Clinical Allergology – Original Paper

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2017;173:51–60
DOI: 10.1159/000475498

Received: October 26, 2016
Accepted after revision: April 5, 2017
Published online: May 16, 2017

Use of Epinephrine in Patients with Drug-Induced Anaphylaxis: An Analysis of the Beijing Pharmacovigilance Database

Tiansheng Wang[a, e, g] Xiang Ma[a] Yan Xing[d] Shusen Sun[h] Hua Zhang[b] Til Stürmer[g] Bin Wang[c] Xiaotong Li[e] Huilin Tang[a, i] Ligong Jiao[f] Suodi Zhai[a]

Departments of [a]Pharmacy, [b]Epidemiology, and [c]Emergency Medicine, and [d]Division of Pulmonology and Allergy, Department of Pediatrics, Peking University Third Hospital, [e]Department of Pharmacy Administration and Clinical Pharmacy, Peking University Health Science Center, and [f]Beijing Adverse Drug Reaction Monitoring Center, Beijing, China; [g]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, [h]College of Pharmacy, Western New England University, Springfield, MA, and [i]Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University-Purdue University Indianapolis, Indianapolis, IN, USA

Keywords

Drug-induced anaphylaxis · Anaphylaxis · Epinephrine · Overdose · Clinical setting

Abstract

Background: Few studies assessing the use of epinephrine in drug-induced anaphylaxis (DIA) in the hospital setting are available. We utilized the Beijing Pharmacovigilance Database (BPD) to evaluate the appropriateness of epinephrine for DIA management. ***Methods:*** DIA cases collected in the BPD from January 2004 to December 2014 were adjudicated and analyzed for demographics, causative drugs, clinical signs, outcomes, initial treatment, route, dosing, and cardiovascular adverse events (CAE) of epinephrine. ***Results:*** DIA was primarily caused by antibiotics (38.4%), radiocontrast agents (11.9%), traditional Chinese medicine injections (10.9%), and chemotherapeutic drugs (10.3%). Only 708 (59.5%) patients received epinephrine treatment. Patients who received epinephrine were more likely to experience wheezing ($p < 0.001$) and respiratory arrest ($p < 0.001$). Among 518 patients with a complete record of the epinephrine administration route, the percentage of patients receiving it by intramuscular (IM) injection, subcutaneous (SC) injection, intravenous (IV) bolus injection, or IV continuous infusion was 16.9, 31.5, 43.5, and 8.1%, respectively. Among the 427 patients with a record of both the administration route and the dosing, an overdose was more likely with IV bolus (94.1%) in contrast to IM injection (56.6%; $p < 0.001$) or SC injection (43.7%; $p < 0.001$). Among the patients analyzed for CAE ($n = 349$), 17 patients accounted for 19 CAE, and 13 (76.5%) of these patients were overdosed with epinephrine. ***Conclusion:*** Underuse, inappropriate IV bolus use, and overdosing were the 3 major problems with epinephrine use in DIA in China. Educational training for health care professionals on the appropriate use of epinephrine in managing anaphylactic reactions is suggested.

Tiansheng Wang and Xiang Ma contributed equally to this work.

KARGER

E-Mail karger@karger.com
www.karger.com/iaa

Correspondence to: Dr. Suodi Zhai
Department of Pharmacy, Peking University Third Hospital
49 N Huayuan Rd., Haidian District
Beijing 100191 (China)
E-Mail zhaisuodi@163.com

Introduction

Anaphylaxis is a severe life-threatening systemic allergic reaction with a sudden onset that usually develops after exposure to an offending agent. Common triggers of anaphylaxis include food, hymenoptera venom, and drugs [1, 2]. Anaphylaxis is a medical emergency requiring rapid recognition and prompt management. Epinephrine is the recommended first-line treatment [3], and its delayed administration is an important risk factor for fatal anaphylaxis [2, 3].

Drugs are one of the most common causes of anaphylaxis [2]. According to a study by Jerschow et al. [4], drugs were the most common cause of 2,458 anaphylaxis-related deaths (58.8%) in the USA from 1999 to 2010. Recent evidence suggests that the prevalence of drug-induced anaphylaxis (DIA) in inpatients is approximately 0.03%, with a mortality rate of 3–9% [5]. However, most previous studies assessing anaphylaxis management have been limited to patients presenting to emergency departments (ED) [6–11] or outpatient allergy clinics [12–14]. Very few studies have been conducted to assess the use of epinephrine in patients who developed DIA in generalized clinical settings. Considering the prevalence and the potential severity of DIA, it is important for healthcare providers to manage DIA patients appropriately in the various clinical settings including outpatient, inpatient, and ED.

Thus, the objective of our study was to assess the use of epinephrine in patients who developed DIA in clinical settings using the Beijing Pharmacovigilance Database (BPD). Cases from the BPD were reported by health care professionals for patients who had DIA during patient encounters. The outcomes of interests were: (1) to analyze whether epinephrine was used and whether it was used as an initial treatment (first medication administered) to manage anaphylaxis, (2) to assess the route of administration (intramuscular [IM], subcutaneous [SC], intravenous [IV] bolus, or IV continuous infusion) and the dose utilized, and (3) to analyze whether any relationship exists between the dose used and the incidence of cardiovascular adverse events (CAE) associated with epinephrine.

Materials and Methods

Data Sources

The BPD used in this study was provided by the Beijing Adverse Drug Reaction Monitoring Center. The BPD contains records of severe adverse drug event (ADE) cases reported from 94 hospitals in the Beijing region. Its intent is to obtain well-defined, standardized data of affected patients experiencing ADE in the Beijing region of China. In each clinical setting (inpatient, outpatient, and ED), ADE are typically reported by physicians, pharmacists, and nurses to the respective pharmacy department. The widely accepted World Health Organization-Uppsala Monitoring Center (WHO-UMC) criteria were used to assess causality, and Certain and Probable/Likely categories were applied for the identification of an offending agent [15]. Once a case is confirmed as a severe ADE [16] (defined as at least one of the following outcomes: death, life-threatening symptoms, initial or prolonged hospitalization, disability or permanent damage, congenital anomaly or birth defect, requirement of intervention to prevent permanent impairment or damages, and other serious medical events), the patient's data are electronically reported to the BPD by a pharmacist. BPD reports include the following information: the severity of the ADE, demographic variables (gender, age, current disease, history of ADE, and history of family member ADE), triggering prescriptions (brand and generic name, formulation, dose, unit, frequency, route, initial and end dates, and indication), and a description of the ADE. The ADE information includes the reporting time, the category (anaphylaxis, pneumonia, gastrointestinal bleeding, myocardial infarction, etc.), the severity (moderate or severe), the onset date, a detailed description (symptoms, lab data, treatment, etc.), and the outcome (death, recovery, or improvement).

