Renin angiotensin system blockers-associated angioedema in the Thai population: analysis from Thai National Pharmacovigilance Database

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Summary

Background: **Renin-angiotensin-aldosterone system (RAS) blockers are commonly used for cardiovascular diseases. Currently, little information exists for the Asian population on angioedema, a rare yet serious adverse event.**

Objective: **This study aimed to describe characteristics of RAS blockers-associated angioedema (RASBA) in Thai patients.**

Methods: **A retrospective study using the national pharmacovigilance database of Thailand was undertaken. Cases indicating the presence of angioedema with RAS blockers uses from 1984-2011 were identified. Patient demographics, co-morbidities, concomitant drugs, information for the RAS blockers and angioedema were obtained as well as causality assessment and quality of reports.**

Results: **A total of 895 cases were identified. Mean age was 59.9±12.8 years and 66.5% being female. Most angioedema events (48.6%) occurred during the first week of treatment. Angiotensin converting enzyme inhibitors (87.7%) were the most commonly implicated agents followed by angiotensin receptor blockers (10.5%), aldosterone antagonist (2.1%) and direct renin inhibitor (0.2%). Out of the 895 cases incorporated in this study, 165 (18.4%) were classified as serious events and resulted in hospitalization. The overall case fatality rate was 0.4%. Respiratory disturbance occurred in 46 cases (5.1%). Patients with respiratory complications tended to be younger (53.4±13.9 vs 60.3±12.7 years old; p=0.002) and with higher frequency of allergy history (26.1% vs 14.7%; p=0.032) compared to those without respiratory complications. Based on multivariate logistic regression, the adjusted OR for history of allergy was 2.23 (95%CI: 1.04 - 4.78, p = 0.041).**

Conclusions: **RASBA in Thai population occurred mostly in elderly female patients and often led to hospitalization. Since large number of patients is regularly exposed to RAS-blockers, a nationwide attempt to raise awareness of clinicians when prescribing RAS-blockers is prudent.** ***(Asian Pac J Allergy Immunol 2015;33:227-35)***

Keywords: *angioedema, renin-angiotensin-aldosterone system blocking agents, Thai population, Thai National Pharmacovigilance Database, drug safety*

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Introduction

Renin angiotensin system (RAS) blockers are drug classes with proven benefits for various cardiovascular and renal diseases such as hypertension, post myocardial infarction, heart failure and kidney diseases.[1] There are four classes of drugs classified as RAS blockers including angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), aldosterone antagonists (AA) and direct renin inhibitors (DRI). In general, these drugs are very well tolerated with the exception of angioedema, a rare yet potentially serious adverse event. RAS blockers-associated

angioedema (RASBA) is an abrupt and short lived swelling in deep dermal, subcutaneous and/or mucosal levels.[2] Unlike other forms of angioedema, RASBA is non-allergic in nature and more frequently localized in the head and neck area, especially face, lips, tongue, mouth, pharynx, larynx, or periorbital region.[3] In certain cases, clinically significant upper airway obstruction may ensue which can be life-threatening and sometime even fatal.[2,3]

Although the exact mechanism underlying this reaction is still unclear, bradykinin is believed to play an important part in the pathogenesis of this adverse event. Initially thought to occur only with ACEI due to its ability to directly potentiate bradykinin action, reports of angioedema associated with the use of ARB and DRI have surfaced soon after the introduction of these agents in clinical practice.[4,5]

Data from various studies reported an incidence of RASBA in the range of 0.25 – 2.5%.[6-8] Several risk factors have been identified including race (African descendants), age ≥ 65 years, smoking, female sex, a history of hereditary, acquired or idiopathic angioedema, history of allergy, uses of certain drugs (aspirin, non-steroidal anti-inflammatory drugs or NSAIDs, beta-lactam antibiotics, dipeptidyl peptidase IV or DPP-IV inhibitors, immunosuppressants) and respiratory tissue trauma.[9-15] Most angioedema cases occurred within the first month of treatment initiation.[7] However, there are reports of RASBA that occurred months, years or even decades after treatment which made diagnosis of RASBA quite challenging.[16,17] Incidence of respiratory complications varied from 10-22 % from different reports.[7,17,18] In recent years, exponential growth of RAS blockers usage is evident worldwide.[19-21] This, in turn, results in increasing number of RASBA along with increasing hospitalization, healthcare resource consumption and loss of lives.[19-21]

