

Critical Review

Idiosyncratic Adverse Reactions to Antiepileptic Drugs

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Summary: Idiosyncratic drug reactions may be defined as adverse effects that cannot be explained by the known mechanisms of action of the offending agent, do not occur at any dose in most patients, and develop mostly unpredictably in susceptible individuals only. These reactions are generally thought to account for up to 10% of all adverse drug reactions, but their frequency may be higher depending on the definition adopted. Idiosyncratic reactions are a major source of concern because they encompass most life-threatening effects of antiepileptic drugs (AEDs), as well as many other reactions requiring discontinuation of treatment. Based on the underlying mechanisms, idiosyncratic reactions can be differentiated into (1) immune-mediated hypersensitivity reactions, which may range from benign skin rashes to serious conditions such as drug-related rash with eosinophilia and systemic symptoms; (2) reactions involv-

ing unusual nonimmune-mediated individual susceptibility, often related to abnormal production or defective detoxification of reactive cytotoxic metabolites (as in valproate-induced liver toxicity); and (3) off-target pharmacology, whereby a drug interacts directly with a system other than that for which it is intended, an example being some types of AED-induced dyskinesias. Although no AED is free from the potential of inducing idiosyncratic reactions, the magnitude of risk and the most common manifestations vary from one drug to another, a consideration that impacts on treatment choices. Serious consequences of idiosyncratic reactions can be minimized by knowledge of risk factors, avoidance of specific AEDs in subpopulations at risk, cautious dose titration, and careful monitoring of clinical response. **Key Words:** Antiepileptic drugs—Adverse drug reactions—Idiosyncratic effects—Toxicity—Review.

Preventing and managing adverse effects is a major challenge in optimizing antiepileptic drug (AED) therapy (Perucca and Meador, 2005). Most adverse effects of AEDs belong to the type A category (Table 1), in that they are predictable, dose dependent, and explained by the known pharmacological properties of individual agents (Loiseau, 1996). Although Type A effects can have a major impact on patients' quality of life, they are usually reversible upon dosage adjustment and they rarely require discontinuation of therapy. The situation is different with idiosyncratic type B adverse reactions, which occur unpredictably and whose pathogenesis is apparently unrelated to the known mechanisms of action of the offending drug.

Although idiosyncratic effects only account for 6–10% of all adverse drug reactions in general (Ju and Uetrecht,

2002), they are a major source of morbidity and mortality. This is especially true for AEDs, which in one survey have been found to be the class of drugs most frequently responsible for idiosyncratic reactions with a fatal outcome in children (Clarkson and Choonara, 2002). Non-life-threatening idiosyncratic adverse reactions are also a major concern, because they often require discontinuation of the offending agent with associated consequences in terms of psychological distress and potential loss of seizure control. In a recent study of 470 people with epilepsy, the proportion of patients discontinuing their first AED because of adverse events ranged from 10% to 27% depending on the prescribed drug, and some of the most common events, such as skin rashes, were idiosyncratic in nature (Kwan and Brodie, 2001).

The purpose of this article is not to provide a comprehensive review of idiosyncratic AED reactions, but to appraise their importance by discussing common manifestations, frequency of occurrence, and risk factors involved. Pathogenic mechanisms, as well as preventive and management strategies will also be discussed.

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TABLE 1. Typical features of Type A (pharmacology-related) and Type B (idiosyncratic) adverse effects of antiepileptic drugs

	Type A (pharmacology-related) effects	Type B (idiosyncratic) effects
Underlying mechanisms	A consequence of the known pharmacological actions of individual AEDs	Abnormal interaction between the drug and the individual, usually mediated by cytotoxic or immunologic effects triggered by the drug or reactive metabolites
Predictability	Usually predictable	Mostly unpredictable, though risk factors may be known (e.g., a previous history of a similar reaction with other drugs) and susceptibility tests may be available (e.g., lymphocyte toxicity assays)
Frequency and relationship with dose	Common or relatively common (>1%); incidence and severity typically increases with increasing dose (or dose titration rate) or serum AED concentration	Uncommon (<10%, and <1% for life-threatening reactions). Some effects may be related to dose or titration rate.
Time course	More common at the onset of treatment or after a dose increase, and usually promptly reversible after dose reduction; some chronic effects (e.g., weight gain, osteomalacia) may develop insidiously and are not rapidly reversible	Most commonly observed during the first few weeks of therapy.
Severity	May interfere significantly with quality of life, but they are rarely life-threatening	May range from trivial skin rashes to life-threatening reactions
Action required	Usually managed by dose adjustment	Discontinuation of the offending drug often required
Prevention	Chose AED whose adverse effect profile is predicted to be most favorable for the individual characteristics. Optimize dose carefully	Avoid (or use very cautiously) specific AEDs in high risk groups. Up-titrate drug gradually.
Examples (with putative mechanisms involved, and offending drugs)	<ul style="list-style-type: none"> • Somnolence, dizziness, fatigue, incoordination, cognitive dysfunction, mood changes (sodium channel blockade, GABAergic potentiation, and others: all AEDs) • Vitamin D deficiency, endocrine disorders, adverse drug interactions (enzyme induction: mostly CBZ, PHT, PB and PMD) • Hyponatremia and water intoxication (antidiuretic effects: CBZ and OXC) • Metabolic acidosis, paresthesias, nephrolithiasis (inhibition of carbonic anhydrase: TPM and ZNS) 	<ul style="list-style-type: none"> • DRESS (immunologic) • Skin rashes, including SJS and TEN (immunologic) • Pseudolymphoma (immunologic) • Agranulocytosis, aplastic anemia (cytotoxic, immunologic) • Liver toxicity (cytotoxic, immunologic)

For abbreviations, see text.

DEFINITION

Although the concept of “idiosyncratic” adverse reaction is intuitively simple, the diverse nature of these reactions make a precise categorization elusive and no consistent definition is found in the literature (Edwards and Aronson, 2000; Glauser, 2000; Gruchalla, 2000; Knowles et al., 2000; Jue and Utrecht, 2002; Pirmohamed and Arroyo, 2007). In fact, it is not a single characteristic that differentiates idiosyncratic reactions from other reactions but, rather, a combination of features (Table 1). For the purpose of this article, an idiosyncratic reaction will be defined as “any adverse effect that cannot be explained on the basis of the known mechanisms of action of the drug and occurs mostly unpredictably in susceptible individuals only, irrespective of dosage.” Idiosyncratic reactions as defined above include immune-mediated hypersensitivity reactions as well as adverse effects that involve an unusual nonimmune-mediated reactivity of the individual. Although teratogenicity and carcinogenicity may fall within this definition, traditionally they are classified separately and will not be discussed here.

Because of the difficulty in providing a clearer definition, many adverse reactions caused by AEDs fall within a

gray area which defies precise classification. For example, carbamazepine (CBZ)-induced precipitation of porphyric attacks in an individual with acute intermittent porphyria (AIP) may be regarded by many physicians as idiosyncratic, yet the reaction is related to a known pharmacological action of the drug (indirect interference with the delta-aminolaevulinic acid synthetase pathway) and occurs predictably in the vast majority of people with an inborn defect in porphyrin metabolism. Other examples which fall into a gray area include barbiturates-induced shoulder-hand syndrome (reflex sympathetic dystrophy) and phenytoin (PHT)-induced hirsutism and gingival hyperplasia, all of which are relatively common, yet they are not well understood mechanistically and occur unpredictably only in certain individuals irrespective of dose.

ASSESSMENT AND IDENTIFICATION

Most idiosyncratic adverse reactions have clinical manifestations that cannot go unnoticed. This, however, is not synonymous with saying that such reactions are interpreted correctly and that they are reported readily. In fact, the evaluation of idiosyncratic effects is fraught with methodological difficulties.

TABLE 2. Latency between the introduction of some antiepileptic drugs in the market and the discovery of important idiosyncratic adverse effects

	Adverse effect	Estimated incidence	Year of drug introduction	First report of adverse effect
Phenobarbital	Shoulder-hand syndrome	Up to about 30%	1912	1934
Phenytoin	Pseudolymphoma	82 cases reported in the first 20 years of use	1938	1940
Carbamazepine	Agranulocytosis	1:200,000	1963	1964
Valproic acid	Hepatotoxicity	1:35,000	1967	1977
Lamotrigine	Hepatotoxicity, often as part of DRESS syndrome	About 20 cases published to date	1991	1992
Felbamate	Aplastic anemia	1:7500	1993	1994
Topiramate	Acute closed-angle glaucoma	86 cases reported up to 2006	1996	2001
Zonisamide	Oligohidrosis	1:5000 patient years	1989	1988

For references concerning some of these effects, see text.

One difficulty relates to their rare occurrence. While reactions occurring with a frequency above 1% are usually detected in clinical trials prior to introduction of a drug in the market, those which are less common (or those which are common only in specific patients subgroups excluded from preregistration trials, or occur after prolonged exposure) may only be observed during routine clinical use. Information on their occurrence can be acquired through drug surveillance programs, such as spontaneous reports to regulatory authorities. However, because only a small fraction of unexpected reactions are reported, important adverse effects may go unrecognized for many years (Table 2).

A second problem is the difficulty in establishing cause–effect relationships in the clinical setting. A relationship may be obvious when, for example, a young woman develops rapidly progressive Stevens-Johnson syndrome (SJS) within three weeks of starting an AED. However, what conclusions would a physician draw when a young woman who had been on a combination of two AEDs for the past 7 years presents with symptoms and signs of systemic lupus erythematosus? Is that an unrelated condition, or is it a delayed idiosyncratic reaction, and if so which AED is responsible? What investigations can be done to answer these questions? Should her treatment be changed, and in what way? Establishing the causative link between drug treatment and the condition can be challenging in such cases. At times, discovery of important adverse effects is delayed because patients or their doctors discard incorrectly the plausibility of an event being drug related. For idiosyncratic effects, this is particularly likely to occur because these effects are often bizarre and, by definition, bear no relationship to the known pharmacology of the drug. A typical example is the insidious development of shoulder-hand syndrome during chronic treatment with phenobarbital (PB) or primidone (PMD): although in some populations the incidence of this condition may be close to 30% (De Santis et al., 2000), 22 years elapsed between the introduction of PB and the recognition of this adverse effect (Bériel and Barbier, 1934).

