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# Anticonvulsant Hypersensitivity Syndrome

## Incidence, Prevention and Management

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## Abstract

Although the anticonvulsant hypersensitivity syndrome was first described in 1950, confusion still abounds regarding the syndrome. The triad of fever, rash and internal organ involvement occurring 1 to 8 weeks after exposure to an anticonvulsant heralds this rare (1 in 1000 to 10 000 exposures) but serious reaction. Aromatic anticonvulsants [phenytoin, phenobarbital (phenobarbitone) and carbamazepine] are the most frequently involved drugs; however, there have also been several cases of anticonvulsant hypersensitivity syndrome associated with lamotrigine.

Fever, in conjunction with malaise and pharyngitis, is often the first sign. This is followed by a rash which can range from a simple exanthem to toxic epidermal necrolysis. Internal organ involvement usually involves the liver, although other organs such as the kidney, CNS or lungs may be involved. Hypothyroidism may

be a complication in these patients approximately 2 months after occurrence of symptoms.

The aromatic anticonvulsants are metabolised to hydroxylated aromatic compounds, such as arene oxides. If detoxification of this toxic metabolite is insufficient, the toxic metabolite may bind to cellular macromolecules causing cell necrosis or a secondary immunological response. Cross-reactivity among the aromatic anticonvulsants may be as high as 75%. In addition, there is a familial tendency to hypersensitivity to anticonvulsants.

Discontinuation of the anticonvulsant is essential in patients who develop symptoms compatible with anticonvulsant hypersensitivity syndrome. A minimum battery of laboratory tests, such as liver transaminases, complete blood count and urinalysis and serum creatinine, should be performed. Corticosteroids are usually administered if symptoms are severe. Patients with anticonvulsant hypersensitivity syndrome should avoid all aromatic anticonvulsants; benzodiazepines, valproic acid (sodium valproate) or one of the newer anticonvulsants can be used for seizure control. However, valproic acid should be used very cautiously in the presence of hepatitis. There is no evidence that lamotrigine cross-reacts with aromatic anticonvulsants. In addition, family counselling is a vital component of patient management.

Anticonvulsant hypersensitivity syndrome is a rare but potentially life-threatening syndrome that occurs after exposure to an anticonvulsant, most commonly the aromatic anticonvulsants phenytoin, carbamazepine or phenobarbital (phenobarbitone).[1-9] Moreover, cross-reactivity among the aromatic anticonvulsants is reported to be as high as 75%; this may explain why some patients' symptoms continue to progress or re-occur after switching to another aromatic anticonvulsant.[4]

A triad of fever, skin eruption and internal organ involvement is the defining presentation of the syndrome; however, variable presentations encompassing a spectrum of clinical features often result in a delay in diagnosis.[5] As well, in many case reports, the hypersensitivity syndrome is often not recognised or diagnosed. The syndrome may mimic infectious, neoplastic or collagen vascular disorders, further delaying the correct diagnosis. In fact, the adverse event is likely to be reported solely as the most prominent or severe organ manifestation. For example, there are a large number of cases in the literature which have been termed as 'hepatotoxicity', yet closer investigation of these cases reveals that a rash and fever were also evident, heralding a diagnosis of 'anticonvulsant hypersensitivity syndrome'.[10-14] Another complicating factor is a lack of consensus of a generally accepted term for the syndrome. For example, terms such as 'Dilantin hypersensitivity reaction', 'phenytoin/Dilantin syndrome', 'Kawasaki-like syndrome', or 'mononucleosis-like syndrome', have been used to describe a similar constellation of symptoms.[15]

## 1. Incidence and Epidemiology

Phenytoin was associated with severe reactions as early as 1938,[16] and the systemic symptoms of anticonvulsant hypersensitivity syndrome were described in 1950.[17] Although this reaction has been estimated to occur in between 1 in 1000 and 1 in 10 000 exposures, its true incidence is unknown because of the variable presentation and inaccurate reporting. In a recent record linkage study, the risk for developing an anticonvulsant hypersensitivity syndrome within 60 days of the first or second prescription in new users of phenytoin or carbamazepine was estimated to be 2.3 to 4.5 per 10 000 and 1 to 4.1 per 10 000, respectively.[18]