This study was exempt from further review by the Institutional Review Board of Peking University Third Hospital. Informed consent was not required from patients because this was a retrospective study using only deidentified data.

Database Inquiry

We downloaded the BPD database for the period covering January 1, 2004, to December 31, 2014, and assembled a base cohort that included all patients with a reported drug-induced acute allergic reaction or anaphylaxis using the following search terms: "anaphylaxis," "anaphylactic shock," "allergy," "allergic reaction," and "hypersensitivity." Prior to excluding mild hypersensitivity reactions from the base cohort, mutually exclusive definitions for drug-related allergic reactions and anaphylaxis using standard definitions [3, 6] were created by 2 physicians, i.e., an emergency physician (B.W.) and a pediatric allergist (Y.X.) (detailed information on the definition and severity of anaphylaxis is shown in online suppl. Appendix 1; see www.karger.com/doi/10.1159/000475498 for all online suppl. material). Patients with acute allergic reactions (grade 1) had only cutaneous involvement, whereas patients with anaphylaxis were those presenting with grade 2 or 3 reactions; patients with grade 2 reactions had mild-to-moderate manifestations of anaphylaxis, and those with grade 3 reactions had severe presentations with cutaneous, gastrointestinal, and potentially life-threatening respiratory or cardiovascular signs and symptoms [6].

Then the search terms "anaphylaxis," "anaphylactic reaction," "shock," "convulsion," "cardiac arrest," "respiratory arrest," "cyanosis," and "death" were used to identify patients with a potential anaphylaxis (grade 2 and 3 reactions). Eligibility required a complete record that included the patient's age, gender, trigger medications, anaphylactic symptoms, and treatment. Approximately 14.9% of the patients were excluded due to incomplete records.

Data Extraction

For patients with a potential anaphylaxis identified by the search terms in the BPD, we developed a data extraction form to validate the diagnosis and severity of anaphylaxis and the use of epinephrine. The following free-text information was collected:

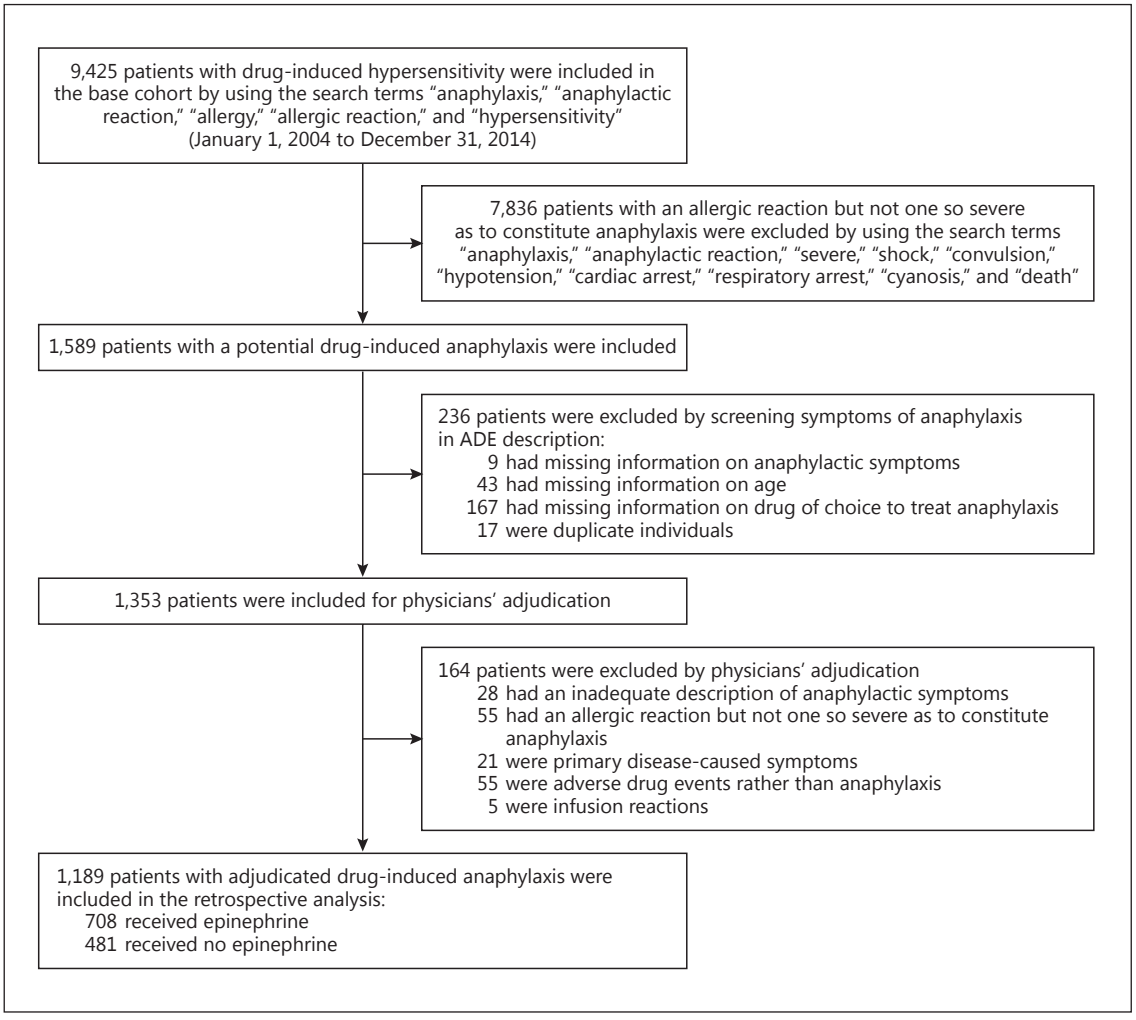

Fig. 1. Number of patients in the base cohort and the study cohort. ADE, adverse drug event.

