COMMENTARY

Pediatric Dermatology Vol. 19 No. 1 82–84, 2002

Erythema Multiforme: A Practical Approach to Recent Advances

James E. Rasmussen, M.D.

Department of Dermatology, University of Michigan Medical Center, Ann Arbor, Michigan

In this edition of *Pediatric Dermatology* Samimi and Siegfried report the interesting and provocative case of a 9-year-old girl with hypocomplementemic systemic lupus erythematosus and severe nephritis. Over an approximate 3-week time span this very ill patient was treated with seven different agents including intravenous and oral corticosteroids. Within 2–3 weeks (and while on steroids) she developed a fever and a widespread eruption involving her face, trunk, and the mucous membranes of her eyes, mouth, and vulva. Intravenous cefuroxime was then added. At that time a dermatology consultant suggested a diagnosis of bullous lupus erythematosus or Stevens–Johnson syndrome (SJS). The skin biopsy favored SJS and a direct immunofluorescence study was negative. Furosemide was discontinued as "the most likely cause" but the disease progressed over the next 2 days. At this point a 4-day course of intravenous immunoglobin (IVIg) (750 mg/kg/day) and the reinstitution of intravenous methylprednisolone 1 mg/kg every 12 hours was begun. Hydroxychloroquine and cefuroxime were discontinued and replaced by vancomycin and cefazidime. Her condition continued to deteriorate for the next 3 days with critical care management including skin debridement, transfusion of blood and albumin, and intubation with mechanical ventilation. Gradual improvement began 4 days after starting IVIg and the patient was discharged 3 weeks later.

There are several important new points regarding severe erythema multiforme (EM) that are illustrated by this case report and other recent publications. This article will comment on the practical importance for the involved clinician of increased susceptibility to EM in high-risk patient groups (disease predisposition), genetic predisposition, and the role of drugs in causing and treating SJS/toxic epidermal necrolysis (TEN).

HIGH-RISK PATIENT GROUPS

The discussion section of Samimi and Siegfried's manuscript points out that there are certain groups at somewhat higher risk for the development of SJS, specifically focusing on systemic lupus erythematosus (SLE). Patients with HIV infection and malignancies treated with radiation also appear somewhat more susceptible to SJS and TEN (1). Another recent publication investigates the role of human herpesvirus 6 in these severe adverse drug reactions (ADRs) (2). Unfortunately the dermatologist, although aware that a patient is "high risk," cannot usually defer therapy because of the serious nature of the underlying illness, so not much practical advantage is gained here except heightened suspicion. Although it is commonly suggested that drugs be used with "caution" in these situations, I am not certain what this entails since I presume that all medications are administered in this manner. Perhaps a more appropriate caveat would be to treat all new eruptions as if they are life threatening and proceed directly to avoidance and aggressive therapy.

GENETIC PREDISPOSITION

It is becoming increasingly apparent that many patients who have severe ADRs such as SJS/TEN do so because of their metabolic predisposition. Wolkenstein et al (3)

This is a Commentary on the article: Samimi SS, Siegfried E. Stevens–Johnson Syndrome Developing in a Girl with Systemic Lupus Erythematosus on High-Dose Corticosteroid Therapy. Pediatr Dermatol 2002;19:52–55.

Address correspondence to James E. Rasmussen, M.D., Department of Dermatology, University of Michigan Medical Center, 1910 Taubman Health Center, Ann Arbor, MI 48109-0314.

studied the reaction of lymphocytes from patients with severe cutaneous ADRs to metabolites of sulfonamides and anticonvulsants, family members of those affected, and a group of nonaffected, unrelated controls. In all situations, affected patients' lymphocytes suffered more toxicity when exposed to metabolites of the suspected drug than did those of controls. Family members of those who suffered ADRs also had higher reaction rates to these metabolites, suggesting that these reactions were in some way genetically determined by inherited metabolism. These abnormalities have been linked to the cytochrome P-450 system and certain human leukocyte antigen (HLA) subtypes.

Anticonvulsant hypersensitivity syndromes may be related to individuals' inability to properly metabolize arene oxide by-products of these medications, the actual immunologic reaction being not to the medication itself but to a metabolic degradation product. The immunologic mechanism has been recently described in detail by Sullivan and Shear (4).

Is there some practical way to screen users of the most likely drug causes of EM for this predisposition? In addition to the method described in the preceding paragraphs, there are numerous other mechanisms that can be used for in vitro testing for ADRs as outlined by Rieder (5): in vitro challenge, radioallergosorbent test (RAST), basophil degranulation, determination of specific antibodies, determination of immune mediators, and study of enzymic pathways. Unfortunately these modalities are usually not commercially available and are impractical for pretreatment evaluation. Even though the risk may be increased many fold in these groups of patients, systemic therapy with high-risk drugs is frequently necessary. While having a higher risk, the rate of ADR remains low in "slow metabolizers" and there is still no practical way to avoid EM in this group of patients. Therefore a clinician should also have a higher degree of concern for drug eruptions in these high-risk groups and act accordingly, with close monitoring and early drug discontinuation.