The economic impact of treating an anticonvulsant hypersensitivity syndrome can be significant. A recent Canadian study suggests that the median direct medical cost of an anticonvulsant hypersen-

sitivity syndrome is $Can3128 (1996 values) [range $Can1149 to $Can21 293] per patient.[19]

Other drugs that have been associated with hypersensitivity syndrome include sulfonamide antibacterials, dapsone, allopurinol,[18,20] sorbinil[21] and minocycline.[22] Although not considered to be an aromatic anticonvulsant, lamotrigine has also been associated with anticonvulsant hypersensitivity syndrome.[23]

No gender variation in the risk for developing anticonvulsant hypersensitivity syndrome has been reported in the literature. Different series have reported similar numbers of male and female patients.[4,5,8] The literature, mainly case reports, has been interpreted to suggest that the incidence of anticonvulsant hypersensitivity syndrome is higher in Blacks than in other ethnic groups.[14,24,25] A retrospective review of a university-based teaching hospital clinical database identified 55 patients with anticonvulsant hypersensitivity syndrome to phenytoin, phenobarbital or carbamazepine who were referred for diagnostic testing. The major ethnic groups were Caucasians (71%), Blacks (13%), Asians (13%) and mixed origin (3%). Epilepsy occurs 1.8 times more frequently in Blacks than Caucasians[26] and local census data revealed that Blacks comprised 6% of the population. This study suggests that ethnic origin does not predict an increased risk of aromatic anticonvulsant hypersensitivity syndrome.[27]

## 2. Clinical Features

Anticonvulsant hypersensitivity syndrome occurs most frequently on first exposure to the drug, with initial symptoms starting 1 to 8 weeks after exposure to the drug. For phenytoin, the mean interval to onset is 17 to 21 days, and for carbamazepine the onset is generally between 21 and 28 days.[4] In previously sensitised individuals, anticonvulsant hypersensitivity syndrome may occur within 1 day on rechallenge. Anticonvulsant hypersensitivity syndrome is not related to dosage or serum concentration of anticonvulsants.

Fever and malaise, which can be accompanied by pharyngitis and cervical lymphadenopathy, are the presenting symptoms in most patients. Biopsies indicate benign lymphoid hyperplasia with preservation of normal lymph node architecture.[1] The fevers are generally low grade but may be as high as 40°C. When present, atypical lymphocytosis occurs in the first week of the reaction, with a subsequent eosinophilia noted by the second week in a subset of patients.[4]

### 2.1 Cutaneous Effects

The frequency of skin rash, without fever or internal organ involvement, ranges from 2 to 13% for phenytoin, carbamazepine and phenobarbital.[28,29] Often the drug eruption is related to higher plasma concentrations of either phenytoin[30] or carbamazepine.[31] The cutaneous eruption occurs within days to 2 weeks after the introduction of the drug. It should be noted that a more extensive work-up of the patient is required and the anticonvulsant must be discontinued if a fever accompanies the drug eruption, since it could mark the initiation of the anticonvulsant hypersensitivity syndrome reaction.

A drug eruption occurs in approximately 90% of patients with anticonvulsant hypersensitivity syndrome and can range from an exanthematous eruption to more serious Stevens-Johnson syndrome or toxic epidermal necrolysis (table I). In most cases, the cutaneous eruption starts as a macular erythema that often evolves into a red, symmetrical, pruritic, confluent, papular rash. Pustules, either follicular or nonfollicular, may also be present. Initially, the upper trunk and face are affected with later involvement of the lower extremities. The incidence of severe skin reactions as part of the anticonvulsant hypersensitivity syndrome was found to be as high as 9% among 53 patients with anticonvulsant hypersensitivity syndrome induced by an aromatic anticonvulsant[4] or 13% among 38 cases of anticonvulsant hypersensitivity syndrome induced by phenytoin.[5] Other dermatological findings include periorbital or facial oedema and conjunctivitis.