(1) demographic variables and trigger prescriptions, (2) anaphylactic symptoms from different organ systems according to previous guidelines and literature [3, 10, 17, 18], (3) drugs that were used to treat the anaphylaxis (nonepinephrine anaphylaxis treatment included corticosteroids, antihistamines, and bronchodilators), and (4) the use of epinephrine (whether it was used as an initial treatment, the administration route, the dosing, and adverse events). We pretested the extraction form on database records from 250 patients and revised the form based on this pretest. Then, 2 trained extractors independently performed the extraction to ensure consistency; discrepancies were resolved by an investigator with experience in standardized medical record extraction (T.W.).

Adjudication

The physician adjudicators (B.W. and Y.X.) independently reviewed the information extracted from each case, determining the diagnosis of anaphylaxis and the case severity, as well as any CAE associated with the use of epinephrine. Physician reviewers used the published clinical diagnosis of anaphylaxis [1] and the severity definition [6] as a gold standard and referred to a recent publication by Campbell et al. [19] to judge the occurrence of epinephrine adverse events. Disagreement was dealt with through discussion. Patients with an acute allergic reaction were excluded and only those who met the diagnostic criteria for anaphylaxis were included in the analysis.

Study Design

The frequency of the initial administration route of epinephrine was assessed according to the severity of anaphylaxis reported. To analyze overdosage of epinephrine, epinephrine overdose for adults was defined as a dose that exceeded the recommended dose, i.e., 0.01 mg/kg body weight, with a maximum dose of 0.5 mg for IM and SC injections or 0.1 mg given by IV bolus [19–23]. Accordingly, the initial epinephrine dosing for adults was analyzed by different administration routes (IM, SC, and IV) and categorized as nonoverdose or overdose (≤0.5 vs. >0.5 mg for both IM and SC, and ≤0.1 vs. >0.1 mg for IV bolus). The initial pediatric epinephrine dosing was categorized as nonoverdose or overdose [21, 24,

Table 1. Demographic and clinical characteristics of patients with drug-induced anaphylaxis

Variable	Value	95% CI
Mean age ± SD, years	47.6±20.1	
Patients aged <18 years	91 (7.7)	6.3–9.3
Females	627 (52.7)	49.8–55.5
Triggers[a]		
Antibiotics	457 (38.4)	36.2–43.8
Radiocontrast agents	141 (11.9)	10.2–14.3
TCM (injection)	130 (10.9)	9.4–13.2
Chemotherapeutic drugs	122 (10.3)	8.8–12.4
Biologics	49 (4.1)	3.0–5.4
Anesthetics	25 (2.1)	1.3–3.0
Plasma substitutes	25 (2.1)	1.3–3.0
Parenteral nutrition	20 (1.7)	1.0–2.5
Hormones	16 (1.3)	0.8–2.1
NSAID	11 (0.9)	0.4–1.6
Associations[b]	110 (9.3)	7.8–11.5
Others[c]	82 (6.9)	5.6–8.8
Organ system involvement		
Mucocutaneous	563 (47.4)	44.6–50.5
Respiratory	659 (55.4)	52.5–58.3
Gastrointestinal tract	372 (31.3)	28.8–33.9
Cardiovascular	996 (83.8)	81.3–85.8
Central nervous system	596 (50.1)	47.4–53.1
Origin		
Inpatient	1,128 (96.2)	95.1–97.3
Outpatient	1 (0.1)	0.0–0.3
ED	43 (3.67)	2.6–5.0
Outcome		
ICU admission	73 (6.1)	4.9–7.8
Death	39 (3.3)	2.3–4.3

Values are presented as numbers (%) unless otherwise stated. Data were available for 708 patients in the epinephrine group and 481 patients in the nonepinephrine group, and from 1,172 patients with a clearly reported occurrence setting (inpatient, outpatient, or ED). [a] Sorted by groups of drugs most frequently implicated in drug-induced anaphylaxis. The classification of culprit medications was based on a publication by Baldo and Pham [5]. [b] Defined as cases in which more than one medication was suspected to cause the anaphylaxis, and these medications belonged to different pharmacotherapy classes. [c] Only the top 10 common culprit drugs are listed; detailed information on the Others category is presented in online supplementary Appendix 4. TCM, traditional Chinese medicine; NSAID, nonsteroidal anti-inflammatory drugs; ICU, intensive care unit; ED, emergency department.

25] based on weight-based dosing (≤0.01 vs. >0.01 mg/kg for IM and SC, with a maximum dose of 0.5 mg, or 0.001 mg/kg for the IV bolus route, with a maximum dose of 0.1 mg). When body weights were not available, pediatric IM/SC epinephrine dosing was assessed according to the child's age group (<6, 6–12, or >12 years) as suggested in the literature [21]. For IV bolus injections, age was used to estimate the body weight [26] to calculate the dose. In both adults and children, overdosing with IV continuous infusion was not analyzed since continuous infusion is usually titrated to clinical effects and not all of the information necessary to calculate the total dose was available.

The inclusion criteria for evaluation of CAE of epinephrine were: (1) records reporting both the administration route and the dosing of epinephrine (35.2% patients with missing values were excluded), (2) signs and symptoms of cardiovascular complications that developed after epinephrine administration where the onset was temporally related (within several minutes or noted on the next set of vital signs) to epinephrine administration, and (3) no concurrent use of epinephrine-like medications (e.g., norepinephrine and dopamine) or reporting of CAE prior to the use of such epinephrine-like drugs. CAE were defined according to Campbell et al. [19]. Hypertension was considered an adverse event if there was a recorded systolic blood pressure ≥180 mm Hg or a diastolic blood pressure ≥120 mm Hg. Cardiac ischemia required both a documented troponin T level elevation and symptoms suggestive of cardiac ischemia, such as chest tightness, pressure, or pain (detailed information is shown in online suppl. Appendix 2).

Variables that influenced the choice of therapy (epinephrine or nonepinephrine) for DIA patients were identified. The key baseline information, organ system involvements, and other nonepinephrine acute therapies to treat anaphylaxis in epinephrine and nonepinephrine users were compared.

