ORIGINAL RESEARCH ARTICLE

Drug Safety 2008; 31 (8): 695-702
0114-5916/08/0008-0695/$48.00/0

Influence of Chemical Structure on Hypersensitivity Reactions Induced by Antiepileptic Drugs

The Role of the Aromatic Ring

Kim B. Handoko,[1,2] *Eugène P. van Puijenbroek*,[3] *Annemarie H. Bijl*,[3] *Walter A.J.J. Hermens*,[2] *Jeannette E.F. Zwart-van Rijkom*,[4] *Yechiel A. Hekster*[5] and *Toine C.G. Egberts*[1,4]

1 Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute of Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, the Netherlands
2 Hospital Pharmacy, 'Ziekenhuisapotheek Noordoost-Brabant', 's-Hertogenbosch, the Netherlands
3 Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands
4 Department of Clinical Pharmacy, University Medical Centre Utrecht, Utrecht, the Netherlands
5 Department of Clinical Pharmacy, University Medical Centre Nijmegen, Nijmegen, the Netherlands

Abstract

Objective: Antiepileptic drugs (AEDs) can cause various 'idiosyncratic' hypersensitivity reactions, i.e. the mechanism by which AEDs induce hypersensitivity is unknown. The aim of this study was to assess whether the presence of an aromatic ring as a commonality in chemical structures of AEDs can explain symptoms of hypersensitivity.

Methods: Between January 1985 and January 2007, all adverse drug reactions (ADRs) reported to the Netherlands Pharmacovigilance Centre Lareb related to AEDs as suspected drugs were included in this study. ADRs were analysed using a case/non-case design. Cases were defined as those patients with ADRs involving symptoms of hypersensitivity. Non-cases were patients with all other ADR reports. Symptoms of hypersensitivity were classified according to the Gell and Coombs classification (type I–IV) and the organ involved (e.g. cutaneous, hepatic). AEDs were classified as aromatic anticonvulsant if their chemical structure contained at least one aromatic ring. All other AEDs were classified as non-aromatic. We assessed the strength of the association between aromatic AEDs versus non-aromatic AEDs and reported hypersensitivity reactions with logistic regression analysis and expressed these as reporting odds ratios (RORs).

Results: In total, 303 cases of hypersensitivity associated with the use of AEDs were reported. Aromatic AEDs were suspected in 64.4% of these reports versus 41.3% (574/1389) of the non-hypersensitivity reports. A significant ROR of 2.15 (95% CI 1.63, 2.82) was found for aromatic AEDs and all hypersensitivity reactions. Aromatic AEDs were significantly associated with immunoglobin E-mediated type I hypersensitivity reactions (ROR 2.15; 95% CI 1.23, 3.78) and

T-cell-mediated type IV reactions (ROR 6.06; 95% CI 3.41, 10.75). Type II and III reactions did not show an association. Cutaneous symptoms represented 39.9% of the hypersensitivity-related ADRs. Aromatic AEDs were significantly associated with cutaneous hypersensitivity reactions (ROR 5.81; 95% CI 3.38, 9.99).
Conclusion: This study confirms that the presence of an aromatic ring as a common feature in chemical structures of AEDs partly explains apparent 'idiosyncratic' hypersensitivity reactions. Symptoms of hypersensitivity were reported twice as frequently with aromatic AEDs than with non-aromatic AEDs. Strong associations for aromatic AEDs versus non-aromatic AEDs were found for T-cell-mediated (type IV) reactions, as well as for cutaneous reactions.

Background

It is well known that the use of antiepileptic drugs (AEDs) may cause hypersensitivity reactions in susceptible patients with a varying clinical presentation, such as skin involvement, eosinophilia and/or systemic symptoms like hepatitis. Hypersensitivity reactions also differ in severity, ranging from mild urticarial eruptions to potentially life-threatening events.[1-3] The most feared AED-related adverse reactions are 'Stevens-Johnson syndrome (SJS)', 'toxic epidermal necrolysis (TEN)' and 'anticonvulsant hypersensitivity syndrome'. The estimated incidence of these events ranges from 1 per 1000 to 1 per 10 000 users of AEDs.[4] Clinical symptoms appear usually 2–8 weeks after initiation of therapy and typically start with fever, rash and lymphadenopathy, followed by involvement of various internal organs leading to hepatitis, eosinophilia, blood dyscrasias and nephritis. In the case of SJS and TEN, rash with extensive mucosal blistering or erosions is characteristic.[5-7] Rash alone is a much more common hypersensitivity reaction with an average rate of approximately 3 per 100 AED users.[8]

