Original Article

Cutaneous Adverse Drug Reactions (CADRs) between Aromatic and Non-Aromatic Antiepileptic Drugs: Clinical Presentation and Severity

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Background: Drug hypersensitivity is the most common adverse effect of drug use. Major cutaneous adverse drug reactions (CADRs) represent the higher rates of morbidity and mortality, with up to 5.2% of cases. Current reports revealed the non-aromatic antiepileptic drugs had increasing rates of CADRs from the past.

Objective: To study the clinical presentations and the severity of CADRs due to aromatic and non-aromatic antiepileptic drugs.

Materials and Methods: A retrospective cohort study was conducted with inpatients and outpatients with CADRs receiving antiepileptic drugs in Phramongkutklao Hospital between January 2009 and December 2018.

Results: Among 77 patients with CADRs, 61 patients received aromatic antiepileptic drugs and 16 patients took non-aromatic antiepileptic drugs. Among the patients with aromatic antiepileptic drugs 52.46% developed minor cutaneous drug reactions. The rest, 47.54%, developed major cutaneous drug reactions including Steven-Johnson syndrome or toxic epidermal necrolysis (SJS/TEN) 13.11% and drug rash with eosinophil and systemic symptoms (DRESS) 31.15%. Among the patients with non-aromatic antiepileptic drugs, 62.5% developed minor cutaneous drug reactions. The rest, 37.5%, developed major CADRs including SJS/TEN 12.5% and DRESS 25%. Of the patients receiving aromatic antiepileptic, the major CADRs group showed significant higher level of eosinophil compared with minor CADRs (10.35% and 2.1%, respectively, $p<0.001$). The study showed significant higher alkaline phosphatase (ALP) levels in 138.5 IU/L among patient with major CADRs who received aromatic antiepileptic drugs compared with minor CADRs in 87 IU/L ($p=0.006$). No significant difference of laboratory was found among CADRs patients in non-aromatic group.

Conclusion: Aromatic antiepileptic drugs tended to cause more severe cutaneous drug reactions than non-aromatic antiepileptic drugs, especially DRESS. The internal organ involvements were significantly identified in the aromatic antiepileptic group regarding to serum eosinophil and ALP level.

Keywords: Adverse skin reaction, Aromatic antiepileptic drugs, Non-aromatic antiepileptic drug

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Cutaneous adverse drug reactions (CADRs) are the most common presentation of drug hypersensitivities that may be associated with other systems. Major drug reactions such as anaphylaxis, drug hypersensitivity syndromes, Steven Johnson syndrome, and toxic epidermal necrolysis (SJS/TEN) have increased the morbidity and mortality rate in patients. The studies of Thong et al revealed that 5.2% of the patients have major drug reactions from all adverse reactions[1]. The clinical presentation of delayed hypersensitivity results in CADRs including maculopapular exanthema (MP), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), fixed drug eruption (FDE), and SJS/TEN[2]. In 2010, Sangasapasviliya et al found that the common CADRs in Phramongkutkloa Hospital were maculopapular rash (34.99%), followed by non-specific erythrematous rash (16.42%), FDE

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(9.28%), and SJS (8.57%), respectively. Severe and lethal of CADRs accounted for 10.0% and 0.71%, respectively[3].

Antiepileptic drugs can be divided into two groups by structures, aromatic, and non-aromatic. The aromatic antiepileptic drugs reveal higher rates of CADRs, such as phenobarbital (15%), phenytoin (13%), carbamazepine (11%), and lamotrigine (7.3%), compared with the non-aromatic antiepileptic drugs such as topiramate (<1%)[4].

The authors aimed to study the clinical presentations and severity of CADRs due to aromatic and non-aromatic antiepileptic drugs.