When rare adverse reactions are reported, determining their incidence (a major consideration in assessing the risk/benefit ratio of treatment) can be very difficult, due to uncertainties about reporting rates, number of exposed patients (denominator), and ascertainment of cause–effect relations (Edwards and Aronson, 2000). Prospective case-control or cohort studies may be needed to determine whether an adverse event is drug related, and the magnitude of the risk. Similar considerations apply to identification of risk factors.

In the light of the above considerations, it is understandable that for most serious idiosyncratic reactions we still lack information about true incidence, risk factors, and optimal management strategies. Given the delay with which many of these reactions are discovered, this information is even less for AEDs introduced in the last few years.

UNDERLYING MECHANISMS

Classification of mechanisms and role of reactive metabolites

In view of the different chemical and pharmacological properties of the causative agents, and the heterogeneity of the clinical presentations, it is not surprising that idiosyncratic reactions involve a broad range of mechanisms, and more than one mechanism may be involved in any single event. A classification which has didactic value, but may not be always easily applicable to individual cases, distinguishes three broad mechanisms: (1) direct cytotoxicity, whereby a drug or a metabolite cause direct cellular damage; (2) immune-mediated hypersensitivity reactions; (3) off-target pharmacology, whereby a drug or a metabolite interact directly with a system other than that for which the drug is intended.

Many idiosyncratic reactions are initiated by reactive drug metabolites, which bind covalently to macromolecules and either cause direct cell damage or trigger an immune response (Guengerich, 2006). Reactive metabolites often have a very short half life, which explains why their sites of formation, and the liver in particular, are

also the major targets of tissue damage (Ju and Uetrecht, 2002). Extrahepatic damage may be seen when reactive metabolites are formed at multiple sites, when long-lived metabolites travel from the liver to other organs, or when a locally initiated immune response spreads systemically.

There are many examples of AEDs producing idiosyncratic reactions via formation of toxic metabolites. For instance, the ability of CBZ to cause liver toxicity, blood dyscrasias, skin reactions and multiorgan hypersensitivity syndromes seems to be related, at least in some cases, to reactive metabolites such as carbamazepine-2,3-epoxide (Madden et al., 1996) and an iminoquinone which is sufficiently long-lived to be detectable in the urine of patients treated with this drug (Ju and Uetrecht, 1999). Covalent binding of CBZ metabolites to proteins has been observed in vitro using both liver microsomal and myeloperoxidase activation systems (Naisbitt et al., 2003b), whereas in vivo most of the reactive epoxides are detoxified to dihydrodiols by microsomal epoxide hydrolase 1 or to glutathione conjugates by glutathione transferase (Lillibridge et al., 1996). A reactive arene oxide intermediate is also known to be formed during the conversion of PHT to its primary para-hydroxy-phenyl-metabolite (p-HPPH): although this intermediate has never been isolated from plasma or urine, presumably because it is too unstable, it is considered to be involved in PHT-induced idiosyncratic reactions affecting the liver, the blood and other organs (Browne and Leduc, 2002). Similar reactive intermediates produced by cytochrome P450 (CYP) enzymes may play a role in hypersensitivity reactions associated with PB (Knowles et al., 2000) and lamotrigine (LTG) (Maggs et al., 2000; Schaub and Bircher, 2000). In the case of LTG, most of the drug is cleared by glucuronide conjugation and only minor amounts are converted by CYP enzymes to an arene oxide intermediate. Since valproic acid (VPA) inhibits LTG glucuronidation, in patients comedicated with VPA a higher percentage of the LTG dose is converted through the alternative CYP-mediated pathway to the oxide intermediate, which may explain the greater susceptibility of these patients to LTG-induced skin rashes (Anderson, 2002). As discussed in the next section, the hepatotoxicity of VPA and felbamate (FBM) is also related to formation of toxic metabolites.

Variability in the rate of formation and detoxification of reactive metabolites can explain why some reactions only occur in susceptible individuals (Glauser, 2000). Susceptible individuals may produce excessive amounts of reactive metabolites, for example, as a result of intake of high doses of the drug and/or abnormally high activity of bioactivating enzymes, or they may have impaired cellular defense mechanisms, for example, abnormally low levels of detoxifying enzymes such as epoxide hydrolases or substrates such as glutathione (Johnson, 2003; Lee et al., 2004; Gerber and Pichler, 2006; Guengerich, 2006). Variability in response is also related to the fact that not all covalent

binding to macromolecules is pathogenic, and some may even play a protective role by sequestering and/or inactivating reactive species. In particular, covalent binding to serum proteins is less likely to lead to idiosyncratic reactions than binding to membrane proteins (Ju and Uetrecht, 2002; Seguin and Uetrecht, 2003).

Direct cytotoxicity

Some idiosyncratic reactions appear to be caused by a direct cytotoxic effect of the drug or its metabolites, without pathogenetic involvement of the immune system (Ju and Uetrecht, 2002). As far as AEDs are concerned, the best example of such reactions is probably VPA-induced hepatotoxicity. While a direct role of the parent drug in causing or contributing to liver damage cannot be excluded, there is experimental and clinical evidence for a direct cytotoxic effect of two metabolites, namely 4-en VPA and its β -oxidation derivative 2,4-dien VPA (Sadique et al., 1997). The formation of 4-en VPA is largely catalyzed by CYP2C9, whose activity is inducible and is higher in young children (Johnson, 2003), which may explain why the risk of VPA-induced liver toxicity is highest in infants comedicated with enzyme inducing AEDs. 4-en VPA is further metabolized in mitochondria to 2,4-dien VPA (Walgren et al., 2005), which is a reactive species capable of causing inhibition of β -oxidation and mitochondrial dysfunction.

Considerable evidence indicates that FBM-induced liver and bone marrow toxicity is mediated by the reactive metabolite atropaldehyde (Thompson et al., 1996, 1997). Both atropaldehyde and another FBM metabolite, alcohol carbamate, have been shown to inhibit glutathione transferase and to cause cytotoxicity in human hepatocytes (Kapetanovic et al., 2002). Likewise, FBM metabolites have been shown to form covalent adducts with human serum albumin (Walgren et al., 2005). Since the half-life of the atropaldehyde precursors CPPA (3-carbamoyl-2-phenylpropionic acid) and 4-hydroxy-5-phenyl-(1,3)-oxazinan-2-one is in the order of hours, it has been suggested that these FBM metabolites may travel from the liver and release atropaldehyde to other sites such as the bone marrow (Dieckhaus et al., 2001a; Walgren et al., 2005). Whether immune mechanisms play an important role in the toxicity of FBM metabolites is unclear, but their involvement is suggested by experimental studies on the immunogenic potential of reactive FBM metabolites (Popovic et al., 2004) and by the observation that patients with a history of hypersensitivity reactions and autoimmune disease are at greater risk of developing FBM-induced aplastic anemia (Pellock et al., 2006). Evidence for a key role of reactive metabolites in FBM toxicity provides a rationale for the development of fluorofelbamate, a FBM analogue that is not converted to atropaldehyde and is currently under clinical evaluation as a potentially safer AED (Bialer et al., 2007).

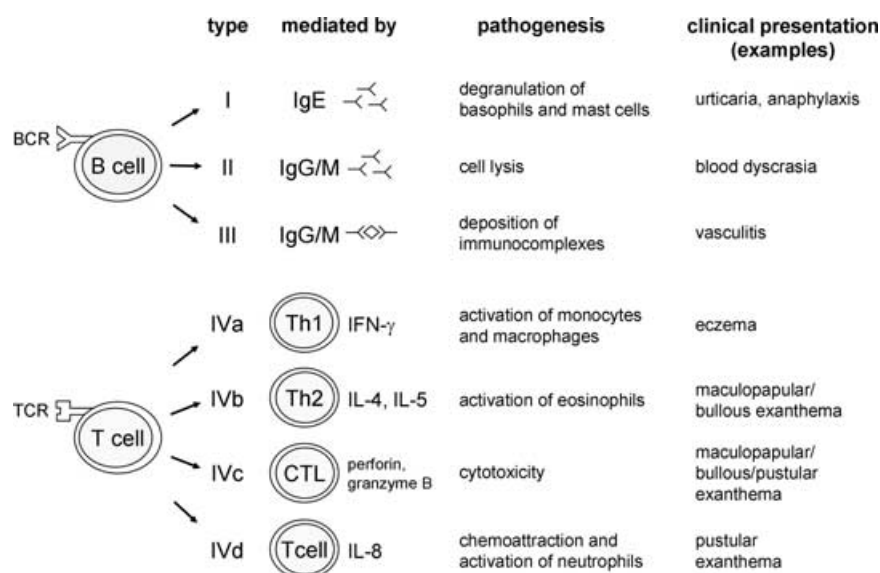


FIG. 1. Classification of reactions responsible for immune-mediated hypersensitivity to drugs according to Coombs and Gell (1968), as updated by Pichler (2003). The different subtypes of type IV reactions may yield similar clinical phenotypes. BCR, B-cell receptor; IFN, interferon; IL, interleukin; TCR, T-cell receptor; Th1, T helper type 1 lymphocyte; Th2, T helper type 2 lymphocyte; and CTL, cytotoxic T lymphocyte.

Immune-mediated hypersensitivity

Immune-mediated hypersensitivity reactions, which result from an evolutionary derangement of the main defense mechanisms against infectious agents, involve abnormal humoral- or cell-mediated responses. AEDs may initiate these responses by interacting with cells of adaptive immunity through incompletely understood mechanisms. Fig. 1 summarizes known types of immune-mediated drug reactions, and their main clinical correlates. These reactions can be broadly divided into two classes, namely those involving an interaction of B cells, which are able to recognize antigenic determinants through B cell receptors (BCRs), and those whereby T cells recognize, through T-cell receptors (TCRs), molecules that have been phagocytized, modified and presented by antigen presenting cells (APCs). These two arms of adaptive immunity are cooperative, since B cells can act as APCs or recognize processed antigens, and T cells can act as helper cells towards B cells.