Hypersensitivity reactions are often classified as idiosyncratic ('type B') adverse effects because they cannot be explained easily on the basis of known pharmacological mechanisms and occur mostly unpredictably in susceptible patients only, irrespective of dosage.[9] Because of the serious nature of most idiosyncratic reactions, extensive research to unravel the mechanism explaining these effects has been carried out.[9,10] One of the most widely proposed theories of hypersensitivity reactions in general is based on the hapten hypothesis of immune recognition of drugs by specific antibodies or T cells.[11-13] Evidence shows that drugs associated with a high incidence of hypersensitivity are converted to protein-reactive intermediates in the normal processes of drug metabolism. The drug-protein complex may then act as an immunogenic complex and elicit the production of specific antibodies (humoral response) and/or the generation of specific T lymphocytes (cellular response), thus being responsible for the allergic effects.[14]

Various reports have shown that specific AEDs such as carbamazepine, phenytoin, phenobarbital and lamotrigine were connected with hypersensitivity.[3-5] The mechanism by which these AEDs induce hypersensitivity is unknown. One of the main hypotheses is that AEDs containing an aromatic ring in their chemical structure can form an arene-oxide intermediate (figure 1).[6] This chemically reactive product may become immunogenic through interactions with proteins or cellular macromolecules in accordance with the hapten hypothesis, suggesting that this structural commonality between AEDs may be responsible for hypersensitivity reactions.[15] This hypothesis is based on incidental case reports and

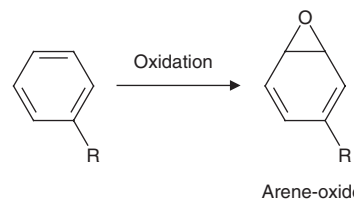

Fig. 1. Possible metabolic pathway for production of toxic metabolites of aromatic antiepileptic drugs.

in vitro experiments. So far, no *in vivo* experimental or observational studies supporting this theory have been published. Therefore, we conducted this study to investigate the association between the presence of an aromatic ring as a structural commonality in AEDs and hypersensitivity reactions using the spontaneous reporting database of our national pharmacovigilance centre.

Objective

The aim of this study was to assess whether an aromatic ring as a commonality in chemical structures of AEDs is associated with the occurrence of symptoms of hypersensitivity.

Methods

Setting

The Netherlands Pharmacovigilance Centre Lareb maintains the spontaneous adverse drug reaction (ADR) reporting system in the Netherlands on behalf of the Dutch Medicines Evaluation Board. Its objective is to detect, record and analyse ADRs and, by doing so, to contribute the safe and rational use of drugs.[16] ADRs are reported by healthcare professionals and patients on a voluntary basis and include relevant clinical information about the patient (age and sex), the suspected ADR, medication used at time of the event ('suspected' and 'concomitant'), source (physician, pharmacist, marketing authorisation holder or patient) and year of reporting. Each report is evaluated by a qualified assessor (physician or pharmacist) and is coded according to the Medical Dictionary for Regulatory Activities (MedDRA).[17] For this study, all suspected ADRs associated with AEDs reported to the Netherlands Pharmacovigilance Centre were taken into account.

Selection and Stratification of Cases and Non-Cases

All ADRs related with AEDs as the suspected drug reported between January 1985 and January 2007 were included in this study and categorized into hypersensitivity or non-hypersensitivity reports. The reported hypersensitivity reactions were stratified according to the Gell and Coombs classification[18-20] (table I). This procedure was executed by two of the authors (Annemarie Bijl and Eugène van Puijenbroek) independently of each other. Differences were discussed until consensus was reached. Furthermore, since hypersensitivity reactions are often clustered in the literature by the involved organ, these were also distinguished if applicable as cutaneous, hepatic, haematological and pulmonary hypersensitivity reactions[6,8,20] (table II). ADRs were analysed using a case/non-case study design. A case was defined as a patient with a report of hypersensitivity related to a suspected AED. All patients with non-hypersensitivity ADR reports related to AEDs, namely reports without any of the included MedDRA terms mentioned in tables I and II, were defined as non-cases. If more than one AED was suspected in the report, then these were included as separate cases. As such, the number of cases and non-cases may exceed the number of reports, and thus the number of patients,