Materials and Methods

The present research protocol was reviewed and approved by the Ethics Committee of Phramongkutklao College of Medicine (IRBRTA 325/2561). The retrospective cohort study was conducted with inpatients and outpatients with CADRs receiving antiepileptic drugs at Phramongkutklao Hospital between January 2009 and December 2018. The inclusion criteria consisted of patients aged above 18 years receiving any form of antiepileptic drugs including oral, intravenous, and intramuscular or other route who developed CADRs. The clinical diagnosis was made by multi-department consultants including dermatologists, internists, neurologists, and pharmacists. The exclusion criteria were patients with immunodeficiency, those who received immunosuppressive, or with abnormal immunological symptoms. All patient data were recorded in OPD cards by e-documents from the Phramongkutklao Hospital database.

The patients were divided into two groups, aromatic and non-aromatic antiepileptic drug groups according to the drug received. The demographic data recorded were sex, age, underlying disease, renal function, smoking, alcohol consumption, blood pressure, pulse rate, associated drug and other drug, and food allergy. The authors separated the major CADRs including SJS/TEN, DRESS, AGEP and urticarial or angioedema. The minor skin reactions included MP rash and FDE.

Statistical analysis was performed using Stata/MP 12 (StataCorp LP, College Station, TX, USA). Data were analyzed using multiple logistic regressions, and categorical data were compared using chi-square test or Fisher's exact test as applicable, and independent t-test or Mann-Whitney U test for continuous data. A p-value of less than 0.05 was considered significant.

Table 1. Demographic characteristic of patients receiving aromatic and non-aromatic epileptic drugs (n=77)

Baseline characteristics	Aromatic (n=61) n (%)	Non-aromatic (n=16) n (%)	p-value
Sex			0.861[a]
Male	32 (52.46)	8 (50.00)	
Female	29 (47.54)	8 (50.00)	
Age (year)			0.155[b]
Mean±SD	62.49±16.02	55.88±17.91	
Min-max	(20 to 90)	(26 to 86)	
HT	21 (34.43)	4 (25.00)	0.474
DM	6 (9.84)	2 (12.5)	0.668[c]
DLP	17 (27.87)	4 (25.00)	1.000[c]
CVA	32 (52.46)	4 (25.00)	0.050
CAD	3 (4.92)	1 (6.25)	1.000[c]
Renal	7 (11.48)	4 (25.00)	0.226[c]
Smoke	5 (8.20)	0 (0.00)	0.577[c]
Alcohol	11 (18.03)	0 (0.00)	0.107[c]
SBP			0.711[b]
Mean±SD	127.74±22.93	125.25±26.93	
Min-max	(91 to 209)	(90 to 179)	
DBP			0.577[b]
Mean±SD	74.79±12.20	72.94±9.70	
Min-max	(50 to 115)	(57 to 89)	
PR			0.199[b]
Mean±SD	84.98±12.75	80.19±14.82	
Min-max	(60 to 120)	(51 to 103)	
Associated drug	47 (77.05)	15 (93.75)	0.173[c]
Drug allergy	7 (11.48)	4 (25.00)	0.226[c]

HT=hypertension; DM=diabetes mellitus; DLP=dyslipidemia; CVA= cerebrovascular accident; CAD=coronary artery disease; SBP= systolic blood pressure; DBP=diastolic blood pressure; PR=pulse rate; SD=standard deviation

[a] Chi-square test, [b] Independent t-test, [c] Fisher's exact test, Significant if p<0.05

Results

Seventy-seven patients were enrolled in the present study, including 40 (51.94%) men and 37 (48.05%) women. Sixty-one patients (79.22%) received aromatic antiepileptic drugs such as phenytoin, phenobarbital, carbamazepine, and lamotrigine, and 16 patients (20.77%) received non-aromatic antiepileptic drugs such as valproate, levetiracetam, gabapentin and topiramate. The mean age was 61 years and mean time of rash onset after the prescription was 15.9 days. Table 1 shows the demographic data of the patients.

