Current Understanding of Delayed Anticonvulsant Hypersensitivity Reactions

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Hypersensitivity syndrome (HSS) reactions are one of the most feared idiosyncratic drug reactions and are most common with exposure to antiepileptic drugs (AEDs), sulfonamides, nonsteroidal antiinflammatory drugs, corticosteroids, and allopurinol. HSS is associated with chemotoxic and T-cell–mediated inflammatory injuries in barrier tissue systems that contain cytochrome oxidases (e.g., skin, mucosa, liver, and lungs) and can be seen as a derangement in the defense system against xenobiotics—bioactive foreign molecules. The mechanisms for anticonvulsant HSS are incompletely understood but involve genetic susceptibility, with accumulation of AEDs and oxidized metabolites causing major histocompatibility complex (MHC) and non–MHC–dependent clonal activation of T cells and subsequent cytokine/chemokine production in T cells, keratinocytes, and other target cells. This review discusses the classification and possible mechanisms for anticonvulsant HSS.

Antiepileptic Drug-Induced Hypersensitivity Syndrome

Hypersensitivity syndrome (HSS) is a partially understood disorder, with serious idiosyncratic drug reactions that most commonly develop 2–6 weeks after exposure to antiepileptic drugs (AEDs), sulfonamides, nonsteroidal antiinflammatory drugs, corticosteroids, and allopurinol (1). The classification of AED-associated HSS recently has been reworked to groupings of three related disorders—Stevens–Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and anticonvulsant-induced HSS (2). Patients with SJS have fever, mucosal blistering, erythematous skin eruptions, and frequently have hepatitis or other organ involvement. TEN is similar to SJS, but patients have >30% delamination of epidermis and usually require treatment in burn units. An anticonvulsant-induced HSS denotes a subset of patients with systemic and cutaneous features of SJS and TEN but without extensive mucosal involvement or skin delamination.

Bocquet and colleagues designated a new syndrome "DRESS," which is an acronym for drug reactions with eosinophilia and systemic signs, to distinguish a systemic drug reaction with features of lymphoma (i.e., lymphocytic skin infiltration) from cutaneous drug-induced pseudolymphoma (3). Most patients with DRESS, however, otherwise have typical clinical features of severe HSS (4,5). Erythema multiforme major is an older term used to describe patients with HSS and remains grouped with HSS in in standard diagnostic (ICD9) classification. The term now usually is reserved to denote acute mucocutaneous reactions triggered by herpes simplex virus. Other serious cutaneous and systemic acute drug reactions associated with AEDs include acute fixed drug reactions, phototoxic reactions, and porphyric exacerbations.

Risks for Hypersensitivity Syndrome

The risks for AED-induced HSS range from 1 to 10 per 10,000 for phenytoin, carbamazepine, phenobarbital, lamotrigine (6–8). Although not formally studied, risks for zonisamide are probably similar, since spontaneous reports of HSS were 4.9 per 100,000 (9). HSS is not reported during monotherapy treatment with topiramate, gabapentin, or levetiracetam. HSS is reported rarely with valproic acid. Risks for HSS with oxcarbazepine administration are increased only slightly: 3–10 times the background risk for the general public, which is 0.5–6 cases per million people per year (10).

Mechanisms of Hypersensitivity Syndrome

Recent evidence suggests that AED-related HSS is due to a sequence of chemotoxic and immunologically mediated injury; however, the pathogenesis of HSS may vary somewhat among AEDs. HSS may depend more on skin and mucosal bioactivation of AEDs and on MHC-dependent clonal expansion of T cells than was previously suspected.

Spielberg and Shear showed that lymphocytes cultured from patients with prior HSS have increased rates of necrosis when the putative AED is added compared with lymphocytes taken from unexposed control patients and cultured with the same AED (2). The investigators found that lymphocyte toxicity for the aromatic amines (i.e., phenytoin, carbamazepine,

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and phenobarbital) depended on oxidation by cytochrome P-450 isozymes into reactive arene oxide metabolites. Lymphocyte toxicity was increased when epoxide hydrolase, the detoxifying enzyme that removes the reactive intermediate, was inhibited or defective. This finding suggests that HSS was partially caused by loss of detoxification capacity, which resulted in an accumulation of reactive epoxide intermediates. There is considerable evidence for this hypothesis, including the fact that rapid accumulation of AEDs or their metabolites increase risks for HSS in susceptible patients. Rapid infusion of phenytoin or rapid initiation of lamotrigine, for example, increases risks for HSS.