Table I. Included hypersensitivity symptoms based on reported suspected adverse drug reactions as classified by Gell and Coombs[18-20] (Medical Dictionary for Regulatory Activities terms)

Type	Reaction
I	Anaphylactic reaction, anaphylactic shock, angioneurotic oedema, eye swelling, eyelid oedema, face oedema, oedema mouth, periorbital oedema, pharyngeal oedema, shock, urticaria
II	Agranulocytosis, increased ALT, anaemia, increased AST, increased hepatic enzymes, hepatic failure, abnormal hepatic function, (cholestatic) hepatitis, toxic hepatitis, hepatocellular damage, leukopenia, abnormal liver function test, rhabdomyolysis, thrombocytopenia
III	Arthralgia, arthritis, arthropathy, lymphadenopathy, myalgia, nephritis interstitial, pleural effusion, pleurisy, pneumonia, pneumonitis
IV	Dermatitis (allergic, bullous), drug rash with eosinophilia and systemic symptoms, erythema multiforme, rash (erythematous, maculo-papular, papular, pustular), skin exfoliation, Stevens-Johnson syndrome, toxic epidermal necrolysis

Table II. Classification of hypersensitivity symptoms on organ involvement based on reported adverse drug reactions (Medical Dictionary for Regulatory Activities terms)

Type	Reaction
Cutaneous	Dermatitis (allergic, bullous), drug rash with eosinophilia and systemic symptoms, erythema multiforme, rash (erythematous, maculo-papular, papular, pustular), skin exfoliation, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
Hepatic	Increased ALT, increased AST, increased hepatic enzymes, hepatic failure, abnormal hepatic function, (cholestatic) hepatitis, toxic hepatitis, hepatocellular damage, abnormal liver function test
Haematological	Agranulocytosis, anaemia, leukopenia, thrombocytopenia
Pulmonary	Pleural effusion, pleurisy, pneumonia, pneumonitis

since one report could contain more than one suspected AED.

Exposure Definitions

AEDs were classified as aromatic anticonvulsants if their chemical structure contained at least one aromatic ring (carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenytoin, phenobarbital, primidone and zonisamide). All other AEDs were classified as non-aromatic (figure 2).

Data Analysis

The Chi-squared test, Student's t-test or Mann-Whitney test were used to compare cases and non-cases as appropriate. The strength of the association between the different types of hypersensitivity reactions and the aromatic AEDs in comparison with non-aromatic AEDs was calculated using the ADR reporting odds ratio (ROR) as a measure of disproportionality.[21] The calculation of a ROR is comparable to the calculation of an odds ratio from a case-control study. RORs, adjusted for age, sex, year of reporting and the source of reports (health professional or patient), were calculated by means of logistic regression analysis and expressed as point estimates with corresponding 95% confidence intervals.

Results

A total of 1692 cases and non-cases of ADRs with AEDs as suspected medication involving 1593 patients were included. There were no significant differences in patients with or without hypersensitivity reactions in terms of age, sex or reporting source ($p > 0.05$). A significant difference in the year of reporting was detected (table III).

In total, 303 cases of hypersensitivity were reported. Aromatic AEDs were suspected in 64.4% (195/303) of cases versus 41.3% (574/1389) of non-cases. The presence of an aromatic ring in the chemical structure was associated with a significant increased risk of hypersensitivity reactions (adjusted ROR 2.15; 95% CI 1.63, 2.82). Among the aromatic AEDs, hypersensitivity was significantly associated with carbamazepine (adjusted ROR 2.04; 95% CI 1.46, 2.85), lamotrigine (adjusted ROR 2.89; 95% CI 1.98, 4.23) and phenytoin (adjusted ROR 1.88; 95% CI 1.12, 3.15) [table IV].

Of 303 cases of hypersensitivity, 62 (20.5%) represented immunoglobin E (IgE)-mediated response reactions (type I), 94 (31.0%) corresponded with immunoglobulin-mediated cytotoxic reactions (type II), 36 (11.9%) were suggestive for immune complex deposition reactions (type III) and 111 (36.6%) for T-cell-mediated hypersensitivity reactions (type IV). Type I reactions were significantly associated with aromatic AEDs (adjusted ROR 2.15; 95% CI 1.23, 3.78). Furthermore, a high adjusted ROR of 6.06 (95% CI 3.41, 10.75) was found for aromatic AEDs and type IV reactions. The use of aromatic AEDs was not associated with type II (adjusted ROR 0.93; 95% CI 0.61, 1.45) and type III reactions (adjusted ROR 1.17; 95% CI 0.58, 2.36) [table V].