**Table I.** Spectrum of presentation (mild to severe) of patients with anticonvulsant hypersensitivity syndrome

| Organ involved | Presentation | | |
|---|---|---|---|
| | mild | moderate | severe (organ- or life-threatening) |
| Skin | Exanthematous eruption | Urticarial eruption | Stevens-Johnson syndrome/toxic epidermal necrolysis |
| Bone marrow | Leucopenia | Agranulocytosis | Aplastic anaemia |
| Liver | Mild elevations in liver function tests | Hepatitis | Fulminant hepatic necrosis |
| Muscle | Elevated creatine kinase level | Myositis | Rhabdomyolysis |
| Kidney | Haematuria | Nephritis | Acute renal failure |
| Heart | Pericarditis | Carditis | Congestive heart failure |
| Lung | Cough | Pneumonitis | Adult respiratory distress syndrome |
| Other | Pharyngitis, epididymitis, hypogammaglobulinaemia, pancreatitis, thyroiditis, aseptic meningitis, inappropriate antidiuretic hormone secretion, colitis | | |

### 2.2 Extracutaneous Effects

Internal organ involvement may not develop for 1 to 2 weeks into the reaction and may even develop 1 month later (table I).[32] Internal organ involvement may be symptomatic or asymptomatic and should be routinely searched for. The liver is the most frequently involved internal organ in anticonvulsant hypersensitivity syndrome, although other organs such as the kidney (e.g. interstitial nephritis, vasculitis), CNS (e.g. encephalitis, aseptic meningitis), heart (e.g. myocarditis)[33] or the lungs (e.g. interstitial pneumonitis, respiratory distress syndrome, vasculitis)[34,35] may be involved. Tender hepatomegaly with or without splenomegaly is possible. Liver involvement can range from mild elevations in transaminase levels, marked abnormalities in liver function tests with hepatomegaly to granulomatous hepatitis or fulminant hepatic necrosis.[4,10,36] Severe hepatitis with jaundice increases the risk of mortality to between 12 and 50%.[37] The degree of hepatitis is related to the interval between the onset of the syndrome and the discontinuation of the anticonvulsant.[1] This emphasises the importance of the prompt recognition of the syndrome.

In some patients, extensive organ involvement evolves as part of the anticonvulsant hypersensitivity syndrome. For example, a woman developed skin rash, fever and eosinophilia 3 weeks after starting carbamazepine. Fulminant respiratory and renal failure ensued. Autopsy showed pneumonitis, nephritis, serositis, pancreatitis, hepatitis and carditis.[38] Other studies have shown that 62% of reactions involved more than 2 organs.[4]

Although most patients improve following discontinuation of the medication, some patients may flare 3 to 4 weeks after the start of the reaction. Patients redevelop the skin eruption, fever and malaise, and may have a recurrence of internal organ involvement such as hepatitis;[32] this relapse is often seen after rapid withdrawal of a corticosteroid. In addition, once the culprit drug is discontinued, organs initially involved may show progressive changes or organs that were previously uninvolved may manifest involvement.

Thyroid involvement has also been seen in a small subgroup of patients. The hyperthyroid phase of the illness, which develops during the acute phase of the reaction, may be missed by the clinician, because fever, tachycardia and malaise appear to be part of the anticonvulsant hypersensitivity syndrome. These patients will then become hypothyroid as part of an autoimmune thyroiditis within 2 months of initiation of symptoms.[39] A low thyroxine level, an elevated level of thyroid-stimulating hormone and autoantibodies, including antimicrosomal antibodies, characterises this. Resolution of the autoimmune thyroid disease associated with anticonvulsant hypersensitivity syndrome occurs over

the ensuing 12 to 18 months, allowing eventual discontinuation of thyroid hormone replacement.