Statistical Analysis

The statistical analysis was performed using SPSS version 22 (SPSS Inc., USA). Continuous variables were subjected to normality tests using a single-sample Kolmogorov-Smirnov test, and data with a normal distribution were expressed as means ± SD, those with a nonnormal distribution were expressed as medians (range), and the dichotomous variables were described as frequencies (%). Continuous variables were compared using an independent samples *t* test, while dichotomous variables were compared using the Pearson χ^2 test or Fisher's exact test. To identify independent clinical features (risk factors) associated with patients receiving epinephrine, bivariate logistic regression was used to derive OR and 95% CI of different variables. Variables with p values <0.2 in the bivariate analysis were included in a multivariate logistic regression analysis using forward stepwise selection processes. All tests were 2-tailed, and $p < 0.05$ was considered statistically significant.

Results

Demographic and Clinical Characteristics

Using our search terms, 9,425 patients with drug-induced hypersensitivity reactions were identified from the BPD. Of those, 1,189 patients with adjudicated anaphylaxis were included in our analysis (Fig. 1). Among these patients, the mean age was 47.6 years, 627 (52.7%) were female, and 91 (7.7%) were children (age <18 years) (Table 1). Among the 1,172 DIA cases with a clearly reported occurrence setting (inpatient, outpatient, or ED), the majority of the patients (1,128; 96.2%) developed anaphylaxis during their hospital stays. Forty-three patients present-

Table 2. Clinical features associated with epinephrine therapy

Variable	Epinephrine	Nonepinephrine	Bivariate analysis		Multivariate analysis	
			OR (95%)	*p* value	OR (95%)	*p* value
N	708 (59.5)	481 (40.5)				
Mean age ± SD, years	46.6±20.2	49.1±19.8	0.94 (0.89–0.99)	0.033	0.91 (0.86–0.97)[a]	0.003
Patients aged <18 years	62 (8.8)	29 (6.0)	1.50 (0.95–2.36)	0.082		
Patients aged ≥18 years	646 (91.2)	452 (94.0)	reference			
Females	368 (52.0%)	259 (53.8%)	0.93 (0.74–1.17)	0.526		
Current disease						
Asthma/COPD	14 (2.0)	5 (1.0)	1.91 (0.68–5.34)	0.210		
Cardiovascular disease	103 (14.5)	64 (13.3)	1.10 (0.79–1.54)	0.570		
Hypertension	38 (5.4)	22 (4.6)	1.18 (0.69–2.02)	0.553		
Mucocutaneous symptoms	346 (48.9)	217 (45.1)	1.16 (0.92–1.47)	0.203		
Flushing	120 (16.9)	100 (20.8)	0.78 (0.58–1.04)	0.094	0.70 (0.52–0.96)	0.024
Pruritus	137 (19.4)	88 (18.3)	1.07 (0.80–1.44)	0.648		
Diffuse urticaria	179 (25.3)	96 (20.0)	1.36 (1.03–1.80)	0.033	1.43 (1.06–1.91)	0.018
Angioedema	70 (9.9)	34 (7.1)	1.44 (0.94–2.21)	0.091		
Conjunctivitis	50 (7.1)	27 (5.6)	1.28 (0.79–2.07)	0.319		
Gastrointestinal tract symptoms	204 (28.8)	168 (34.9)	0.75 (0.59–0.97)	0.026		
Emesis	125 (17.7)	97 (20.2)	0.85 (0.63–1.14)	0.268		
Nausea	138 (19.5)	113 (23.5)	0.79 (0.60–1.04)	0.097		
Abdominal cramping	41 (5.8)	32 (6.7)	0.86 (0.54–1.39)	0.543		
Diarrhea	6 (0.8)	11 (2.3)	0.36 (0.13–0.99)	0.040		
Respiratory symptoms	431 (60.9)	228 (47.4)	1.73 (1.37–2.18)	<0.001		
Rhinorrhea	8 (1.1)	2 (0.4)	2.74 (0.58–12.95)	0.186		
Cough	26 (3.7)	12 (2.5)	1.49 (0.74–2.98)	0.257		
Voice change	37 (5.2)	25 (5.2)	1.01 (0.60–1.69)	0.983		
Dyspnea	138 (19.5)	105 (21.8)	0.87 (0.65–1.15)	0.326		
Wheezing	216 (30.5)	91 (18.9)	1.88 (1.42–2.49)	<0.001	1.96 (1.47–2.62)	<0.001
Cyanosis	129 (18.2)	55 (11.4)	1.73 (1.23–2.42)	0.001		
Respiratory arrest	68 (9.6)	16 (3.3)	3.09 (1.77–5.39)	<0.001	3.67 (2.07–6.49)	<0.001
Hypoxemia	69 (9.7)	39 (8.1)	1.22 (0.81–1.85)	0.335		
Cardiovascular symptoms	596 (84.2)	400 (83.2)	1.08 (0.79–1.47)	0.639		
Hypotension	587 (82.9)	398 (82.7)	1.03 (0.76–1.40)	0.857		
Cardiac arrest	44 (6.2)	9 (1.9)	3.48 (1.68–7.19)	<0.001		
Incontinence	34 (4.8)	31 (6.4)	0.73 (0.44–1.21)	0.221		
Central nervous system	350 (49.4)	246 (51.1)	0.93 (0.74–1.18)	0.563		
Presyncope	186 (26.3)	129 (26.8)	0.97 (0.75–1.26)	0.834		
Syncope	204 (28.8)	146 (30.4)	0.93 (0.72–1.20)	0.567		
Convulsions	53 (7.5)	39 (8.1)	0.92 (0.60–1.41)	0.693		
Other medications to treat anaphylaxis						
Corticosteroid	612 (86.4)	365 (75.9)	2.03 (1.50–2.74)	<0.001	2.02 (1.48–2.76)	<0.001
Bronchodilator	19 (2.7)	21 (4.4)	0.60 (0.32–1.14)	0.114	0.44 (0.23–0.84)	0.013
Antihistamine	197 (27.8)	147 (30.6)	0.88 (0.68–1.13)	0.307		

Values are presented as numbers (%) unless otherwise stated. COPD, chronic obstructive pulmonary disease. [a] Per 10-year increase in age.