Loss of detoxification capacity, however, does not explain individual susceptibility to HSS. Only a small subset of patients with HSS due to aromatic AED administration have defective production of epoxide hydrolase (2). Moreover, patients without HSS often have several-fold increases in lymphocyte toxicity when their lymphocytes are cultured with carbamazepine or phenytoin and microsomal cytochrome P-450 is added. First-degree relatives of patients with phenytoin-induced HSS have rates of lymphocyte toxicity that are lower than that of relatives with HSS, but are elevated compared with unrelated control subjects intermediate. These findings suggest that rapid accumulation of reactive metabolites may trigger cellular injury in susceptible patients but does not explain HSS susceptibility.

Only recently has it been appreciated that epidermal keratinocytes and mucosal cells are major sites of oxidative and conjugative processing of drugs. A simple example of this action is the ability of grapefruit juice to inhibit CYP3A4 in intestinal mucosa; consequently, patients being administered carbamazepine may have marked increases in blood concentrations when the drug is ingested with grapefruit juice (11). The major site of drug bioactivation and injury with HSS appears to occur in skin epidermis and other target tissues (e.g., epidermal keratinocytes, mucosal cells, and hepatocytes).

The pathogenesis of HSS in epidermis is probably best illustrated for the sulphonamide, sulfamethoxazole. Reilly et al. (12) showed epidermal keratinocytes convert sulfamethoxazole into a reactive hydroxylamine intermediate. This reactive epoxide is formed in a manner similar to the formation of arene oxides by cytochrome oxidation of an aryl-amine side-chain. In culture, hydroxylamine covalently binds to keratinocytes but is cytotoxic only when keratinocytes are depleted of glutathione. The pattern is similar to the lymphocyte toxicity assay discovered for the aromatic AEDs—keratinocyte toxicity depends on drug bioactivation and loss of enzyme detoxification capacity. However, as with the aromatic amines, accumulation of reactive drug intermediates, alone, is unlikely to be sufficient to trigger HSS. Recently it was shown that sulfamethoxazole triggers T-cell–mediated responses in keratinocytes. In a patient with a bullous skin reaction, sulfamethoxazole stimulated production of T-lymphocyte clones when cultured with cytochrome P-450 (13). Hydroxylamine–keratinocyte adducts can trigger MHC-dependent clonal proliferation of T-cell lymphocytes (12). This finding suggests that individual genetic susceptibility to HSS may be mediated by MHC expression in keratinocytes and other target cells.

AEDs are likely to share similar mechanisms for HSS (14). The AED zonisamide does not appear to share cross-reactivity with sulfamethoxazole; however, it is a comparable sulfonamide and is likely to cause HSS via similar mechanisms. Naisbitt et al. showed that patients with carbamazepine-induced HSS have clonal proliferation of CD4+ or CD4+/CD8+ cells that secrete interferon-γ and are cytotoxic (15). T-cell recognition of carbamazepine was dependent on human leukocyte antigen (HLA) class II matched antigen-presenting cells. Posadas et al. (16) showed that patients with TEN, as a result of aromatic AED administration, had early activation of peripheral blood T cells with skin homing receptors (CLA-T cells). They linked epidermal injury to accumulation of T cells and cytokines in skin, including tumor necrosis factor-α. In Han Chinese patients, carbamazepine-induced SJS correlates strongly with an HLA marker: 100% (44 of 44 patients) had the human leukocyte antigen *HLA–B*1502*, while the same genetic marker was present in only 3% (3 of 101) of patients who tolerated carbamazepine and in 8.6% (8/93) of the general population (17). This association possibly explains why Chinese have a several-fold higher incidence of SJS resulting from carbamazepine administration compared to Caucasians.