Cutaneous symptoms represented 39.9% (121/303) of cases. Rash (erythematous, maculo-papular, papular, pustular or unspecified) was the most frequently reported hypersensitivity symptom 79/303 (26.3%). Of all cases, 51/303 (16.8%) were hepatic, 41/303 (13.5%) were haematological and 7/303

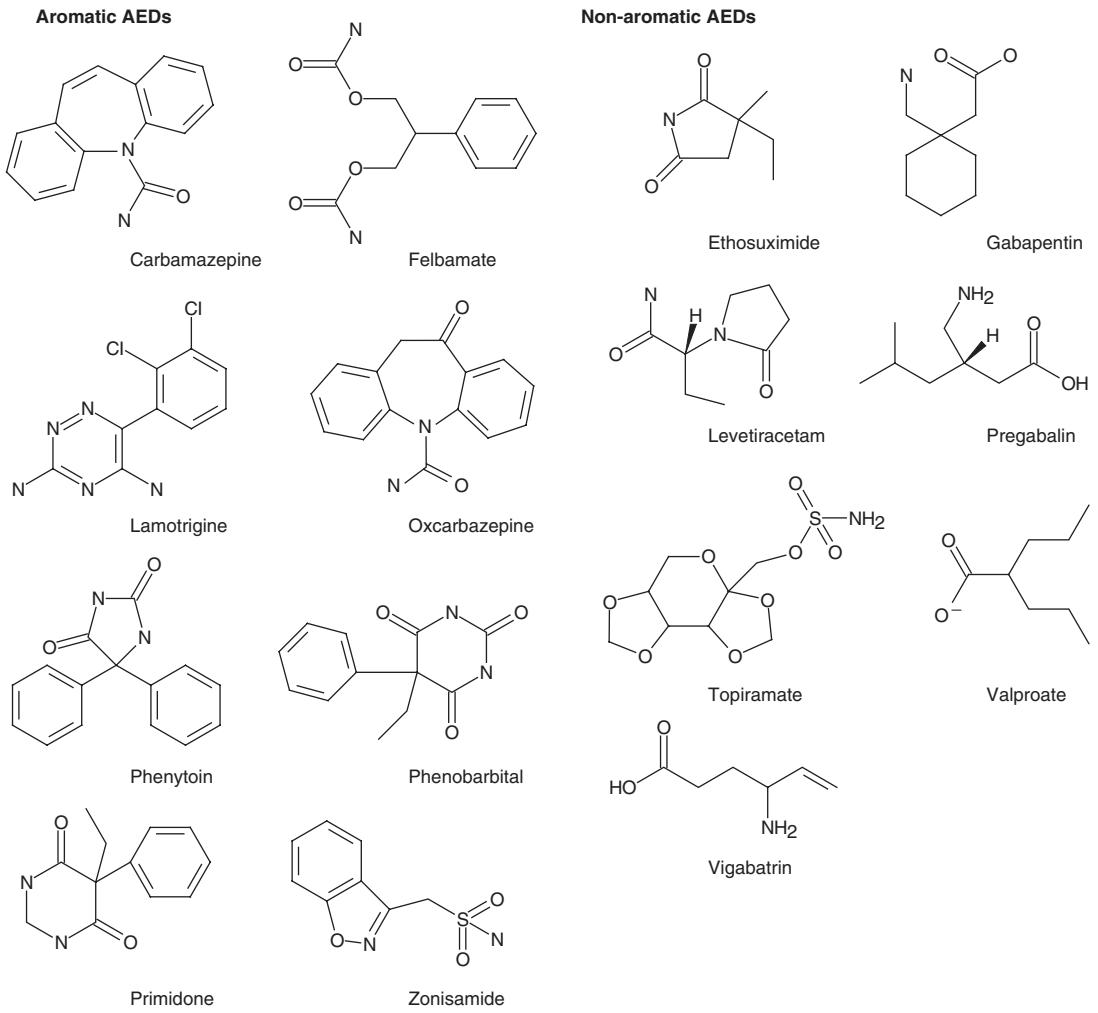

Fig. 2. Aromatic and non-aromatic antiepileptic drugs (AEDs)

(2.3%) were pulmonary. Aromatic AEDs were significantly associated with cutaneous hypersensitivity reactions, adjusted ROR 5.81 (95% CI 3.38, 9.99), but not with hepatic, haematological or pulmonary hypersensitivity reactions.