Despite its seriousness, increasing importance and increasing usageof RAS blockers in Asia, there is very limited information regarding RASBA in the Asian population. Currently, available information is limited to case reports, case series or studies with too small sample size to be meaningful.[22-24] Considering large population exposed to RAS blockers, more information is required to better understand this rare yet important adverse event among threatening the Asian population. This study therefore aimed to describe the patterns of RAS blockers use, patient characteristics, and outcomes among cases reported with angioedema in the Thai population.

Methods

Data source

Relevant data from 1984 to 2011 was extracted from the Health Product Vigilance Center (HPVC) database (called "Thai Vigibase"), the national pharmacovigilance database of Thailand. Thai vigibase is under the direct supervision of HPVC which was established in 1983 under the Thai Food and Drug Administration, Ministry of Public Health (http://thaihpvc.fda.moph.go.th). The HPVC has been collecting and managing case reports submitted from spontaneous reporting systems, intensive monitoring programs, and clinical trials nationwide since 1984. Currently, HPVC has a network of more than 900 public and private hospitals and health service centers and now contains over 500,000 reports from across the nation.

Inclusion criteria

To be included in this study, a case had to 1) receive any RAS blockers either as a suspected or concomitant drug and 2) contain any terms related to angioedema. The World Health Organization – Adverse Reaction Terminology (WHO-ART) was used to determine the presence of angioedema. Those terms include angioedema, angioneurotic (o)edema, angioneurotic (o)edema aggravated, Giant urticarial, Giant hives, Qunicke's (o)edema, larynx (o)edema, face (o)edema, (o)edema periorbital, urticaria. For cases identified as having urticaria, such cases were included only if the description of cases identified head and neck as area of involvement. All products containing RAS blockers in Thailand were included in this study. They were angiotensin converting enzyme inhibitors (captopril, enalapril, lisinopril, ramipril, quinapril, perindopril, fosinopril, delapril, imidapril and cilzapril), angiotensin receptor blockers (losartan, irbesartan, valsartan, candesartan, eposartan, telmisartan and olmesartan), aldosterone antagonists (spironolactone) and direct renin inhibitor (aliskiren).

Data extraction

From each identified unique HPVC number, a detail information of basic patient's demographic, history of allergy, co-morbidities, history of any RAS-blocker intolerance, both suspected and concomitant drugs, dosage, dosing regimen and duration of use prior to adverse event, site of angioedema, seriousness of angioedema, presence of respiratory involvement, management and outcome were obtained. Furthermore, effect of re-challenge, causality assessment and the quality of reports were

extracted from reports when available. Causality assessment was classified as "certain", "probable", "possible" and "unlikely". Health professionals carried out the assessment at the time of report submission. The assessment for the quality of reports was done by the HPVC using the modified WHO-Uppsala Monitoring Center (WHO-UMC) documentation grading.[25]

Data analyses

Descriptive statistics were used to describe patients' characteristics. Percentage for each type of RAS blockers usage, mean daily doses, onset of adverse events, affected areas, seriousness of events, clinical outcome and the quality of reports were also analyzed descriptively. Subgroup analysis was performed to compare characteristics between patients with and without respiratory complication. Statistical significance was tested using chi-square or t-test statistics. Odd ratios were calculated where appropriate. The data were manipulated and analyzed using STATA version 12.0 (StataCorp, College Station, Texas).