Table 3. Route of epinephrine administration according to the severity of anaphylaxis

Severity of anaphylaxis	IM injection (n = 83)	SC injection (n = 155)	IV bolus (n = 214)	IV continuous infusion (n = 40)
Mild to moderate	15 (18.1)	24 (15.5)	25 (11.7)	4 (10.0)
Severe	68 (81.9)	131 (84.5)	189 (88.3)	36 (90.0)

Values are presented as numbers (%). Data were available for 518 patients in the epinephrine group with clearly documented administration routes (among these, 26 patients with cardiac or respiratory arrest prior to administration of epinephrine were excluded). The percentage of patients with IM injection, SC injection, IV bolus, and IV continuous infusion is 16.9, 31.5, 43.5, and 8.1%, respectively. IM, intramuscular; SC, subcutaneous; IV, intravenous. A significant difference was noted in the use of the different administration routes ($p < 0.001$). Overall, there was no significant difference in the percentage of patients with severe anaphylaxis between each administration route group ($\chi^2 = 2.931$, $p = 0.402$).

ed to an ED, and only 1 patient developed anaphylaxis in the outpatient setting and did not receive any treatment (Table 1). Among the 1,128 inpatients, the number of patients who received anaphylaxis treatment in an ED and in a non-ED setting was 123 and 1,005, respectively. The top 4 triggers of DIA were antibiotics (38.4%), radiocontrast agents (11.9%), traditional Chinese medicine injections (10.9%), and chemotherapeutic drugs (10.3%). The majority of patients (83.8%) experienced cardiovascular anaphylactic symptoms (82.8, 4.5, and 5.5% for hypotension, cardiac arrest, and incontinence, respectively). The percentage of patients who developed mucocutaneous compromise, respiratory compromise, and central nervous system symptoms was 47.4, 55.4, and 50.1%, respectively. Only 31.3% of the patients had gastrointestinal anaphylactic symptoms. Overall, 73 (6.1%) patients were admitted to an intensive care unit and 39 (3.3%) patients died of anaphylaxis during hospitalization.

Analysis of Therapies for the Treatment of Anaphylaxis

Of the 708 patients (59.5%) who received epinephrine treatment (Table 2), 699 had adequate documentation for analysis. Among them, 518 patients (74.1%) were administered epinephrine as an initial treatment, and 409 of 518 patients were coadministered corticosteroids. Of the 518 patients, 26 were excluded since they presented cardiac or respiratory arrest prior to the administration of epinephrine. The number of patients who received IM, SC, IV bolus injection, and IV continuous infusion was 83 (16.9%), 155 (31.5%), 214 (43.5%), and 40 (8.1%), respectively (Table 3). The median dosing for the IM, SC, and IV bolus injection routes was 1.0 (0.10–5.00), 0.5 (0.10–3.00), and 1.0 mg (0.04–5.00), respectively. Of the 1,189 anaphylactic patients, 977 (82.2%) received corticosteroids, and for 904 (92.5%) of them it was the initial therapy; 344 (28.9%) received antihistamines, and only 40 (3.4%) received bronchodilators.

Patients who received epinephrine during the course of anaphylactic treatment did not differ significantly from those who did not receive it with regard to gender or current disease (Table 2). In contrast, there was a significant difference between those who received epinephrine and those who did not in terms of age (mean 46.6 vs. 49.1 years, $p = 0.032$), risk of mortality (34 vs. 5 patients, OR 4.81; 95% CI 1.87–12.39), and intensive care unit admission (53 vs. 20 patients, OR 1.86; 95% CI 1.10–3.16). The severity of anaphylaxis was significantly different between the epinephrine group and the nonepinephrine group. There was a higher proportion of respiratory arrest (OR 3.09; 95% CI 1.77–5.39) and cardiac arrest (OR 3.48; 95% CI 1.68–7.19) in the epinephrine group compared to the nonepinephrine group. In cases of death in the epinephrine group, 19 of 34 (55.9%) patients experienced the onset of respiratory or cardiac arrest prior to the administration of epinephrine. Fifteen of 34 (44.1%) patients did not receive epinephrine as the initial treatment (online suppl. Appendix 3). Among 9 patients who received epinephrine as the initial treatment prior to respiratory or cardiac arrest, 2 were treated in community hospitals and underwent a referral process, and 3 experienced contrast media-induced anaphylaxis, resulting in severe anaphylaxis within 10 min. In the multivariate analysis, clinical features associated with receiving epinephrine were age (OR per 10-year increase in age: 0.91; 95% CI 0.86–0.97), flushing (OR 0.70; 95% CI 0.52–0.96), diffuse urticaria (OR 1.43; 95% CI 1.06–1.91), wheezing (OR 1.96; 95% CI 1.47–2.62), and respiratory arrest (OR

Table 4. Route of epinephrine administration and overdose according to the severity of anaphylaxis

Severity of anaphylaxis	IM injection (n = 76)			SC injection (n = 142)			IV bolus (n = 187)		
	overdose	nonoverdose	p value	overdose	nonoverdose	p value	overdose	nonoverdose	p value
Mild to moderate	10 (23.3)	3 (9.1)	0.104	12 (19.4)	10 (12.5)	0.263	20 (11.4)	2 (18.2)	0.843
Severe	33 (76.7)	30 (90.9)		50 (80.6)	70 (87.5)		156 (88.6)	9 (81.8)	

Values are presented as numbers (%) unless otherwise stated. Among 427 patients with a clearly reported administration route (IM injection, SC injection, or IV bolus) and dose of epinephrine (among these, 22 patients with cardiac or respiratory arrest prior to administration of epinephrine were excluded). The initial epinephrine dosing for adults was categorized as nonoverdose or overdose (≤0.5 vs. >0.5 mg for both IM and SC, and ≤0.1 vs. >0.1 mg for IV bolus). IM, intramuscular; SC, subcutaneous; IV, intravenous. Overall, there was no significant difference regarding the severity of anaphylaxis for each administration route (χ^2 = 1.638, p = 0.441). There was no significant difference in the percentage of severe anaphylaxis between the overdose and nonoverdose groups in each administration route group. Overall, there was significant difference regarding the overdose rate for each administration route (χ^2 = 103.944, p < 0.001). IV bolus was more likely to be associated with overdose compared to IM injection (p < 0.001) and SC injection (p < 0.001). There was no significant difference in overdose rates between IM injection and SC injection (p = 0.286).