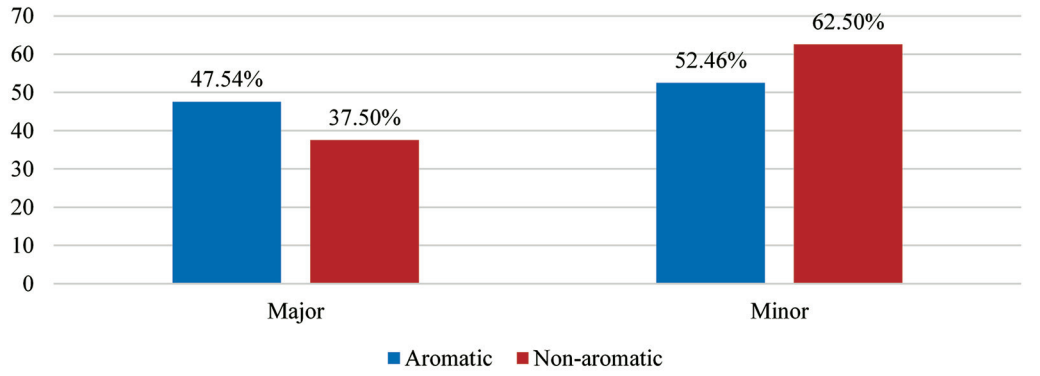

Figure 1. Rate of CADRs among patients receiving aromatic and non-aromatic antiepileptic drugs (p=0.473).

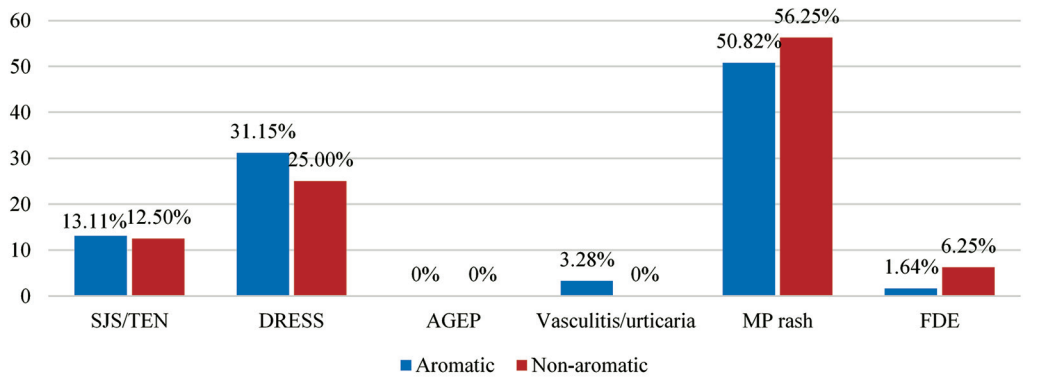

Figure 2. Rate of CADRs among patients receiving aromatic and non-aromatic antiepileptic drugs (p=0.784).

In all, 32 patients (52.46%) receiving aromatic antiepileptic drug developed minor cutaneous reaction, 31 MP rashes (50.82%) and one FDE (1.64%). The rest, 29 patients (47.54%), developed major cutaneous reaction including eight SJS/TEN (13.11%), 19 DRESS (31.15%), and two urticaria (3.28%). Of the patients receiving non-aromatic antiepileptic drugs, ten (62.5%) developed minor skin reaction including nine MP rashes (56.25%), one FDE (6.25%). The rest, six (37.5%) patients, developed major skin reaction, two SJS/TEN (12.5%) and four DRESS (25%). No significant difference was observed according to cutaneous presentation between the two drug groups (Figure 1, 2).

Among 77 patients presenting adverse cutaneous reaction, 48 patients were sensitized to phenytoin (62.33%), ten to carbamazipine (12.9%), five to valproate (6.49%), four to levetiracetam and topiramate (5.19%), three to gabapentin (3.89%), two to lamotrigine (2.59%), and one to phenobarbital (1.29%). The comparison between major and minor CADRs regarding to each antiepileptic drug is shown in Figure 3. Otherwise no significant difference was found.

Of the patients receiving aromatic antiepileptic, the major CADRs group showed significantly higher level of eosinophil compared with the minor CADRs group (10.35% and 2.1%, respectively, $p<0.001$). The present study showed significant higher alkaline phosphatase (ALP) levels of 138.5 IU/L among patient with major CADRs receiving aromatic antiepileptic drugs, compared with minor CADRs of 87 IU/L ($p=0.006$), as shown in Table 2. No significant difference of laboratory was found among CADRs patients in the non-aromatic group.