Discussion

This study shows that a commonality in chemical structures of AEDs partly explains specific types of hypersensitivity reactions. We found that symptoms of hypersensitivity were reported twice as frequently with aromatic AEDs than with non-aromatic AEDs. The association was strongest for T-cell-mediated (type IV) reactions. Also, IgE-mediated response (type I) reactions showed a significant ROR for the relation with aromatic AEDs. Furthermore, a strong association was found for aromatic AEDs and cutaneous hypersensitivity reactions.

In general, it is assumed that small molecules with molecular weights <1 kDa cannot directly induce an immune response. AEDs, as well as the majority of other drugs, fall into this category. Therefore, it is assumed that they must covalently bind to components of the immune system in order

Table III. Main patient characteristics

Patient characteristics	Patients with hypersensitivity (n = 293)	Patients without hypersensitivity (n = 1300)	p-Value
Sex			
female [n (%)]	180 (61.4)	779 (59.9)	0.663[a]
Mean age (y) ± SD	44.4 ± 22.1	46.1 ± 21.1	0.228[b]
Source			0.074[a]
healthcare professional, [n (%)]	281 (95.9)	1210 (93.1)	
patient, [n (%)]	12 (4.1)	90 (6.9)	
Reporting year (range)	1986–2006	1987–2006	
mean ± SD	2000 ± 4.7	2002 ± 4.0	<0.001[c]

a Pearson χ^2 test.
b Student's t-test.
c Mann-Whitney test.

to cause hypersensitivity reactions. This principle forms the basis of the hapten hypothesis, which proposes that drugs or reactive metabolites of drugs act as haptens and bind to proteins or other endogenous macromolecules. Covalently modified macromolecules are immunogenic and elicit an immune response.[22] In 1974, Jerina and Daly[23] described the metabolic formation of arene-oxides. According to them, arene-oxides were responsible for many toxic and carcinogenic properties of aromatic hydrocarbons. Although the involvement of alternative reactive metabolites of AEDs have been proposed in experimental systems, the formation of arene-oxides is believed to be the most likely mechanism of hypersensitivity reactions.[24] Another argument supporting this theory is the cross-sensitivity that has been reported among patients using aromatic AEDs.[25] This phenomenon has also been studied *in vivo* and *in vitro* in patients that showed clinical hypersensitivity reactions to phenytoin, phenobarbital and carbamazepine. A rechallenge with a possible cross-reactive AED resulted in hypersensitivity reactions in up to 87% of patients.[26]

Apart from the hapten formation hypothesis, another immune mechanism might be involved. In this hypothesis, there is direct, non-covalent binding of the drug to the T-cell receptor of specific T-cell clones. Drug-specific T cells have been identified for lamotrigine and carbamazepine.[19,27] Our findings of the strong association with T-cell-mediated (type IV) hypersensitivity reactions in these aromatic AEDs might support this hypothesis.

Arif et al.[8] recently studied predictors of rash associated with AEDs. They found higher rash rates in patients treated with phenytoin, lamotrigine and

Table IV. Use of aromatic and non-aromatic antiepileptic drugs (AEDs) in cases and non-cases

AED	Cases	Non-cases	ROR (95% CI)	
	n = 303 [n (%)]	n = 1389 [n (%)]	crude	adjusted[a]
Non-aromatic AEDs	108 (35.6)	815 (58.7)	1.00 (reference)	1.00 (reference)
Aromatic AEDs	195 (64.4)	574 (41.3)	2.56 (1.98, 3.32)	2.15 (1.63, 2.82)
carbamazepine	97 (32.0)	275 (19.8)	2.66 (1.96, 3.62)	2.04 (1.46, 2.85)
felbamate	3 (1.0)	0 (0)	NE	NE
lamotrigine	55 (18.2)	135 (9.7)	3.07 (2.12, 4.46)	2.89 (1.98, 4.23)
oxcarbazepine	12 (4.0)	56 (4.0)	1.62 (0.84, 3.11)	1.45 (0.75, 2.79)
phenobarbital	4 (1.3)	21 (1.5)	1.44 (0.48, 4.27)	1.23 (0.41, 3.71)
phenytoin	24 (7.9)	77 (5.5)	2.35 (1.43, 3.88)	1.88 (1.12, 3.15)
primidone	0 (0)	10 (0.7)	NE	NE

a Adjusted for age, sex, source and year of reporting.
NE = not estimable; **ROR** = reporting odds ratio.

