
Anticonvulsant hypersensitivity syndrome: cross-reactivity with tricyclic antidepressant agents

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Background: Aromatic anticonvulsant agents such as carbamazepine and phenytoin can induce anticonvulsant hypersensitivity syndrome (AHS) at a frequency of 1 in 10,000 to 1 in 1,000 treated patients. The hypersensitivity syndrome is a potentially life-threatening adverse drug reaction with multiorgan involvement, and incidental reexposure must be strictly avoided. Patients and treating physicians must be informed and educated about the causal drug and its potential immunologic or toxicologic cross-reactivity with other compounds. It has been well established that for future antiepileptic drug therapy, carboxamides (carbamazepine and oxcarbazepine), phenytoin, and barbiturates (phenobarbital and primidone) have to be avoided owing to their high degree of cross-reactivity. Other anticonvulsant agents, such as valproic acid, benzodiazepines, and gabapentin, may be prescribed.

Objectives: To present the clinical data for and to describe the potential cross-reactivity between aromatic anticonvulsant and tricyclic antidepressant agents in patients with carbamazepine- and phenytoin-induced AHS.

Methods: The knowledge of cross-reactivity among aromatic anticonvulsant agents mainly emerged from clinical experience and observations because diagnostic challenge tests are not advisable. Thirty-six patients with the diagnosis of AHS were instructed to contact our unit if the symptoms relapsed.

Results: Despite better knowledge of AHS, one third of the patients had avoidable recurrences after exposure to cross-reactive drugs. Besides the known cross-reactivity among aromatic anticonvulsant agents, we observed a recurrence of the hypersensitivity syndrome in 5 patients after the administration of tricyclic antidepressant agents.

Conclusion: The important potential cross-reactivity between aromatic anticonvulsant and tricyclic antidepressant drugs should be brought to the attention of treating physicians.

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INTRODUCTION

Anticonvulsant hypersensitivity syndrome (AHS) is a rare but potentially severe multiorgan adverse effect of anticonvulsant drug therapy recognized by the classic symptoms of fever, rash, hepatitis, and lymphadenopathy.^{1,2} Because this syndrome is often associated with eosinophilia, it is also termed *drug reaction with eosinophilia and systemic symptoms* (DRESS). The clinical symptoms, course, and complications of this adverse drug reaction have been the topic of several reviews in the past few years and, therefore, have been described in detail.^{3–5} Rash can range from a maculopapular or pustular exanthema to severe bullous eruptions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis.^{6,7} The underlying pathogenic mechanism of AHS has not yet been elucidated, but possible explanations are an immunologic T-cell-mediated delayed-type hypersensitivity, a toxic reaction of specific metabolites (especially against keratinocytes and hepatocytes), or a combination of both.^{8,9}

Classic triggers of AHS are aromatic anticonvulsant agents, such as carbamazepine, phenytoin, and phenobarbital, with a latency of 1 to 12 weeks after first exposure to the

drug. The clinical symptoms are similar for each anticonvulsant drug, and each has the potential to produce severe, life-threatening symptoms. Other drugs besides anticonvulsants that have been associated with this syndrome include sulfonamides, dapsone, allopurinol, and tricyclic antidepressants.^{1,2,5,10} Cross-reactivity rates among aromatic anticonvulsant agents may be as high as 80%, and patients who have had AHS should, therefore, avoid all aromatic anticonvulsants. Valproic acid, benzodiazepines, and gabapentin, which are structurally and metabolically different from the 3 previously mentioned aromatic anticonvulsant agents, have been used successfully to control seizures in patients with AHS.^{1,2}

In this study of 36 patients with carbamazepine- and phenytoin-induced AHS, we present the clinical data and describe the potential cross-reactivity between aromatic anticonvulsant and tricyclic antidepressant agents. This cross-reactivity should be recognized by treating physicians to avoid AHS recurrences in affected patients in the future.

METHODS

Patients

Thirty-six patients (20 females and 16 males) were evaluated between January 1, 2001, and December 31, 2005, with the diagnosis of AHS (Table 1). The diagnosis was based on dermatologic and systemic symptoms, a detailed history, skin biopsy findings, and laboratory test results. Because some

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Table 1. Clinical Data for the 36 Patients Studied and the Anticonvulsant Agents Causing Anticonvulsant Hypersensitivity Syndrome

Characteristics	No. of patients*
Age, mean (range), y	59 (13–92)
Sex, M/F	16/20
Symptoms	
Fever	29
Exanthema	31
Bullous skin reaction	5
Hepatitis	25
Hematologic abnormalities	21
Lymphadenopathy	10
Causal anticonvulsant agent	
Carbamazepine	23
Phenytoin	12
Lamotrigine	1

* Data are presented as number of patients unless otherwise indicated.

