Research Article

Drug-induced anaphylactic reactions in Indian population: A systematic review

Tejas K. Patel, Parvati B. Patel, Manish J. Barvaliya[1], C. B. Tripathi[1]

Abstract

Background: Epidemiological data on drug-induced anaphylactic reactions are limited in India and are largely depending on studies from developed countries. **Aim:** The aim was to analyze the published studies of drug-induced anaphylaxis reported from India in relation with causative drugs and other clinical characteristics. **Materials and Methods:** The electronic databases were searched for Indian publications from 1998 to 2013 describing anaphylactic reactions. The information was collected for demographics, set up in which anaphylaxis occurred, causative drugs, incubation period, clinical features, associated allergic conditions, past reactions, co-morbid conditions, skin testing, IgE assays, therapeutic intervention and mortality. Reactions were analyzed for severity, causality, and preventability. Data were extracted and summarized by absolute numbers, mean (95% confidence interval [CI]), percentages and odds ratio (OR) (95% CI). **Results:** From 3839 retrieved references, 52 references describing 54 reactions were included. The mean age was 35.31 (95% CI: 30.52–40.10) years. Total female patients were 61.11%. Majority reactions were developed in perioperative conditions (53.70%), ward (20.37%) and home (11.11%). The major incriminated groups were antimicrobials (18.52%), nonsteroidal antiinflammatory drugs-(NSAIDs) (12.96%) and neuromuscular blockers (12.96%). Common causative drugs were diclofenac (11.11%), atracurium (7.41%) and β-lactams (5.96%). Cardiovascular (98.15%) and respiratory (81.48%) symptoms dominated the presentation. Skin tests and IgE assays were performed in 37.03% and 18.52% cases, respectively. The fatal cases were associated with complications (OR =5.04; 95% CI: 1.41–17.92), cerebral hypoxic damage (OR =6.80; 95% CI: 2.14–21.58) and preventable reactions (OR =14.33; 95% CI: 2.33–87.97). **Conclusion:** Antimicrobials, NSAIDs, and neuromuscular blockers are common causative groups. The most fatal cases can be prevented by avoiding allergen drugs.

Keywords: Anaphylaxis, causative drugs, hypersensitivity reactions, preventable reactions

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.146313

Quick Response Code:

Introduction

The anaphylaxis is a rare life-threatening hypersensitivity reactions. Its incidence in Europe is 1.5–7.9/1,00,000 person-years.[1] In Turkey, incidence is 1.95/1,00,000 person-years based on hospital admission.[2] In USA, an age-adjusted incidence rates for male and female are 6.6/1,00,000 male/year and 8.7/1,00,000 female/year, respectively.[3] The anaphylaxis occurs suddenly after contact with an allergen.[4] Anaphylactoid and anaphylactic reactions are clinically difficult to distinguish. Anaphylactoid do not require any previous exposure with an offending agent and occurs by nonimmunological mechanisms that trigger the release of mediators from mast cells and basophils. Their management remains the same.[5]

The common offenders for anaphylaxis are drugs, food, insect bites, venom, contrast materials, and latex.[4,6] The common drugs causing anaphylaxis are antimicrobials, nonsteroidal antiinflammatory drugs (NSAIDs) and muscle relaxants.[6,7] However, no testing

From:
Department of Pharmacology, GMERS Medical College, Gotri, Vadodara, [1]Department of Pharmacology, Government Medical College, Bhavnagar, Gujarat, India

Correspondence:
Dr. Tejas K. Patel, Department of Pharmacology, GMERS Medical College, Gotri, Vadodara - 380 021, Gujarat, India.
E-mail: dr.tkp2006@yahoo.co.in

methods or known risk factors avail to differentiate individuals at risk for an anaphylactic reaction from a simple allergic reaction. Individuals with asthma are exception to this, who may suffer a more severe reaction.[5]

Most of the epidemiological data on anaphylaxis are based on studies in developed countries. The data regarding its causative agents and other clinical patterns are limited in developing countries. The aim of our study was to analyze published studies and cases of drug-induced anaphylaxis reported from India and compared the data with the other foreign studies.

Materials and Methods

The publications describing anaphylactic reactions in Indian population were searched through following key terms: "Anaphylactic reaction" odds ratio (OR) "immediate reaction" OR "anaphylactic shock" AND ("India" OR "Indian population"). The electronic databases "PubMed, MEDLINE, PubMed Central, Google Scholar" and bibliographies of relevant articles were searched. Articles published in English from 1998 to 2013 were included in the review. Two reviewers (TKP, PBP) independently searched the articles. Title, abstract and full text articles if necessary were assessed for possible inclusion in the study. The protocol of this study was registered in PROSPERO (CRD42014007347) register for systematic review.

Inclusion criteria

- Studies conducted in Indian population only
- Prospective or retrospective studies related to drug-induced anaphylactic reactions
- Cohort, case-control, case series related to anaphylactic reactions
- Case reports, letter to editors related to drug-induced anaphylactic reactions and fulfilling the clinical case criteria defined by second symposium of the national institute of allergy and infectious disease/food allergy and anaphylaxis network[8]
- Studies related to adverse drug reactions (ADR) those have described the anaphylactic reactions
- All age groups and clinical settings (Inpatient or outpatient).

Exclusion criteria

- Studies not based on Indian population
- Studies related to other etiologies of anaphylactic reactions (e.g. food, insects, parasitic diseases, etc.)
- Editorials, review articles, nonresearch letters and discussion papers
- Animal studies.