Mechanisms for lamotrigine-induced HSS are less well understood than those for carbamazepine; however, they are similar structures and are likely to share mechanisms similar to sulphonamides—that is, they are likely to have drug bioactivation that triggers clonal expansion of T cells in skin, liver, and other injury sites. HLA linkages have not been performed for patients with lamotrigine-induced HSS. Valproic acid inhibits glucuronidation, the major elimination pathway for lamotrigine in humans, and studies indicate that the majority of patients with lamotrigine-related HSS also were taking valproic acid (18). The finding suggests a possible diversion of lamotrigine from glucuronidation to an oxidative elimination pathway, as found in rodents, with production of a reactive epoxide intermediate (19). However, this hypothesis remains to be demonstrated in humans, and a patient with lamotrigine-induced HSS had direct binding of T-cell receptors with lamotrigine (14). Lamotrigine binding of T cells subsequently triggered clonal production of CD4+ cells and some CD8+ cells in culture. It remains unclear, however, whether direct T-cell–receptor binding was the result of previous sensitization and whether initial lamotrigine-induced HSS reactions are MHC dependent.

The mechanisms producing HSS can be seen as a defect in the human ecological barrier system. Cytochrome enzymes are present in skin, mucosal (oropharyngeal, intestine, vagina, conjunctiva), lung, and hepatic tissue. These tissues also are sites of MHC-dependent T-cell–mediated immunity and together the oxidative and immunologic systems are adaptable to removing xenobiotics (20). MHC proteins coordinate T-cell–responses for foreign molecules, including some AEDs that are processed as antigens by keratinocytes. It remains unclear whether small molecules, such as AEDs, may bind directly to specific T-cell–receptors without prior T-cell–sensitization or drug-antigen presentation by MHC (20).

The variability in the clinical presentation of HSS, such as epidermal eruptions and mucosal blistering in SJS, epidermal necrosis and delamination in TEN, or eosinophilia in DRESS, is likely to reflect host-specific metabolic and immunologic reactions associated with T-cell–mediated responses in these tissues (14–16,20). These reactions include varying levels of cytochrome induction; MHC- and non–MHC–dependent T-cell–activation; involvement of cytotoxic CD8+ and CD4+ mediated responses; expression of adhesion and homing molecules on keratinocytes; and chemokine release with infiltration by monocytes/macrophages and eosinophils. Keratinocytes are apt to be directly involved in drug bioactivation and T-cell–mediated injury, since they express monocyte adhesion molecules; form adducts with AEDs; and secrete cytokines, such as TNF-α, and chemokines involved in immune cell migration and cell injury. (21). Possible mechanisms of AED-induced HSS, adapted from Pichler's schemata for sulfonamides (20), are illustrated in Figure 1. This figure shows MHC-mediated binding between keratinocyte–AED adducts and T cells with eventual cytotoxic T cell release of granzyme and perforin—enzymes that cause membrane perforations and apoptosis.

Hypersensitivity Syndrome Cross-Reactivity

HSS cross-reactivity for patients switching among the three aromatic amines, phenytoin, carbamazepine, and phenobarbital, is between 40% and 70% (22). This range reflects differences in the signs and severity of rash necessary to define recurring HSS. Similarly, 15–25% of patients with carbamazepine-associated rashes have cross-reactions to oxcarbazepine, detected either clinically or by in vitro lymphocyte screening; however, serious HSS cross-reactions are rare. AEDs that do not induce cytochromes and do not have cyclic amine structures generally are not associated with HSS—a factor that can help focus safety surveillance for newer AEDs.

