Erythema multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

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Pharmacology Literature Reviews

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Formulary Update

Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis are mucocutaneous disorders that are thought to be related, constituting a spectrum of reactions. Erythema multiforme (EM) has the most benign presentation, and is followed in severity by Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Additionally, EM is generally a postinfectious process, while SJS and TEN are drug-induced reactions. As a result, SJS and TEN will therefore be discussed in greater detail than EM in this newsletter article.

Erythema multiforme
EM, first described in 1860 by von Hebra, is characterized by symmetrical target-like lesions. These lesions are described as erythematous papules surrounded by a raised, erythematous ring, which is in turn encircled by an erythematous outer ring. The lesions are generally located on the extremities. As previously mentioned, EM is often a recurrent, postinfectious process, frequently associated with herpes simplex and mycoplasmal infections. It has a self-limited and acute course, and is associated with low morbidity.

**Stevens-Johnson syndrome**

In 1922, Stevens and Johnson described two cases of children who presented with disseminated cutaneous eruptions of dark-red macules with necrotic centers. The children also had erosive stomatitis and severe ocular involvement. The syndrome, now known as SJS, is characterized by irregularly shaped purpuric lesions that often have overlying blisters or necrotic centers. The lesions predominate on the face, trunk, and mucous membranes, but also may be located on the linings of the respiratory and gastrointestinal tracts. SJS differs from EM in that it is a more severe disease, and is commonly drug-induced. Epidermal detachment may occur in SJS, but less than 10% of the body surface area is involved. Morbidity with this disease is high, and can include photophobia, burning eyes, visual impairment, and blindness.

**Toxic epidermal necrolysis**

In a 1956 article, Lyell coined the term "toxic epidermal necrolysis" to describe the reaction he observed in four patients who had presented with extensive epidermal loss due to necrosis. Because TEN, by definition, involves greater than 30% loss of epidermis, it is considered to be the most severe of the drug-induced skin reactions. The characteristic lesions of TEN are similar to those seen in SJS, although the degree of epidermal loss and subsequent dermis exposure is greater. TEN is often associated with leukopenia, high fever, and extensive lesions in the respiratory and gastrointestinal tract. Morbidities associated with TEN are similar to those of SJS, including the ocular involvement, although the mortality associated with TEN is significantly higher (25-30% versus 5% with SJS).

**Diagnosis**

SJS and TEN are generally clinically evident, but diagnoses should be confirmed by direct immunofluorescence studies and skin biopsies to exclude conditions not related to drug therapy such as bullous diseases.

**Etiology**

Drugs are the most common cause of SJS and TEN. An offending agent is found in 50% of SJS cases and in 70% to 90% of cases of TEN. Over 100 different drugs have been reported as causing these reactions. The top three drugs associated with SJS and TEN reactions are carbamazepine (14 cases per 100,000 users), long-acting combinations of sulfadoxine and pyrimethamine (10 cases per 100,000 users), and cotrimoxazole (1-3 cases per 100,000 users). Other common offenders include:

- sulfonamides
- barbiturates
- piroxicam
- aminopenicillins
- hydantoin
- allopurinol
- phenylbutazone

Less commonly reported agents include:
- cephalosporins
- tenoxicam
- fluoroquinolones
- non-steroidal anti-inflammatory agents
- vancomycin
- rifampin
- ethambutol
- thiabendazole
- corticosteroids

Identifying the causative agent is often difficult. Special attention should be paid to drugs initiated one to three weeks before the onset of the skin reaction. A mean time of 14 days from initiation of therapy to onset of reaction was noted by one source. In general, patients appear to be at the greatest risk for developing these reactions within the first two months of therapy. Other possible causes of these reactions include infections with Mycoplasma or Streptococcal sp., genetic predisposition to autoimmune diseases, graft versus host disease, viral infection, allergy, immunization, radiotherapy, and malignancy.

**Epidemiology**

SJS and TEN have been reported in both sexes and all age groups, including infants and children. However, SJS is more common in people younger than 30 or older than 65, and TEN has a much higher incidence in the elderly. Both conditions occur more commonly in patients on drug therapy, particularly those on regimens involving multiple drugs. Patients at higher risk for developing SJS and TEN include bone marrow transplant recipients, patients with systemic lupus erythematous, and those with HIV infection and AIDS.