### 2.3 Pseudolymphoma Versus Anticonvulsant Hypersensitivity Syndrome

Although some clinicians have used the term drug-induced pseudolymphoma interchangeably with anticonvulsant hypersensitivity syndrome, pseudolymphoma applies only to patients who have both clinical and histological features suggestive of lymphoma. The drug eruption is subacute, usually composed of single or multiple nodules, with no accompanying general signs.[40] It is not considered a premalignant state. The syndrome occurs after 1 week to 2 years of exposure to the drug (table II).[41] Within 7 to 14 days of drug discontinuation, the symptoms generally resolve. Histopathologically, 2 types of pseudolymphomas are distinguished: T cell pseudolymphoma (band-like pattern which simulates mycosis fungoides) and B cell pseudolymphoma (nodular pattern). Management of drug-induced pseudolymphoma often involves no treatment other than withdrawal of the offending agent. Complete blood cell count and serum chemistries are usually within normal limits. Long term follow-up is necessary to rule out the possibility of pseudo-pseudolymphoma[42] (i.e. patients who, after withdrawal of phenytoin following pseudolymphoma and resolution of symptoms, later develop malignant lymphoma[43]). Although the pathophysiology is unknown, immunosuppression induced by the drug and increased CD4/CD8 ratio in the blood inducing lymphocyte proliferation have been reported.[44]

There are numerous case reports in the literature describing pseudolymphoma in association with either phenytoin[41,45-47] or carbamazepine[42,46,48,49] therapy. A case of nodular drug-induced pseudolymphoma of the skin following carbamazepine therapy is also described.[50] Mycosis fungoides–like lesions, which often manifest as scaly patches or plaques, have also been associated with phenytoin[44,51-53] and carbamazepine[51,54] administration.

In contrast to anticonvulsant hypersensitivity syndrome, it is unknown whether cross-reactivity exists among the anticonvulsants for pseudolymphoma. In 1 patient who developed mycosis fungoides–like lesions, withdrawal of phenytoin and initiation of phenobarbital and carbamazepine resulted in complete regression of skin lesions.[52] However, because pseudolymphoma shares the symptomatology of the anticonvulsant hypersensitivity syndrome, it is recommended that all aromatic anticonvulsants be avoided in patients who develop pseudolymphoma.

**Table II.** Clinical features of drug hypersensitivity syndrome, pseudolymphoma and serum sickness–like reaction (after Knowles et al.,[22] with permission)

| Syndrome | Rash | Onset of symptoms | Fever | Internal organ involvement | Arthralgia | Lymphadenopathy |
|---|---|---|---|---|---|---|
| Drug hypersensitivity syndrome | Exanthematous<br>Exfoliative dermatitis<br>Urticarial plaques<br>Pustular eruptions<br>Severe cutaneous adverse reactions ('SCAR'), i.e. Stevens-Johnson syndrome, toxic epidermal necrolysis | 1-8 weeks | Present | Present (either symptomatic or asymptomatic) | Absent | Present |
| Pseudolymphoma | Single or multiple papulonodules | 6 months | Absent | Absent | Absent | Present (biopsy shows atypical hyperplasia simulating malignancy) |
| Serum sickness–like reaction | Urticarial<br>Exanthematous | 7-14 days | Present | Absent | Present | Present |

## 3. Anticonvulsants Associated with the Hypersensitivity Syndrome

The anticonvulsants phenytoin, carbamazepine and phenobarbital have in common an aromatic benzene ring that is metabolised to toxic arene oxides. The aromatic anticonvulsants have all been associated with the development of anticonvulsant hypersensitivity syndrome.[5,55,56] The symptoms associated with the reaction,[37] as well as the severity of the reaction, are similar for all 3 drugs. Although there have been more cases associated with phenytoin and carbamazepine, this may simply reflect the greater use of these agents as compared with phenobarbital.[15] There is 1 report of anticonvulsant hypersensitivity syndrome related to therapy with valproic acid (sodium valproate).[57]

Lamotrigine has been shown to cause a rash in approximately 25% of children treated,[58,59] although most occur without fever and resolve upon discontinuation of the drug. There have been cases of anticonvulsant hypersensitivity syndrome associated with lamotrigine reported in adults[60-68] and 1 case in a child.[69] We have recently reviewed and analysed both published and unpublished cases of lamotrigine-associated anticonvulsant hypersensitivity syndrome.[23] The majority of the dermatological eruptions were exanthematous rashes (77%). However, 19% of patients had severe skin eruptions, including 2 cases of Stevens-Johnson syndrome and 3 cases of toxic epidermal necrolysis. It is unknown whether the risk of developing a severe cutaneous reaction in association with lamotrigine-induced anticonvulsant hypersensitivity syndrome is higher than with aromatic anticonvulsants. However, the incidence of a severe lamotrigine-induced rash without any internal organ involvement is approximately 1 per 1000 in adults and 1 per 50 to 100 in children,[70] which is higher than that associated with the aromatic anticonvulsants.[20]