Review methods

The following data were collected from each publications: Demographic, set up in which anaphylaxis occurred, lag period, causative drugs, clinical features, systems involved, co-morbid conditions, risk factors, allergen testing, complications, hospitalization, mortality and therapy administered.

The "CARE guideline" was used to assess the quality of case reports.[9] The severity of anaphylaxis were graded (I–IV) according to Ring's classification.[10] The causality assessment was performed as per Naranjo's algorithm.[11] It classifies drug-ADR pair as "certain," "probable," "possible" and "unlikely" categories. Anaphylaxis cases were assessed for the preventability of reactions by modified Schumock and Thorton criteria by Lau *et al*.[12] It classifies ADR as "definitely preventable," "probably preventable" and "not preventable" reaction.

Outcome analysis

Data for primary outcome variable (causative drugs) and secondary outcome variables were extracted and summarized using absolute numbers and percentage. Demographic data were presented as mean (95% confidence interval [CI]), percentage of various age groups and male to female ratio. A subgroup analysis was performed for the male and female gender for age groups, grading, setup and involvement of systems, causative drugs and their route of administration by Chi-square test. Incubation period, grading, set up, systems involved, common presenting features, allergen tests, complications, co-morbid conditions and therapy administered were pooled and presented as proportions. Subgroup analysis was performed between expired and survived cases for gender, set up, systems involved, co-morbid conditions, complications, treatment administered and preventable reactions by Fisher's exact test and their OR (95% CI) were calculated. The disagreements were discussed and resolved by consensus. Graph Pad Prism version 6.0 (GraphPad Software, Inc., La Jolla, CA 92037 USA) was used for statistical analysis. P <0.05 was considered to be statistically significant.

Results

Literature search

The search yielded 3839 references. Totally 3739 references were excluded. Out of 100 fully evaluated, 52

references were included in the analysis as per selection criteria.[13-64] The flow diagram for the article selection is presented as Figure 1.

Characteristic and quality of the included studies

Total 34 case reports, 13 letter to editors, 4 correspondence and 1 image in medicine were included in the study [Table 1]. Two studies had described two cases in one report.[45,61] Total 54 cases were analyzed. We did not find any cohort, case-control, and case-series studies. The two Indian hospitals were part of the "International Collaborative Study of Severe Anaphylaxis" during 1992–1997. No separate Indian data were described in any of two publications from this study and were excluded.[65,66] The set-up in which anaphylaxis occurred were: Perioperative-29, ward-11, home-06, outpatient department-03, procedure room-02, intensive care unit-01 and primary health care center-01. One study did not specify a setting.[23] As per "CARE guideline," the most studies did not mention important timelines in the form of tables or figures, strengths, limitations, follow-up data and informed consent or permission from the institutional committee to publish the report.[9]

Characteristics of the patients

The mean (95% CI) age of the patients was 35.31 (30.52–40.10) years. The age group distributions for 0–20, 21–39, 40–60 and >60 years were 25.93%, 42.59%, 20.37%, and 11.11%, respectively ($P < 0.0001$; Chi-square test). The youngest patient was a 7-day-old male child and eldest was 70-year-old male patient. Total female patients were 33 (61.11%). Male: Female ratio was 1:1.57. The mean (95% CI) age of the male and female patients were 39.81 (30.39–49.23) and 32.45 (27.20–37.71) years, respectively. The gender was not significantly associated with age groups, setup, grading, system involved, common causative drugs and route of administration ($P > 0.05$, Chi-square test/Fisher's exact test).

Causative drugs

Thirty-five different drugs were suspected. As shown in Table 2, major causative groups were antimicrobials (18.52%), NSAIDs (12.96%) neuromuscular blockers (12.96%), and anesthetic agents (9.26%). β-lactams (5.96%) were the most commonly incriminated antimicrobials. The most common causative drug was