3.67; 95% CI 2.07–6.49). Patients who received epinephrine were also more likely to receive corticosteroids (OR 2.02; 95% CI 1.48–2.76) and less likely to receive bronchodilators (OR 0.44; 95% CI 0.23–0.84).

Analysis of the Initial Administration Route and the Initial Dosing of Epinephrine

There was a significant difference in the use of different administration routes (p < 0.001), but there was no significant difference in terms of anaphylaxis severity between the administration routes (p = 0.402; Table 3). There was a significant difference between overdose rates per administration route (p < 0.001; Table 4). An overdose was more likely with the IV bolus route (94.1%) compared to IM (56.6%, p < 0.001) and SC routes (43.7%, p < 0.001). There was no association with anaphylaxis severity for any administration route (p = 0.441; Table 4). Among a total of 178 patients who experienced perioperative DIA, 78 patients received epinephrine administration with a clearly documented administration route, including 2 (2.6%) via the IM route, 7 (9.0%) via the SC route, 20 (25.6%) via IV continuous infusion, and 49 (62.8%) via IV bolus.

Analysis of CAE of Epinephrine

Among a total of 349 patients eligible for analysis of CV complications associated with epinephrine (Table 5), 17 patients developed 19 CAE, and 13 (76.5%) of them were overdosed. Patients who received IM epinephrine had no adverse events, 2 (11.8%) patients who received SC epinephrine had arrhythmia events, and 15 (88.2%) patients, including 1 child, who received an IV bolus injection had 17 CV events. Patients who received an epinephrine IV bolus (9.62%) were more likely to have adverse CV events than patients who received epinephrine via IM (0.00%, p = 0.016) or SC (1.64%, p = 0.006) injections.

Discussion

As far as we know, our study is the first to assess epinephrine use in patients with DIA using a large pharmacovigilance database from China. Use of the BPD permitted the collection of data on patients who received epinephrine for DIA in both ED and non-ED settings. Therefore, we are able to present the largest community-based cohort of patients with DIA. To our knowledge, this is the first study to evaluate epinephrine use in patients with DIA in a variety of clinical settings. The number of patients treated in an ED was lower than the number of inpatients and, because the BPD database includes patients with drug adverse events only, other triggers (food, venom, etc.) of anaphylaxis from ED were not included in our study. Consistent with previous studies [4, 5, 27, 28], the most common triggers of DIA in our patient population were antibiotics, radiocontrast agents, and chemotherapeutic drugs. Notably, our data suggests that, in addition to these known triggers, traditional Chinese medicine injections are one of the top triggers of DIA in Beijing, which is consistent with a recent study by Jiang et al. [11]. Further studies regarding the safety of traditional Chinese medicine injections are thus warranted [29]. A high proportion of patients developed cardiovascular symptoms (83.8%), and the mortality rate of

Table 5. Cardiovascular adverse events associated with routes of epinephrine administration

Cardiovascular adverse events[a]	IM injection (n = 0)		SC injection (n = 2)		IV bolus (n = 17)[b]	
	overdose	nonoverdose	overdose	nonoverdose	overdose	nonoverdose
Hypertension	0	0	0	0	8 (47.1)	1 (5.9)
Arrhythmia	0	0	1 (50.0)	1 (50.0)	5 (29.4)	2 (11.8)
Ischemia	0	0	0	0	1 (5.9)	0
Stroke	0	0	0	0	0	0
Angina	0	0	0	0	0	0

Values are presented as numbers (%). We included 349 patients for cardiovascular event analysis, including 71 patients with IM injection, 122 with SC injection, and 156 with IV bolus. IM, intramuscular; SC, subcutaneous; IV, intravenous; cardiovascular adverse events. [a] The signs and symptoms of cardiovascular complications that developed after epinephrine administration where the onset was temporally related (within several min or noted on the next set of vital signs) to the epinephrine administration. [b] One patient presented with both hypertension and arrhythmia, and 1 patient presented with both arrhythmia and myocardial ischemia. One pediatric patient presented with arrhythmia. Overall, there was a significant difference regarding the CAE rate in each administration route ($\chi^2 = 16.728$, $p < 0.001$). IV bolus was more likely to be associated with CAE compared to SC injection ($p = 0.006$) and IM injection ($\chi^2 = 5.835$, $p = 0.016$). There was no significant difference in overdose rates between IM injection and SC injection ($p = 0.532$).

3.3% was comparable to those of previous studies [5, 30]. Most cases of DIA developed during patient hospitalizations and were managed by non-ED health care providers. The analysis suggests that epinephrine use in patients with DIA could be improved in the region studied.

Utilization of Epinephrine in Anaphylaxis Management

Epinephrine should be administered to anaphylaxis patients as a first-line treatment because a delayed administration has been shown to result in poor outcomes and fatality [10, 20]. Corticosteroids are not effective in acute anaphylaxis management [2, 3, 20, 31], and neither are antihistamines [31–33]. Overall, epinephrine is underused for DIA in the Beijing region, which is in line with previous studies [11, 34]. Our data indicates a low rate (59.5%) of epinephrine use and a suboptimal timing of use, with only 74.1% of patients receiving it as the initial treatment. Clinicians are more inclined to administer epinephrine to patients with respiratory symptoms (e.g., respiratory arrest and wheezing). We observed a higher mortality rate in epinephrine users (34 vs. 5), which was probably due to a delayed administration of epinephrine (in epinephrine users, 56% of the death cases experienced respiratory or cardiac arrest prior to epinephrine administration, and 47% of the death cases did not receive epinephrine as the initial treatment). This demonstrated the importance of early use of epinephrine for severe anaphylactic patients. Although the rate of use of antihistamines was not high (28.9%), the use of corticosteroids was considerable (977 of 1,189; 82.2%). Among the patients who received corticosteroids, the number of patients who received corticosteroids as a first-line treatment was substantial (904 of 977; 92.5%). The importance of a timely administration of epinephrine should be stressed in DIA management.