patients were receiving other drugs concomitantly, the diagnosis of AHS to an anticonvulsant agent was established only in cases with a chronological sequence and clinical improvement after anticonvulsant drug withdrawal. Using the Naranjos probability scale for causality evaluation, scores between 7 (the presence of previous conclusive reports describing similar reactions, symptoms appeared after administration of the drug, symptoms improved when the suspected drug was discontinued, the absence of alternative causes of the symptoms, and an adverse reaction confirmed by objective evidence) and 10 (the adverse reaction reappeared when the drug was readministered and similar symptoms to similar drugs on previous exposure) were obtained, and the reactions could be evaluated to be “probably” or “highly probably” caused by the suspected anticonvulsant drug.¹¹

Cross-reactivity

Cross-reactivity was considered if after (1) withdrawal of the anticonvulsant agent because of hypersensitivity and (2) complete healing of the skin and systemic symptoms a new episode with similar symptoms appeared after exposure to a second drug (11 patients). In 6 patients with substitution of carbamazepine to phenytoin or vice versa, no complete resolution of clinical symptoms was reached owing to the short interval. In these patients, worsening of clinical symptoms was considered to be cross-reactivity, ie, recurrence of fever, repeated elevation of liver enzyme levels, and increased skin symptoms. The clinical course of AHS is variable, and some patients experience a brief flare-up of especially skin symptoms 2 to 3 weeks after initial improvement.^{1,2} At least in some instances this may represent a “rebound flare” due to the withdrawal of systemic corticosteroids. However, the 6 patients in the present series who reacted to a second aromatic anticonvulsant agent experienced not a brief flare-up but rather a longer-lasting AHS episode, making cross-reactivity much more likely than a flare-up of the initial AHS.

Skin Tests

Skin prick tests on the forearm and patch tests on the upper back were performed according to international standards.¹² Late reactions were evaluated after 2, 3, and 4 days. Late reactions to skin prick tests were documented according to patch test reactions, ie, faint macular erythema (doubtful reaction), erythematous infiltration (weak positive reaction), erythematous infiltration with papules and vesicles (strong positive reaction), and bullous reaction (extreme positive reaction). For skin prick and patch testing, tablets were ground in a mortar and diluted with 30 μ L of physiologic saline solution. This approach is based on the previous experience of our group in avoiding irritant reactions. The agents were freshly reconstituted, and isotonic sodium chloride solution was used as a negative control.

RESULTS

Patients

The average age of the 36 patients at the time of AHS was 59 years (range, 13–92 years). Two patients had experienced the hypersensitivity symptoms within 1 week of anticonvulsant drug therapy, 20 patients between 1 and 4 weeks, and 14 patients between 5 and 12 weeks. In 23 patients, carbamazepine was the suspected anticonvulsant agent, followed by phenytoin. In this case series we found the manifestations of AHS in the following order of frequency: rash, fever, elevation of liver enzyme levels, hematologic alterations (eosinophilia and leukocytosis), and lymphadenopathy (Table 1). When the patients were evaluated for skin lesions, macular, maculopapular, or pustular exanthemas were observed in 31. Five patients had severe bullous skin reactions, ie, Stevens-Johnson syndrome ($n = 4$) or toxic epidermal necrolysis ($n = 1$). Treatment of AHS was initially directed toward symptomatic relief once use of the causal anticonvulsant agent was discontinued. Topical corticosteroid creams and ointments and antihistamines were generally helpful for the discomfort. Systemic corticosteroid therapy was justified in 19 of 31 patients with AHS and exanthema. Patients with Stevens-Johnson syndrome or toxic epidermal necrolysis received symptomatic treatment with intense monitoring, fluid replacement, antiseptic therapy, nutrition, and special skin, eye, and mucous membrane care. In 23 patients with AHS, the hypersensitivity reaction continued to progress 3 to 4 days after use of the culprit anticonvulsant drug was stopped before skin symptoms improved.^{1,2} Twenty patients achieved clinical clearing of symptoms and normalization of laboratory findings within 14 days. In the remaining 16 patients, including the 5 with severe bullous skin reactions, the AHS resolved gradually for 3 to 5 weeks until complete resolution.