NEW INFORMATION REGARDING CAUSATIVE DRUGS AND THERAPY

The discussion section of Samimi and Siegfried's article also reviews the controversy regarding systemic steroids and their effect on EM. They mention the recent knowledge that corticosteroids may on occasion be a culprit drug (6).

The increased risk for the use of corticosteroids was originally reported by Roujeau et al (6), who noted "no explanation is apparent for the high risk we observed with recently initiated corticosteroid therapy." After correcting for concomitant disease and drug use, the authors concluded "the relative risk remains significantly elevated when subjects with these factors were excluded" (6). It is not clear from this information whether physicians treating patients who developed EM while receiving steroids should have discontinued these medicines or increased the dose.

A more useful method of suspecting the presence of an ADR is the "length of exposure" rule. Roujeau et al (6) have attempted to define the risk of developing SJS or TEN during the short- and long-term use of a large number of medications. They noted greatly increased risks for patients whose medication had been recently started (less than 2 months duration) with most of the commonly suspected agents, including anticonvulsants, antibiotics, and antiarthritic drugs. However, they noted that a significant risk still existed for the long-term use of both phenobarbital and valproic acid even after 2 months, so it isn't enough to withdraw the most recently introduced agents when the SJS appears.

The clinician is then left as the primary detective to determine which drug from the most likely of causative agents also fits the time use rule. That is, agents which have been in use for many months are highly unlikely to have caused EM. Those who fit in the 7- to 21-day period are most likely and those within a 2-month window are still considered possible causes and should be discontinued. The most difficult aspect of this decision making is illustrated by the patient described in this case report—multiple medications used for a variety of reasons including lupus and presumed infection. Sometimes you simply have to toss them all out and start over again. This, however, is a very difficult therapeutic choice and usually isn't attempted unless the clinician has no clear alternative.

The accurate determination of the causative agent may have a substantial influence on survival regardless of the patient's underlying medical condition. Garcia-Doval et al (7) recently published a retrospective review suggesting that early discontinuation of some drugs is associated with a substantial decrease in mortality. They noted that for drugs with a short half-life (less than 24 hours), early withdrawal (within 1 day of the onset of blistering) was associated with a 5% mortality. When the drug was stopped after that point the death rate was 26%. These effects were apparent even when adjustment had been made for variables such as maximum surface area blistered or other associated underlying diseases. Such benefits were not noted for patients who were taking drugs with a half-life longer than 24 hours.

The study of Garcia-Doval et al (7) raises many questions. Several drugs which are common causes of SJS/TEN such as phenytoin were not included in the

list of causative agents. Corticosteroids were also not among the drugs that were considered causative in this series. In addition, half-life was determined from a 1985 edition of Goodman and Gilman, *The Pharmacological Basis of Therapeutics* (8). It wasn't explained why a more current source such as the *Physician's Desk Reference* wasn't utilized.

In an editorial accompanying the Garcia-Doval et al publication, Robert Stern (9) noted the pros and cons of discontinuing all non-life-sustaining medications versus only the suspected one, correctly commenting that many medicines will be unnecessarily withdrawn. This is very difficult to do in hospitalized patients who have major organ involvement due to other diseases. Not discussed by either the Garcia-Doval group or Stern is the fact that certain drugs are metabolized more slowly in the older patient or in those with diseased organs (e.g., declining renal function) or through modification by other agents that induce changes in the cytochrome P-450 system. In these situations a clinician has no clear choice—pick the most likely drug, discontinue it, and monitor closely.

My approach has usually been to try to identify the most likely culprit based on reputation, introduction during the preceding 1- to 4-week period, and prior history of allergy. I am not sure what to do about the patient who is already on corticosteroids when the EM begins, although I usually continue them for a short period of time and increase the dose if early in the course of SJS/TEN.

I think the picture is clearer when only a single agent is used but much more complex when the patient is hospitalized with significant underlying medical problems and is using multiple drugs.

REFERENCES

1. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331:1272–1284.
2. Descamps V, Valance A, Edlinger C, et al. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. Arch Dermatol 2001;137:301–304.
3. Wolkenstein P, Charue D, Laurent P, Revuz J, Roujeau JC, Bagot M. Metabolic predisposition to cutaneous adverse drug reactions. Arch Dermatol 1995;131:544–551.
4. Sullivan RJ, Shear NH. The drug hypersensitivity syndrome. Arch Dermatol 2001;137:357–364.
5. Rieder MJ. In vivo and in vitro testing for adverse drug reactions. New Front Pediatr Drug Ther 1997;44:93–110.
6. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333:1600–1607.
7. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens–Johnson syndrome. Does early withdrawal of causative drugs decrease the risk of death? Arch Dermatol 2000;136:323–327.
8. Gilman AG, Goodman LS, Rall TW, Murad F, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 1985, New York: MacMillan.
9. Stern RS. Improving the outcome of patients with toxic epidermal necrolysis and Stevens–Johnson syndrome [editorial]. Arch Dermatol 2000;136:410–411.