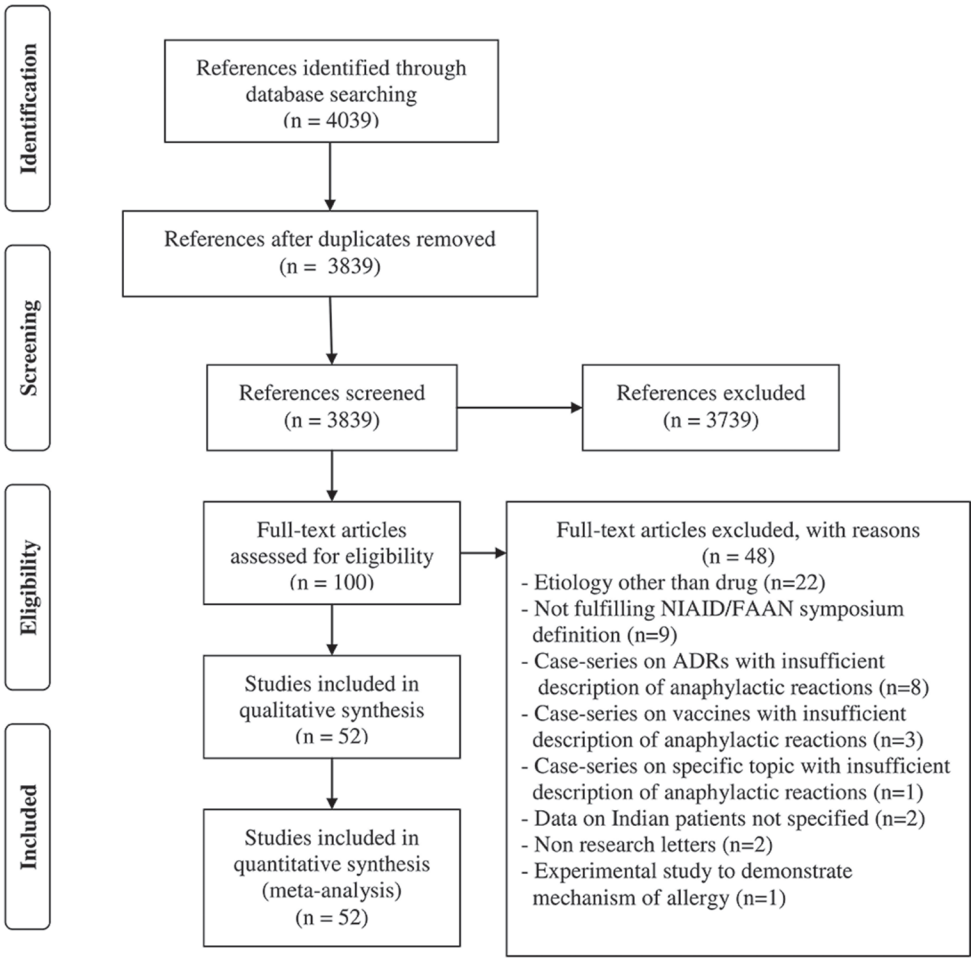

Figure 1: Study selection flow diagram

Table 1: Characteristic of included studies in systemic review

Article name	Type of study	Age (years)	Gender	Set up
Afonso *et al.*[13]	Letter to editor	30	Female	Home
Ansari *et al.*[14]	Letter to editor	55	Female	Perioperative
Awasthi and Tripathi[15]	Case report	38	Female	Perioperative
Babu and Sharmila[16]	Case report	7 days	Male	Ward
Basu *et al.*[17]	Case report	57	Female	Ward
Bhagwat and Saxena[18]	Case report	52	Male	Perioperative
Choudhury *et al.*[19]	Letter to editor	35	Male	Procedure room
Chowdhry *et al.*[20]	Letter to editor	48	Female	Perioperative
Das and Mondal[21]	Case report	06	Female	OPD
Dube *et al.*[22]	Case report	30	Female	Perioperative
Elangovan *et al.*[23]	Image in medicine	30	Female	Not stated
George and Williams[24]	Letter to editor	26	Male	OPD
Ghai *et al.*[25]	Letter to editor	48	Female	Perioperative
Gowrinath and Balachandran[26]	Case report	58	Female	Ward
Gupta *et al.*[27]	Letter to editor	18	Female	Perioperative
Gupta *et al.*[28]	Letter to editor	40	Female	Ward
Hiremath[29]	Case report	35	Female	Perioperative
Kalra *et al.*[30]	Case report	28	Female	Perioperative
Kothur *et al.*[31]	Case report	15	Female	Home
Koul *et al.*[32]	Case report	56	Male	Perioperative
Kumar *et al.*[33]	Case report	52	Male	Perioperative
Mallick *et al.*[34]	Case report	18	Female	Perioperative
Miraj *et al.*[35]	Case report	58	Female	Perioperative
Mishra *et al.*[36]	Case report	20	Female	PHC
Mishra *et al.*[37]	Case report	63	Male	Perioperative
Mohapatra *et al.*[38]	Correspondence	20	Male	Ward
Mukherjee and Bhattacharya[39]	Letter to editor	56	Female	Ward
Murthy *et al.*[40]	Case report	70	Male	Perioperative
Neki *et al.*[41]	Case report	40	Female	OPD
Pant *et al.*[42]	Case report	34	Female	Perioperative
Parikh *et al.*[43]	Correspondence	40	Female	Perioperative
Pattnaik *et al.*[44]	Letter to editor	18	Male	Perioperative
Ravi *et al.*[45]	Case report	43	Female	Perioperative
Ravi *et al.*[45]	Case report	24	Female	Perioperative
Ray *et al.*[46]	Letter to editor	09	Female	Home
Samanta *et al.*[47]	Letter to editor	32	Male	Perioperative
Samanta *et al.*[48]	Case report	15	Male	Ward
Sen *et al.*[49]	Correspondence	09	Female	Home
Sengupta and Kohli[50]	Case report	35	Female	Perioperative
Shah *et al.*[51]	Case report	30	Male	Procedure room
Shankar *et al.*[52]	Case report	20	Female	Perioperative
Shanthi *et al.*[53]	Case report	18	Male	Ward
Shrivastava[54]	Case report	37	Male	Perioperative
Singbal and Rataboli[55]	Correspondence	30	Male	Home
Singh *et al.*[56]	Case report	25	Female	ICU
Sinha and Sinha[57]	Case report	65	Male	Perioperative
Sripriya *et al.*[58]	Case report	25	Female	Perioperative
Swamy *et al.*[59]	Case report	28	Female	Ward
Tiwari *et al.*[60]	Case report	64	Male	Ward
Tomar *et al.*[61]	Case report	31	Female	Perioperative
Tomar *et al.*[61]	Case report	26	Male	Perioperative
Tummala *et al.*[62]	Case report	62	Male	Home
Vaidya *et al.*[63]	Case report	20	Female	Ward
Vyas *et al.*[64]	Letter to editor	65	Male	Perioperative

PHC: Primary health center; OPD: Outpatient department; ICU: Intensive care unit

diclofenac (11.11%). Other commonly implicated drugs were atracurium (7.41%), vecuronium (5.56%), ranitidine (5.56%), fentanyl (3.70%), midazolam (3.70%), ceftriaxone (3.70%), artesunate (3.70%), iron sucrose (3.70%) and gelofusine (3.70%).

