acid when used as antiseizure monotherapy alone has a low independent association with the skin eruptions, Dr. Elston said.

A diagnosis of anticonvulsant hypersensitivity disorder should be presumed if the rash is morbilliform or scarlatiniform and is accompanied by facial edema, fever, and/or lymphadenopathy.

Additional clinical features often include hepatitis, eosinophilia, and atypical lymphocytosis.

Acute-onset rashes that present as severe mucosal erosions with epidermal detachment and widespread erythematous macules may be either SJS or TEN. The former, associated with 5% mortality, is often defined by purpuric macules and atypical target lesions, full-thickness epidermal necrosis, mucous membrane involvement, and detachment of less than 10% of the total cutaneous surface.

Possibly a more severe variant of the same process, TEN shares the histologic features of SJS, but detachment affects more than 30% of the cutaneous surface and the mortality is significantly higher. Acute onset of intense skin tenderness also indicates TEN, Dr. Elston said.

When a diagnosis is confirmed, the

most important treatment is to withdraw the anticonvulsant immediately and switch to an alternative medication for seizure control. "Doing so requires extreme care because of the high degree of cross-reactivity" among the various agents—particularly, but not exclusively, the aromatic drugs, Dr. Elston said.

"If you put a patient on an alternative antiseizure drug that has a high degree of cross-reactivity, not only is the eruption likely to recur, the course will probably be quicker and more devastating."

Dr. French noted that when anticonvulsant therapy is withdrawn, there is no "one best" alternative medication for seizure control. "There are many options, but they depend on the patient's history and their seizure type," she said.

While the newer-generation antiepileptic drugs have proved to be at least as effective as the older agents in most settings and are associated with fewer side effects and adverse events, care must still be taken when prescribing them to patients who have reacted to previous drugs.

Anecdotal reports linking gabapentin to recurrence of hypersensitivity syndrome, for example, suggest this second-generation drug should be avoided in patients with a previous sensitivity.

The coadministration of lamotrigine and valproate should be avoided as well, given the increased risk of TEN, according to Dr. French.

Dr. Elston noted that in addition to withdrawing the offending anticonvulsant, intravenous fluid replacement is a mainstay of therapy for these syndromes. For the more severe exfoliative conditions, symptomatic treatment is the same as for burns—de-

bridement, dressings, growth factors, and aggressive monitoring for infection and for fluid and electrolyte disturbances.

In fact, "patients should be transferred to a burn center if possible," he noted. Burn center care can improve mortality, primarily because of the specialized and intensive nursing support, he said.

It has been hypothesized that the severe anticonvulsant-induced skin reactions might be associated with reactivation of human herpesvirus 6.

If research bears this out, neurologists and dermatologists will gain more insight into—as well as possible tools for—the prevention and treatment of these conditions. ■



This patient developed full-thickness necrosis of toxic epidermal necrolysis on the trunk.



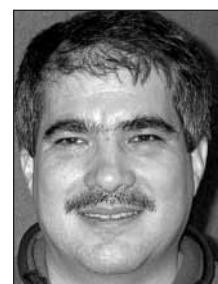
A drug hypersensitivity reaction resulted in follicular prominence on this patient's arm.

PHOTOS COURTESY DR. DIRK M. ELSTON

## Breast-Feeding Allows Gradual Neonatal AED Weaning

BY BRUCE JANCIN  
Denver Bureau

BRECKENRIDGE, COLO. — A strong case can be made for encouraging a few weeks or months of breast-feeding by epileptic women who have heeded neurologic advice to continue their seizure medication throughout pregnancy, Jose



**'I suggest breast-feeding for the first several weeks, then weaning from the breast.'**

DR. CAVAZOS

E. Cavazos, M.D., said at a conference on epilepsy syndromes sponsored by the University of Texas at San Antonio.

In addition to all the usual benefits of breast-feeding, such as enhanced maternal-infant bonding, this practice greatly reduces the likelihood of neonatal antiepileptic drug (AED) withdrawal syndrome, said Dr. Cavazos, a neurologist at the university's South Texas Comprehensive Epilepsy Center.

Transplacental passage of AEDs occurs readily. Studies have shown maternal serum and umbilical cord blood concentrations of AEDs are generally similar. After being exposed to therapeutic AED concentrations throughout fetal life, a baby who experiences abrupt postpartum discontinuation often develops a withdrawal syndrome marked by increased irritability.

This can be avoided by taking advantage of the fact that most AEDs enter breast milk in concentrations similar to those found in maternal serum.

"Many women have an irrational atti-

tude of 'I don't want to give my baby this medicine.' I tell such a patient that for the last 9 months, her baby has been exposed to an AED. I suggest breast-feeding for the first several weeks, then weaning from the breast and, in that way, gradually weaning the baby off the medication. When it's presented in that light, it's more often that breast-feeding will occur," the neurologist explained.

There is little downside to such an approach, he added. Idiosyncratic drug reactions are extremely unlikely in a neonate exposed in utero. There have been no large prospective studies of the neurodevelopmental impact of breast-feeding by mothers on AEDs, although several studies suggest in utero exposure is associated with mild, partially reversible delays in motor coordination.

Breast-feeding while the mother is on an AED can result in neonatal sedation, but it's typically mild and of little concern un-

less the mother is taking large doses of phenobarbital.

And speaking of phenobarbital, some obstetricians still favor it for seizure control in pregnancy, although the practice is no longer recommended. "In fact, in the past year, I've had two women who were switched from other AEDs to phenobarbital because they became pregnant and happened to visit their ob.gyns. before seeing their neurologists.

"This is not necessarily the best way to go," Dr. Cavazos noted during his presentation.

A recent report from the North American AED Registry is instructive. Of 77 pregnancies exposed to phenobarbital monotherapy from conception and followed prospectively, 5 (6.5%) resulted in major malformations identified by 5 days of age. This represented a 4.2-fold elevation over the background risk (Arch. Neurol. 2004;61:673-8). ■