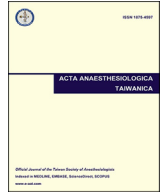




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## Research Paper

## Epidemiology of anaphylaxis: A retrospective cohort study in Taiwan

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## ABSTRACT

**Objective:** Medication-induced anaphylaxis is a potentially fatal event. Little is known at present about the patterns of medication-induced anaphylaxis in Asian countries. The current study aims to examine the pattern of documented incidences of drug-associated anaphylaxis in Taiwan over a 9-year period.

**Methods:** Cases of medication-associated anaphylaxis documented in the Taiwan National Health Insurance claims database during a span of 9 years (from January, 1997 to December, 2005) encompassing approximately 23 million person-years were reviewed. The database quantifies the drugs dispensed, clinical diagnoses, and patient demographics.

**Results:** Overall, 92 reports of medication-associated anaphylaxis in 92 patients were identified with potential causative agents documented. In this group, nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics were the main classes of medications most frequently implicated as the causative agent(s) in 89% of the cases. NSAIDs alone were implicated in 28% of cases, whereas antibiotics alone were implicated in another 28% of these cases. The use of multiple medications including either antibiotics or analgesics was documented in an additional one-third of the cases. A number of different NSAIDs including aspirin, diclofenac, ketoprofen, ketorolac, and meperidine were documented as the causative agents. Among the reported cases of antibiotics-induced anaphylaxis, cefazolin was the most frequently reported causative agent with 11 cases, followed by amoxicillin with four cases.

**Conclusion:** Antibiotics and NSAIDs were the two main classes of medications most frequently implicated in the reports of anaphylaxis in the Taiwanese population. Although this may be related to the frequent use of these medications in the Taiwanese population, the observation here does advocate for reduced combination of NSAIDs and antibiotics, and more careful patient monitoring when they are combined.

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## 1. Introduction

Anaphylaxis is a serious and occasionally fatal adverse event. The American College of Allergy, Asthma and Immunology describes anaphylaxis as an acute systemic reaction caused by immunoglobulin E (IgE)-mediated immunological release of mediators from mast cells and basophils to allergenic triggers, such as food, insect venoms, latex, and medication.<sup>1</sup> Etiologically, anaphylaxis can be divided into anaphylaxis and anaphylactoid reaction, the later also known as pseudoanaphylaxis. The difference between the two is that anaphylactoid reaction is an IgE-mediated reaction

whereas anaphylactoid reaction is not. The severity, onset, and appearance of both reactions shows significant overlap clinically. Thus, according to the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group, the IgE- and non-IgE-mediated reactions are considered under a single term, anaphylaxis; this combined definition is used in the current study.

In a review by the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group, an estimated 1.2% to 15% of the total United States population is believed to be at risk of anaphylactoid reaction.<sup>2</sup> Most studies speculate that the prevalence of anaphylaxis is underestimated from underreporting.<sup>3,4</sup> In addition, some studies examined a relatively small number of participants that are not representative of the general population.<sup>5</sup> The most common causes of anaphylaxis are food, drug, and idiopathic reactions.<sup>6–10</sup> The most

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common medication causes of anaphylaxis found by earlier studies include antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs), particularly when the drugs are administered parenterally.<sup>4</sup> However, there appear to be several differences in the profiles of causative drugs for anaphylaxis across different populations.<sup>2,11–13</sup>

The aim of this study is to examine patterns of drug association in documented cases of anaphylaxis in the Taiwanese population when the drugs are administered parenterally.

## 2. Methods

### 2.1. Study population

This cohort study was based on a review of a subset of data from the National Health Insurance Database, provided by the Taiwan National Health Research Institutes. The National Health Insurance program, which was initiated in 1995, covers 99% of the entire population (more than 23 million people) in Taiwan. This National Health Insurance Database consisted of detailed healthcare data including demographic data, visiting date, visiting department, diagnostic codes, procedures, prescriptions, and medical expenses. The International Classifications of Diseases, ninth Revision, Clinical Modification format (ICD-9), was used for disease diagnosis. The data subset used in the analysis consists of 1 million randomly selected population-representative individuals with no significant difference in age, sex, and medical expenses from the entire insured population.