Table 2: Causative drugs for anaphylaxis in Indian population

Causative drugs	Total *n* (%)
Antimicrobials	10 (18.52)
β-lactam antibiotics	5 (9.26)
Cefotaxime	2
Ceftriaxone	2
Amoxycillin + clavulanic acid	1
Other antibiotics	5 (9.26)
Artesunate	2
Co-trimoxazole	1
Ciprofloxacin	1
Tinidazole	1
NSAIDs	7 (12.96)
Diclofenac	6
Paracetamol	1
Neuromuscular blockers	7 (12.96)
Atracurium	4
Vecuronium	3
Anesthetic agents	5 (9.26)
Fentanyl	2
Midazolam	2
Propofol	1
Colloids	4 (7.41)
Gelatin 3.5%	1
Gelofusine	2
Hydroxyethyl starch	1
H_2 receptor antagonists	3 (5.56)
Ranitidine	3
Local anesthetics	2 (3.70)
Bupivacaine	1
Lidocaine	1
Hemetinics	2 (3.70)
Iron sucrose	2
Oxytocics	2 (3.70)
Oxytocin	1
Dinoprostone	1
Contrast media	2 (3.70)
Iohexol	1
Diatrizoate	1
Blood products	2 (3.70)
Whole blood	1
Random donor platelet	1
Others	6 (11.11)
Tetanus toxoid vaccine	1
Anti-snake venom	1
Mephenteramine	1
Palonosetron	1
Protamine sulfate	1
Cetrizine	1
Cisplatin	1
Atropine	1
Total	54 (100)

NSAIDs: Nonsteroidal antiinflammatory drugs

Among the perioperative cases, neuromuscular blockers (24.13%) and anesthetic agents (13.79%) were commonly incriminated groups. Atracurium (13.79%), vecurnium (10.34%) and ranitidine (10.34%) were common causative drugs.

Intravenous medication produced 74.07% reactions. Other reported routes were oral (14.81%), intramuscular (5.56%), intracervical (1.85%), intraurethral (1.85%) and intraspinal (1.85%).

Incubation period, clinical feature and severity of the reaction

It was not possible to calculate the mean (95% CI) for the incubation period. Many reports described the incubation period as "Immediate/soon after the administration of the drug (25.93%)" and "within few min (11.11%)." It was within 1–5 min in 18.52%, >5–30 min in 24.07%, >30 min in 11.11% and not stated in 9.26% cases. Cardiovascular features dominated (98.15%) followed by respiratory (81.48%), cutaneous (72.22%) and gastrointestinal symptoms (9.26%). Almost 50% cases showed simultaneous involvement of cardiovascular, respiratory and cutaneous systems [Table 3]. The second common presentation was a combination of cardiovascular and respiratory features (20.37%). The common presenting features were hypotension (81.48%), difficulty in breathing (74.07%), tachycardia (42.59%), pruritus (33.33%), morbilliform rash (29.63%), urticaria (25.93%) and wheezing (20.37%) [Table 4]. On severity assessment, most patients belonged to grade III (57.41%) followed by grade II (22.22%) and grade IV (20.37%) at the time of presentation.

History of allergy, previous experience of drug reactions and co-morbid conditions

The associated allergic conditions were bronchial asthma (1.85%),[37] idiopathic urticaria (1.85%),[28] household detergent allergy (1.85%)[35] and latex allergy (1.85%).[13] History of anaphylaxis with same drugs (ranitidine and tinidazole) was positive in two cases.[55,64] In the case of tinidazole induced anaphylaxis, norfloxacin + tinidazole fixed dose combination caused oral mucosal lesions on first exposure; anaphylaxis and erythema multiforme on second exposure. On third exposure to tinidazole alone, patient developed anaphylaxis and Stevens Johnson syndrome. However, patient tolerated metronidazole in between second and third exposure of tinidazole.[55] Previous hypersensitivity reaction to the same group of drug was observed in one case[26] and to the different group of drug was observed in two cases.[25,30] Grading of anaphylaxis cases were comparable for previous experience of allergic or drug reactions (P = 0.2283; Chi-square test).

The most common co-morbid condition was pregnancy (14.81%).[36,42,50,52,56,58,59,63] The drugs linked with anaphylaxis in pregnancy are iron sucrose (2), ranitidine (2), oxytocin (1), dinoprostone (1), cefotaxime (1) and diclofenac (1). Other co-morbid conditions were cardiovascular diseases (9.26%),[18,33,35,37,64] diabetes mellitus (3.70%),[37,64] chronic obstructive pulmonary disease (1.85%),[64] epilepsy (1.85%)[34] and cerebral malaria (1.85%).[53]

Allergen testing

Allergens were tested in 25 (46.30%) cases. Skin tests, IgE and serum tryptase were performed in 37.03%, 18.52% and 11.11% cases, respectively [Table 5]. Eighteen positive allergen skin testing were linked to the following

Table 3: Systems involved in anaphylaxis

System involved	*n* (%)
CVS+RS+cuteneous	28 (51.85)
CVS+RS	11 (20.37)
CVS+cuteneous	07 (12.96)
CVS+RS+cutaneous+GIT	02 (3.70)
CVS+RS+GIT	02 (3.70)
CVS alone	02 (3.70)
CVS+cutaneous+GIT	01 (1.85)
RS+cuteneous	01 (1.85)
Total	54 (100)