**Incidence**

Both SJS and TEN are rare reactions. SJS occurs slightly more often at 1-7 cases per million per year, while TEN occurs in 0.4-1.3 cases per million per year.

**Clinical Manifestations**

These reactions generally begin with non-specific flu-like symptoms including high fever, cough, sore throat, and burning eyes, which are followed in one to three days by skin and mucous membrane lesions. A painful, burning rash rapidly spreads from the face and trunk to the extremities. In two to five days (or sometimes even in hours) the lesions are maximally extended, and the epidermis is raised by flaccid blisters that spread upon pressure. In the most severe cases of TEN, close to 100% of the epidermis may slough off. Ninety percent of patients with SJS or TEN have lesions involving the mucosa, and experience painful erosions and crusting of these areas. The most commonly affected sites in order include the oropharynx, eyes, genitalia, and anus. These painful and widespread lesions cause crusted lips, salivation, photophobia, and painful micturation. Ocular lesions need particular attention due to high risk of sequelae. Other systems that are affected include the gastrointestinal and respiratory tracts. In the gastrointestinal tract, esophageal sloughing is very common, and can cause bleeding and diarrhea. In the respiratory tract, tracheobroncheal erosions can lead to hyperventilation, interstitial edema, and acute respiratory disease syndrome (ARDS). Complications are similar to those seen in extensively burned patients. They may include: the loss of large areas of skin; massive edema, fluid loss and electrolyte abnormalities; multiorgan toxicity, including pneumonia, esophageal strictures, hepatitis, and nephritis; and blood dyscrasias including anemia due to blood loss, lymphopenia and neutropenia. Asthenia, pain, and anxiety are commonly seen.
**Pathogenesis**

The pathogenesis of these reactions is largely unknown. However, two possible mechanisms have been reported. The first postulated mechanism is an alteration in drug metabolism, which has previously been shown in patients with hepatitis and hypersensitivity syndromes. For example, patients with sulfonamide-induced TEN are usually slow acetylators. Their reduced rate of metabolism may cause them to accumulate reactive metabolites. These metabolic by-products may act as haptens, adhering to proteins on epidermal cells and inducing an immunologic response. This leads into the second possible mechanism of the reaction, which is a cell-mediated cytotoxic reaction directed toward the epidermis. The epidermis of SJS/TEN patients becomes infiltrated by T lymphocytes and macrophages. It has been proposed that the immunologic reaction is directed toward epidermal cells that have drug particles bound to them. These drug/cell complexes may create antigenicity and stimulate a hypersensitivity reaction.²

**Prognosis**

As mentioned previously, patients with SJS have a mortality rate around 5%, while patients with TEN have a much higher rate at 25-30%.¹³ As might be expected, elderly patients and those with more extensive lesions have a higher mortality rate. Sepsis is the most common cause of death, followed by pulmonary complications.⁵ Patients who survive the reaction typically heal in three to four weeks. Unfortunately, 30% to 50% of patients will have lingering sequelae, especially ocular problems such as synechiae (adhesion of the iris to the cornea or lens) and erosions, which can result in blindness.²

**Treatment**

The most important aspect of patient management is to immediately withdraw the offending drug.² Following drug withdrawal, treatment is generally symptomatic and should include volume replacement, aggressive nutritional support, and insulin (which may be necessitated by a patient’s hypercatabolic state). It has been suggested that the environmental temperature should be raised to decrease the patient’s caloric losses. Many sources also suggest that these should receive anticoagulants due to the risk of thromboembolism during recovery. Clinicians should use aseptic techniques when applying topical products to the skin to avoid infection. The use of silver sulfadiazine should be avoided. The patient should receive routine eye care, including antibiotic and antiseptic eye drops, oral and nasal debris should be removed, and the mouth should be sprayed with antiseptic agents. Finally, appropriate antacids, sedatives, and analgesics should be administered. Antibiotic prophylaxis is not recommended, but should be started if increasing numbers of bacteria are cultured from the skin, a single bacterial strain appears to be selected, there is a sudden drop in fever (a sign of worsening prognosis), or the patient’s clinical condition worsens. Corticosteroids should be avoided, as they may be a precipitating cause of SJS and TEN. They may worsen prognosis and increase mortality.²