The risk of a cutaneous reaction is significantly increased when lamotrigine and valproic acid are administered concomitantly;[71] valproic acid interacts with lamotrigine metabolism, leading to a reduced total clearance and a marked increase of the elimination half-life of lamotrigine.[72] Whether concomitant valproic acid increases the risk of lamotrigine-induced anticonvulsant hypersensitivity syndrome in not known, although valproic acid was concurrently administered in 58% of cases of lamotrigine-induced anticonvulsant hypersensitivity syndrome.[23] Other factors which increase the risk of a cutaneous eruption include exceeding the initial lamotrigine dosage and exceeding the recommended dosage escalation schedule. In contrast, in the analysis of cases of lamotrigine-induced anticonvulsant hypersensitivity syndrome, a wide range of dosages was observed; this may suggest that the reaction is not dose-dependent.

## 4. Diagnostic Tests

The lymphocyte toxicity assay is an *in vitro* drug metabolite toxicity system that was developed in the early 1980s. It uses murine hepatic microsomes as a source of cytochrome P450, which are incubated with the drug in question to generate reactive metabolites. Human lymphocytes are used as surrogate peripheral target cells to investigate individuals susceptible to drug toxicity. Lymphocytes are used since they are readily accessible, do not contain the enzymes which produce toxic metabolites from the parent drug, and contain detoxification enzymes (e.g. epoxide hydrolases). If the cells are susceptible to damage by reactive metabolites, this cytotoxicity can be quantified by a variety of methods. However, the lymphocyte toxicity assay is expensive and cumbersome to perform; currently it is only being used in certain research centres.[73]

Several studies have evaluated the usefulness of patch testing in the diagnosis of anticonvulsant hypersensitivity syndrome.[74-79] However, many of the studies have shown inconsistent results (see table III). For example, in 5 patients with carbamazepine-induced anticonvulsant hypersensitivity syndrome, oral challenges were performed with positive results; 2 of these patients had negative patch tests.[76] If patch testing is to be performed in patients with a history of anticonvulsant hypersensitivity syndrome, a 1 and 10% carbamazepine or phenytoin in petrolatum compound is recom-

**Table III.** Carbamazepine hypersensitivity reactions – use of patch tests

| Description of carbamazepine-induced reaction | Interval between reaction and testing | Carbamazepine concentration and vehicle used | Results | Other diagnostic test(s) performed |
|---|---|---|---|---|
| Male, 39y; maculopapular rash, lymphadenopathy, hepatomegaly, fever[74] | Not stated | 1%, 5% in petrolatum | Both positive | Phenytoin patch test negative; LTT positive for phenytoin and carbamazepine |
| 5 patients with erythroderma and 4 with moderate increases in LFTs[75] | 5mo to 2y | 1% in petrolatum | Positive in 4/5 patients | None |
| 7 patients with fever, rash, lymphadenopathy, impaired liver function[80] | 14wk to 5y | 10%, 20%, 40% in petrolatum | Positive results in 6/7 patients | Lymphocyte stimulation tests positive in 7/7 patients |
| 1 patient each with exfoliative dermatitis, photosensitivity reaction, erythematous dermatitis[81] | 4mo | 1%, 10% in petrolatum | Positive in 3/3 patients | None |
| Female, 19y; malaise, fever, rash, lymphadenopathy, leucocytosis with eosinophilia, increased LFTs[78] | 3y | 10% in yellow soft paraffin<br>20% in yellow soft paraffin<br>40% in yellow soft paraffin | Negative<br>Positive<br>Positive | NS |
| 7 patients with symptoms consistent with hypersensitivity syndrome[76] | 2mo to 8y | 3%, 10% in petrolatum | Both positive in 5/7 patients | Oral challenge positive in 5/5 patients with AHS (2 of these patients had negative patch tests) |
| Male, 20y; maculo-erythematous eruption with fever, increased LFTs | Not stated | 1%, 10% in petrolatum | Both positive | None |

**AHS =** anticonvulsant hypersensitivity syndrome; **LFTs** = liver function tests; **LTT** = lymphocyte transformation test.

mended. In addition, at least 2 months should elapse from the eruption to the testing date since either false positive reactions due to increased reactivity or false negative reactions due to a refractory state may exist. As with any diagnostic test, diagnosis is dependent on clinical recognition and judgement.