Results

A total of 1,369 cases were extracted from the HPVC database using the screening criteria (usage of at least one RAS blockers plus at least one adverse event term related to angioedema). After case record validation, 474 cases were excluded; 3 cases for miscoding of drug names and 471 cases for adverse event term "urticarial" in areas other than face and neck. Therefore, 895 cases were included into data analysis. Among these cases, angioedema (55.7%) was the most common term used for reporting followed by face edema (39%), edema periorbital (11.2%), edema mouth (7.5%), angioneurotic edema (0.4%), facial urticarial (0.5%) and tongue edema (0.2%). Number of reports increased exponentially with time. During 1994-1996, there were only 4 reports. During 1997-99, 2000-02, 2003-05, 2006-08, 2009-11, there were 16, 62, 136, 246, 431 reports, respectively. Approximately 90% of cases were reported by either a physician or a pharmacist. Baseline characteristics of these 895 cases are shown in Table 1. Age ranged from 1-98 years, with a mean ($\pm$ SD) age of 59.9$\pm$12.8 years. Female was the predominant gender (66.5%). Hypertension (55.6%), diabetes mellitus (7.6%) and dyslipidemia (7.5%) were the three most common comorbidities. History of drug allergies was documented in 137 cases (15.3%) with 6 cases (0.7%) having previous history of adverse reaction to RAS blockers. Interestingly, 2 out of these 6 cases received enalapril despite having previous history of angioedema to the same drug. The other 2 cases were switched to different classes of RAS blockers and angioedema reaction appeared.

Angiotensin converting enzyme inhibitors (ACEI) were the most commonly implicated drug class (87.7%) with enalapril (83.3%) as the predominant agent (mean dose of 10.1 $\pm$ 9.8 mg/day). Among angiotensin receptor blockers (ARB), losartan (5.7%) with mean dose of 56.4 $\pm$ 37.8 mg/day and valsartan (2.6%) with mean dose of 86.2 $\pm$ 58.6 mg/day were the two most commonly implicated agents. Angioedema due to aldosterone antagonist (spironolactone) was found in 19 patients (2.1%). There were also 2 case reports (0.2%) of angioedema with aliskiren. RAS blockers monotherapy was prescribed in 176 patients (19.7%). Among the concomitant drugs, the top five most common drugs were hydrochlorothiazide (22.8%), aspirin (19.9%), amlodipine (15.6%), simvastatin (15.2%) and metformin (12.1%). NSAIDs and beta-lactam antibiotics were used as concomitant drugs in very small number of cases. None of the cases received any DPP-IV inhibitors. Causality assessment was mostly classified as probable (65.8%). Regarding the quality of reports, most were graded at quality level 2 (63.6 %).

The patterns of angioedema events and outcomes are shown in Table 2. Approximately half of angioedema cases occurred within the first week of treatment initiation. Angioedema report during the second week through the first 6 month sharply decreased but remained evident. However, reports of angioedema from patients receiving RAS blockers for more than 6 months were small and sporadic. There was one case report where the patient had an event after taking ACEI for 9 years. The most commonly affected areas were face (41.3%), periorbital region (13.6%) and mouth (9.7%). However, details of area involvement were not reported in almost half of the cases (48.8%). Among 895 cases, 46 patients (5.1%) were documented as experiencing respiratory involvement. While the majority (80.5%) of reported events was classified as non-serious, 18.4% (165/895) were classified as serious. Among those with serious events, 87% (144/165) required either hospitalization or prolongation of hospital stay. Overall, there were 4 dead cases (case fatality rate of 0.4%).

Table 1. Baseline characteristics of cases with RAS blockers-associated angioedema from HPVC database