To overcome the limitation of being too small to trigger immune responses, the drug or a metabolite need to behave as haptens (from Greek *haptein*, to fasten), for example, they have to covalently bind and modify a macromolecule (usually, a self-peptide) to become immunogenic (Landsteiner and Jacobs, 1935; Park, 1998). Alternatively, electrophilic metabolites can react with nucleophilic groups on proteins without covalent binding (Park et al., 1987). The drug-peptide complex, which is recognized as foreign, is thus processed by APCs which, in turn, can trigger B- or T cell-mediated responses.

Type I, II, and III reactions involve activated B cells (plasma cells) which produce antibodies directed against antigenic determinants located on the drug itself or generated by an interaction of the drug (or a reactive metabolite) with macromolecules of the host organism (Coombs and Gell, 1968). In type I reactions, which include anaphylactic reactions (a rare event with AEDs) and some

urticarioid skin rashes, an antigen to which the organism is sensitized binds to IgE antibodies at the surface of mast cells and basophils, resulting in their degranulation and release of inflammatory factors. Among the released factors, histamine is responsible for vasodilation and leakage of fluids in the interstitial space, with chemoattraction of T helper 2 (Th2) cells (Bryce et al., 2006) and upregulation of proallergic, Th2-related cytokines. Type II reactions, conversely, include complement-mediated cytotoxic effects triggered by an interaction of IgG and/or IgM antibodies with antigenic determinants at the surface of target cells in the tissue affected by the reaction, such as the blood or the bone marrow (Parr and Doukas, 1999). In Type III reactions (serum sickness-like reactions), the interaction of the antigen with IgG and/or IgM antibodies results in the formation of immunocomplexes, whose accumulation in the affected tissue results in vasculitic changes and tissue damage (Calabrese and Duna, 1996).

Type I to III reactions seem to occur less frequently than previously suspected. In fact, many immune-mediated reactions to AEDs, including the large majority of those affecting the skin, consist in delayed (type IV) hypersensitivity reactions mediated by different T cell subpopulations (Krauss, 2006). Histopathological examination of these skin lesions shows that CD4+ T cells predominate in dermis, and CD8+ T cells in epidermis (Barbaud et al., 1997). Interestingly, these subpopulations include phenotypes, such as T helper 1 (Th1) cells, with predictable protective roles in allergy (Woodfolk, 2006). These observations weaken the "Th1/Th2 paradigm" (Maggi, 1998), in which T cells and related mediators such as interleukins (ILs) and interferons (IFNs) are differentiated into proallergic (Th2 cells, IL-4, and IL-5) and antiallergic (Th1 cells, IFN- γ , and IL-12) subtypes.

The discovery of T cells with specific reactivity for antibiotics (Yawalkar et al., 2000), CBZ (Naisbitt et al.,

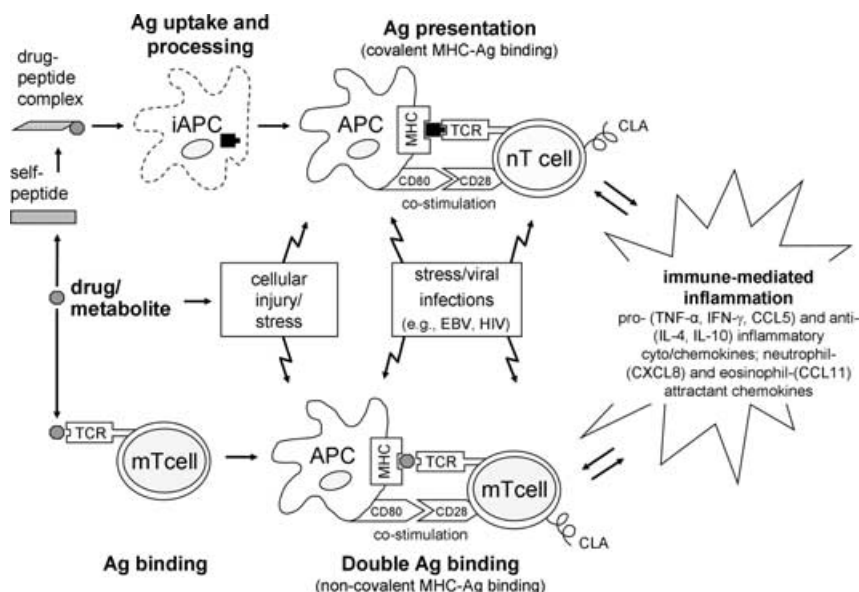


FIG. 2. Possible pathways of T-cell priming and activation in immune-mediated hypersensitivity reactions to drugs. To trigger immune-mediated inflammation, the drug or a metabolite has to interact with one of the indicated pathways. The classical pathway involves covalent binding to a macromolecule (self-peptide) and antigen processing and presentation (upper part). An alternative pathway exploits noncovalent antigen binding after antigen recognition by crossreactive T cells. Additional "danger signals" from the environment, which act on antigen presenting cells (e.g., substances derived from a cytotoxic effect of the drug or a metabolite) or simultaneously on antigen presenting cells and T cells (e.g., a concomitant viral infection with production of cyto/chemokines), may be needed to trigger immune-mediated inflammation. Locally released cyto/chemokines foster the amplification of the immune response. T cells may express the skin-homing receptor CLA (cutaneous lymphocyte antigen) (see text for details). Ag, antigen; APC, antigen presenting cell; CCL, chemokine (C-C motif) ligand; CD28 and CD80: T-cell activation antigens CD28 and CD80; CXCL, chemokine (C-X-C motif) ligand; iAPC, immature APC; IL, interleukin; MHC, major histocompatibility complex; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; nT cell, naive T cell; mT cell, memory T cell; TCR, T cell receptor; and TNF, tumor necrosis factor.

2003a), and LTG (Naisbitt et al., 2003b) in the blood of patients hypersensitive to the respective drug helped in identifying the mechanisms by which delayed hypersensitivity reactions occur (Fig. 2). Beside the classical model of APC-T cell interaction, which is characterized by a covalent binding between major histocompatibility complex (MHC) molecules and the exposed peptide, followed by priming of naive T cells, an alternative mechanism by which delayed hypersensitivity may occur is outlined by the so-called "p-i concept," that is, pharmacological interaction with immune receptors (Pichler, 2002). According to this concept, drugs or metabolites can interact first with T cells and then, through noncovalent binding, with APCs, without previous uptake and intracellular processing. In this case the reaction does not involve naive T cells but, instead, crossreactive memory T cells, which can account for allergic reactions without antecedent drug exposure. The "p-i concept" can also explain drug-induced skin reactions that occur a few hours after administration (Christiansen et al., 2000; Gerber and Pichler, 2006) and were previously ascribed to IgE-mediated responses. Experiments on mouse T-cell hybridomas transfected with drug-specific human TCRs seem to confirm the "p-i concept" (Schmid et al., 2006). However, further confirmations from in vivo studies are awaited, especially on the postulated existence of TCRs with double specificity for a

drug and a self-peptide. The reason why the skin is the organ most commonly affected by these reactions is unclear, but studies on cutaneous lymphomas suggest that Langerhans cells, which act as APCs in the skin, play a pivotal role in the epidermotropism of lymphocytes (Twersky and Nordlund, 2004). The presence of skin-homing molecules, such as cutaneous lymphocyte antigen (CLA), has been reported in peripheral blood mononuclear cells of patients with hypersensitivity reactions to both CBZ (Leyva et al., 2000) and LTG (Naisbitt et al., 2003a).

Irrespective of the pathogenetic pathway, the role for APCs in immune-mediated hypersensitivity reactions is crucial (Pirmohamed et al., 2002). These cells contribute to inflammation through production of specific cytokines and chemokines that can boost or even suppress the process, depending on the role of co-stimulatory stimuli. Boosting stimuli involve an interaction of APCs with additional, incompletely defined environmental "signals." Such signals can possibly derive from cells that have been damaged by the drug or a metabolite, or from the immune activation that follows infections or nonspecific "cellular stress" (in the latter case, T cells are also involved as targets) (Fig. 2). The occurrence of boosting stimuli, which is part of the "danger hypothesis" (Uetrecht, 1999; Matzinger, 2002), would explain both the low incidence of hypersensitivity reactions in the general population as

well as the increased risk of such reactions under stressful conditions (surgery, viral infections, certain associated disorders). Some of these mechanisms may be reciprocally reinforcing. For example, evidence has been provided that the AED-induced syndrome of drug-related rash with eosinophilia and systemic symptoms (DRESS) may trigger latent virus reactivation and massive nonspecific immune-inflammatory responses, leading to sensitization to other drugs administered during the course of the reaction (Gaig et al., 2006).

The immune-inflammatory responses triggered by the processes described above are polymorphic and show predominant infiltration by specific T cell subtypes (particularly CD4⁺ though CD8⁺ may be prevalent in severe clinical presentations), and scattered monocytes and eosinophils (Pichler et al., 2002). The cellular heterogeneity mirrors the complex and overlapping production of cytokines and chemokines (Fig. 2). Eotaxin (CCL11) and IL-5 act as key factors as attractants and activators of eosinophils. IL-8, a neutrophil-attracting chemokine that can also be produced by T cells, is particularly up-regulated in SJS, where it contributes to the severe clinical manifestations and intense leukocytosis (Greenberger, 2006). The role of regulatory T cells, which are important in autoimmunity and allergy, has been little studied in immune-mediated hypersensitivity to AEDs. These cells can exert suppressive functions in hapten-allergic individuals, mainly through production of IL-10 (Girolomoni et al., 2004). Advances in knowledge regarding their role in drug-related hypersensitivity bear promise for application in specific immunotherapies.

Off-target pharmacology

Certain idiosyncratic adverse reactions cannot be explained by the mechanisms discussed above. In such cases, the pathogenesis must involve alternative events which, while diverse at molecular level, share as a common feature an unusual interaction of the drug (or a metabolite) with the host organism. By definition, these reactions cannot be explained by the primary pharmacological properties of the offending agents, and one must consider or postulate the presence in the affected organism of specific peculiarities, which result in unexpected effects.