Cross-reactivity

After the first anticonvulsant drug was withdrawn because of hypersensitivity symptoms, 17 patients developed a new episode of hypersensitivity symptoms due to exposure to cross-reactive compounds. Seven patients with carbamazepine-induced AHS developed cross-reactivity to phenytoin, and 5

with phenytoin-induced AHS experienced cross-reactivity to carbamazepine (Table 2). In 5 patients, cross-reactivity between carbamazepine and tricyclic antidepressants occurred. Four of these patients experienced moderate hypersensitivity symptoms, including fever, maculopapular rash, and elevation of liver enzyme levels, after treatment with amitriptyline (n = 2) and doxepin (n = 2). After intake of amitriptyline tablets, 1 patient with carbamazepine-induced AHS developed severe hypersensitivity symptoms, with fever, pustular exanthema, marked eosinophilia and leukocytosis, and elevation of liver enzyme levels, followed by a prolonged course of healing (>3 weeks). In these 5 patients with cross-reactivity between carbamazepine and tricyclic antidepressant agents, the interval between the first AHS and initiation of the antidepressant drug therapy that induced the repeated hypersensitivity symptoms was at least 6 months. Antiepileptic therapy with valproic acid (n = 16), benzodiazepines (n = 8 taking clobazam and n = 1 taking clonazepam), and the newer drug gabapentin (n = 3) was tolerated by 18 patients with AHS.

Skin Tests

In summary, we observed 4 clearly positive reactions in 15 skin tests. All the tested patients (8 with carbamazepine-induced AHS and 7 with phenytoin-induced AHS) had exanthematous skin symptoms. No immediate skin reaction was observed in any of the patients. One patient with carbamazepine-induced AHS had a positive reaction with carbamazepine in the skin prick and patch tests (positive at day 2 to maximum day 4). Two patients showed only positive patch test reactions with either carbamazepine or phenytoin.

DISCUSSION

During the past few years, AHS has been well documented in the medical literature, not only in case reports but also in several reviews.^{1,2,4-6} Today physicians and medical students can find information about this relatively rare but potentially life-threatening adverse drug reaction of aromatic anticonvulsants in textbooks of pharmacology, neurology, and dermatology. After AHS, incidental reexposure has to be strictly avoided. Therefore, patients and treating physicians have to be informed not only about the causal drug leading to AHS but also about potential cross-reactivity to other compounds and possible alternative medications. The present data show

that despite better education and knowledge regarding AHS, one third of the patients still experienced avoidable recurrences after exposure to cross-reactive drugs. Besides the known cross-reactivity among aromatic anticonvulsant agents, we suggest that patients with a history of AHS due to anticonvulsant agents should not receive tricyclic antidepressant agents.

Patients who develop AHS to an anticonvulsant drug are susceptible to the syndrome when exposed to other aromatic anticonvulsant agents. The incidence of cross-reactivity among aromatic anticonvulsant agents is greater than 80%.^{1-6,13-15} Twelve patients experienced a recurrence after withdrawal of carbamazepine and substitution with phenytoin or vice versa because the treating physician was not aware of such potential cross-reactivity. Eighteen patients received the appropriate antiepileptic medication with valproic acid, benzodiazepines, or gabapentin. Six patients who were prescribed carbamazepine not as an anticonvulsant agent but because of trigeminal neuralgia or neuropathic pain had it discontinued after AHS without introducing an alternative medication. Although cases of AHS due to lamotrigine have been reported, no evidence has been found of cross-reactivity between lamotrigine and aromatic anticonvulsant agents.^{16,17} Five of the present patients (14%) with carbamazepine-induced AHS developed a recurrence of hypersensitivity symptoms after administration of 1 of 2 tricyclic antidepressants: amitriptyline or doxepin.

Aromatic compounds follow a common metabolic pathway primarily leading to toxic intermediate metabolites. The so-called phenolic conversion of carbamazepine is mediated by the cytochrome P450 pathway, leading to toxic epoxide intermediates of aromatic rings, the unstable and reactive arene oxides.^{18,19} Arene oxides are capable of covalent binding to proteins, thereby perturbing cell function and initiating immune responses.²⁰ Thus, it is at least likely that arene metabolites of aromatic ring structures are responsible for the cross-reactivity among aromatic anticonvulsant agents. Arene oxides have to be effectively detoxified by epoxide hydratase or glutathione transferase. Immediate toxicity and antigen formation are possibly results of a reduced detoxification, eg, by a deficiency in or decreased activity of enzymes or a genetic predisposition for an immune response.^{21,22} A familial occurrence has been reported, and first-degree relatives of an affected individual have a 4-fold higher risk of AHS than the

Table 2. Cross-reactivity and Alternative Medication

Causal anticonvulsant agent	Cross-reactive anticonvulsant agent	Tolerated anticonvulsant agents	Cross-reactive antidepressant agents
Carbamazepine (n = 23)	Phenytoin (n = 7)	Valproic acid (n = 10) Clobazam (n = 4) Gabapentin (n = 3)	Amitriptyline (n = 3) Doxepin (n = 2)
Phenytoin (n = 12)	Carbamazepine (n = 5)	Valproic acid (n = 6) Clobazam (n = 4) Clonazepam (n = 1)	None

population at large.^{2,5,23,24} Hence, family counseling is important in the management of these patients.