## 5. Pathophysiology

The availability of toxic metabolites of phenytoin, carbamazepine and phenobarbital may play a pivotal role in the development of anticonvulsant hypersensitivity syndrome (see fig. 1)[4,82,83] and of serious dermatological reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis.[84] Phenytoin, carbamazepine and phenobarbital are metabolised to hydroxylated aromatic compounds. Reactive intermediates (such as arene oxides) are produced by cytochrome P450 oxidative metabolism and are capable of binding to cellular macromolecules. The identity of the metabolite is unknown but evidence supports detoxification by epoxide hydrolase; however, if detoxification is insufficient, the toxic metabolite may bind to cellular macromolecules that could lead directly to cell necrosis or apoptosis, or may initiate secondary immunological responses.[82,85] In addition, T cells regulate the immune response and may cause the release of cytokines that result in cell destruction.[86,87] Use of the lymphocyte toxicity assay in patients who have had anticonvulsant hypersensitivity syndrome showed increased cytotoxicity in these patients compared with both healthy volunteers and patients with epilepsy who tolerated therapy.[4,88]

Other theories that have been postulated include that anticonvulsant hypersensitivity syndrome represents a form of graft-versus-host disease[89] or that the reaction is an allergic hypersensitivity reaction. As with all immunological reactions, the

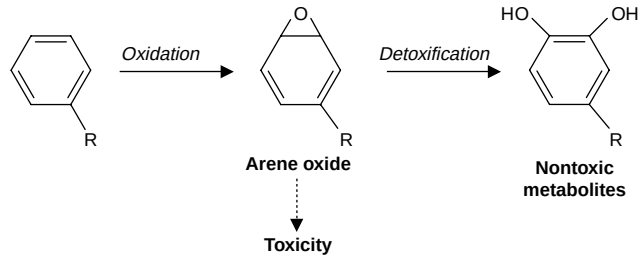


**Fig. 1.** Possible metabolic pathway for production of toxic metabolites of aromatic anticonvulsants [phenytoin, phenobarbital (phenobarbitone), carbamazepine].

anticonvulsant hypersensitivity syndrome requires an induction period after initial exposure, reappearance occurs after rechallenge and the reaction is not related to dosage or serum concentration.[1]

The mechanism of an isolated skin eruption without fever or internal organ involvement is unknown. The exanthem often subsides despite continued anticonvulsant treatment in some patients.[30] Alternatively, a reduction in dosage and treatment with prednisone and/or antihistamines[90,91] may be sufficient to treat the exanthem and allow the patient to continue on the implicated anticonvulsant.[92]

The development of anticonvulsant hypersensitivity syndrome during therapy with aromatic anticonvulsant drugs is not related to DNA sequence variation within the coding regions of the human microsomal epoxide hydrolase gene; this suggests that structural defects altering epoxide hydrolase function are unlikely to contribute to the anticonvulsant hypersensitivity syndrome.[93] However, defects occurring in regulatory regions of the epoxide hydrolase gene may alter expression of this protein.

A recent case of carbamazepine-induced anticonvulsant hypersensitivity syndrome showed increased cytotoxicity with the lymphocyte toxicity assay; however, the patient's epoxide hydrolase activity was no different from control patients. The possibility of a qualitative abnormality of the enzyme, such as a mutant form with altered substrate specificity or affinity, has been raised.[94] Another case similarly described a patient with a carbamazepine-induced anticonvulsant hypersensitivity syndrome with positive lymphocyte toxicity assay and the presence of a specific autoantibody directed against a human liver microsomal protein.[95]

Additional work has shown circulating immunoglobulin G antibodies in 9 patients with anticonvulsant hypersensitivity syndrome presenting with a variety of clinical patterns. These antibodies were directed against cytochrome P450 3A1.[96] Theoretically, covalent adduct formation with the cytochrome P450 generating the reactive species could lead to neoantigen formation and to an immune response that includes antibody formation. It is then possible that multiorgan involvement in anticonvulsant hypersensitivity syndrome is a function of the expression of the antigen in different tissues.