**References**

Pharmacology Literature Review

Adverse Effects from Anesthetics

This extensive review covers complications related to the administration of regional anesthetics in children. The authors have included not only adverse effects arising from the medications themselves, but also complications resulting from the types of devices and insertion techniques used. The complication rates provided in this review are from the extensive cumulative data collected by the French-Language Society of Paediatric Anaesthesiologists. The authors conclude with a brief, but useful, section on preventing the more common complications of this technique. Dalens BJ, Mazoit J. Adverse effects of regional anaesthesia in children. Drug Safety 1998;19:251-68.

Frequency of Adverse Drug Reactions

There has been considerable attention paid recently to the issue of preventing adverse drug reactions (ADRs) in hospitalized children. The authors of this study have conducted a prospective evaluation of the frequency and characteristics of ADRs in 219 pediatric patients hospitalized at the Universidad Catolica hospital in Santiago, Chile. Using an intensive screening and surveillance system, it was estimated that ADRs occurred in 13.7% of the children studied. The most frequently reported ADRs were, as anticipated, diarrhea, abdominal pain, and emesis. While the majority of the ADRs reported were considered mild, 27.9% were described as severe. These included 3 cases of erythema multiforme, 2 anaphylactic reactions, and 1 case each of vascular purpura, hyperglycemia, hypertension, and acute pancreatitis. The drugs most commonly associated with ADRs were antineoplastics, anticonvulsants, antibiotics, albuterol, and methylprednisolone. Age was not a factor, but the length of hospitalization was directly correlated with the likelihood of developing an ADR. Gonzalez-Martin G, Caroca CM, Paris E. Adverse drug reactions in hospitalized pediatric patients. A prospective study. Internat J Clin Pharmacol Ther 1998;36:530-3.

Grapefruit Juice with Carbamazepine

Although this trial involved only adults, the results may have significant impact on pediatric patients taking carbamazepine. Ten patients were included in this randomized cross-over clinical trial. All patients had been taking 200 mg carbamazepine three times daily for at least 3 weeks. Patients received either 300 ml of grapefruit juice or water with their morning dose. After a two day "wash-out" period, a second trial was done with the alternative drink. Serum concentrations taken after grapefruit juice administration showed a significant increase in peak concentrations (9.20 mcg/ml versus 6.55 mcg/ml in the water group) and trough concentrations (62.0 mcg/ml versus 44.0 mcg/ml with water). No difference in the time to achieve peak concentrations was found. Based on these results and previous research, the authors concluded that grapefruit juice increases the bioavailability of carbamazepine by inhibition of CYP3A4 enzymes in the gut wall and liver. Garg SK, Kumar N, Bhargava VK, et al. Effect of grapefruit juice on carbamazepine bioavailability in patients with epilepsy. Clin Pharmacol Ther 1998;64:286-8.

Formulary Update
The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 10/23/98:

1. Irinotecan (Camptosar®) was added to the formulary for the treatment of refractory metastatic carcinoma of the colon or rectum. This agent is one of the new class of topoisomerase inhibitors.
2. Gemcitabine (Gemzar®) was also added to the formulary. This antineoplastic agent is indicated for the treatment of adenocarcinoma of the pancreas and certain lung cancers.
3. Trastuzumab (Herceptin®) was also approved for use. This agent is a monoclonal antibody that binds to human epidermal growth factor receptor 2 (HER2), inhibiting proliferation of tumor cells that overexpress HER2. It is indicated for treatment of metastatic breast cancer in patients known to have HER2 overexpression.
4. Efavirenz (Sustiva®) was added as a Category A (restricted) antiviral agent. It is a non-nucleoside reverse transcriptase inhibitor used for HIV infection.
5. Dalteparin (Fragmin®), a low-molecular-weight heparin (LMWH), was removed from the formulary. Enoxaprin will remain on formulary for patients requiring therapy with a LMWH.
6. Antimicrobial guidelines for adults, developed by members of the Antimicrobial Utilization Committee were approved by the full P&T Committee.