Parameter	Number of reports (%) [N = 895]
Age (years)	
Mean ± SD	59.9±12.8
< 30	10 (1.1)
31-40	33 (3.7)
41-50	157 (17.5)
51-60	236 (26.4)
61-70	223 (24.9)
71-80	161 (18.0)
≥ 81	29 (3.3)
Not reported	46 (5.1)
Gender [n (%)]	
Female	595 (66.5)
Male	298 (33.3)
Not reported	2 (0.2)
Co-morbidities[a] [n (%)]	
Hypertension	498 (55.6)
Diabetes mellitus	68 (7.6)
Dyslipidemia	67 (7.5)
Gout	25 (2.8)
Ischemic heart disease	10 (1.1)
Heart failure	8 (0.9)
Asthma/COPD	5 (0.6)
Gastrointestinal disorder	4 (0.4)
Chronic kidney disease	3 (0.3)
History of drug-allergies [n (%)]	
No	711 (79.4)
Yes	137 (15.3)
Not reported	47 (5.3)
Type of RAS blockers [n (%)]	
Angiotensin converting enzyme inhibitors	785 (87.7)
Enalapril	745 (83.3)
Perindopril	12 (1.3)
Quinapril	11 (1.2)
Ramipril	8 (0.9)
Captopril	7 (0.8)
Lisinopril	1 (0.1)
Delapril	1 (0.1)
Angiotensin receptor blockers	94 (10.5)
Losartan-based products	51 (5.7)
Valsartan-based products	24 (2.6)
Irbesartan	6 (0.7)
Telmisartan	5 (0.6)
Candesartan	5 (0.6)
Olmesartan	3 (0.3)
Aldosterone antagonist (spironolactone)	19 (2.1)
Direct renin inhibitor (aliskiren)	2 (0.2)
Use of concomitant drugs	
Mean number of concomitant drugs (items)	2.47 ± 2.01
1-2 items	321 (35.9)
3-5 items	327 (36.5)
> 5 items	71 (7.9)
None	176 (19.7)
Use of aspirin	177 (19.8)
Use of NSAIDs	81 (9.1)
Use of beta-lactam antibiotics	50 (5.6)
Causality assessment [n (%)]	
Certain	42 (4.7)
Probable	589 (65.8)
Possible	255 (28.5)
Unlikely	2 (0.2)
Not reported	7 (0.8)
Quality of reports[b] [n (%)]	
Quality 3	51 (5.7)
Quality 2	569 (63.6)
Quality 1	247 (27.6)
Quality 0	17 (1.9)
Not reported	11 (1.2)
Diagnosis person [n (%)]	
Physicians	605 (67.6)
Pharmacists	177 (19.8)
Others	93 (10.4)
Unknown	13 (1.4)
Nurses	7 (0.8)
Reporter [n (%)]	
Pharmacists	826 (92.3)
Others	51 (5.7)
Physicians	9 (1.0)
Missing	5 (0.6)
Unknown	9 (1.0)

[a]Each case may have > 1 co-morbidities.
[b]World Health Organization-Uppsala Monitoring Center (WHO-UMC) documentation grading.
COPD = chronic obstructive pulmonary disease; NSAIDs = non-steroidal anti-inflammatory drugs; RAS = renin angiotensin system

Since aspirin and NSAIDs are known causes of angioedema and may increase the risk of angioedema development when used in combination with RAS blockers, separate analyses were performed comparing cases with or without aspirin/NSAID use using multivariate logistic regression. However, we were unable to identify significant differences on any parameters of interest.

Since one of known serious consequences of angioedema is airway obstruction, we therefore performed a subgroup analysis comparing cases with versus without respiratory involvement. (Table 3) Patients with respiratory involvement were significantly younger (53.4 ± 13.9 vs 60.3 ± 12.7 years old; *p*-value = 0.002) and with more frequent previous history of drug allergy (26.1% vs 14.7%; p-value = 0.032). Onset of angioedema tended to occur faster with a borderline significance (average time to event; 20.5 days vs 108.7 days; *p*-value = 0.053). Cases with respiratory involvement had significantly higher rate of face, mouth or tongue as one or more of the affected areas compared to those without respiratory involvement ($p = 0.032$). Most importantly, the event had a significantly higher probability of being serious (37.0% vs 17.4%; OR: 2.7; 95%CI: 1.3 – 5.3, $p < 0.001$). However, there were no fatal cases in the group with respiratory involvement.

Based on multivariate logistic regression analysis with gender, underlying diseases and aspirin or NSAIDs use in the model, previous history of drug allergy was independently associated with the risk of respiratory involvement (OR: 2.23; 95%CI: 1.04 - 4.78, $p = 0.041$).