In one study, 40 out of 50 patients with an anticonvulsant hypersensitivity syndrome to 1 aromatic anticonvulsant showed *in vitro* cross-reactivity to the other 2.[4] Seven out of 10 patients who had received all 3 anticonvulsants (i.e. phenytoin, carbamazepine and phenobarbital) had adverse reactions to each. In addition, 40 out of 50 patients rechallenged *in vitro* with all 3 drugs had positive results to all 3. Another report described 4 children who manifested symptoms of anticonvulsant hypersensitivity syndrome with carbamazepine. In 3 patients, the syndrome was exacerbated after treatment with another aromatic anticonvulsant. Discontinuation of the aromatic anticonvulsant resulted in resolution of symptoms; valproic acid was well tolerated in 3 patients who required continued anticonvulsant therapy.[97]

*In vitro* testing has shown that there is a familial occurrence of hypersensitivity to anticonvulsants, with an autosomal pattern of inheritance.[4,98] This

suggests that the patients' siblings' risk of having a reaction to an aromatic anticonvulsant may be as high as 1 in 4. In one study, 3 siblings from a family of 12 siblings (8 available for study) developed hypersensitivity reactions to phenytoin characterised by fever, rash, lymphadenopathy and hepatitis. Following this reaction, 1 sibling tolerated phenobarbital. Using the lymphocyte toxicity assay, cells from each of the patients who had experienced an anticonvulsant hypersensitivity syndrome exhibited increased toxicity from metabolites of phenytoin and carbamazepine, while the response to phenobarbital was within normal limits. Of the other siblings, 4 showed an abnormal response to phenytoin metabolites, whereas 1 sibling detoxified phenytoin metabolites normally.[98]

The pathophysiology of lamotrigine-induced anticonvulsant hypersensitivity syndrome is unknown. Although lamotrigine is extensively metabolised, the main metabolic pathways are conjugation reactions, predominantly *N*-glucuronidation.[99] Only minor fractions of lamotrigine undergo phase I metabolism, resulting in the 2-*N*-oxide and the 2-*N*-methylated metabolites. Whether one of the phase I biotransformation products might in fact act as a toxic metabolite is not known. As well, cross-reactivity among lamotrigine and the aromatic anticonvulsants is not known, although structurally lamotrigine is not an aromatic anticonvulsant.

## 6. Management

### 6.1 Differential Diagnosis

The differential diagnosis includes other cutaneous drug reactions, acute infections (e.g. Epstein-Barr virus, hepatitis virus, influenza virus, streptococcus), lymphoma or pseudolymphoma, collagen vascular diseases and serum sickness–like reaction (table II). The main distinguishing features between serum sickness–like reactions and anticonvulsant hypersensitivity syndrome are the development of arthralgias and the lack of internal organ involvement with the former.

### 6.2 Treatment

Discontinuation of the anticonvulsant following the development of a fever and rash, with or without lymphadenopathy, is essential to avoid potential progression of symptoms. There are a minimum of laboratory tests that will help to evaluate internal organ involvement which may be asymptomatic (table IV). Liver transaminase levels, complete blood count and urinalysis and serum creatinine level should be done; in addition, the clinician should be guided by the presence of symptoms that may suggest specific internal organ involvement (e.g. respiratory symptoms). Thyroid function tests, as well as antimicrosomal thyroid antibodies, should be measured, and repeated in 2 to 3 months.[39] A skin biopsy may be helpful if the patient has a blistering or a pustular eruption. Antihistamines and/or topical corticosteroids can also be used to help alleviate symptoms.[100]