Treating Hypersensitivity Syndrome

Patients with HSS can suffer serious epidermal scarring, mucosal inflammation, hepatic failure, pneumonitis, and with TEN, sepsis and shock. The most effective treatment for HSS is immediate discontinuation of the drug involved, along with symptomatic support with hydration and skin care. There have been no successful controlled trials for treatment of HSS, and reports vary considerably as to whether patients benefit from treatment with corticosteroids (23). Recently, several uncontrolled series suggested that treatment with high-dose intravenous immunoglobulin hastens recovery from SJS and TEN for some patients (24,25). Tan et al., for example, treated eight patients with TEN and four with SJS using high dose intravenous

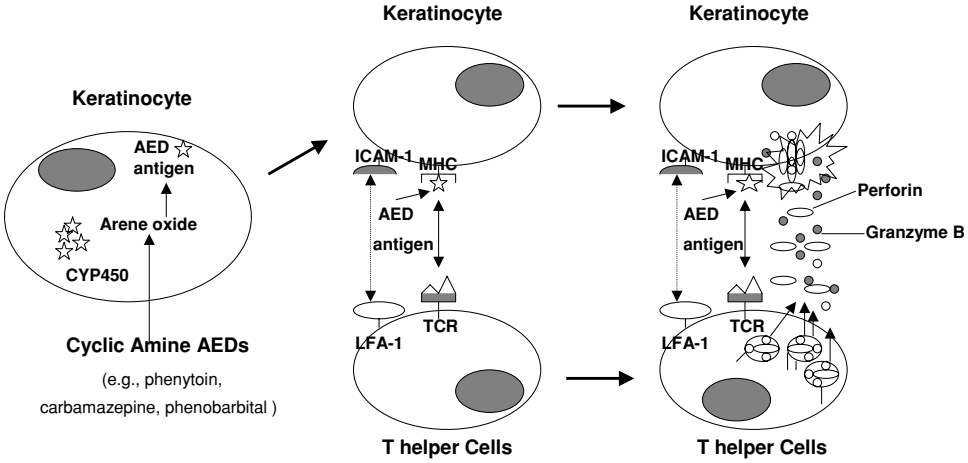

FIGURE 1. Possible stages in the development of keratinocyte injury with hypersensitivity syndrome. Cytochrome oxidation of aromatic AEDs to reactive arene oxides eventually leads to MHC-dependent presentation of AED antigen and binding with T-cell receptors. Keratinocyte toxicity may be caused directly by injury from reactive intermediates, by CD8+ T cell cytotoxicity, or by perforin and granzyme B release by T-helper (CD4+) cells. AED, antiepileptic drug; ICAM-1, intercellular adhesion molecule 1; LFA-1, leukocyte function-related antigen-1; MHC, major histocompatibility complex; TCR, T-cell receptor. Adapted from *J of Invest Derm* 2000;114(6):1164–1173 and *Ann Intern Med* 2003;139(8):683–693.

immunoglobulin (2 g/kg body weight) (26). One patient died, the remaining 11 patients recovered relatively rapidly, with initial recovery noted after 3 days of therapy. Keratinocytes secrete TNF-α in areas of blistering and epidermal injury in TEN; in a recent case report, treatment with anti-TNF-α appeared to hasten recovery for a patient with TEN (27). Visual loss, as a result of conjunctivitis and corneal scarring, is one of the most serious complications of SJS and TEN (28). Corneal injury appears to be due to keratinization of the eyelid margin, with microtrauma from blinking, and may be treated topically (29).

Conclusion

HSS is a delayed idiosyncratic drug reaction strongly linked to genetic susceptibility for T-cell–mediated responses to bioactive molecules. The efficacy of intravenous immunoglobulin for treating HSS requires evaluation; thus, the major current treatment for HSS is immediate removal of the offending drug. Future treatment for HSS may also involve reducing buildup of reactive intermediates and blocking target cell reactions, such as keratinocyte secretion of TNF-α (27). Since MHC proteins expressed by human chromosome 6 help determine whether molecules, such as AEDs, are presented as foreign antigens, it may be possible to develop a MHC library to determine individual susceptibility to HSS. An example is the previously described study of Han Chinese with antigen *HLA–B* 1502*, placing patients at risk for HSS when treated with carbamazepine. If libraries of MHC and enzyme-subtypes associated with serious drug reactions can be developed, it may be feasible to develop individual panels showing susceptibility to HSS and other serious drug reactions.

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