CVS: Cardiovascular system; RS: Respiratory system; GIT: Gastrointestinal tract

Table 4: Commonly observed clinical features of anaphylaxis

Clinical features	*n* (%)
Cardiovascular	
Hypotension	44 (81.48)
Tachycardia	23 (42.59)
Peripheral pulse absent/impalpable pulse	12 (22.22)
Bradycardia	11 (20.37)
Dysrythmia	06 (11.11)
Respiratory	
Difficulty in breathing	40 (74.07)
Bilateral wheezing/bilateral rhonchi	11 (20.37)
Increased peak airway pressure	07 (12.96)
Cyanosis	07 (12.96)
Diminished air entry	06 (11.11)
Cutaneous	
Pruritus	18 (33.33)
Morbiliform rash	16 (29.63)
Urticaria (hives)	14 (25.93)
Angioedema	06 (11.11)
Flushing	06 (11.11)
Gastrointestinal tract	
Nausea/vomiting	05 (9.26)
Other	
Altered mental status/drowsy/restless/irritable	19 (35.19)

Table 5: Allergen tests used for the diagnosis of anaphylaxis

Types of allergen tests	*n* (%)
Skin testing	20 (37.03)
Prick test	04 (7.41)
Intradermal testing	10 (18.52)
Prick and intradermal	05 (9.26)
Patch	01 (1.85)
Serum tryptase, during anaphylaxis	10 (18.52)
Serum tryptase, baseline-after 24 h	02 (3.70)
IgE	06 (11.11)
Methylhitamine level in urine	01 (1.85)

drugs: Atracurium (3), vecuronium (3), midazolam (2), artesunate (2), ranitidine (2), gelofusine (2), fentanyl (1), oxytocin (1), propofol (1) and amoxicillin + clavulanic acid (1). Two negative skin testing were linked to the ceftriaxone. IgE assay was positive in 5 of the 6 stated cases. Positive IgE assays were linked to the one case each with propofol, ranitidine, oxytocin, mephenteramine and random donor platelet while it was within normal range in cisplatin-induced reaction.

Therapeutic interventions

Adrenaline was administered in 45 (83.33%) cases. Adrenaline was not administered due to insignificant fall of blood pressure (2),[17,63] use of alternative vasopressors (2),[44,57] rise of blood pressure (1)[61] and lack of diagnosis on presentation (1).[53] Three cases did not state its use.[39,49,55] Most common used route was intravenous (55.56%). Dose of the first injection of adrenaline varied from 0.01 to 1 mg. In one case, acute myocardial infarction was developed following intramuscular administration of 1 mg (1:1000) adrenaline.[62] Corticosteroid, antihistaminic, inotropes, bronchodilators, H_2 receptor antagonists and vasopressors were used in 87.04%, 53.70%, 25.93%, 24.07%, 18.52% and 16.67% cases, respectively [Table 6]. Ventilator support was required in 46.30% cases.

Morbidity and mortality

Anaphylaxis required intensive care unit admission in 29 cases (53.7%). The complications were present in 7 (12.96%) cases. The observed complications were cerebral hypoxic damage (5.55%), acute renal failure (5.55%) and fetal death (3.7%), septicemia (3.7%), acute respiratory distress syndrome (1.85%), abnormal coagulation profile (1.85%), pulmonary edema (1.85%) and abnormal liver function (1.85%).[18,19,33,37,48,50,59] The mortality for anaphylaxis was observed in 7 (12.96%) cases.[19,33,36,37,46,49,53] One case did not mention the outcome.[23] The expired and survived cases showed no association with gender, set up, systems involved, route of administration for causative drugs and not administration of adrenaline. The expired cases were significantly associated with a high rate of complications, cerebral hypoxic damage and preventable reactions than survived cases [$P < 0.05$; Table 7]. Seven expired cases were linked to the following drugs: Diclofenac (2), protamine sulfate (1), ceftriaxone (1), iohexol (1), random donor platelet (1) and iron sucrose (1).

Assessment of anaphylaxis cases

Fifty-three cases belonged to "probable" category on causality assessment. Only one case belonged to "certain" category.[55] The "definitely preventable," "probably preventable" and "not preventable" cases were 12.96%, 1.85%, and 85.86%, respectively. Reasons for the preventability were past allergic reaction to the same drug (3),[26,55,64] immediate type of cutaneous reactions while ongoing treatment (2),[46,49] anaphylactic reaction with ongoing treatment (2)[37,39] and test dose not administered (1).[36]

Table 6: Treatment administered for anaphylaxis

Therapy	*n* (%)
Adrenaline	45 (83.33)
Number of doses required	-
One	34 (62.96)
Two	09 (16.67)
Three	01 (1.85)
Infusion	11 (20.37)
Route of administered	-
Intravenous	30 (55.56)
Intramuscular	03 (5.56)
Subcutaneous	04 (7.41)
Not stated	08 (14.81)
Corticosteroid	47 (87.04)
Hydrocortisone	36 (66.67)
Methylprednisolone	02 (3.70)
Hydrocortisone+dexamethasone	04 (7.41)
Hydrocortisone+methylprednisolone	01 (1.85)
Name not stated	04 (7.41)
Antihitaminics	29 (53.70)
Chlorpheniramine	12 (22.22)
Diphenhdramine	06 (11.11)
Pheniramine	06 (11.11)
Promethazine	01 (1.85)
Name not stated	04 (7.41)
Inotropes	14 (25.93)
Dopamine	10 (18.52)
Dobutamine	01 (1.85)
Name not stated	03 (5.56)
Bronchodilators	13 (24.07)
Salbutamol	04 (7.41)
Deriphylline	04 (7.41)
Salbutamol+ipratropium bromide	03 (5.56)
Levosalbutamol+ipratopium bromide	01 (1.85)
Aminophylline	01 (1.85)
H_2 receptor antagonists	10 (18.52)
Ranitidine	08 (14.81)
Name not stated	02 (3.70)
Vasopressors	09 (16.67)
Mephenteramine	03 (5.56)
Ephedrine	03 (5.56)
Phenylephrine	01 (1.85)
Phenylepherine+ephedrine	01 (1.85)
Norepinephrine+vasopressine	01 (1.85)

Discussion

In this study, drug-induced anaphylactic reactions in Indian population were systematically reviewed from selected published studies from 1998 to 2013. Only case reports and letter to editors were included as no case-series, cohort or case-control study was conducted in India in last 15 years.