On some occasions, the mechanism underlying these reactions are explained by genetically or disease-mediated alterations in susceptible individuals. Examples include the precipitation of hemolytic attacks by several therapeutic agents in patients with 6-phosphate dehydrogenase deficiency (favism) (Mehta et al., 2000), or the induction of porphyric attacks by a variety of AEDs in patients with AIP (Hahn et al., 1997). In most cases, however, the pathogenic mechanism is unknown, and these reactions stand out for their unpredictability, low frequency and, at times, dramatic presentation. Many unusual CNS adverse effects fall within this category: examples include the pre-

cipitation of choreoathetoid reactions by PHT (Zaccara et al., 2004), Parkinsonian symptoms by VPA (Masmoudi et al., 2006), and severe psychiatric reactions by AEDs not commonly associated with such effects (Wong et al., 1997). While the classification of some of these reactions as idiosyncratic may be questioned, their unpredictability, low frequency, occurrence (at times) at low dosages and uncertain pathogenesis, possibly related to interaction with altered neuronal circuitries, are reminiscent of idiosyncratic mechanisms.

RISK FACTORS

Genetic factors

The occurrence of similar idiosyncratic reactions to AEDs in identical twins and in families suggests a genetically determined predisposition (Edwards et al., 1999), possibly with an autosomal pattern of inheritance. Siblings of patients who had immune-mediated idiosyncratic reactions to an aromatic AED such as PHT, CBZ, PB, and PMD may have an up to 25% probability of experiencing a similar reaction when exposed to a drug of the same class, suggesting that counseling of family members is crucial for clinical management (Shear and Spielberg, 1988).

To date, evaluation of genetically determined alterations in AED metabolism as predisposing factors to idiosyncratic reactions has yielded conflicting results. Impaired detoxication of reactive metabolites has been demonstrated *in vitro* in peripheral blood mononuclear cells from patients with hypersensitivity reactions to PHT and CBZ and their siblings (Gennis et al., 1991). However, potential genetic defects altering the structure or function of epoxide hydrolase 1, an enzyme that detoxifies epoxide metabolites, could not be identified in individuals with CBZ-induced idiosyncratic reactions (Green et al., 1995). Lee and coworkers (2004) reported that PHT-induced cutaneous reactions were associated with a polymorphism of the CYP2C9 gene, which codes for a major enzyme involved in the conversion of PHT to pHPPH. A heterozygous CYP2C9*3 variant allele was found in 3 of 10 patients with such reactions. Since the CYP2C9*3 allele codes for a CYP enzyme with reduced activity, this observation questions the role of reactive pHPPH precursors in the pathogenesis of PHT-induced hypersensitivity.

Interesting results have been obtained from investigations on genes that control immune-inflammatory responses. Pirmohamed et al. (2001) reported that a polymorphism in the promoter region (position -308) of the tumor necrosis factor (TNF)- α gene may act as a predisposing factor for CBZ hypersensitivity, although the polymorphic allele, being part of the TNF2-DR3-DQ2 haplotype, could not be associated with the predisposition. The polymorphic TNF2 variant allele is considered to lead to higher TNF α production, which, in turn, could sustain early pathogenetic events in serious skin reactions.

More recently, an association has been found between serious CBZ-induced hypersensitivity reactions and the heat shock protein (HSP)70 gene cluster (Alfirevic et al., 2006a). However, the association may not be causative, but merely reflect linkage disequilibrium with another closely located gene. Interestingly, HSP70 genes code for proteins that are upregulated under stress, and can thus be involved at various stages (e.g., antigen processing, inflammation, cell damage) of immune-mediated hypersensitivity.

Results obtained in a Han Chinese population, but not confirmed in whites, suggest that the human leukocyte antigen (HLA)-B*1502 allele is strongly associated with CBZ-induced SJS and toxic epidermal necrolysis (TEN), but not with CBZ-induced maculopapular reactions or DRESS (Chung et al., 2004; Hung et al., 2006). Because HLA genes code for proteins involved in antigen presentation, the HLA-B*1502 allele could play a primary role in the pathogenesis of SJS and TEN. Hung and coworkers (2006) also showed that CBZ-associated maculopapular eruptions were associated with the HLA-A* 3101 variant allele, while CBZ hypersensitivity syndrome was associated with polymorphisms in the motilin gene, which is located terminal to the MHC class II genes. Overall, these data suggest that genetic susceptibility may account for the much higher incidence of CBZ-induced SJS in Chinese compared with whites. The role of ethnicity in these reactions is emphasized by recent data confirming that an association between CBZ-induced SJS and the HLA-B*1502 allele is present in Asians (Lonjou et al., 2006), but does not appear to occur in whites (Alfirevic et al., 2006a; Lonjou et al., 2006).

As research in this area advances rapidly, it is likely that genetic testing will become an important tool to identify patients at risk for idiosyncratic reactions.

Age

The risk of many idiosyncratic reactions is age-dependent. This is in part a consequence of age-related differences in drug metabolism (Perucca, 2006). In particular, the reduction in glucuronide conjugation in young infants, and the faster rates of CYP-mediated reactions in infants and children compared with adults may result in the increased production of reactive metabolites and increased susceptibility of idiosyncratic effects in younger age groups (Johnson, 2003).

The best example of an idiosyncratic reaction that occurs more frequently in children than in adults is provided by LTG-induced serious and nonserious skin rashes (Messenheimer et al., 1998; Hirsch et al., 2006). In particular, the incidence of SJS in children started on LTG has been estimated to be as high as 1:100, compared with 1:1,000 in adults (Messenheimer et al., 2000), even though these high frequencies may reflect early use of high initial dosing rates and the risk may have decreased with cur-

rently recommended dosing schemes (Mockenhaupt et al., 2005).

Young age has been identified as a major risk factor for VPA-induced hepatic injury, for which the highest risk is recorded in infants below 2 years (Dreifuss et al., 1987). This might be related to a higher prevalence of predisposing conditions such as inborn errors of metabolism in infants, as well as to pharmacokinetic factors such as accumulation of the toxic metabolite 4-en-VPA, whose concentration is negatively correlated with age (Kondo et al., 1992).

Idiosyncratic reactions also tend to occur at a relatively high frequency in old age. In a controlled trial in elderly patients with new onset epilepsy, as many as 19% of those exposed to CBZ withdrew because of skin rashes, despite use of a low dose (100 mg/day) in the first two weeks (Brodie et al., 1999). The susceptibility of the elderly to idiosyncratic reactions can be explained by a number of factors, including age-related pharmacokinetic alterations (Perucca, 2006), interactions with highly prevalent comedications, altered homeostatic mechanisms, and occurrence of comorbid conditions predisposing to adverse reactions (Perucca et al., 2006).

Starting dose and titration rate

A common misconception is that allergic reactions share no relationship with dose. In fact, immune-mediated reactions only occur when a critical dose threshold is reached. Drugs that produce their therapeutic effects at low doses (below 10 mg/day) are unlikely to be associated with immune-mediated reactions (Seguin and Uetrecht, 2003). The rate of dose titration is also important: as a general rule, the risk of allergic reactions is decreased when treatment is started at a low dose and is increased gradually, possibly because slow titration may allow desensitization to occur.

A relation between starting dose (and titration rate) and the incidence of cutaneous reactions is particularly evident for LTG (Messenheimer et al., 1998), CBZ and PHT (Wilson et al., 1978; Chadwick et al., 1984). For example, in LTG monotherapy trials in adults, rash occurred in 6.1% of patients when the dose in the first treatment week was <31 mg/day, and in 20.5% when the dose was between 62.5 and 125 mg/day (Messenheimer et al., 1998). The dose and titration rate dependency of immune-mediated idiosyncratic reactions provides the rationale for desensitization procedures, which involve rechallenging hypersensitive individuals with extremely low doses that are then increased very slowly under careful clinical surveillance (Knowles and Shear, 2000). Because these procedures are not without risk, they should only be attempted by experienced physicians and only when no alternative treatments exist and when the nature of the hypersensitivity reaction previously exhibited by the patient was not life threatening.

The mechanisms by which starting at a low dose and increasing it slowly can reduce the incidence of immune-mediated hypersensitivity reactions are incompletely understood. For IgE-mediated reactions, antigen-specific mast-cell desensitization may be involved (Naclerio et al., 1983; Woo et al., 2006). For T cell-mediated reactions, a key role may be played by dendritic cells, whose ability to either facilitate or inhibit immunogenic responses is also dependent on the antigen dose (Roncarolo et al., 2006). A direct role of regulatory T cells in the dose dependency of the response, however, cannot be excluded (Girolomoni et al., 2004).

The dependence of idiosyncratic reactions from starting dosage and titration rate is not confined to hypersensitivity reactions. In particular, the risk of many idiosyncratic CNS reactions can be minimized by gradual dose titration (Perucca et al., 2001). Gradual titration may prevent such reactions by allowing the development of pharmacodynamic tolerance through adaptative changes at the level of molecular drug targets (Löscher and Schmidt, 2006). Another mechanism by which slow titration minimizes CNS (or CNS-mediated) reactions is by permitting early detection of subtle or prodromal signs which limit the extent of further dose increases, thereby preventing exposure of susceptible patients to dosages associated with prominent manifestations.

Disease-related factors

Rheumatoid arthritis, systemic lupus erythematosus, Hashimoto thyroiditis, panhypogammaglobulinemia, idiopathic thrombocytopenic purpura, high serum antinuclear antibody titers, and a history of cytopenia or hypersensitivity to other AEDs are considered as risk factors for FBM-induced aplastic anemia (Pellock et al., 2006). Systemic lupus erythematosus, other immune system disorders, corticosteroid therapy and a family history of serious rashes are also risk factors for hypersensitivity reactions to other AEDs (Pichler, 2003).