The potential cross-reactivity between aromatic anticonvulsant and tricyclic antidepressant agents is not mentioned in recent review articles about AHS, and we found only 2 case reports.^{25,26} One article dealing with drug toxicologic screening describes false-positive results when screening with a tricyclic antidepressant immunoassay in patients with a history of ingestion of carbamazepine.²⁷ Considering the chemical structure (tricyclic antidepressants share the tricyclic nucleus with carbamazepine), cross-reactivity between carbamazepine and tricyclic antidepressant agents seems more likely than among anticonvulsant agents (Fig 1), eg, phenytoin shares fewer structural similarities with carbamazepine and is as a 5,5-diphenyl derivivate merely an aromatic compound. On the other hand, numerous drugs have aromatic ring structures, such as benzodiazepines, which are appropriate alternative medications after carbamazepine- or phenytoin-induced AHS. Therefore, it seems likely that the toxicity and immunogenicity of an aromatic compound depend not only on the aromatic rings but also on the structure as a whole and the side chains.

Owing to the risk of potential life-threatening reactions, challenge tests are not advisable in the case of AHS, and the application of alternative in vivo or in vitro test methods has been attempted. Skin tests with suspected drugs are basically

not standardized and have to be interpreted carefully. However, skin tests with some drugs yield reproducible results, including penicillins and aromatic anticonvulsants.^{25,28} In this context, Alanko²⁹ reported a series of 7 patients with maculopapular exanthema due to carbamazepine and observed positive patch test reactions to carbamazepine in 4. Most of the present patients refused further diagnostic skin tests; the main reasons were a currently well-tolerated and effective alternative antiepileptic drug therapy, no therapeutic need for anticonvulsant agents, and the fear of skin test adverse effects after a serious cutaneous adverse drug reaction. Therefore, only a few of the patients agreed to skin testing, and we observed 4 positive reactions in 15 skin tests. The lymphocyte transformation test (LTT) with drugs is also not standardized and should be performed only in specialized laboratories. One distinct problem of the LTT with aromatic anticonvulsant agents is the direct cytotoxicity of arene metabolites, and, therefore, interpretation of results, particularly regarding cross-reactivity, has to be done carefully.^{3,30} However, further studies will demonstrate whether the LTT is a helpful tool in the diagnosis of cross-reactivity between aromatic anticonvulsant and tricyclic antidepressant agents.

After AHS, education of patients is imperative to prevent hypersensitivity reactions in the future. Detailed allergologic documents with mentioning of the causal drug and the other cross-reactive aromatic anticonvulsants (carbamazepine, oxcarbazepine, phenytoin, phenobarbital, and primidone) is essential. Therapeutic alternatives and structurally or metabolically dissimilar anticonvulsant drugs are valproic acid, benzodiazepines, and gabapentin. Antidepressants are relatively frequently prescribed not only for depression but also for eating and anxiety disorders and for neuropathic pain. The potential cross-reactivity of aromatic anticonvulsant agents with tricyclic antidepressant agents should be mentioned in allergy documents and also brought to the attention of treating physicians.

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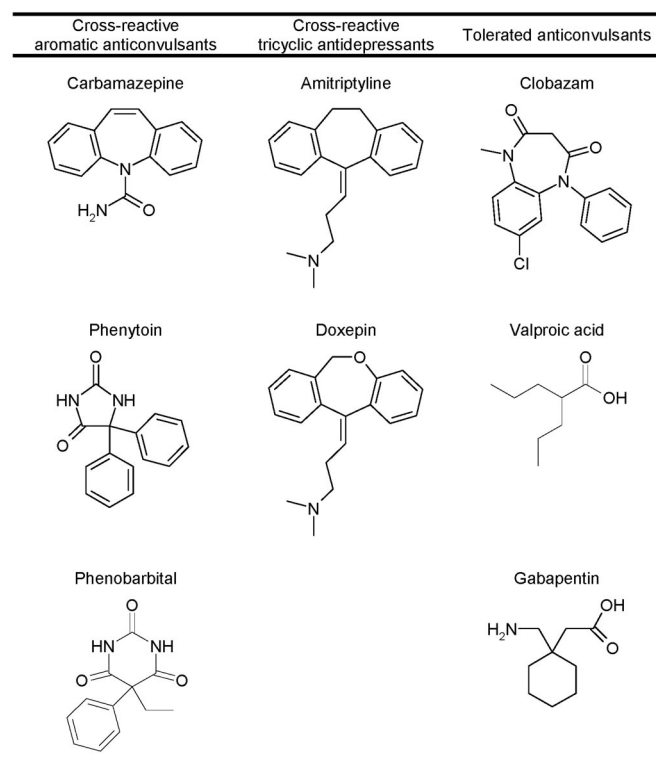


Figure 1. Cross-reactivity and chemical structure of anticonvulsant and tricyclic antidepressant agents.

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