Table 2. Characteristics of angioedema events and outcomes

Parameter	Number of reports % [N = 895]
Time to event	
Median **(days)**	5
Mean ± SD **(days)**	104.19 ± 328.41
1 – 7 days	435 (48.6)
8 days – 1 month	131 (14.6)
> 1 – 6 months	94 (10.5)
> 6 months – 1 year	21 (2.4)
> 1 – 2 years	16 (1.8)
> 2 – 3 years	22 (2.5)
> 3 years	19 (2.1)
Not reported	157 (17.5)
Affected area[a] [n (%)]	
Face	370 (41.3)
Periorbital (including eyelid)	122 (13.6)
Mouth (including tongue)	87 (9.7)
Others[b]	24 (2.7)
Not specified	436 (48.7)
Number of edema area [n (%)]	
1	328 (36.6)
2	118 (13.2)
3	13 (1.5)
Not reported	436 (48.7)
Respiratory involvement [n (%)]	
Yes	46 (5.1%)
No	849 (94.9%)
Seriousness of events [n (%)]	
Non-serious	720 (80.5)
Serious	165 (18.4)
Hospitalization-initial or prolonged	144 (16.1)
Medical significant	7 (0.8)
Life-threatening	8 (0.9)
Death	4 (0.4)
Seriousness not defined	2 (0.2)
Not reported	10 (1.1)
Outcomes after treatment [n (%)]	
Recovered without sequelae	661 (73.8)
Not yet recovered	102 (11.4)
Recovered with sequelae	57 (6.4)
Lost to follow up	58 (6.5)
Recovering	13 (1.4)
Died	4 (0.4)

[a]Each case may have >1 edema associated area.

[b]Others include body, arms and legs.

Discussion

To the best of our knowledge, this study is the first of its kind to characterize RASBA using pharmacovigilance database from Asia. Findings from this study provide useful information on this rare yet serious adverse event. Results from this study lend support to previous studies suggesting that female sex had a higher tendency to experience RASBA.[2,6,8] Although there is no clear and universally accepted explanation for this phenomena, estrogen was proposed to be a part of potential factors due to its ability to increase gene expression of pre-kallikrein or bradykinin type 2 receptor and decrease gene expression of angiotensin converting enzyme.[26-28] The overall effect is therefore potentiation of bradykinin, a potent vasodilator believed to be a key player in the pathogenesis of RAS-blockers related angioedema. Nevertheless, such sexual preference is not overwhelming and caution should be equally taken when both sexes are prescribed RAS-blockers.

Consistent with previous findings, ACEI is the most frequently implicated drug class in our study followed by ARB. Enalapril and losartan were the most commonly reported agents of each drug class in our report. This was most likely due to their widespread use in Thailand as the main representative of ACEI and ARB listed in Thailand's National Essential Drug Lists. Despite being on a market for a relatively short time, there were two reports involving aliskiren monotherapy suggesting that angioedema could potentially occur with this agent. This finding is consistent with a previous study which suggested that aliskiren can cause angioedema to a larger extent than ARB but to a lesser extent than ACEI.[29] We also found 19 cases of angioedema in patients receiving spironolactone in which reaction occurred after spironolactone initiation. Nevertheless, spironolactone has never been implicated as an important cause of angioedema despite its long history of use. In addition, plausible biological theory that could substantiate this reaction is still lacking. Combined with the inherent limitation of pharmacovigilance study to identify cause and effect relationship, one should not conclude that spironolactone was the true cause of angioedema in these cases. Therefore, this finding needs to be taken with caution and require further investigation and validation.

Since ACE inhibition leading to bradykinin potentiation is believed to be the main mechanism of angioedema, occurrence of angioedema with ARB

Table 3. Subgroup analyses on the presence versus absence of respiratory involvement among RAS blockers-associated angioedema patients.