Table 7: Comparison of expired and survived cases

Variable	Expired (*n*=7)	Survived (*n*=47)	*P*	OR (95% CI)
Male patient	4 (57.14)	17 (36.17)	0.411	2.35 (0.47-11.79)
Setting				
Perioperative	02 (28.57)	28 (59.57)	0.221	0.27 (0.05-1.55)
Home	02 (28.57)	04 (8.51)	0.169	4.30 (0.62-29.75)
Systems involved				
2 system involvement	02 (28.57)	16 (34.04)	1.000	0.77 (0.13-4.45)
>2 system involvement	05 (71.43)	25 (53.19)	0.443	2.20 (0.39-12.50)
Routes of causative drugs				
Oral	02 (28.57)	05 (10.64)	0.221	3.36 (0.51-22.11)
Intravenous	05 (71.43)	35 (74.47)	1.000	0.86 (0.15-5.01)
Co-morbid conditions				
Pregnancy	01 (14.29)	08 (17.02)	1.000	0.83 (0.11-6.11)
Cardiovascular conditions	02 (28.57)	03 (6.38)	0.120	3.92 (1.00-15.24)
Complications	03 (42.85)	04 (8.51)	0.039	5.04 (1.41-17.92)
Cerebral hypoxic damage	02 (28.57)	01 (2.13)	0.041	6.80 (2.14-21.58)
Acute renal failure	01 (14.29)	02 (4.25)	0.346	2.83 (0.48-16.61)
Treatment				
Adrenaline not administered	01 (14.29)	05 (10.64)	1.000	1.14 (0.12-11.18)
Preventable reactions	04 (57.14)	04 (8.51)	0.006	14.33 (2.33-87.97)

P value by Fisher's exact test. 95% CI: 95% confidence interval, OR: Odds ratio

In demographics, maximum cases of anaphylaxis occurred in 3rd to 4th decades in our study. This is in contrast with the European studies where peak rate of anaphylaxis occurs in fifth to sixth decade.[6,7,65,67,68] In European literature, it coincides with high incidence of overall ADRs in these age groups.[6,68] Female preponderance for the anaphylaxis is in accordance with the previous studies.[7,67,69,70] The observed rate of anaphylaxis in female gender is ranged from 61.9% to 72.7%[7,67,70,71] and male to female ratio varies from 1:2 to 1:3 in various case-series studies.[67,69] One Italian case–control study reports 56.9% female anaphylaxis cases. However, there was no significant difference between the anaphylaxis cases and other ADRs (56.9% vs. 60.1%) in terms of female gender.[6] It was in line with the high number of overall ADRs in females.

In this study, antimicrobials are reported as the most common offending agents in line with the various studies abroad.[7,71-73] β-lactam antibiotics are major causative antimicrobials that coincide with reported literature.[6,7,70,72-75] In the international collaborative study, incidence of β-lactams-induced anaphylaxis was 5.7–32/100000 exposed patients.[66] Amoxicillin,[7,72] amoxicillin + clavulanic acid,[74] cephalosporins[73] are the commonly incriminated among β-lactam antibiotics. One Italian study reported OR (95% CI) for commonly observed antimicrobials: Penicillins 1.64 (1.30–2.05), cephalosporins 2.36 (1.76–3.17), glycopeptides 2.46 (1.14–5.30) and quinolones 2.17 (1.69–2.79).[6] For OR calculation, cases were considered as a number of anaphylaxis with suspected drugs and control as the number of other ADRs with the same drug. Artesunate is the second most common antimicrobial agent which is in contrast with the European literature.[6,7,70,72,73] It may be due to its widespread use in India due to malaria. IgE mediated mechanism was confirmed in both cases of artesunate by positive skin testing.

Diclofenac is the most commonly reported NSAID in literature.[72] In one Italian study, diclofenac was the only NSAID with a significant reporting OR of 3.23 (95% CI: 2.21–4.73).[6] As per van Puijenbroek *et al*. OR of diclofenac-induced anaphylaxis to all other drugs was 17.2 (95% CI: 12.1–24.5) and was quite higher than other NSAIDs.[68] The incidence rate (95% CI) for diclofenac-induced anaphylaxis as per different routes were: Oral-7.2 (2.6–20), parenteral-9.0 (2.7–30) and suppository-16 (3.4–74) per 100000 exposed patients.[66] We have observed 3 cases each with oral and parenteral routes and none with diclofenac suppository. Risk of anaphylaxis is reported higher with the use of heteroaryl acetic acids (diclofenac, tolmetin and ketorolac) than arylpropionic acid NSAIDs (ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen and oxaprozin) as per their OR (19.7, 95% CI: 13.8–28.1 vs. 6.7, 95% CI: 4.2–10.6).[68] In contrast to this study, Renaudin *et al*.[7] had reported paracetamol and ibuprofen while Moro Moro *et al*.[74] had reported ibuprofen and acetylsalicylic acid as common causative NSAIDs.