Table V. Association of aromatic vs non-aromatic antiepileptic drugs (AEDs) and type of hypersensitivity reaction

Hypersensitivity reaction	Aromatic AEDs [n(%)]	Non-aromatic AEDs [n (%)]	ROR (95% CI) crude	adjusted[a]
All	195 (100)	108 (100)	2.56 (1.98, 3.32)	2.15 (1.63, 2.82)
Allergic reactions: Gell and Coombs[18] classification				
Type I	40 (20.5)	22 (20.3)	2.45 (1.32, 3.82)	2.15 (1.23, 3.78)
Type II	42 (21.5)	52 (48.1)	0.97 (0.64, 1.47)	0.93 (0.61, 1.45)
Type III	17 (8.7)	19 (17.6)	1.08 (0.56, 2.08)	1.17 (0.58, 2.36)
Type IV	96 (49.2)	15 (13.9)	8.64 (4.97, 15.01)	6.06 (3.41, 10.75)
Allergic reactions: organ classification				
Cutaneous	104 (53.3)	17 (15.7)	8.34 (4.94, 14.05)	5.81 (3.38, 9.99)
Hepatic	23 (11.8)	28 (25.9)	0.96 (0.56, 1.73)	0.96 (0.53, 1.74)
Haematological	18 (9.2)	23 (21.3)	0.94 (0.50, 1.75)	0.86 (0.45, 1.66)
Pulmonary	2 (10.3)	5 (4.6)	0.48 (0.09, 2.48)	0.56 (0.10, 3.24)

a Adjusted or age, sex, source and year of reporting.

ROR = reporting odds ratio.

carbamazepine (all aromatic AEDs) and lower rates with levetiracetam, gabapentin and valproate (all non-aromatic AEDs). When we reanalysed their data, we found an odds ratio of 2.18 (95% CI 1.80, 2.56) for the association between aromatic AEDs versus non-aromatic AEDs and rash. These findings are in accordance with our data.

Recently, a study was published in which an association was found between the HLA-B*1502 allele and AED-induced cutaneous reactions in a small sample size of Han Chinese.[28] If confirmed in larger studies and other ethnic cohorts, identification of genetic polymorphisms predisposing AED-induced hypersensitivity and subsequent avoidance of aromatic AED treatment could help to prevent life-threatening hypersensitivity events.

Not all reactions included in this study are necessarily based on hypersensitivity. Some reactions are more likely to have an allergic basis (i.e. urticaria or pneumonitis), whereas in other reactions, such as rash or hepatic reactions, immunopathology is less certain. This might have led to a relative overestimation of the proportion of allergic reactions and subsequent overestimation of the point estimates involved.

Spontaneous reporting, the major system used by national pharmacovigilance centres, has been found to be especially effective in detecting idiosyncratic adverse events. One of the limitations of this system as a source of collecting data on suspected ADRs is that it is known to represent only a fraction of the drug-related adverse events; therefore, no relative incidence can be obtained from our data.[29] It is recognised that <10% of all serious and only 2–4% of non-serious adverse reactions are reported.[30] Thus, this may have led to both over- and underestimation of the RORs. In this study, an underestimation is expected, as it is well accepted by potential reporters that some of the aromatic AEDs lead to hypersensitivity.

The approach outlined in this study should be replicated with other study designs, such as prescription event monitoring, case control surveillance or record linkage by use of large automated databases.[31] Unravelling the association between a commonality in chemical structures of AEDs and hypersensitivity reactions with these methods could provide additional evidence for the association we found.

Conclusion

In conclusion, this study demonstrates that apparently 'idiosyncratic' hypersensitivity reactions can partly be explained by a commonality in chemical structures of AEDs. A significant association was found for aromatic versus non-aromatic AEDs and hypersensitivity reactions. When stratifying for different types of hypersensitivity, the association was

strongest for T-cell-mediated (type IV) reactions and cutaneous reactions.

Acknowledgements

No sources of funding were used in the preparation of this study. The authors have no conflicts of interest that are relevant to the content of this study.

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Correspondence: Professor *Toine C.G. Egberts*, Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, PO Box 80.082, Utrecht, 3508 TB, the Netherlands.
E-mail: A.C.G.Egberts@uu.nl