Assessment of the Epinephrine Administration Route

There is significant discrepancy between guidelines [2, 3] and actual practice in the Beijing region regarding the administration route of epinephrine. Based on a previous pharmacokinetic study in children not experiencing anaphylaxis, IM injection of epinephrine into the anterolateral thigh results in a higher and more rapid peak plasma concentration compared to SC injection in the arm [35], and thus IM should be the preferred administration route [3]. However, more patients in our study received SC epinephrine compared to IM administration (31.5 vs. 16.9%). IV continuous infusion of epinephrine should only be given to patients not responding to IM injection [3]. Nevertheless, our data showed that in 8.1% of cases the initial administration route of epinephrine was by continuous infusion. A possible explanation is that physicians' lack of knowledge regarding anaphylaxis treatment guidelines contributes to a high utilization of the IV route of administration. IV bolus administration of epinephrine should be avoided whenever possible due to the risk of cardiac

arrhythmias and the increased potential for inappropriate dosing [19, 36–38]. It should only be considered when a patient is experiencing an actual or impending cardiovascular collapse and is unresponsive to an epinephrine continuous infusion or when an epinephrine continuous infusion is not feasible due to time constraints [20]. However, our data showed that IV bolus injection was the most frequently (43.5%) used initial administration route; it was used about 5.4 times more than the IV continuous infusion route (8.1%). The data showed that there was no statistically significant relationship between the severity of the anaphylaxis and the treatment administration route selected. In this analysis, we excluded patients with cardiac or respiratory arrest prior to administration of epinephrine, since the route and dose of epinephrine should follow the guidelines for resuscitations. Furthermore, a relatively low proportion of perioperative cases could not account for the highly frequent choice of the IV route. The data support a need for further education of clinicians regarding the appropriate route of epinephrine administration in the management of anaphylaxis.

Implications of Overdosing of Epinephrine and CAE

The observation of the significantly higher risk of overdose subsequent to IV bolus administration of epinephrine is consistent with prior research [19]. Our finding of a significantly higher risk of cardiovascular complications associated with IV bolus injection compared to IM administration confirms the relative safety of IM administration reported by Campbell et al. [19]. Excluding patients with multiple presentations of CAE, 12 of the 15 patients (80%) who developed adverse CAE were in the overdose group, suggesting that bolus administration of IV epinephrine is associated with inappropriate dosing [19, 35–38].

Limitations

Our retrospective analysis was based on self-reported cases by health care professionals to the BPD database, and therefore our study has the following limitations: (1) we could not assess the prevalence of anaphylaxis in the region studied as we did not have information for the total patient base, (2) reporting biases may exist (most reported cases were hospitalized patients in the non-ED setting, and only severe anaphylactic cases may have been reported), (3) we may not have included all DIA patients in the BPD (cases were missed if clinicians did not report using terms related to allergy or anaphylaxis or hypersensitivity; e.g., a patient had bronchospasm, wheeze, and vomiting but was not described as "allergy" by clinicians when reporting to the BPD, and some reported cases were not included due to a lack of sufficient information), and (4) the causative drugs were identified using WHO-UMC criteria [15]. The drug hypersensitivity diagnostic workup could increase sensitivity when determining the causative drug for anaphylaxis [39–43]. However, such information was not recorded in the BPD. Despite this, the method we used should be robust against some of the reporting biases; rigorous inclusion/exclusion criteria were utilized and all potential anaphylaxis cases were adjudicated by trained physician/allergists, and only patients with confirmed anaphylaxis and a complete data record were included in the analysis.

Conclusion

Our study suggests that epinephrine use in DIA management in Beijing should be improved. Underuse of epinephrine, overuse of IV bolus administration, and overdosing of epinephrine are the 3 major problems. Our results highlight the risk of overdosing and CAE associated with IV bolus administration. Targeted educational programs on the utilization of consensus anaphylaxis management guidelines for optimal patient care are necessary.

Disclosure Statement

Til Stürmer received investigator-initiated research funding and support as principal investigator (R01/R56 AG023178) from the National Institute on Aging (NIA), and as coinvestigator (R01 CA174453, R01 HL118255, and R21-HD080214) from the National Institutes of Health (NIH). He also receives salary support as director of the Comparative Effectiveness Research (CER) Strategic Initiative from the NC TraCS Institute, he is a recipient of the UNC Clinical and Translational Science Award (UL1TR001111), and he receives support as director of the Center for Pharmacoepidemiology (current members: GlaxoSmithKline, UCB BioSciences, and Merck) and research support from pharmaceutical companies (Amgen and AstraZeneca) to the Department of Epidemiology, University of North Carolina at Chapel Hill. Dr. Stürmer does not accept personal compensation of any kind from any pharmaceutical company. He owns stock in Novartis, Roche, BASF, AstraZeneca, and Novo Nordisk. The remaining authors have no conflict of interests to disclose. This research received no funding from any funding agency in the public, commercial, or not-for-profit sectors.