Neuromuscular blockers are most commonly account for anaphylaxis in perioperative cases that matches with the foreign studies.[67,70,76-78] Rocuronium, succinylcholine, atracurium and vecuronium are commonly incriminated drugs in the literature.[7,67,70,76,79] The observed rate of anaphylaxis for rocuronium, atracurium and vecuronium are 8.0, 4.01, and 2.8/1,00,000 administrations, respectively.[79] We observed anaphylaxis with atracurium and vecuronium only in this study.

Anaphylaxis to contrast media is reported lower than previous studies.[6,67] In contrast to previous studies, no latex-induced anaphylactic reaction was observed.[7,67,74] Only one case of anti-snake venom induced anaphylaxis is published from India in spite of common occurrence.[66]

In this study, diagnosis was mainly based on clinical presentation. Skin testing, serum tryptase and IgE assay were carried out in <50% cases. This frequency is lower than foreign studies.[7,67] IgE mediated mechanism can be established by positive skin tests and IgE assay for the anaphylaxis.[7] This study supports it for neuromuscular blockers and anaesthetic agents. High

frequency of cross-reactivity (63.4–82.6%) is reported among neuromuscular blockers.[67,70,76,78] Rocuronium and vecuronium in Laxenaire *et al*.[67] and vecuronium, atracurium and pancuronium in Karila *et al*.[78] show highest rate of cross reactivity. Skin testing should be done with all the neuromuscular blockers in a sensitized individual to find the safer alternative.[80] Negative skin prick testing with ceftriaxone in this study are in line with the low frequency of positive prick tests for cephalosporins (58.5%) reported in literature.[7] NSAIDs-induced reactions can be immune or nonimmmune mediated. One French study reported most cases of paracetamol and ibuprofen due to nonimmune mediated hypersensitivity or unknown mechanism while all cases of diclofenac were IgE mediated as suggested by positive intradermal and basophil activation tests.[7] In our study, allergen testing was performed in only one dicolofenac case which reported elevated serum tryptase at 1 h and methylhistamine level in urine at 4 h. Serum tryptase was not repeated after 24 h to check for baseline.[56]

Both intravenous[6] and oral[7,74] medications are commonly incriminated in the literature. More frequent reporting among inpatients than outpatients are in accordance with previous studies.[6,75] This may be because most cases of anaphylaxis in our study are perioperative and intravenous drugs are exclusively used in hospital settings than outpatient setting. Our findings suggest slight lower rate of cutaneous involvement (72.22%) than expected of >80% by Sampson *et al*.[8] In contrast with our findings, de Silva *et al*.[73] and Moro Moro *et al*.[74] had reported high rate of cutaneous and respiratory systems while low rate of cardiovascular involvement. However, they have included all cases of anaphylaxis irrespective of the etiology. A study of fatal anaphylaxis in UK showed most common involvement of cardiovascular system with drug-induced and respiratory system with food-induced anaphylactic reactions.[81] In line with our findings, cardiovascular symptoms were predominant than cutaneous and respiratory in a study of perioperative anaphylaxis cases by Laxenaire *et al*.[67] Overall grading for the severity of reactions (grade III > II > IV) are in accordance with the literature.[67,79] Allergic conditions are less frequently observed than previous study.[67] Bronchial asthma was associated with fatal outcome as reported in literature.[5]

The adrenaline was used in 83.33% patients as against 57.6% in Renaudin *et al*.[7] and 76% in de Silva *et al*.[73] A recent systematic review for the management of anaphylaxis suggests prompt administration of adrenaline may be life-saving. Repeat dose of adrenaline is also require frequently.[82] Subcutaneous route is not considered optimal for case of anaphylaxis particularly in the presence of shock as absorption may be impaired. Adrenaline concentrations were significantly higher after intramuscular injection into the thigh than after intramuscular or subcutaneous injection into the upper arm in healthy adults.[83] Optimum site of intramuscular injection is vastus lateralis muscle.[82] Use of subcutaneous route for adrenaline is lower than previous study.[73] Almost 50% of patients received intravenous adrenaline and 20% received intravenous infusion in this study. Continuous low dose adrenaline infusion is most effective and safe due to ease of titration as per desired response.[8] A recent systematic review did not identify any suitable randomized control trials (RCTs) or quasi-RCTs for the steroids and antihistaminics in the management of anaphylaxis.[82] Because of anti-allergic mechanisms, steroids are routinely incorporated in management.[8] They are not the part of initial management due to slow onset of action. Steroids should never be used in place of or prior to adrenaline.[84] However, they can prevent biphasic reaction.[8,85] H_1 antihistaminics should be used as a second line treatment because of slow action and little effect on blood pressure and respiratory symptoms.[8,85] The combination of H_1 antihistaminics and H_2 receptor antagonists are superior to H_1 antihistaminics alone for urticaria but not for the angioedema and pruritus.[82] Vasopressors should be given if adrenaline and fluid resuscitation are not able to maintain systolic blood pressure >90 mm Hg.[8] Inhaled β_2-agonist should be used for the bronchospasm resistant to adequate doses of adrenaline.[84]

The pregnancy was the most common co-morbid condition. This may be correlated with female preponderance in child bearing age. It was associated with maternal death in one case and adverse neonatal outcome in two cases. In contrast with previous studies, iron sucrose is the commonly incriminated drug during pregnancy.[86,87] This may be because of high prevalence of anemia during pregnancy in India, which may lead to its frequent use than western countries.

