

ORIGINAL ARTICLE

Drug-induced angioedema without urticaria: prevalence and clinical features

C Leeyaphan,[†] K Kulthanan,^{†,*} K Jongjarearnprasert,[‡] N Dhana[‡][†]Departments of Dermatology and [‡]Pharmacy, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

*Correspondence: K Kulthanan. E-mail: sikkt@mahidol.ac.th

Abstract

Background Angioedema without urticaria can be caused by drugs. The purpose of our study was to assess the prevalence and clinical features of patients with drug-induced angioedema without urticaria.

Methods This study retrospectively reviewed case records at Siriraj Hospital, between January 2007 and December 2008. Patients aged at least 15 years were included.

Results The prevalence of drug-induced angioedema without urticaria among patients with adverse drug reactions was 2.3%/year. Non-steroidal anti-inflammatory drugs (NSAID) were the most common cause (50%), followed by antibiotics (20%). The commonest NSAID which induced angioedema were ibuprofen and diclofenac. The common sites were periorbital area (67.3%) and lips (27.6%). The median duration of suspected drug therapy before the development of angioedema was 1 day with the range of 10 min to 23 days.

Conclusions Non-steroidal anti-inflammatory drugs and antibiotics were the most common drugs causing angioedema without urticaria. The duration of onset ranged from minutes to days. After stopping the suspected drugs, symptoms disappeared within 2–5 days in most patients.

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Keywords

angioedema, clinical features, drug-induced, prevalence

Conflicts of interest

All authors have neither conflicts of interest nor financial supports from the drug companies.

Introduction

Angioedema is an abrupt localized swelling of the skin and mucous membranes of the face, lips, mouth, throat, larynx, extremities and genitalia. If the mucosa of the upper airways and gastrointestinal tract is affected, this can lead to life-threatening asphyxia and violent abdominal pain, vomiting and/or diarrhoea respectively. Angioedema generally develops over minutes to hours and resolves in 24–48 h. Pruritus is usually absent, unless the angioedema is associated with urticarial lesions. Pain and heat are variably present. Angioedema may occur in isolation, accompanied by urticaria or as a component of anaphylaxis.^{1,2}

Angioedema results from the release of inflammatory mediators that cause dilation and increase permeability of capillaries and venules.^{1–3} The common vasoactive mediators are histamine and proteases that are associated to acute allergic angioedema. Moreover, cyclooxygenase (COX) products such as prostaglandin D₂, cysteinyl leukotrienes, cytokines and chemokines may be involved in the pathogenesis of angioedema. Some forms of angioedema are mediated by bradykinin and complement components that derive from plasma and tissue fluids.¹

Angioedema without urticaria is the clinical syndrome that can be caused by an adverse drug reaction (ADR).^{1,3} Naldi *et al.*⁴ showed that 171 of 2224 patients with ADR (7.7%) reported to the spontaneous surveillance systems of four Italian regions, had angioedema pattern and it was the most frequent serious skin reaction. Patel *et al.*⁵ reported that 35 of 200 patients with cutaneous drug eruptions (17.5%) had urticaria and angioedema pattern. Kulthanan *et al.*² reported that 34 of 105 angioedema patients (32%) resulted from drugs.

The pathogenesis of angiotensin converting enzyme inhibitor (ACEI)-induced angioedema appears to be associated with a decreased degradation and catabolism of bradykinin. Non-steroidal anti-inflammatory drugs (NSAID) can cause angioedema with or without urticaria. The pseudoallergic reaction can be explained by the shunting of arachidonic acid metabolites from COX pathway to the lipoxygenase pathway. Some studies suggested that only COX 1 inhibitors caused pseudoallergic angioedema.^{1,3,6–9} However, other reports demonstrated that preferential or selective COX 2 inhibitors were the ones to induce angioedema or urticaria.^{10–16} Angioedema associated

with antibiotic drugs such as penicillin and sulfa drugs had been reportedly caused by an acute allergic angioedema. Urticaria is commonly present in this setting. This type of angioedema is dependent on sensitization of the mast cells by specific IgE that is bound to the high affinity IgE receptor FcεR1. Exposure to specific antigen in causative drug causes cross-linking of receptors leading to mast cell degranulation. The mediators such as histamine, tryptase and chymase lead to angioedema.¹

Some cases of angioedema have been reported after treatments with fibrinolytic agents in patients with acute myocardial infarction, acute ischemic stroke and deep vein thrombosis.^{17–21} Previous reports suggested the possibility of angioedema associated with the use of oestrogen, psychotropic drugs, metoprolol, calcium channel antagonist, amiodarone, voriconazole and bupropion.^{3,22–29}

The purpose of our study was to assess the prevalence of patients with drug-induced angioedema without urticaria among patients with ADR and to study the clinical features of these patients, including culprit drugs and outcome, in the setting of a university hospital.