References

1 Sampson HA, Munoz-Furlong A, Campbell RL, et al: Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–397.
2 Simons FE, Ebisawa M, Sanchez-Borges M, et al: 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J 2015;8:32.
3 Muraro A, Roberts G, Worm M, et al: Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014;69:1026–1045.
4 Jerschow E, Lin RY, Scaperotti MM, McGinn AP: Fatal anaphylaxis in the United States, 1999–2010: temporal patterns and demographic associations. J Allergy Clin Immunol 2014;134:1318–1328.e7.
5 Baldo BA, Pham NH: Classification and descriptions of allergic reactions to drugs; in: Drug Allergy: Clinical Aspects, Diagnosis, Mechanisms, Structure-Activity Relationships. New York, Springer, 2013.
6 Brown AF, McKinnon D, Chu K: Emergency department anaphylaxis: a review of 142 patients in a single year. J Allergy Clin Immunol 2001;108:861–866.
7 Cianferoni A, Novembre E, Mugnaini L, et al: Clinical features of acute anaphylaxis in patients admitted to a university hospital: an 11-year retrospective review (1985–1996). Ann Allergy Asthma Immunol 2001;87:27–32.
8 Lieberman P, Decker W, Camargo CA Jr, Oconnor R, Oppenheimer J, Simons FE: SAFE: a multidisciplinary approach to anaphylaxis education in the emergency department. Ann Allergy Asthma Immunol 2007; 98:519–523.
9 Oren E, Banerji A, Clark S, Camargo CA Jr: Food-induced anaphylaxis and repeated epinephrine treatments. Ann Allergy Asthma Immunol 2007;99:429–432.
10 Baalmann DV, Hagan JB, Li JT, Hess EP, Campbell RL: Appropriateness of epinephrine use in ED patients with anaphylaxis. Am J Emerg Med 2016;34:174–179.
11 Jiang N, Yin J, Wen L, Li H: Characteristics of Anaphylaxis in 907 Chinese patients referred to a tertiary allergy center: a retrospective study of 1,952 episodes. Allergy Asthma Immunol Res 2016;8:353–361.
12 Jarvinen KM, Sicherer SH, Sampson HA, Nowak-Wegrzyn A: Use of multiple doses of epinephrine in food-induced anaphylaxis in children. J Allergy Clin Immunol 2008;122: 133–138.
13 Kelso JM: A second dose of epinephrine for anaphylaxis: how often needed and how to carry. J Allergy Clin Immunol 2006;117:464–465.
14 Korenblat P, Lundie MJ, Dankner RE, Day JH: A retrospective study of epinephrine administration for anaphylaxis: how many doses are needed? Allergy Asthma Proc 1999;20: 383–386.
15 The Uppsala Monitoring Centre: The use of the WHO-UMC system for standardized case causality assessment. https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf (accessed March 11, 2017).
16 US Food and Drug Administration: What is a serious adverse event? https://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm (accessed March 3, 2017).
17 Simons FE, Sheikh A: Anaphylaxis: the acute episode and beyond. BMJ 2013;346:f602.
18 Brown SG: Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004;114:371–376.
19 Campbell RL, Bellolio MF, Knutson BD, et al: Epinephrine in anaphylaxis: higher risk of cardiovascular complications and overdose after administration of intravenous bolus epinephrine compared with intramuscular epinephrine. J Allergy Clin Immunol 2015;3:76–80.
20 Campbell RL, Li JT, Nicklas RA, Sadosty AT: Emergency department diagnosis and treatment of anaphylaxis: a practice parameter. Ann Allergy Asthma Immunol 2014;113: 599–608.
21 Soar J, Pumphrey R, Cant A, et al: Emergency treatment of anaphylactic reactions – guidelines for healthcare providers. Resuscitation 2008;77:157–169.
22 Lieberman P, Nicklas RA, Randolph C, et al: Anaphylaxis – a practice parameter update 2015. Ann Allergy Asthma Immunol 2015; 115:341–384.
23 Kemp SF, Lockey RF, Simons FER, et al: Epinephrine: the drug of choice for anaphylaxis – a statement of the World Allergy Organization. Allergy 2008;63:1061–1070.
24 Hegenbarth MA: Preparing for pediatric emergencies: drugs to consider. Pediatrics 2008;121:433.
25 Lane RD, Bolte RG: Pediatric anaphylaxis. Pediatr Emerg Care 2007;23:49–56.
26 Tinning K, Worth AC: Make your best guess: an updated method for paediatric weight estimation in emergencies. Emerg Med Australas 2007;19:528–534.
27 Demoly P: Drug hypersensitivity. Immunol Allergy Clin North Am 2014;34:xv–xvi.
28 Ribeiro-Vaz I, Marques J, Demoly P, Polonia J, Gomes ER: Drug-induced anaphylaxis: a decade review of reporting to the Portuguese Pharmacovigilance Authority. Eur J Clin Pharmacol 2013;69:673–681.
29 Guo YJ, Wang DW, Meng L, Wang YQ: Analysis of anaphylactic shock caused by 17 types of traditional Chinese medicine injections used to treat cardiovascular and cerebrovascular diseases. Biomed Res Int 2015;2015: 420607.
30 Fisher M, Baldo BA: Anaphylaxis during anaesthesia: current aspects of diagnosis and prevention. Eur J Anaesthesiol 1994;11:263–284.
31 Choo KJ, Simons E, Sheikh A: Glucocorticoids for the treatment of anaphylaxis: Cochrane systematic review. Allergy 2010;65: 1205–1211.
32 Sheikh A, Ten BV, Brown SG, Simons FE: H1-antihistamines for the treatment of anaphylaxis: Cochrane systematic review. Allergy 2007;62:830–837.
33 Sheikh A, ten Broek VM, Brown SG, Simons FE: H1-antihistamines for the treatment of anaphylaxis with and without shock. Cochrane Database Syst Rev 2007;1:CD006160.
34 Asai Y, Yanishevsky Y, Clarke A, et al: Rate, triggers, severity and management of anaphylaxis in adults treated in a Canadian emergency department. Int Arch Allergy Immunol 2014;164:246–252.
35 Simons FE, Roberts JR, Gu X, Simons KJ: Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol 1998;101:33–37.
36 Manivannan V, Campbell RL, Bellolio MF, Stead LG, Li JT, Decker WW: Factors associated with repeated use of epinephrine for the treatment of anaphylaxis. Ann Allergy Asthma Immunol 2009;103:395–400.
37 Karch SB: Coronary artery spasm induced by intravenous epinephrine overdose. Am J Emerg Med 1989;7:485–488.
38 Kanwar M, Irvin CB, Frank JJ, Weber K, Rosman H: Confusion about epinephrine dosing leading to iatrogenic overdose: a life-threatening problem with a potential solution. Ann Emerg Med 2010;55:341–344.
39 Rebelo Gomes E, Geraldes L, Gaspar Â, et al: Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs among adults: clinical features and risk factors for diagnosis confirmation. Int Arch Allergy Immunol 2016; 171:269–275.
40 Kepil Özdemir S, Öner Erkekol F, Ünal D, et al: Management of hypersensitivity reactions to proton pump inhibitors: a retrospective experience. Int Arch Allergy Immunol 2016; 171:54–60.
41 Blanca-López N, Pérez-Sánchez N, Agúndez JA, et al: Allergic reactions to metamizole: immediate and delayed responses. Int Arch Allergy Immunol 2016;169:223–230.
42 Guvenir H, Dibek Misirlioglu E, Capanoglu M, et al: Proven non-β-lactam antibiotic allergy in children. Int Arch Allergy Immunol 2016;169:45–50.
43 Pineda F, Ariza A, Mayorga C, et al: Role of histamine release test for the evaluation of patients with immediate hypersensitivity reactions to clavulanic acid. Int Arch Allergy Immunol 2015;168:233–240.