Parameter	Number of reports (%)		
	Presence of respiratory involvement [N = 46]	Absence of respiratory involvement [N = 849]	p-value
Mean age (years±SD)	53.4±13.9	60.3±12.7	0.002
Gender [n (%)]			
Female	30 (65.2)	565 (66.6)	0.835
Male	16 (34.8)	282 (33.2)	
Not reported	0 (0)	2 (0.2)	
Co-morbidities[a] [n (%)]			
Hypertension	20 (43.5)	478 (56.3)	0.088
Diabetes mellitus	3 (6.5)	65 (7.7)	0.777
Dyslipidemia	3 (6.5)	64 (7.5)	0.799
Gout	-	25 (2.9)	0.238
Ischemic heart disease	1 (2.2)	9 (1.1)	0.484
Heart failure	-	8 (0.9)	0.508
Asthma/COPD	-	5 (0.6)	0.602
Gastrointestinal disorder	-	4 (0.5)	0.641
Chronic kidney diseases	-	3 (0.4)	0.686
Affected area[b] [n (%)]			
Face	24 (52.2)	346 (40.8)	0.032
Periorbital	14 (30.4)	108 (12.7)	
Mouth including tongue	8 (17.4)	79 (9.3)	
History or allergic to product			
No	31 (67.4)	680 (80.1)	0.032
Yes	12 (26.1)	125 (14.7)	
Not reported	3 (6.5)	44 (5.2)	
Type of RAS blockers [n (%)]			
Angiotensin converting enzyme inhibitors	38 (82.6)	747 (87.9)	0.313
Angiotensin receptor blockers	8 (17.4)	86 (10.1)	
Aldosterone antagonist	0 (0)	19 (2.2)	
Direct renin inhibitor	0 (0)	2 (0.2)	
Mean dose of enalapril	11.03±10.17	10.08+9.83	0.694
Mean dose of losartan	60±22.36	55.91+39.87	0.587
Median time to event (days)	3	5	
Mean time to event (days)	20.47±40.78	108.7+336.5	0.053
Use of aspirin	13 (28.3)	164 (19.3)	0.138
Use of NSAIDs	5 (10.9)	78 (9.2)	0.607
Seriousness of events [n (%]			
Serious	17 (37.0)	148 (17.4)	0.001
Non-serious	29 (63.0)	691 (81.4)	
Case fatality rate	0 (0)	4 (0.4)	0.554

[a]Each case may have > 1 co-morbidities.

[b]Each case may have > 1 oedema associated area.

Table 4. Multivariate logistic regression analysis to identify independent risk factors for angioedema with respiratory involvement among RAS blockers-associated angioedema patients.

Characteristics	OR	S.E.	z	95% CI	p value
Gender	1.258617	0.5016541	0.58	0.5762688 - 2.748918	0.564
Hypertension	0.6585074	0.2492511	-1.10	0.3222215 - 1.417312	0.270
Diabetes	0.7461786	0.5826697	-0.37	0.1614967- 3.44764	0.708
Dyslipidemia	0.40735	0.4254217	-0.86	0.0526021 - 3.154511	0.390
NSAIDs/aspirin use	1.781316	0.6980331	1.47	0.8263917 - 3.839688	0.141
History of allergy	2.224783	0.8690011	2.05	1.034684 - 4.783737	0.041

and aliskiren that are devoid of ACE inhibition may require further explanation. A recent study conducted among hypertensive patients indicated that treatment of losartan led to a 2-fold increase in plasma bradykinin level.[30] Initial pharmacodynamic studies with aliskiren reported no effect on bradykinin plasma levels.[31] However, recent studies suggested that aliskiren was capable of increasing bradykinin level in certain tissues and leading to activation of bradykinin B2 receptors.[32] Recent analysis of the US Adverse Event Reporting System (AERS) using Multi-item Gamma Poisson Shrinker data mining algorithm suggested that aliskiren was associated with angioedema (empiric Bayes geometric mean or EBGM value of 3.9, 95% CI: 3.2–4.7).[5] Based on the fact that this is a rare event, it is therefore proposed that RAS-blockers may facilitate angioedema in predisposed individuals rather than cause angioedema independently.[3,10] Several genetic polymorphisms have recently been identified to associate with increased risk of angioedema which may lend support to this theory.[11, 16, 33]

For angioedema reaction, many aspects of our findings are consistent with previous studies. We found that angioedema onset was highest in the first month after initiating the treatment.[6-8] However, delayed reaction was also identified in our study similar to previous studies.[16] Face, periorbital and mouth are the most associated area with RASBA like those reported in previous studies. Interestingly, presence of respiratory involvement in our study was only 5.1% which is lower than the 10-22% reported from various studies.[7,17,18] Possible explanations are differences in study design, missing information from the reports about such complications and potentially less respiratory complications in Asian subjects. Nevertheless, this issue requires further study.