Discussion

Gaeta et al found that the three most common CADRs of aromatic antiepileptic drugs were MP rash (5% to 10%) follow by TEN (0.1%) and SJS (0.01%). The non-aromatic antiepileptic drugs such as gabapentin developed MP rash (1.8%) and showed

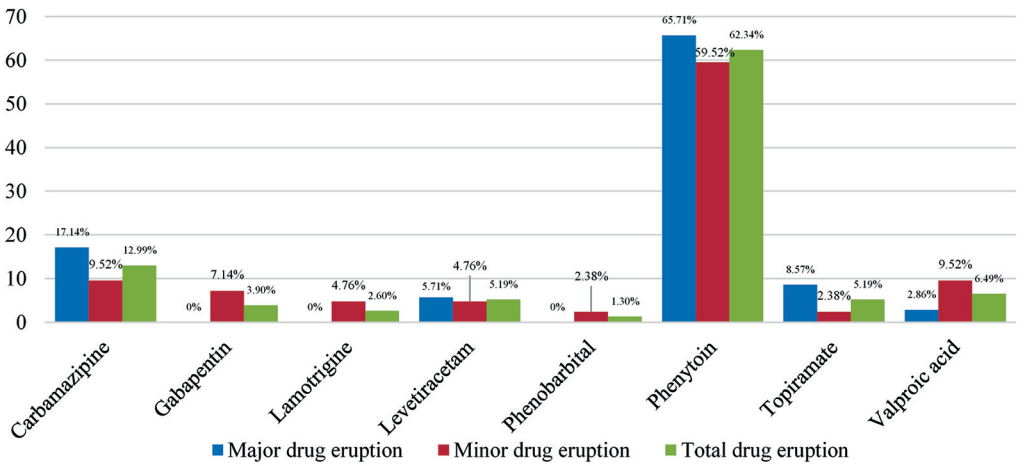

Figure 3. Rate of major and minor CADRs regarding to each antiepileptic drugs (p=0.321).

Table 2. Laboratory results in aromatic and non-aromatic antiepileptic drugs

Lab - subgroup skin	Major		Minor		p-value
	n	Median (min-max)	n	Median (min-max)	
Aromatic					
WBC	28	9,300 (4,200 to 19,800)	31	7,300 (1,300 to 19,200)	0.017
%Eo	28	10.35 (0 to 58)	31	2.1 (0 to 36)	<0.001
BUN	27	15.4 (5.6 to 89.5)	30	14.5 (6.3 to 98.8)	0.879
Cr	27	0.8 (0.3 to 4)	30	0.8 (0.4 to 9.26)	0.778
Alb	23	3.4 (1.6 to 4.5)	28	3.5 (1.6 to 4.9)	0.292
Glob	23	3.4 (2.4 to 4.7)	28	3.1 (2.5 to 5.5)	0.436
TB	24	0.3 (0.1 to 3.1)	28	0.3 (0.1 to 1.4)	0.874
DB	25	0.2 (0.1 to 3,017)	28	0.18 (0.1 to 0.6)	0.323
AST	27	37 (13 to 3,340)	29	25 (9 to 161)	0.209
ALT	27	43 (5 to 327)	29	25 (4 to 174)	0.090
ALP	26	138.5 (53 to 406)	29	87 (20 to 224)	0.006
Onset	28	19.5 (4 to 270)	32	16.5 (1 to 768)	0.467
Non-aromatic					
WBC	6	6,650 (5,100 to 13,100)	9	8,800 (3,300 to 20,300)	0.953
%Eo	6	3.95 (1.6 to 12.7)	9	3.4 (1.3 to 11)	0.406
BUN	5	17.7 (8.3 to 26.6)	10	13.15 (5 to 23.3)	0.220
Cr	6	1.23 (0.55 to 2.2)	10	0.75 (0.21 to 1.3)	0.354
Alb	6	3.6 (2.5 to 4.1)	9	3.8 (2.8 to 4.5)	0.406
Glob	6	3.35 (2.4 to 3.9)	9	3.1 (2.9 to 3.6)	0.632
TB	6	0.2 (0.2 to 0.4)	9	0.4 (0.3 to 0.9)	0.007
DB	6	0.1 (0.1 to 0.3)	9	0.2 (0.1 to 0.5)	0.095
AST	6	28 (16 to 469)	9	22 (11 to 66)	0.595
ALT	6	42.5 (6 to 117)	9	21 (7 to 224)	0.637
ALP	6	90 (58 to 170)	9	68 (20 to 215)	0.554
Onset	6	14 (4 to 14)	10	20 (6 to 93)	0.403