Infectious diseases can be associated with a higher frequency of allergic drug reactions the best example being hypersensitivity reactions to cotrimoxazole and other chemotherapeutic agents in patients with HIV infection (Pirmohamed and Arroyo, 2007). HIV infection may also be a risk factor for hypersensitivity reactions to AEDs (Pichler, 2003), which is intriguing because HIV-infected patients are typically anergic, T-cell depleted and, therefore, expected to be less prone to immune-mediated hypersensitivity. A possible explanation for the higher incidence of hypersensitivity reactions in these patients may be found in the occurrence of HIV-related glutathione deficiency, which could impair the efficiency of processes involved in detoxification of reactive metabolites (Chosidow et al., 1994), even though there are studies that failed to identify an association between drug hypersensitivity and glutathione levels in HIV-infected patients (Eliasiewicz

et al., 2002). There is also evidence for a complex relationship between other viral infections and AED-induced DRESS (Ogihara et al., 2004; Gaig et al., 2006): in particular, the finding of high antihuman herpes virus (HHV)-6 IgG/IgM concentrations and HHV-6 DNA copies in the serum of five patients with CBZ-induced DRESS suggests that this virus might be reactivated by DRESS, and simultaneously play a pathogenetic role in this condition (Descamps et al., 2001). Reactivation of HHV-7, Cytomegalovirus and/or Epstein-Barr virus may also occur in association with hypersensitivity reactions (Seishima et al., 2006). Although these herpes viruses at times may also be detected in peripheral blood mononuclear cells from healthy individuals, there is evidence that immunologic processes involved in drug hypersensitivity can lead to viral reactivation which probably contributes to development and chronicity of inflammatory tissue damage (Pichler, 2003). With respect specifically to the role of viral infections in hypersensitivity reactions to AEDs, however, it should be stressed that a cause-effect relationship has not been ascertained.

The risk of VPA-induced liver toxicity is increased in patients with various metabolic disorders, including urea cycle defects, organic acidurias, multiple carboxylase deficiency, mitochondrial or respiratory chain dysfunction, cytochrome *aa₃* deficiency in muscle, pyruvate carboxylase deficiency, and pyruvate dehydrogenase complex deficiency (Willmore and Pellock, 1997). Patients with GM₁ gangliosidosis type 2, spinocerebellar degeneration, Friedreich ataxia, Lafora body disease, Alpers-Huttenlocher disease, and myoclonic epilepsy with ragged red fiber (MERRF) disease are also more susceptible to VPA hepatotoxicity (Willmore and Pellock, 1997; König et al., 1999). In a review of 23 cases of fatal VPA liver toxicity, about one-half of the affected patients had neurodegenerative diseases such as Friedreich ataxia, progressive myoclonic epilepsies, or ornithine carbamoyl transferase deficiency (König et al., 1999). In the case of Friedreich ataxia, the toxicity of VPA might be explained by impaired activity of antioxidant enzymes, resulting in increased sensitivity to oxidative stress (Tozzi et al., 2002). Patients with urea cycle disorders, particularly those with ornithine transcarbamylase deficiency, are also at high risk for other manifestations of serious VPA toxicity, including death associated with severe hyperammonemic encephalopathy (Oechsner et al., 1998).

Cerebral damage may predispose to some idiosyncratic central nervous system (CNS) reactions. For example, basal ganglia damage and mental retardation are frequently reported in patients with PHT-induced choreoathetosis, and patients with severe myoclonic epilepsy may also be particularly vulnerable to this complication (Zaccara et al., 2006). Patients with cerebral damage and intellectual disability may also be more prone to VPA-induced encephalopathy (König et al., 1999).

Other factors

Idiosyncratic reactions to a given drug occur at a higher frequency in patients with a history of similar reactions to other medications, particularly structurally related compounds. The best example is the apparent crossreactivity for hypersensitivity reactions to aromatic AEDs (Ruble and Matsuo, 1999). In a retrospective assessment of 633 patients who had 1875 exposures to 14 AEDs, 14 had rashes from two or more drugs. Of 17 patients who had a rash from PHT, 10 (58%) also had a rash from CBZ; likewise, 10 of 25 patients (40%) who had a rash from CBZ also had a rash from PHT. Four of five patients who had a rash from PB also developed a rash on PHT or CBZ (Hyson and Sadler, 1997). Apparent cross-sensitivity between aromatic AEDs and LTG is also not uncommon: in a recent multivariate analysis of factors influencing the probability of cutaneous reactions to LTG, a history of rash with another AED was the strongest predictor of a LTG rash (13.9% vs. 4.6%; OR = 3.62) (Hirsch et al., 2006). In children with a rash attributed to another AED, 18.2% experienced a rash on LTG, whereas in adults without a rash from another AED, 3% experienced a LTG-associated rash (Hirsch et al., 2006). Whether these findings reflect true cross-sensitivity or simply the fact that, as suggested by a large epidemiological study on sulfonamide hypersensitivity (Strom et al., 2003), some individuals are predisposed to allergic reactions, remains to be clarified. In any case, VPA or benzodiazepines are safer alternatives in patients who had a rash associated with aromatic AEDs (Hyson and Sadler, 1997), although there are patients who are hypersensitive to both aromatic and nonaromatic AEDs other than LTG (Chan and Tan, 1997).

Comedication can influence susceptibility to idiosyncratic reactions. Concomitant treatment with VPA, in particular, increases the risk of LTG-induced hypersensitivity, particularly when the LTG starting dose is not reduced and its titration rate slowed appropriately (Messenheimer et al., 1998). Enzyme inducing AEDs increase the incidence of VPA-induced liver toxicity, pancreatitis, hyperammonemia and encephalopathy (Johannessen and Johannessen, 2003). There are also concerns that the association of pivaloyl-conjugated antibiotics with VPA may be hazardous, because these agents can determine carnitine depletion via independent and possibly additive mechanisms. This interaction could have been at play in a woman who developed hyperammonemic encephalopathy after pivmecillinam was added to VPA (Lokrantz et al., 2004).

Malnutrition, intellectual disability and use of the ketogenic diet are often associated with reduced carnitine stores and may therefore increase the risk of VPA-induced hyperammonemic encephalopathy and hepatotoxicity (De Vivo et al., 1998). The interaction between VPA and the ketogenic diet may also involve inhibition of fatty acid oxidation by VPA, with potential risk of mitochondrial dysfunction (De Vivo et al., 1998), although there is no

agreement on whether VPA treatment should be considered as a relative contraindication to the use of the diet (Freeman et al., 2006).

MOST COMMON IDIOSYNCRATIC REACTIONS TO AEDs

Cutaneous reactions

Cutaneous manifestations of hypersensitivity are the most common idiosyncratic reactions to AEDs and range from mild urticarioid/maculopapular eruptions to potentially life-threatening DRESS, SJS and TEN.

DRESS

DRESS is a severe acute drug reaction characterized by fever, skin eruption, eosinophilia, atypical lymphocytosis, arthralgia, lymphadenopathy and multiorgan involvement (blood dyscrasias, hepatitis, nephritis, myocarditis, thyroiditis, interstitial pneumonitis and encephalitis) (Peyrière et al., 2006). Other features may include facial edema, exudative tonsillitis, pharyngitis, mouth ulcers, hepatosplenomegaly, flu-like symptoms, myopathy, and disseminated intravascular coagulation (Schlienger and Shear, 1998). This syndrome was first described in association with AEDs and it was therefore named anticonvulsant hypersensitivity syndrome (Shear and Spielberg, 1988). DRESS is observed most frequently with PHT (2.3–4.5 cases per 10,000 exposures) and CBZ (1.0–4.1 cases per 10,000) (Tennis and Stern, 1997). Several cases have been reported with LTG, with features comparable to those observed in patients exposed to aromatic AEDs, apart from a somewhat higher incidence of severe skin rashes and a lower frequency of eosinophilia and lymphadenopathy (Schlienger et al., 1998). The clinical manifestations of DRESS typically occur within 1–12 weeks after initiating therapy and usually resolve when the offending agent is discontinued (Gogtay et al., 2005). A fatal outcome is reported in 10–40% of affected individuals (Peyrière et al., 2006).

The symptoms of DRESS have been recently reviewed in more than 400 patients, half of whom collected within the French Pharmacovigilance database (Peyrière et al., 2006). Almost 50% of these were treated with AEDs: in 80–100% of such cases, skin lesions, typically characterized by a diffuse maculopapular inflammatory rash and erythroderma, were reported. A few patients had skin lesions typical of SJS, TEN, or erythema multiforme. Fever was present in 60–100% of patients; eosinophilia was very common (58–100%) with PB, PHT, and CBZ, and rare (0–21%) with LTG. Liver abnormalities (mainly hepatocellular necrosis) were observed in more than 60% of cases. Renal and lung involvement were infrequently associated with AEDs. Heart abnormalities (pericarditis, tachycardia) were seen in less than 10% of cases associated with PHT and CBZ.

SJS and TEN

SJS and TEN are bullous reactions consisting in a rapidly developing blistering exanthema with purpuric macules and target-like lesions, accompanied by mucosal involvement and skin detachment. They are classified according to the degree of skin detachment, which is less than 10% in SJS, and more than 30% in TEN. A skin detachment between 10% and 30% is named SJS–TEN overlap syndrome. Systemic involvement is variable, and may affect the gastrointestinal tract in some cases, and respiratory airways in one third of cases. Leukocytosis is a relatively common finding at onset (Kamaliah et al., 1998), and may be associated with a clonal expansion of drug-specific CD8+ cytotoxic lymphocytes (Chave et al., 2005). In advanced cases, the presence of neutropenia, lymphopenia and thrombocytopenia is indicative of a poor prognosis (Revuz et al., 1987). High serum concentrations of liver enzymes are occasionally reported (Chave et al., 2005). Mortality relates to the extent of skin involvement and is higher in the older age groups. The prognosis is better when the offending agent has a short half-life and is withdrawn no later than the day when blisters or erosions first occur (Garcia-Doval et al., 2000).

In the general population, the annual incidence of SJS and TEN ranges from 0.4 to 1.2 cases per million (Chan et al., 1990; Chave et al., 2005). It is estimated that about 80% of TEN cases and 50% of SJS cases are caused by drugs (Chang et al., 2006). Over 100 medications have been implicated in the development of these disorders, and AEDs are among those most frequently involved (Chang et al., 2006). In the first few years since its introduction in the market, LTG was associated with a relatively high risk of SJS, particularly in children in whom incidence was estimated to be as high as 1:100 (Messenheimer et al., 2000). These reactions were probably related in part to use of high starting dosages and a fast titration. More recent data suggest that the risk of SJS and TEN during the first two months of therapy is between 1 and 10 per 10,000 new users of CBZ, LTG, PHT and PB, and consistently lower for VPA (Tennis and Stern, 1997; Mockenhaupt et al., 2005). Occasional cases of SJS or TEN have been reported with other AEDs (Table 3).