Although the role of corticosteroids is controversial, if symptoms are severe most clinicians would elect to start prednisone at a dosage of 1 to 2 mg/kg/day.[101] Pulse therapy with high dose methylprednisolone has been used in a patient who developed toxic epidermal necrolysis and severe hepatitis.[102] Uncontrolled studies have shown that plasmapheresis[103] and human intravenous

**Table IV.** Management of patients with anticonvulsant hypersensitivity syndrome

| |
|---|
| **Patients with non–life-threatening or non–organ-threatening disease** |
| Discontinue anticonvulsant |
| Supportive therapy (e.g. antihistamines, topical corticosteroids) |
| Obtain complete blood count, liver function tests, urinalysis, serum creatinine, baseline thyroid function tests, other tests based on symptom presentation |
| Skin biopsy, if blistering or pustular eruption |
| Advise patient regarding potential for cross-reactivity |
| Counsel family members and first degree relatives regarding increased risk |
| Advise patient to obtain a MedicAlert |
| **Patients with life-threatening or organ-threatening disease** |
| All above measures *plus* |
| Use of oral prednisone or pulse methylprednisolone |
| Intravenous immunoglobulin |

immunoglobulin[104] may be efficacious in the treatment of toxic epidermal necrolysis. However, these techniques have not been validated for the management of anticonvulsant hypersensitivity syndrome. Upon discontinuation of the anticonvulsant, symptoms generally begin to abate within days, but this may vary from weeks to months. In addition, careful weaning of the corticosteroid is essential; we have observed patients who have relapsed when their corticosteroid has been discontinued too abruptly.[101]

Successful carbamazepine desensitisation has been described in 12 patients after isolated skin rash[105,106] and in 1 patient with an urticarial rash and mild periorbital oedema[107] following carbamazepine administration. A 23-year-old male patient developed fever, generalised erythematous rash, lymphadenopathy and leucocytosis with an eosinophilia following carbamazepine administration. When oxcarbazepine was substituted, a similar reaction developed within 12 hours of the first dose. Desensitisation with oxcarbazepine was well tolerated.[108] Desensitisation is not recommended for patients with a true anticonvulsant hypersensitivity syndrome. No internal organ involvement was described in any of the patients in whom desensitisation was successful.

### 6.3 Advice to the Patient

Because of the potential for cross-reactivity with other aromatic anticonvulsants, patients with anticonvulsant hypersensitivity syndrome should avoid phenytoin, phenobarbital and carbamazepine. As well, since primidone is metabolised to phenobarbital, it will also probably have a high rate of cross-reactivity. Oxcarbazepine may be an alternative to carbamazepine;[109] however, because results are conflicting,[88] oxcarbazepine should be considered potentially cross-reactive with carbamazepine.

The patient should obtain a MedicAlert stating a reaction to phenytoin, carbamazepine and phenobarbital. Benzodiazepines, valproic acid (not in the acute phase because of the risk of hepatitis), or one of the newer anticonvulsants (gabapentin, topiramate, vigabatrin) can be used for seizure control.[110] There is no evidence that lamotrigine cross-reacts with the aromatic anticonvulsants.

Family counselling is a critical part of patient management because first degree relatives are at an increased risk. Anticonvulsant hypersensitivity syndrome is estimated to occur in 1 in 1000 to 10 000 exposures, but first degree relatives of an afflicted individual may have a risk that approaches 1 in 4.

## 7. Conclusions

Systemic hypersensitivity reactions to drugs are characterised clinically by fever, rash and internal organ involvement. Anticonvulsants such as phenytoin, phenobarbital, carbamazepine and lamotrigine are among the most common causes. The pathogenesis is unknown but research has supported the role of reactive metabolites in mediating toxicity. This is likely to be under genetic control. Patients who develop symptoms suggestive of a hypersensitivity reaction need to be recognised early and the culprit drug discontinued immediately. Investigations should be directed at determining target organ involvement. Therapy is controversial. The potential for cross-reactivity among phenytoin, phenobarbital and carbamazepine is approximately 75%. Patients and close relatives should be warned of risk associated with use of these anticonvulsants.

Current studies are investigating specific enzyme defects at the genomic level, and the chemical and immunological risk factors that contribute to the anticonvulsant hypersensitivity syndrome.

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