WBC=white blood cell; Eo=eosinophil; BUN=blood urea nitrogen; Cr=creatinine; Alb=albumin; Glob=globumin; TB=total bilirubin; DB=direct bilirubin; AST=aspartate aminotransferase; ALT=alanine aminotransferase; ALP=alkaline phosphatase

no serious adverse drug skin reaction[5]. Similar to the present study, the most common cutaneous reactions due to both aromatic drugs were MP rash follow by DRESS, SJS/TEN, and FDE. The study of Baba et al found that major CARDs, up to 15.6% in SJS/TEN of patient, received aromatic antiepileptic drugs[6]. The present study found aromatic antiepileptic drugs tended to develop major CADRs especially DRESS than in the non-aromatic group. Furthermore, non-aromatic antiepileptic also tended to provide minor CADRs such as MP more than in the aromatic group.

The pharmacological review of Blaszczyk et al in 2015 found a higher rate of hypersensitivity among patients receiving aromatic antiepileptic drugs compared with those receiving non-aromatic antiepileptic drugs[4]. The highest rates were reported for phenobarbital (15%), phenytoin (13%), carbamazepine (11%), and oxacarbarzepine (5%). This is comparable with the present study as the authors found that patients receiving aromatic antiepileptic drugs presented a higher rate of major cutaneous reactions involving phenytoin (62.33%), carbamazipine (12.9%), valproate (6.49%), and levetiracetam and topiramate (5.19%), but was rarely found among patients receiving phenobarbital. The different rate of drug allergy in the present study may be explained by the frequency of prescription among the physicians and neurologists together with the wide variety of drugs in the authors' hospital.

A study in 2013 showed a high rate of hepatitis at 9.2% by elevate aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels among patients receiving non-aromatic antiepileptic drugs such as gabapentin and pregabalin[7]. Drug-induced liver injury (DILI) is an important cause of morbidity and mortality. Devarbhavi found 11% of DILI cases caused by antiepileptic drugs such as phenytoin, carbamazepine, and lamotrigine[8]. The elevation of ALP level without jaundice represented a mild case of DILI. The present study showed significantly increase ALP levels without jaundice among patients with major CADRs receiving aromatic antiepileptic drugs.

The present study also found significant higher level of serum eosinophil in major CADRs in the aromatic antiepileptic group. This could be explained by the most common major CADR of the group was DRESS, which often involved with hyper-eosinophilia.

Limitation

The present study was performed in a mono-center, which had a limited number of patients recruited into the study.

Conclusion

Aromatic antiepileptic drugs tended to provide more severe CADRs than non-aromatic antiepileptic drugs, especially DRESS. The internal organ involvements were significantly identified in the aromatic antiepileptic group regarding to serum eosinophil and ALP level.

What is already known on this topic?

Drug hypersensitivity is the most common side effect of drug uses. CADRs are most common presentation of drug hypersensitivity. Aromatic antiepileptic drugs have higher hypersensitivity rate compared with non-aromatic antiepileptic drugs.

What this study adds?

Aromatic antiepileptic drugs tended to provide more severe CADRs than non-aromatic antiepileptic drugs, especially DRESS. Significant higher eosinophil level and higher ALP levels without jaundice were found in major CADRs with aromatic antiepileptic group.

Conflicts of interest

The authors declare no conflict of interest.

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