It has been suggested that the incidence of SJS and other cutaneous reactions caused by PHT and, possibly, other AEDs, is increased in patients with brain tumors who undergo cranial irradiation (Khafaga et al., 1999). The findings, however, are not univocal and altered immune function related to the underlying disease, or chemotherapy, could also be pathogenetic factors in these reactions (Mamon et al., 1999). Duncan and coworkers (1999) described a 53-year-old man who was started on PB in association with radiation therapy, and developed multiple skin lesions that were limited to the sites of irradiation. These observations are especially important in view of the fact that some physicians often initiate AED prophylaxis in seizure-free patients with brain tumors, despite lack of adequate evidence supporting this practice.

Nonserious skin rashes

Benign isolated drug-related eruptions are spotty, non-confluent and nontender, and are usually described as morbilliform or maculopapular in appearance. They typically occur between day 5 and week 8 after the start of therapy, facial involvement is usually minor and there is no facial or neck edema. This rash is relatively common with aromatic AEDs such as PB, PHT, CBZ, with a frequency ranging from 5% to 15% (Chadwick et al., 1984). In 40–60% of cases the rash recurs when a patient is switched from one aromatic AED to another, indicating a high level of crossreactivity (Hyson and Sadler, 1997; Krauss, 2006). Oxcarbazepine (OXC), the keto analogue of CBZ, is associated with a lower incidence of hypersensitivity reactions than CBZ, though in 30% of patients who develop a rash on CBZ the rash recurs after switching to OXC (Jenson et al., 1986).

LTG is structurally different from aromatic AEDs, but it may also cause skin rashes: in a recent analysis of double-blind studies in bipolar disorder, 8.3% of patients started on LTG developed a rash, though a 6.4% rash rate was also reported in patients randomized to placebo. In epilepsy trials, the incidence of rash was consistently higher when LTG was added on to VPA than when it was added on to enzyme inducing AEDs (19.5% vs. 6.7%, respectively) (Messenheimer et al., 1998). This is largely a consequence of excessively high starting dosages and fast titration schemes used in earlier studies, and lower rash rates in all patients groups are reported with currently recommended dosing schemes (Hirsch et al., 2006). A history of rash on other AEDs, and age below 13 years are also risk factors for LTG-induced rashes (Hirsch et al., 2006).

Skin rashes may occur with all other EDs, but their frequency is generally lower than that observed with aromatic AEDs or LTG.

Hematological reactions

In drug-induced blood dyscrasias, the offending agent causes reduced survival and apoptosis of bone marrow cells, leading to selective or global suppression of hematopoiesis. Apoptotic death of progenitor cells can result from deprivation of survival factors (Wickremasinghe and Hoffbrand, 1999), but it may also be induced by immune reactions. In the latter case, it is often a reactive metabolite that binds covalently to a bone marrow protein, and triggers an immune response.

The most serious blood dyscrasia is aplastic anemia, which occurs in the general population with an incidence of two to six cases in one million (Thomson, 1996). The AED with the by far the highest potential for causing aplastic anemia is FBM, which has been associated with a risk rate of 1 in 5,000 or 10,000 (Kaufman et al., 1997). Whether screening for risk factors such as in-

TABLE 3. A selection of serious idiosyncratic reactions associated with individual AEDs

	SJS/TEN ^a	Liver toxicity	Pancreatitis	Aplastic anemia	Agranulocytosis	Systemic lupus erythematosus
Carbamazepine	*	*	*	**	**	*
Ethosuximide	*	*	—	*	*	*
Felbamate	*	**	*	**	**	*
Gabapentin	*	*	—	—	—	—
Lamotrigine	**	*	*	*	—	—
Levetiracetam	—	*	*	—	—	—
Oxcarbazepine	*	*	—	—	—	—
Phenobarbital	*	*	—	—	*	*
Phenytoin	*	*	—	*	*	*
Pregabalin	—	—	—	—	—	—
Primidone	*	*	—	—	*	*
Tiagabine	*	—	—	—	—	—
Topiramate	*	*	*	—	—	—
Valproic acid	*	**	**	—	—	*
Vigabatrin	—	*	*	—	—	—
Zonisamide	*	*	—	*	*	—

The table is based on information sourced from Battino et al. (2000) and supplemented with information from the latest available U.S. prescribing information monographs and from the *Drug Information Monographs, Clinical Pharmacology*, Version 6.09 (updated September 2006), Gold Standard, Tampa, FL (<http://cponline.hitchcock.org>). For some of the reactions reported, information is insufficient to draw definitive conclusions about causality. An asterisk (*) indicates that the specified reaction has been reported for that drug. A double asterisk (**) identifies reactions associated with a warning box in the U.S. prescribing information monographs. — indicates that the reaction has not been reported based on the sources of information stated above.

^aSJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

creased urinary production of atropaldehyde and HLA typing could reduce the risk of FBM-induced aplastic anemia is unclear (Pellock, 1999). FBM is not the only AED that can cause aplastic anemia. In a recent study, 16 (9.2%) of 173 patients with aplastic anemia were found to be receiving AEDs, none of which was FBM, whereas only 0.8% of patients in the control population received these drugs, which translates into a ninefold increase in risk (Handoko et al., 2006). Rare cases of aplastic anemia have been associated with CBZ, PHT, ETS and VPA (Seip, 1983; Yanez-Rubal et al., 2002; Blain et al., 2002; Handoko et al., 2006). The incidence of CBZ-induced aplastic anemia has been estimated at between 1:50,000 and 1:200,000 exposed patients (Pellock et al., 2006).

Agranulocytosis has an incidence of 1.6–3.5 cases per million inhabitants per year and a fatality rate around 10% (Medina and George, 2001). In a recent population-based study, CBZ was found to be associated with an increased risk of developing this condition, with an odds ratio (OR) of 10.96 (95% confidence interval, 1.17–102.64) (Ibanez et al., 2005). PHT was also associated with an increased risk, which could not be quantified precisely in the primary analysis because of insufficient exposure data. Other AEDs have also been occasionally associated with agranulocytosis (Battino et al., 2000).

Pure red cell aplasia is rare, and sporadic cases have been described with PHT, CBZ and VPA (MacDougall et al., 1982; Tagawa et al., 1997). A LTG-induced erythroblastopenic crisis, which resolved after treatment with folinic acid, occurred in a 29-year-old woman with Diamond-Blackfan anemia (Pulik et al., 2000).

Pseudolymphoma syndrome is a rare condition that was initially associated with PHT (Saltzstein and Ackerman,

1959), but can occur with other AEDs, particularly those with an aromatic structure (Choi et al., 2003). It may be part of the DRESS syndrome spectrum, and it may mimic histologically other lymphomas, including mycosis fungoides. Therefore, it may be misdiagnosed as malignant lymphoma, leading to unnecessary chemotherapy (Choi et al., 2003).

Sporadic cases of thrombocytopenia, probably immune mediated, have been reported with CBZ, PHT, LTG, FBM, PMD, and tiagabine (TGB) (Parker, 1974; Ney et al., 1994; Holtzer and Reisner-Keller, 1997; Willert et al., 1999; De Berardis et al., 2003; Goraya and Viridi, 2003; Ural et al., 2005). Due to their dose dependency and relatively high incidence at serum drug concentrations in the upper range (Beydoun et al., 1997), VPA-induced thrombocytopenia and abnormal platelet function cannot be regarded as idiosyncratic and will not be discussed here. Likewise, macrocytosis and anemia related to folate deficiency caused by enzyme inducing AEDs are not idiosyncratic in nature.

Reactions affecting the liver and pancreas

Hepatotoxicity

The liver is exposed to high concentrations of drugs during the absorptive phase and is also the primary organ responsible for drug metabolism. Therefore, it is particularly vulnerable to drug toxicity (Table 3). Hepatotoxicity may be part of the spectrum of DRESS, particularly with aromatic AEDs, or it may occur in isolation. In the latter case, the reaction may be caused by immune-mediated mechanisms or by direct cytotoxic damage (Kaplowitz, 2004).

Aromatic AEDs have been recognized as a cause of severe immune-mediated liver toxicity since 1950 (Reynolds et al., 1972). Hepatotoxicity from these AEDs typically develops shortly after initiating treatment (usually 4 weeks, with a range of 1–16 weeks). Characteristic features include fever, rash, eosinophilia, and autoantibodies, and there is rapid recurrence on rechallenge (Kaplowitz, 2005). The pathological substrate is usually consistent with an immune-mediated reaction with granulomatous infiltration of the liver (Dreifuss and Langer, 1987). There may also be cholestatic injury and jaundice, often caused by damage to cholangiocytes. Cholestatic features seem to be more common with CBZ than with PHT. The exact incidence of liver toxicity associated with aromatic AEDs is unknown: with CBZ, the risk has been estimated at 16 cases per 100,000 treatment years (Askmark et al., 1990). Many of these events are associated with DRESS, and in these cases severe liver involvement is indicative of a poor prognosis (Syn et al., 2005).

About 20 cases of severe LTG-induced liver toxicity have been reported to date (Overstreet et al., 2002; Mecarelli et al., 2005; Chang et al., 2006; Fix et al., 2006). The condition has been described often within the context of DRESS, and sometimes in association with multisystem organ failure and disseminated intravascular coagulation (Schaub et al., 1994). LTG-induced acute liver failure is usually reversible after drug discontinuation, although in at least one case progressive hepatic necrosis led to death (Overstreet et al., 2002).

VPA and FBM cause the greatest concerns with potential liver toxicity. The incidence of fatal VPA-induced hepatotoxicity varies in relation to age and associated therapy. The highest risk (1:500) is in children younger than 2 years on polytherapy, particularly in the presence of an inborn metabolic disorder. In older patients, the risk has been estimated at 1:12,000 with polytherapy and 1:37,000 with monotherapy (Dreifuss et al., 1989). In recent years, the overall incidence of VPA-induced fatal liver toxicity seems to have decreased (Bryant and Dreifuss, 1996), possibly due to greater awareness of the disorder, avoidance of the drug in the highest risk groups and rapid discontinuation when the earliest symptoms appear. Severe VPA-induced hepatic damage usually manifests initially with nausea, vomiting, lethargy, abdominal pain, increased seizure frequency, and coma (Dreifuss et al. 1987, 1989). The condition occurs most commonly during the first 3 months of treatment, and very rarely after more than 6 months (Dreifuss and Langer, 1987). Accurate assessment of residual hepatic function is based on measurement of prothrombin time more than liver enzymes and bilirubin levels. Hyperammonemia occurs commonly. The typical histological features include cellular necrosis and microvesicular steatosis detectable primarily in

the periportal zone (Zimmerman and Ishak, 1982; Konig et al., 1994, 1999). Intrahepatic cholestasis and proliferation of bile ducts may also be present (Konig et al., 1999). These findings suggest a direct toxic action of VPA and/or its metabolites (Gopaul et al., 2003), and differ substantially from those associated with liver toxicity caused by aromatic AEDs, which typically include manifestations of immune-mediated hypersensitivity and eosinophilia. Prompt institution of L-carnitine treatment has been reported to improve survival in patients with VPA-induced liver toxicity (Bohan et al., 2001), and the recommendation has been made that intravenous high dose L-carnitine be given as early as possible in these cases (De Vivo et al., 1998).