Materials and methods

This study was approved by Siriraj Institutional Review Board, Siriraj Hospital, Mahidol University, Bangkok, Thailand. We retrospectively reviewed case records of patients with drug-induced angioedema without urticaria of the ADR centre, Siriraj Hospital, between January 2007 and December 2008. Patients with age at least 15 years were enrolled in this study.

Angioedema was diagnosed by an attending physician by having abrupt swelling of skin and mucous membranes of the face, lips, mouth, throat, larynx, extremities and genitalia without evidence of infection, traumatic or other clear causes of the swelling.² Demographic data, suspected drugs, clinical characteristics, course of angioedema, treatments and outcomes were studied. Moreover, personal history of allergic rhinitis, atopic dermatitis, asthma, allergic conjunctivitis and previous drug allergy was obtained.

Causality assessment of ADR was assessed by physicians and pharmacists at the ADR centre based on history, clinical and laboratory data. The assessment was classified into five levels according to World Health Organization guidelines.³⁰

- 1 Certain means that the adverse reaction has occurred during the time period, which corresponds with the drug usage. However, the reaction cannot be explained by pre-existing disease, other concomitantly used drug or other chemical substance. Furthermore, the adverse reaction obviously improved or disappeared after the patient stopped using the drug, but recurred after they started using it again. Thus, the pharmacological mechanism or the adverse event is clearly evident as an explanation.
- 2 Probable means the adverse reaction has occurred during the time period, which corresponds with the drug usage and is probably not associated with pre-existing disease, concomitantly used drug or other chemical substance.

When the patient stopped using drug, the adverse reaction improved or disappeared. However, information about repeat drug use may not be available.

- 3 Possible means the adverse reaction has occurred during the time period, which corresponds with drug use, but may be explained by pre-existing disease, concomitantly used drug or other chemical substance. Information about the patient stopping use of the drug is not complete or is not available.
- 4 Unlikely means the adverse reaction has occurred during a time period, which does not correspond with the drug use and cannot be explained by pre-existing disease, concomitantly used drug or other chemical substance.
- 5 Unclassified means there is no available information to show the connection between the health product and the adverse event.

Statistical analysis

Prevalence of patients with drug-induced angioedema without urticaria was displayed by number and percentage. Descriptive statistics, e.g. mean, median, minimum, maximum and percentages, were used to describe demographic data, suspected drugs, clinical characteristics, course of disease, treatments and outcomes. The *t*-test and chi-squared test were respectively used for the statistical analysis among continuous and categorical data. As some patients were lost to follow-up, Kaplan–Meier survival curve was applied to determine the probability of symptom resolution at each time point. All statistical data analyses were performed using SPSS for Windows version 10.0.

Results

Ninety-eight Thai patients with drug-induced angioedema without urticaria were enrolled in this study. There were 2163 patients reported to the ADR centre between January 2007 and December 2008. The prevalence of patients with drug-induced angioedema without urticaria was 2.3%/year. Mean (SD) age of patients was 46.1 (17) years. Characteristics of these patients are shown in Table 1.