### 2.2. Study participants

Data from inpatient or outpatient individuals with a diagnosis of anaphylaxis (ICD-9 codes 995.0) between January 1, 1999, and December 31, 2005 were retrieved. As diagnostic validity is often under question, patients who were diagnosed with anaphylaxis repeatedly were excluded, and clinical history was reviewed to ensure that treatment for anaphylaxis was given subsequent to the diagnosis of anaphylaxis. To ensure that anaphylaxis was most likely attributable to medication, patients with diagnoses pertaining to other causes of anaphylaxis were excluded. These diagnoses include ICD-9 codes E905, E905.3, E905.8, E905.9, 997.0, 987.9, 988.0, 989.3, 989.5, 989.8, 989.9, and V048. Detailed prescriptions were reviewed for all cases from the period prior to and after the diagnosis of anaphylaxis, and all medications that were prescribed repeatedly after the diagnosis of anaphylaxis were removed as potential causative agents for anaphylaxis in the respective cases. In this study, potential anaphylaxis-inducing parenteral drugs were categorized into analgesics, antibiotics, and others.<sup>14,15</sup>

### 2.3. Statistical methods

The demographic data and medication list of the study participants were analyzed. Incidence rate estimations were calculated as the number of cases divided by the person-time at risk, which was estimated to be approximately 9 million person-years for the 9-year period of the study.

## 3. Results

Between January 1997 and December 2005, a total of 402 individuals with anaphylaxis reaction were identified. Of this total, 14 individuals were excluded because of repeated diagnosis of anaphylaxis, 42 were excluded because of nonmedication-related anaphylaxis, and 254 were excluded because no potential causative agents for anaphylaxis were identified. A total of 92 individuals

who experienced medication-induced anaphylaxis in which one or several likely causative agents were identified were included in the current study. Treatment for the anaphylaxis reaction in these individuals consisted of a combination of adrenaline, corticosteroids, and antihistamines. Based on the findings of our searches and reviews, we estimated the incidence of medication-induced anaphylaxis to be about 10.2 per 1 million person-years, affecting about 235 Taiwanese patients each year. The demographics of 92 study participants are summarized in Table 1. The mean age of this cohort is 50.37 years (range, 0 to 95 years). Most patients were in their fifth decade of life. Only six patients were younger than 10 years of age. There is a slight male predominance in the study cohort, with 55.4% being male and 44.6% being female.

The profiles of causative medications for anaphylaxis in the current study cohort are shown in Table 2. In cases where a single causative agent was identified, NSAID-type analgesics alone were implicated in 28% of cases whereas antibiotics alone were implicated in 27% of the cases. In 34% of cases, combinations of drug classes were felt to be causative of anaphylaxis; these comprised the following sub-groups: 1) analgesics and antibiotics; 2) either analgesics or antibiotics combined with another medication class; and, 3) analgesics and antibiotics combined together with medication from one or more additional classes. The overall distribution of classes of causative agents is illustrated in Figure 1. In the group with analgesics-only associated anaphylaxis, ketorolac and meperidine were each implicated in seven patients; aspirin was implicated in six patients, and diclofenac and ketoprofen were each implicated in four patients. In the group with antibiotic-only associated anaphylaxis, cephalosporins were the most frequently implicated antibiotic class (used in 19 patients), followed by penicillin and its derivatives, which were used in eight patients. The cephalosporins that were documented to cause anaphylaxis included cefazolin, cefmetazole, ceftriaxone, cefradine, ceftizoxime,

**Table 1**  
Demographic data of medication-induced anaphylaxis cases.

	N	%
Sex		
Male	51	55.4
Female	41	44.6
Age (y)		
Below 10	6	6.5
11–12	7	7.6
21–30	7	7.6
31–40	8	8.7
41–50	11	12.0
51–60	20	21.7
61–70	14	15.2
71–80	11	12.0
Older than 80	8	8.7
Mean age (y)	50.4 (±20.1)	

**Table 2**  
Causative agents in the analgesics group.

Causative agents	N
Aspirin	4
Diclofenac	4
Ketoprofen	4
Ketorolac	4
Meperidine	4
Morphine	1
Tramadol	1
Aspirin + ketorolac	1
Aspirin + meperidine	1
Ketorolac + meperidine	2

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