The risk of fatal hepatic failure due to FBM is estimated at approximately 1 per 26,000 to 34,000 exposures (Pellock et al., 2006). To date, at least 23 cases have been reported, including five deaths (Pellock and Brodie, 1997). Patients usually present with nausea, vomiting, lethargy and evidence of hepatic dysfunction and eosinophilia, which typically appear 4 to 25 weeks after initiation of therapy. Histology reveals submassive to massive necrosis and moderate inflammatory infiltrates (O'Neil et al., 1996). The mechanism of FBM-induced liver toxicity is not clearly understood but may depend on the formation of reactive toxic metabolites, including 3-carbamoyl-2-phenylpropionaldehyde and atropaldehyde (Thomson et al., 1996; Kapetanovic et al., 2002). There is evidence that aldehydes generated from FBM can induce liver damage via a cytotoxic mechanism, whether through direct interaction with critical cellular macromolecules or indirect interference with cellular detoxification mechanisms (Kapetanovic et al., 2002). Immune-mediated mechanisms, however, may also be involved, as suggested by the observation that atropaldehyde irreversibly inhibits the GSTM1-1 isoform of glutathione transferase, whose alkylation could trigger an immunological reaction (Dieckhaus et al., 2001b). Popovic and coworkers (2004) found that administration of 3-carbamoyl-2-phenylpropionaldehyde, which in vivo converts to atropaldehyde in approximately 30 s, determines an immune response in experimental models.

Pancreatitis

Pancreatitis is a rare complication of VPA therapy, with an estimated incidence of 1: 40,000 (Genton and Gelisse, 2002). The condition may develop at any time, but most commonly occurs during the first year of treatment or after an increase in dosage. Age less than 20 years, polytherapy, chronic encephalopathy and hemodialysis are possible risk factors (Ford et al., 1990; Asconape et al., 1993). Initial symptoms include abdominal pain, nausea, vomiting, diarrhea, and anorexia. Patients on VPA who present with abdominal pain and vomiting should have their serum

amylase levels checked. However, in a recent study 25% of children with VPA pancreatitis had serum amylase within the reference range (Grauso-Eby et al., 2003). Moreover, high serum amylase concentrations have been reported in nearly 20% of adults taking VPA without pancreatitis (Balén et al., 2000), and high amylase levels in the absence of symptoms do not require VPA discontinuation if other pancreatic enzymes (elastase, lipase, trypsin) are normal (Pirmohamed and Arroyo, 2007). In comparison to serum amylase, serum lipase is a more specific index of pancreatic damage, and remains elevated for longer time (Grauso-Eby et al., 2003), which make the determination of serum lipase preferable. Mortality rate in VPA-induced pancreatitis has been estimated at 21%, with the worst prognosis in cases with associated liver failure (Binek et al., 1991). Rechallenge often results in recurrence of the pancreatitis (Grauso-Eby et al., 2003), and is strongly contraindicated. Occasional cases of pancreatitis have also been reported with other AEDs (Table 3).

CNS reactions

Adverse CNS effects of AEDs are not usually regarded as idiosyncratic, even when the underlying mechanism is not understood. Yet, a number of CNS reactions stand out for their peculiar presentation, rare occurrence irrespective of dosage, and dependence on individual susceptibility, all of which are suggestive of an idiosyncratic nature.

In some cases, these reactions resemble type A effects, but stand out for their prominent severity and unpredictable occurrence at low dosages in a small subset of individuals: one example is the inability of some patients to tolerate low dosages of one or more AEDs because of exceptionally marked sedative effects. In other instances, it is the quality rather than the intensity of the reaction which is suggestive of an idiosyncratic nature, one example being the severe psychiatric reactions occasionally triggered by AEDs even in individuals who do not have a history of psychiatric disorders.

Additional examples of idiosyncratic CNS reactions include: (1) VPA-induced encephalopathy, which may range from a confusional state to stupor and coma (Zaccara et al., 1984), and even reversible pseudo-atrophy of the brain (Guerrini et al., 1998), with or without Parkinsonian symptoms (Armon et al., 1996); (2) dysknetic movements induced by PHT (Harrison et al., 1993) and other AEDs (Lombroso, 1999; Zaccara et al., 2006); and (3) nonepileptic myoclonus caused by gabapentin (GBP) or pregabalin (PGB) (Reeves et al., 1996; Huppertz et al., 2001). These unusual adverse reactions may reflect alterations in neuronal circuitries in the brain: for example, a dysfunction of dopaminergic circuitries resulting in increased dopaminergic activity in the basal ganglia may play a role in the pathogenesis of AED-induced tics (Okada et al., 1997).

Other reactions

Systemic lupus erythematosus

AEDs which have been reported to induce or activate systemic lupus erythematosus include CBZ and, with a lesser frequency, PHT, ETS, VPA, LTG, and other AEDs (Drory and Korczyn, 1993; Battino et al., 2000). AED-induced systemic lupus erythematosus may not be easily differentiated from the idiopathic form of the disorder. Features which are suggestive of a drug-mediated pathogenesis include: (1) absence of symptoms or other evidence of the disease before initiation of AED therapy; (2) remission within weeks after discontinuation of the putative offending drug; and (3) presence in serum of antihistone antibodies without high titers of antibodies against double-stranded DNA (Verma et al., 2000). Symptoms include musculo-skeletal complaints, fever, pleuro-pulmonary involvement and, infrequently, renal, neurological, or vasculitic involvement. In general, symptoms and serological changes appear more than 1 year and, at times, several years after initiation of the causative drug (Toepfer et al., 1988; Knowles et al., 2000).

Ocular reactions

Topiramate (TPM) can induce in rare cases ocular reactions, including acute secondary angle-closure glaucoma, acute bilateral myopia, and suprachoroidal effusions (Fraunfelder et al., 2004). The most frequent of these is acute secondary angle-closure glaucoma, of which 81 cases were reported up to 2002 (Fraunfelder et al., 2004). Blurred vision is often the presenting symptom and the condition is reversible if the drug is discontinued immediately. Underlying mechanisms are not fully understood, but they seem to be related to the sulfonamide moiety (Craig et al., 2004; Fraunfelder et al., 2004).

Visual field defects caused by vigabatrin (VGB) cannot be regarded as idiosyncratic because of their high prevalence and relationship with dose and duration of exposure.

Miscellanea

AED-induced idiosyncratic reactions may affect every organ and system, either within the context of DRESS or in isolation. Examples of reactions which may result from exposure to various AEDs include: (1) pneumonitis and bronchiolitis; (2) granulomatous interstitial nephritis and tubulo-interstitial nephritis; (3) immune-mediated myocarditis and pericarditis; (4) immunodeficiency syndromes with recurrent infections and panhypogammaglobulinemia; and (5) precipitation of porphyric attacks in AIP patients (Battino et al., 2000).

Reactions that seem to be more specifically, though not exclusively, associated with individual AEDs include VPA-induced Fanconi syndrome (Watanabe, 2005), barbiturates-induced Dupuytren contraction (Matsson et al., 1989) and shoulder-hand syndrome (De Santis et al., 2000), zonisamide (ZNS)-induced oligohidrosis

(Low et al., 2004) and VPA-induced hair-loss (McKinney et al., 1996).

PREVENTION, EARLY IDENTIFICATION AND MANAGEMENT

Prevention

Although idiosyncratic reactions are by definition unpredictable, a number of actions can be taken to minimize their occurrence.

The most important step is to consider carefully the adverse effect profile of individual medications before starting or changing treatment. When more than one drug is expected to be efficacious in a given epilepsy syndrome, the tolerability profile, which includes the risk of idiosyncratic reactions, is a major determinant of drug selection. Irrespective of the drug chosen, initiation of treatment at a low dose and gradual dose titration further ensure that the risk of adverse reactions is minimized.

In determining preference for a specific treatment, assessment of risk factors in the individual is mandatory. In certain conditions associated with a high risk of serious idiosyncratic reactions, the use of specific AEDs may be contraindicated, as for VPA in infants with inborn metabolic disorders predisposing to liver toxicity. Medical history, including familial history, is an important part of risk assessment, because it can provide important clues about risk factors. Given the familial occurrence of some idiosyncratic reactions, counseling of family members is also a component of preventive strategies (Knowles et al., 2000).

When a risk factor is identified, an understanding of the underlying mechanisms is important for correct management. For example, a history of immune-mediated hypersensitivity to a sulfonamide can be an argument against the preferential use of structurally related agents such as TPM and ZNS, while a history of an allergic reaction to PHT is indicative of probable cross sensitivity with other aromatic AEDs and possibly LTG. In general, a history of serious immune-mediated hypersensitivity reactions justifies the preferential use of AEDs with a low allergenic potential such as GBP, LEV, PGB, clobazam, TGB, VPA and, possibly, TPM.

In subjects considered to be at high risk for hypersensitivity reactions to a drug for which no safer alternatives exist, tests for predicting individual reactivity, such as skin tests (Lammintausta and Kortekangas-Savolainen, 2005a) or in vitro laboratory tests such as lymphocyte cytotoxicity (Shear and Spielberg, 1988) or lymphocyte proliferation (Descotes, 2006) assays may be considered. However, none of these tests has full predictivity, partly because they only assess certain mechanisms, which may not be necessarily those implicated in the specific individual, and partly because some idiosyncratic reactions are mediated by metabolites or degradation products which may not be

formed under the conditions of the test (Gruchalla, 2000). In practice, with the current wide array of structurally unrelated AEDs, these tests are generally not needed to establish the optimal drug choice.