Hypoxic brain injury and renal failure had been reported as complications of anaphylaxis in literature.[88,89] Two out of three patients with brain injury were expired in this study. Observed mortality rate (12.96%) in our study is quite higher (0.11–1.8%) than previous studies.[3,7,73] A recent French study had identified male gender, emergency setting, history of cardiovascular disease, obesity and beta-blocker treatment as risk factors for the fatal anaphylaxis due to neuromuscular blockers.[90] We have not observed mortality difference for gender, set up and history of cardiovascular diseases. This may be

because of small sample size for the subgroup analysis. Adrenaline was used in 5 out of 7 fatal cases. It was used in 62% of fatal anaphylaxis cases and before arrest in 14% only in one study from UK.[81] Fatalities can occur even if adrenaline is used correctly.[82] In this study, variables associated with fatal outcome were overall complications (OR =5.04; 95% CI: 1.41–17.92), cerebral hypoxic damage (OR =6.80; 95% CI: 2.14–21.58) and preventable reactions (OR =14.33; 95% CI: 2.33–87.97).

Of included 54 reactions, 53 belonged to "probable" and one to "certain" category in causality assessment with Naranjo's algorithm.[11] No anaphylactic reactions belonged to possible and unlikely category which stat that included cases are more likely due to the incriminated drug rather than the result of other factor. Total 14.81% of reported reactions were preventable as per a Schumock and Thorton criterion that is similar with the previous study showing 15% of preventable cutaneous allergic reactions.[91] One Swedish study observed one fourth of the fatal ADRs could be prevented.[92] A recent systematic review on "preventable ADRs" reported that approximately half of ADRs are preventable among outpatients-52% (95% CI: 42–62%) and inpatients-45% (95 CI: 33–58%).[93] Ignorance of immediate type of reaction while ongoing treatment and past allergic reactions with the same drugs are the common preventable factors which coincide with preventable allergic cutaneous reactions.[91] Kanjanarat *et al*. had observed prescribing of antimicrobials despite a history of allergy is one of the common reasons for the preventable adverse events.[94] Recurrent anaphylaxis can be prevented by identification of risk factors, avoidance of allergen, with caution and constant supervision.[5,73]

There are several limitations of this study. Only case reports were available for the analysis and so the results should be interpreted in this context. There is possibility of bias related to case reports. The main aim of case report is to publish previously unknown ADRs or those occurring with different manner or frequency than expected. This may be the reason for the high rate of observed mortality. There are fewer chances that a well-known reaction is reported. Similarly there are more chances for a new drug induced-reaction to be published. Due to lack of control data, we could not calculate incidence rate for the anaphylaxis and OR for the causative drugs. We could not compare pediatric and adult data due to small sample size. We could not estimate exact incubation period, length of hospital stay, dilution used for the drugs in skin testing and time for administration of adrenaline after symptom onset because of the paucity of data. Site of skin testing was also not mentioned in the included case reports. Skin of forearm is more likely to release histamine non-specifically than patient' back.[67]

Conclusion

In India, the anaphylaxis shows preponderance for the age group 20–40 years and females. This study supports antimicrobials, NSAIDs and neuromuscular blockers as commonly incriminated agents. Cardiovascular features are the predominant manifestation. There is need for the wider use of skin testing and specific IgE assays. High mortality and morbidity is observed for anaphylactic reactions. The complications and preventable reactions are associated with the fatal reactions. Ignorance of previous allergic reaction is the important cause for preventable reactions. In India, registry system and vigilance network are required to strengthen the database for anaphylaxis. The large cohort or case-control study is required from India to confirm the findings of this study.

References

1. Panesar SS, Javad S, de Silva D, Nwaru BI, Hickstein L, Muraro A, *et al.* The epidemiology of anaphylaxis in Europe: A systematic review. Allergy 2013;68:1353-61.
2. Cetinkaya F, Incioglu A, Birinci S, Karaman BE, Dokucu AI, Sheikh A. Hospital admissions for anaphylaxis in Istanbul, Turkey. Allergy 2013;68:128-30.
3. Harduar-Morano L, Simon MR, Watkins S, Blackmore C. A population-based epidemiologic study of emergency department visits for anaphylaxis in Florida. J Allergy Clin Immunol 2011;128:594-6001.
4. Tupper J, Visser S. Anaphylaxis: A review and update. Can Fam Physician 2010;56:1009-11.
5. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: An investigation into its epidemiology. Arch Intern Med 2001;161:15-21.
6. Leone R, Conforti A, Venegoni M, Motola D, Moretti U, Meneghelli I, *et al.* Drug-induced anaphylaxis: Case/non-case study based on an Italian pharmacovigilance database. Drug Saf 2005;28:547-56.
7. Renaudin JM, Beaudouin E, Ponvert C, Demoly P, Moneret-Vautrin DA. Severe drug-induced anaphylaxis: Analysis of 333 cases recorded by the Allergy Vigilance Network from 2002 to 2010. Allergy 2013;68:929-37.
8. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, *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;117:391-7.
9. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D, *et al.* The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development. Glob Adv Health Med 2013;2:38-43.
10. Ring J, Behrendt H, de Weck A. History and classification of anaphylaxis. Chem Immunol Allergy 2010;95:1-11.
11. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al.* A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
12. Lau PM, Stewart K, Dooley MJ. Comment: Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother 2003;37:303-4.
13. Afonso N, Shetgaonkar P, Dang A, Rataboli PV. Cetirizine-induced anaphylaxis: A rare adverse drug reaction. