Recognizing Deadly Anticonvulsant Side Effects

BY DIANA MAHONEY
New England Bureau

STOWE, VT. — "Tell me you have a patient with a rash who also happens to have a seizure disorder [and it's] enough to make me stop what I'm doing and get right over," Dirk M. Elston, M.D., said at a dermatology conference sponsored by the University of Vermont.

The patient might have a drug hypersensitivity syndrome or toxic epidermal necrolysis—both of which have been associated with anticonvulsant therapy, Dr. Elston said in a presentation on life-threatening dermatoses at the conference. Time is critical for such patients, as prompt recognition and appropriate treatment often hold the key to survival, he stated.

Toxic epidermal necrolysis (TEN) is the most severe cutaneous manifestation associated with anticonvulsive therapy. The rare condition is most commonly associated with the aromatic-ring antiepileptic agents (carbamazepine, phenobarbital, and phenytoin), but it has also been reported with other anticonvulsants, such as lamotrigine, particularly when used in combination with valproic acid, said Dr. Elston of Geisinger Medical Center, Danville, Pa.

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 erythematosus macules may be either Stevens–Johnson syndrome (SJS) or TEN. The former, associated with a 5% mortality rate, 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.

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DR. ELSTON

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.

Skin biopsy will show a combination of normal stratum corneum and keratinocyte necrosis, which is important for diagnosis because it rules out other serious dermatologic conditions.

A thorough patient history is also critical for accurate diagnosis and appropriate treatment, Dr. Elston emphasized, noting that delineating a drug exposure timeline is particularly important, as is determining previous exposure history. If the patient has been previously sensitized to the offending drugs, more rapid onset and a worse prognosis are likely, he noted.

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, he noted.

"Lamotrigine [Lamictal] is not an aromatic, yet it has a black box warning about its association with SJS and TEN, especially when used in combination with valproic acid," Dr. Elston said. "I also wouldn't use gabapentin because of the disturbing number of anecdotal reports associating it with recurrence of hypersensitivity reactions."

Valproic acid has a low independent association with the skin eruptions, and "is probably the safest choice for alternative seizure control," Dr. Elston noted.

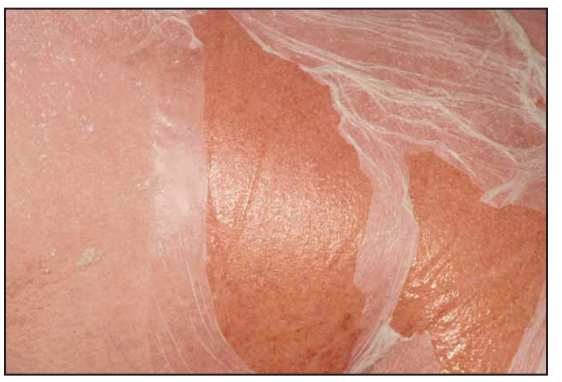
Besides intravenous fluid replacement, the main types of symptomatic treatment for the more severe exfoliative conditions are the same as for burns—debridement, dressings, growth factors, and aggressive monitoring for infection and for fluid and electrolyte disturbances, Dr. Elston said. In fact, "patients 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.

Patients should also be monitored by an ophthalmologist for ocular sequelae, and preventive measures should be taken.

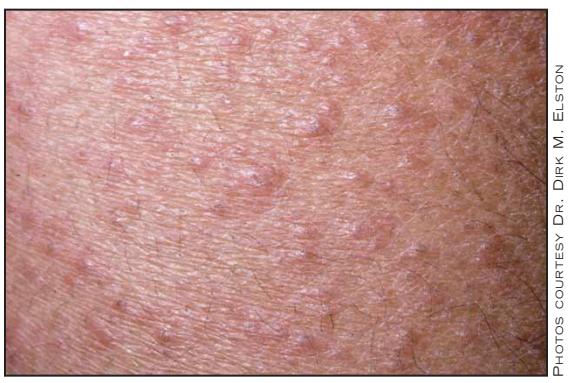
In discussing drug therapy, Dr. Elston said he doesn't recommend systemic corticosteroids because in some studies they have been associated with increased mortality when used for more than 48 hours. Intravenous immunoglobulin is a promising but unproven therapy, he said. Thalidomide, proposed as a treatment for TEN because it is a potent inhibitor of tumor necrosis factor–α action, is not recommended. "A well-designed trial to study its effectiveness was stopped because of excess mortality" in patients receiving the drug, Dr. Elston said.

Although the causative mechanisms are not well established, drug hypersensitivity syndrome may be associated with reactivation of human herpes virus 6.

Prompt diagnosis, withdrawal of the causative drug, avoidance of cross-reactive drugs, and appropriate supportive care appear to be the best way to manage these patients, Dr. Elston said. ■



Toxic epidermal necrolysis resulted in full-thickness necrosis on this patient's trunk.



Follicular prominence, as on this patient's arm, can be caused by anticonvulsant hypersensitivity.

PHOTOS COURTESY DR. DIRK M. ELSTON

Corticosteroids May Promote Favorable Outcome in SJS, TEN

BY BRUCE JANCIN
Denver Bureau

VIENNA — Corticosteroid therapy for Stevens-Johnson syndrome and toxic epidermal necrolysis received a big boost from two observational studies presented at the annual meeting of the European Society for Dermatological Research.

Juergen Schlingman, M.D., reported on 281 patients with Stevens-Johnson syndrome (SJS) or toxic epidermal necrosis (TEN) treated in French and German hospitals under the auspices of the European Registry of Severe Cutaneous Adverse Reactions (EuroSCAR) study group.

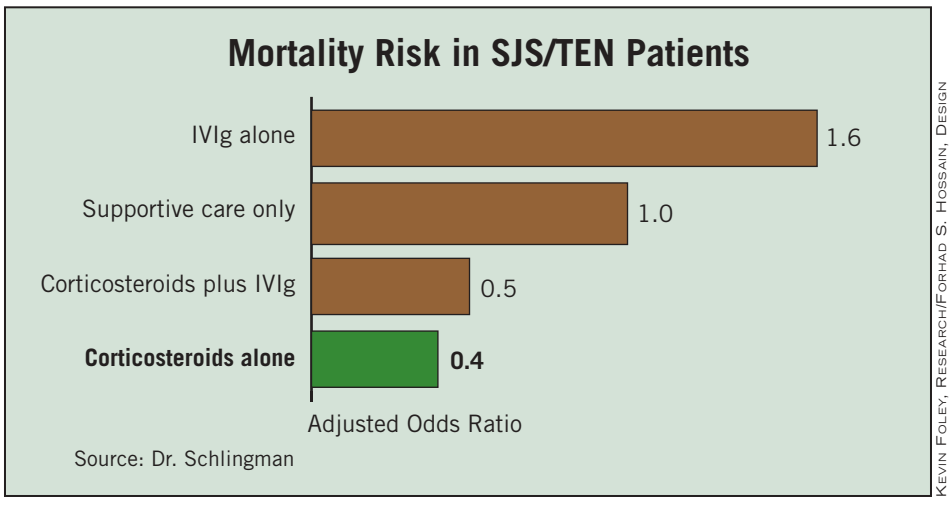
"This is the largest cohort of patients with SJS/TEN ever analyzed for treatment outcomes. It's the best data available, despite having the obvious limitations of an observational study," said Dr. Schlingman of the University of Freiburg (Germany).

The results show that there is no benefit for high-dose intravenous immunoglobulin and that the use of corticosteroids—which has been a subject of controversy—may deserve a randomized therapeutic trial.

An overall death rate of 22.1% was seen in this series, which featured unbiased enrollment. Mortality was 18% in the 119 patients who received corticosteroids. In a multivariate analysis adjusted for age, disease severity, and other relevant variables, corticosteroid-treated patients were 60% less likely to die than were those who got only supportive care. In contrast, patients who got intravenous immunoglobulin (IVIg) alone had a 60% increased risk of mortality relative to those who received supportive care only. (See chart.)

Age proved a significant risk factor for mortality. Patients aged 40-70 years were 3.3-fold more likely to die than were those younger than age 40, and patients older than 70 were at 8.9-fold increased risk.

In recent years, a growing number of physicians have turned to high-dose IVIg based on several favorable published reports. But two recent patient series from Loyola University Chicago and the University of Toronto showed no benefit for IVIg (J. Burn Care Rehabil. 2004;25:81-8, 246-55). Dr. Schlingman said the most likely explanation for the reported favorable outcome with IVIg in some prior series is recruitment bias and exclusion of high-risk patients.



KEVIN FOLEY, RESEARCH/FORHAD S. HOSSAIN, DESIGN

In a separate presentation at the meeting, S.H. Kardaun, M.D., reported on a series of 12 consecutive patients with SJS/TEN treated with dexamethasone pulse therapy, with highly favorable results.

The therapy consisted of one dose of dexamethasone IV 1.5 mg/kg given on each of 3 consecutive days starting as soon as the diagnosis was established. The mean time from the start of dexamethasone pulse therapy to lesion healing was 14.2 days. All cutaneous and mucosal lesions healed within 3 weeks except in two patients, both of whom had disseminated herpes simplex infections.

A single patient died of an underlying malignancy after his skin lesions were nearly healed. Predicted mortality based on the SCORTEN disease severity rating was four cases, said Dr. Kardaun of University Hospital Groningen (the Netherlands). ■