Of importance note, we found that up to one fourth of cases experiencing respiratory complications had previous history of allergy. This is consistent with previous studies and suggests that previous history of allergy is an important risk factor for serious angioedema.[7,17,18] Based on this finding, patients with history of allergy should be closely monitored when a RAS blocker is initiated.

Cross-reactivity is another important concern when prescribing RAS blockers. Previous studies suggested that cross-reactivity occurred in less than 10%.[34,35] In our study, 2 out of 6 patients with previous history of enalapril-induced angioedema, suffered serious life-threatening events when enalapril was rechallenged. Another 2 cases with history of rash, one from enalapril, another from valsartan, were switched to losartan and enalapril, respectively. Both cases suffered angioedema. Based on this finding along with previous studies, switching a patient who is intolerant to other RAS blockers should be considered only when the benefit strongly outweighs the risk. In addition, close monitoring must be implemented after switching occurs.

Several limitations exist in our study. Firstly, we were unable to identify the true incidence of RASBA among RAS blocker users which would give us ability to perform comparative analysis with similar data from other Western countries. Since Thailand has an open drug distribution system, it is therefore impossible to calculate number of prescription or population exposed to a drug accurately. In addition, underreporting of adverse event is one of the major issues of HPVC database especially in the early years of development. Nevertheless, a clear trend for increasing number of angioedema reports in our study may suggest exponential growth in both numbers of prescriptions for RAS blockers along with improved compliance

of healthcare personnel toward spontaneous reporting system.

Similar to other pharmacovigilance studies, limited quality of reports, especially incomplete data, may also affect our analysis. We were unable to collect certain data that have been shown by others as being important risk factors such as detailed smoking status, a history of hereditary, acquired or idiopathic angioedema, history of major operations such as transplantation or respiratory tissue trauma. In addition, information on area of involvement was missing in almost half of all reports. Based on this finding, attempt must be made to improve completeness of reporting in the future.

For case identification, there are two key issues that one must consider when reading this report. First, we used WHO-ART for angioedema as one of the key criteria. Among those terms associated with angioedema, "urticarial" was included. In general, RASBA is not associated with urticaria since the reaction is a kinin-dependent rather than IgE mediated allergic reactions.[3] Therefore, we manually reviewed every case identified as having urticaria and included the case only if the description of cases identified head and neck as area of involvement. In the end, there were only 5 out of 476 of urticaria cases that were included in our data analysis. We believe that such screening help prevent contamination of cases that were not angioedema effectively.

Second, we decided to include all cases whether RAS blockers were listed as suspected agents or concomitant drugs. The main reason for this is to avoid any reporting bias. Based on the natural course of RASBA where a reaction can occur months or years after treatment, RAS blockers are often overlooked as a cause of angioedema. As a result, it is therefore prudent to err on the side of safety in our opinion. Nevertheless, we did a separate analysis of cases that only listed RAS blockers as suspected drugs. Every aspect of the results in such analysis was identical to the overall analysis. Therefore, we believe that our decision did not affect any of our findings.

Conclusion

Our study helps characterize the nature of RASBA in a developing Asian country where no data has been available before. Overall, our results showed that angioedema in the Thai population share similarities and differences from published reports from the Western countries. Similar to those reports, more cases tend to be female and with previous history of drug allergy, especially among those with serious complications. We were able to identify angioedema cases that were associated with every class of RAS blockers, even with a renin inhibitor that was recently introduced into clinical practice. In contrast to reports from the Western world, the incidence of respiratory involvement in our study is relatively low. This interesting finding needs to be further investigated and validated. Nevertheless, with increasing popularity of RAS blockers, Thailand and other Asian nations will experience exponential increase in angioedema cases for years to come. Until more data is available, attempts should be made to improve awareness and educate clinicians about key characteristics of RASBA to minimize the risk of this rare yet potentially devastating adverse event in our society.

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