One hundred and eight drugs were suspected of causing angioedema without urticaria. One patient may have used more than one of the suspected drugs. Suspected drugs which induced angioedema without urticaria are shown in Table 2. Causality assessment of ADR were probable (28.6%) and possible (71.4%). The common sites of angioedema were periorbital area (67.3%) and lips (27.6%). The median duration of suspected drugs therapy before the development of angioedema was 1 day with the range of 10 min to 23 days. All patients stopped using suspected drugs after developing angioedema and received medical alert cards with ADR information. The median duration between stopping suspected drugs and the disappearance of angioedema was 1 day with the range of 0.5–16 days. Twenty-nine of 98 (29.6%) patients had

Table 1 Demographic and clinical data of patients with drug-induced angioedema without urticaria (*n* = 98)

Characteristics	No. patients (%)
Gender	
Female	76 (77.6)
Male	22 (22.4)
Occupation	
Housewife	28 (28.6)
Labourer	24 (24.5)
Officer	15 (15.3)
Department that patients visited	
Outpatient department	95 (96.9)
Inpatient department	3 (3.1)
First attack of angioedema	74 (75.5)
Anaphylaxis	1 (1)
Systemic involvement	7 (7.1)
Breathlessness	4 (4.1)
Rhinitis	1 (1)
Nausea and vomiting	1 (1)
Diarrhoea	1 (1)
Personal history of atopy	21 (21.4)
Allergic rhinitis	15 (15.3)
Asthma	5 (5.1)
Allergic conjunctivitis	1 (1)
Treatment	
None	60 (61.2)
Antihistamine	38 (38.8)
Corticosteroids	15 (15.3)
Epinephrine	1 (1)

previous history of drug allergy (NSAID, 40.4%; antibiotics, 29.8%). The median number of previous drug allergy event was one, with the range of 1–8. Angioedema was the most common feature (55.1%) in patients with previous drug allergy that patients had. Ten of 98 patients (10.2%) had history of receiving drugs that had cross reactivity. NSAID were the most common cross reactive drugs (70%).

Non-steroidal anti-inflammatory drugs were the most frequent cause (50%) of angioedema in this study. The most common drugs were ibuprofen and diclofenac. Single and multiple NSAID which induced angioedema were 77.8% and 22.2% of patients with NSAID-induced angioedema respectively. One-third of patients with multiple NSAID-induced angioedema had a personal history of atopy. The mean onset of angioedema in NSAID and non-NSAID groups was 1.8 and 3.3 days respectively and had significant difference (*P*-value <0.05). There were twelve patients who had selective COX 2 inhibitor-induced angioedema. Among these, three patients (25%) had history of taking other selective COX 2 inhibitors without angioedema. The others had no history of taking selective COX 2 inhibitor other than the one that caused angioedema. Three of 12 patients with selective COX-2 inhibitor-induced angioedema (25%) had histories of conventional NSAID-induced angioedema.

Table 2 Suspected drugs that induced angioedema without urticaria (*n* = 108)

Suspected drugs	<i>n</i> (%)
NSAID	54 (50)
Ibuprofen	13 (12)
Diclofenac	8 (7.4)
Etoricoxib	7 (6.5)
Celecoxib	5 (4.6)
Acetaminophen	4 (3.7)
Naproxen	4 (3.7)
Piroxicam	4 (3.7)
Aspirin	3 (2.8)
Mefenamic acid	2 (1.8)
Nimesulide	2 (1.8)
Meloxicam	1 (0.9)
Tenoxicam	1 (0.9)
Antibiotics	22 (20.4)
Amoxycilin	5 (4.6)
Norfloxacin	3 (2.8)
Ceftriaxone	2 (1.9)
Ciprofloxacin	2 (1.9)
Roxithromycin	2 (1.9)
Ampicillin	1 (0.9)
Azithromycin	1 (0.9)
Cefaclor	1 (0.9)
Cephalexin	1 (0.9)
Clindamycin	1 (0.9)
Dicloxacilin	1 (0.9)
Doxycycline	1 (0.9)
TMP-SMX	1 (0.9)
Muscle relaxants	10 (9.3)
Ophenadrine	8 (7.4)
Eperisone	1 (0.9)
Tolperisone	1 (0.9)
ACEI	4 (3.7)
Enalapril	3 (2.8)
Perindopril	1 (0.9)
Others	
Gabapentin	2 (1.8)
Cimetidine	1 (0.9)
Dexamethasone	1 (0.9)
Dipyrrone	1 (0.9)
Enantone	1 (0.9)
Oestrogen	1 (0.9)
Fenofibrate	1 (0.9)
Glucosamine sulphate	1 (0.9)
Methimazole	1 (0.9)
Pantoprazole	1 (0.9)
Pseudoephedrine + tripolidine	1 (0.9)
Pethidine	1 (0.9)
Pregabalin	1 (0.9)
Propylthiouracil	1 (0.9)
Rabeprazole	1 (0.9)

Table 2 Continued

Suspected drugs	n (%)
Simvastatin	1 (0.9)
Terbinafine	1 (0.9)

NSAID; non-steroidal anti-inflammatory drugs, ACEI; angiotensin converting enzyme inhibitor, TMP-SMX; trimethoprim-sulfamethoxazole.

The common suspected groups of antibiotic drugs causing angioedema without urticaria were penicillins (6.5%) and fluoroquinolones (4.6%). The mean onset of angioedema in antibiotic and non-antibiotic groups was 1.6 and 2.8 days respectively and had significant difference (P -value <0.05). Three of 22 patients with antibiotic-induced angioedema (13.6%) had history of atopy, but there was no significant difference in non-antibiotic groups. Orphenadrine without concomitantly used NSAID was the most common muscle relaxant that caused angioedema without urticaria (7.4%). Four of 98 patients (3.7%) had ACEI-induced angioedema. Beside lips and tongues, abdominal and laryngeal manifestations of angioedema did not develop in all four patients. The mean onset of angioedema in ACEI and non-ACEI groups was 10.2 and 2.3 days respectively and had significant difference (P -value <0.05). Characteristics of patient, classified by groups of suspected drugs are shown in Table 3.

One woman (1%) developed her first episode of angioedema at the age of 21 when she started taking contraceptive pills containing oestrogen. The site of her cutaneous involvement was the whole face. She did not have respiratory or abdominal manifestations. After stopping the drug, she was treated with antihistamine, and angioedema was markedly improved in 1 day.

Only one male patient had anaphylactic symptoms. He was 52 years old. Previously, he took acetaminophen and tolperisone without a problem. Two weeks before admission, he got pruritus

after taking acetaminophen and the symptom disappeared when he stopped the drug. At this time, he developed acute onset of angioedema and hypotension after taking tolperisone and acetaminophen for 5 and 1 h respectively. He was admitted and treated with parenteral antihistamine, adrenaline and corticosteroids. Angioedema disappeared completely after 2 days. Causality assessment was 'possible' for both acetaminophen and tolperisone because rechallenge could not be performed.

Figure 1 shows the Kaplan–Meier curves demonstrating the duration of the disease after stopping the suspected drugs in patients with drug-induced angioedema without urticaria. They were classified as groups of suspected drugs. Mean durations of

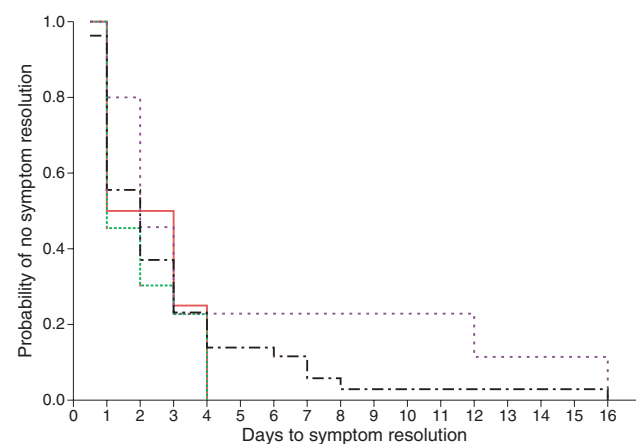


Figure 1 The Kaplan–Meier curves demonstrated the duration of the diseases in patients with drug-induced angioedema without urticaria, classified by groups of suspected drugs. —, angiotensin converting enzyme inhibitors; ---, non-steroidal anti-inflammatory drugs; ···, antibiotic drugs; - · - ·, muscle relaxant drugs.

Table 3 Demographic and clinical data of patients with drug-induced angioedema without urticaria, classified by suspected drug groups

Suspected drug groups characteristics	NSAID	Antibiotic drugs	Muscle relaxants	ACEI
n (%)	54 (50)	22 (20.4)	10 (9.3)	4 (3.7)
Gender, female : male	2.9 : 1	6.3 : 1	2.3 : 1	3 : 1
Mean age $\pm$ SD (years)	44.2 $\pm$ 14.8	43.1 $\pm$ 19	52.2 $\pm$ 16.3	59 $\pm$ 16.4
Personal history of atopy (%)	27.8	13.6	10	0
Median onset (days) (minimum, maximum)	1 (0.04, 14)	1 (0.01, 8)	2.5 (0.04, 9)	8.5 (1, 23)
Site of angioedema (%)				
Lips	18.5	27.3	20	75
Periorbital area	72.2	77.3	50	25
Whole face	35.2	31.8	50	25
Treatment (%)				
None	55.6	63.6	50	50
Antihistamine	44.4	36.4	50	50
Corticosteroids	22.2	13.6	0	25

NSAID, non-steroidal anti-inflammatory drugs; ACEI, angiotensin converting enzyme inhibitor.

NSAID, antibiotic, muscle relaxant and ACEI groups were 2.8, 2, 4.8 and 2.3 days respectively. However, there were no statistically significant differences (log rank *P*-value 0.434).

Discussion

The prevalence of urticaria and angioedema to NSAID in the general populations had been reported to be 0.1–3%.^{2,31,32} Naldi *et al.*⁴ reported that NSAID were causative agents in 60 of 171 patients with drug-induced angioedema (35.1%). The common drugs were aspirin (13.5%) and nimesulide (7%). Patel *et al.* reported that 17 of 35 patients with drug-induced urticaria/angioedema (48.6%) were caused by NSAID; the common ones were ibuprofen (14.3%) and diclofenac (8.6%). Thai FDA report stated that out of 364 cases of drug-induced angioedema in 2006, 101 patients (27.7%) had NSAID-induced angioedema (ibuprofen, 29.7%; aspirin, 10%). Kulthanan *et al.*² reported that 21 of 105 (20%) Thai patients had angioedema that resulted from NSAID. The common NSAID were ibuprofen, aspirin and diclofenac.² Banerji *et al.*³³ reported that 70% of inpatients with angioedema were caused by NSAID. This study demonstrated that 50% of patients with drug-induced angioedema resulted from NSAID. The common drugs were ibuprofen and diclofenac. Aspirin was less commonly suspected of drug-induced angioedema without urticaria. Previous studies reported that the common site of involvement of NSAID-induced angioedema was periorbital areas.^{2,34} Similar results were shown in this study.

Even though some previous studies reported that selective COX 2 inhibitors could induce angioedema or urticaria, it was considered to be a safer alternative for patients with previous adverse reaction to conventional NSAID.^{10–16} The mechanism of selective COX 2 inhibitor-induced angioedema was still unclear. COX-2 inhibitors may bind to proteins, function as haptens and initiate a variety of immune responses, or it is possible that, in susceptible people, inhibition of COX-2 initiates pseudoallergic cutaneous reactions.³² This study demonstrated that selective COX 2 inhibitors were a contributing cause in 12.2% of patients with drug-induced angioedema. Three of 12 patients with selective COX 2 inhibitors-induced angioedema had a history of using other selective COX 2 inhibitor without angioedema. There was no patient who had angioedema from two selective COX 2 inhibitors. Perhaps, ADR for COX 2 inhibitors might be drug specific-, not a class-effect. However, this study had only small sample size of patients with selective COX 2 inhibitors-induced angioedema. Further studies are needed.

The prevalence of ACEI-induced angioedema was reported on 0.1–0.5% of patients taking these drugs.³⁵ Even though the usage of ACEI is popular in our country, Kulthanan *et al.*² reported that 1% of Thai patients with angioedema resulted from ACEI. In the same year, Thai FDA reports stated that seven of 364 (1.9%) cases of drug-induced angioedema were induced by ACEI. This study reported that 3.7% of cases of angioedema were caused by ACEI. Previous studies reported that Black American patients were more

susceptible to this complication compared to White Americans, possibly due to the differences in the kallikrein-kinin system.^{36–38} The racial difference may explain a few cases of ACEI-induced angioedema in this study. ACEI-induced angioedema typically involves the mouth, lips, tongue, larynx, pharynx and subglottic tissues.^{1,39} This study demonstrated that the lips were the most common site of involvement of ACEI-induced angioedema. Previous studies reported that intestinal oedema may also develop and be accompanied of the sudden onset of abdominal pain, diarrhoea and vomiting in patients taking ACEI. However, these manifestations were rare.^{40–42} In this study, no patients reported the abdominal manifestations of angioedema. Angioedema can first manifest from a few hours up to 8 years after an ACEI was first taken. However, approximately 50% of cases of ACEI-induced angioedema occur within the first week of treatment. Moreover, it recurs irregularly while under treatment. Some cases of late-onset angioedema have been observed weeks after discontinuation of the ACEI.^{1,3,37,39,43} Our study demonstrated that median onset of ACEI-induced angioedema was 8.5 days. Kostis *et al.*³⁶ reported that older age (>65 years), history of any previous drug rash and seasonal allergies were additional risk factors. In contrast, no significant risk factor was detected in this study. However, it should be noted that we had a few cases of ACEI-induced angioedema.

Angioedema induced by antibiotic drugs is generally caused by an allergic mechanism.¹ Naldi *et al.* reported that antibiotics were the causative agents in 61 of 171 patients with drug-induced angioedema (35.7%). The most common drugs were amoxycilin (4.7%) and cotrimoxazole (4.1%).⁴ Kulthanan *et al.*² reported that 11.4% of patients with angioedema resulted from antibiotic drugs; the most common was amoxycilin (25%). This study reported that 20.4% of patients resulted from antibiotics; the most common was amoxycilin. Norfloxacin was the second most common cause of angioedema that might be the result of an increased use of fluoroquinolones. Antibiotic-induced angioedema typically occurs within minutes to a few hours following exposure to drugs.¹ This study demonstrated that the median onset of antibiotic-induced angioedema was 1 day. The longer onset may be reliant on prior sensitizing exposure. Urticaria is commonly present in allergic angioedema.¹ However, this study demonstrated that antibiotic-induced angioedema alone was not uncommon. Our study showed that 13.6% of patients with antibiotic-induced angioedema had a personal history of atopy, mostly allergic rhinitis. In 2002, Vichyanond *et al.*⁴⁴ reported that the prevalence of allergic rhinitis and asthma in Thai university students was 26.3% and 8.8% respectively. These data implied that the prevalence of atopy was not increased in our patients with antibiotic-induced angioedema. Reported sites of predilection of allergic angioedema were face, especially lips and periorbital area.¹ This study also demonstrated that face, lips and periorbital area were the common sites of antibiotic-induced angioedema.

Ueno *et al.*⁴⁵ reported one female with eperisone hydrochloride-induced angioedema. Ribi *et al.*⁴⁶ reported four patients with anaphylaxis attributed to the intake of the centrally acting muscle relaxant tolperisone hydrochloride. Orphenadrine is an anticholinergic and *N*-methyl-D-aspartic acid receptor antagonist. The action of orphenadrine was against muscle spasm and the pain produced by it.^{47–49} There were no previous reports of angioedema caused by orphenadrine. This study demonstrated that muscle relaxants, especially orphenadrine, were common as a cause of angioedema.

The relationship between oestrogen and angioedema had been reported in previous studies. Oestrogen can exacerbate the attack of angioedema in patients with hereditary angioedema.^{1,3,50–53} Oestrogen can reduce C1 inhibitor level and functional assay.⁵⁴ This study demonstrated one female who developed her first episode of angioedema when she started taking oestrogen. Unfortunately, the patient refused further investigation for certain diagnosis.

A few previous studies reported cases of anaphylaxis/anaphylactoid reactions to acetaminophen.^{55–57} The intensity of reaction has been found to be dose related and is often unrelated to aspirin hypersensitivity or a history of atopy. Most reports detailed the onset of symptoms within 30–60 min of ingesting acetaminophen, as it occurs with immediate hypersensitivity reactions, but that association has not been confirmed. The mechanism of the anaphylactoid reaction to acetaminophen remains uncertain.^{55–57} This study reported one patient who presumed to have acute onset of angioedema and hypotension after taking acetaminophen and tolperisone.

In conclusion, the prevalence of drug-induced angioedema without urticaria among patients with ADR was 2.3%/year. NSAID and antibiotics were the most common drugs causing angioedema without urticaria among the Thai patients. The duration of onset of drugs causing angioedema without urticaria ranged from minutes to days. The most common affected site was the periorbital area. After stopping the suspected drugs, symptoms disappeared within 2–5 days in most patients.

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