Early identification and diagnosis

For many idiosyncratic reactions, particularly life-threatening hypersensitivity, early identification is important because recovery is dependent on prompt removal of the offending agent. The key strategy for early recognition is to ensure that patients are informed about potential adverse effects of the prescribed AED and instructed to recognize and report heralding symptoms and signs. Such symptoms may include a skin rash, bruising, bleeding, severe malaise, lethargy, nausea, vomiting, jaundice, abdominal pain, infection, and deterioration in seizure control. The appearance of any such symptoms justifies bringing forward any scheduled visit, and some will require immediate medical attention.

Regular follow-up visits with careful history and clinical examinations may facilitate early recognition of many reactions. Package inserts of AEDs include recommendations about laboratory monitoring, and for some high risk drugs, most notably FBM (and VPA in the early age groups), it is wise to follow them, even though their value in reducing mortality and serious morbidity is unproven. In general, intensive monitoring of blood chemistry and hematology parameters is unwarranted (Camfield and Camfield, 2006). Camfield et al. (1989) calculated that testing every patient with epilepsy in North America for blood counts and aspartate aminotransferase three times each year will cost more than \$400 million annually, without a clear evidence of significant benefits. Three prospective studies involving repeated laboratory tests in a total of 1541 patients (Mattson et al., 1985, 1992; Camfield et al., 1986) came to the conclusion that routine screening is neither cost-effective nor of significant value for asymptomatic patients. In particular, blood leukocyte counts as low as $2000/\mu\text{l}$ occur in at least 10% of patients treated with CBZ and PHT, are usually transient, and do not predict the occurrence of aplastic anemia or agranulocytosis (Willmore and Pellock, 1997). Similar considerations apply to moderately high serum liver enzymes or an isolated high serum amylase in patients treated with VPA.

When should routine laboratory monitoring be done? Reasonable indications include (1) before starting treatment (or adding a new AED), to establish a baseline against which to interpret any subsequent change in clinical status; (2) in high risk groups; (3) in patients with impaired ability to communicate; and, most importantly, (4) in the presence of early symptoms or signs possibly prodromal of an adverse reaction (Willmore and Pellock, 1997; Camfield and Camfield, 2006). In the latter event, more specialized tests (e.g., liver and renal enzymes,

serum amylase and lipase, blood ammonia, and immunological tests such as complement 3 and 4 concentrations, or antinuclear antibodies) may be required depending on the nature of the suspected incipient reaction (Gruchalla, 2000). In patients who develop an apparently single-organ hypersensitivity syndrome, the full gamut of laboratory tests should be done to exclude multiorgan involvement (Knowles et al., 2000).

A definitive diagnosis of the nature of a suspected idiosyncratic reaction is based on careful history and physical examination, in addition to laboratory investigations as indicated by the clinical presentation. A causative diagnosis, however, may be difficult and relies on assessing the temporal relationship between initiation of treatment (or a dose increase) and appearance of symptoms, similarities with adverse reactions previously reported for the suspected drug, and recovery after discontinuation (Gruchalla, 2000). While it is tempting to go rapidly to the conclusion that a reaction was drug induced, alternative etiologies must be considered: for example, about 50% of cases of SJS are not drug related, being caused mostly by infectious agents (Gruchalla, 2000). If in doubt, or when investigations would involve potentially harmful delay, the suspected medication should in any case be withdrawn, particularly when this is crucial for recovery of potentially serious conditions.

Confirmatory diagnosis can be important in selected cases, to avoid the situation whereby a patient is labeled as "hypersensitive" to an AED that, in fact, did not cause the reaction. In particular, only a minority of nonserious cutaneous reactions are allergic in origin and will reappear after the next exposure (Lammintausta and Kortekangas-Savolainen, 2005a). Rechallenge remains the only conclusive method to confirm causality, and may be appropriate for certain reactions (e.g., many idiosyncratic effects affecting the CNS) that do not involve immune-mediated hypersensitivity or cytotoxicity. In general, however, rechallenge is rarely justified, because its risks outweigh benefits in most patients, particularly those who experienced serious reactions (Rieder, 1997). Skin tests such as prick and patch tests have been used to assess whether a previous reaction to an AED was caused by immune-mediated hypersensitivity (Lammintausta and Kortekangas-Savolainen, 2005a; Gaig et al., 2006), but their usefulness is limited by the fact that many hypersensitive patients are not identified by such tests (Alanko, 1993; Troost et al., 1996; Knowles et al., 2000; Lee et al., 2004). In vitro tests such as lymphocyte proliferation assays are primarily research tools, and they have been associated with variable sensitivity rates (Shear and Spielberg, 1988; Troost et al., 1996; Rieder, 1997), possibly related to the lack of standardization. Drug provocation tests, involving rechallenge with low and gradually increasing doses of the suspected medication under strict medical surveillance, have been used to confirm the etiology of hypersensitivity reactions in cases

of diagnostic uncertainties, such as negative or dubious responses at skin tests (Aberer et al., 2003; Lammintausta and Kortekangas-Savolainen, 2005b). These tests should never be performed in patients who experienced serious reactions, and even in other patients they are not free from significant risks. Moreover, their reliability in identifying hypersensitive subjects is less than desirable, and their application so far has been mostly confined to testing antimicrobial agents (Aberer et al., 2003).

Because of the above considerations, in vivo or in vitro testing for immune-mediated AED hypersensitivity is rarely conducted. If these tests are performed, results should be interpreted cautiously. If the test turns out to be positive, it is generally unwise to rechallenge the patient with that drug. On the other hand, a negative test result (particularly when the predictive value of such result is not known, which is often the case) does not exclude the possibility of a drug reaction, and rechallenge should be done only when absolutely necessary and under close medical control (Gruchalla, 2000). Rechallenge, in any case, should not be attempted when the patient had experienced a serious reaction, particularly when this showed features typical of cytotoxicity (e.g., VPA-induced liver toxicity) or immune-mediated hypersensitivity (e.g., SJS or TEN) (Knowles et al., 2000).

Management

Given the diverse nature of idiosyncratic reactions, management strategies vary depending on the characteristics of the condition. A number of general rules, however, may be summarized.

Serious reactions (or reactions potentially evolving into severe or life-threatening conditions) require immediate discontinuation of the offending agent. To reduce the risk of recurring seizures or status epilepticus, it is often appropriate to substitute another AED considered to be reasonably safe in the specific context. In patients with hypersensitivity reactions to an aromatic AED, other aromatic anticonvulsants and LTG should be avoided, and agents with a low allergenic potential such as benzodiazepines, LEV and GBP are probably safe. Depending on the clinical presentation, TPM and VPA may also be safe, but they are less suitable for fast titration and VPA, being an inhibitor of epoxide hydrolase, may delay the detoxification of residual reactive metabolites.

The value of corticosteroids in the management of immune-mediated hypersensitivity reactions is controversial (Table 4), though most physicians elect to start prednisone at a dose of 1–2 mg/kg if symptoms are severe (Knowles et al., 2000; Arroyo and de La Morena, 2001). Symptomatic and supportive therapy may be indicated based on the clinical presentation. Patients with specific organ involvement need to be managed by the appropriate specialist. Patients with SJS and TEN in particular should be preferably managed in a burn center to ensure adequate

TABLE 4. Management of AED-induced immune-mediated idiosyncratic reactions

- Prompt recognition of the reaction and withdrawal of the offending drug are essential management steps.
- Most patients need a complete blood count and biochemistry (including thyroid function tests) for the evaluation of internal organ involvement. Such tests should be repeated at 3 months. Additional investigations (e.g., chest radiograph, bone marrow or skin biopsy) may be indicated depending on clinical presentation.
- Patients with drug rash with eosinophilia and systemic symptoms (DRESS) require hospitalization for symptomatic and supportive therapy. Patients with Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) should be preferentially managed in burn units.
- Treatment with corticosteroids is advisable, controversial or contraindicated, depending on the condition. Other treatments (e.g., immunoglobulins, immunosuppressants, organ transplantation, etc.) should be considered depending on clinical presentation.
- An appropriate AED should replace the withdrawn AED, to prevent recurrence of seizures and status epilepticus. AEDs expected to be involved in cross-reactivity reactions or to aggravate the underlying pathology should be avoided.
- Patients with serious hypersensitivity reactions should not be rechallenged. The value of patch tests and in vitro tests for assessing causality and predicting risk of recurrence is limited.

supportive management in terms of wound care, hydration, nutritional support, and prevention of infection and other complications (Letko et al., 2005). In general, prophylactic antibacterials are not recommended in these patients, and many authors advise against the use of steroids due to increased risk of infection and sepsis (Ruble and Matsuo, 1999).

The implications of in vivo and in vitro tests for the assessment of causality have been discussed above. Only when no suitable therapeutic alternatives exist, and only in patients who experienced reactions that are not life-threatening, oral challenge may be considered in a setting which allows timely detection and treatment of potential severe adverse effects. Desensitization procedures have been successfully applied, mostly in patients with nonserious hypersensitivity reactions confirmed or suspected to be IgE mediated. These involve initial administration of very low dosages, to be increased gradually under close medical control over a period of many weeks (Solensky, 2006). Examples of starting dosages applied successfully in these procedures include 1 mg/day CBZ (Hermle and Spitzer, 1993), 1 mg/day PHT (Itomi et al., 2007), and 0.1 mg/day LTG (Besag et al., 2000). The state of immunological unresponsiveness induced by these procedures continues as long as the drug is given and resolves within days after cessation of drug delivery.

CONCLUSIONS

AEDs as a therapeutic class are commonly involved in idiosyncratic adverse reactions, some of which can be life-threatening. Although no AED is free from the potential of inducing these reactions, the magnitude of risk and the nature of the possible reactions vary from one drug to another, a consideration that impacts on treatment choices. Although idiosyncratic adverse reactions are unpredictable, their occurrence or their serious consequences can be minimized by knowledge of risk factors, avoidance of specific AEDs in populations at special risk, cautious dose titration, and careful monitoring of clinical response and, if appropriate, laboratory parameters. Genetic and immunologic tests may become available in the future to recognize patients susceptible to developing specific reactions.

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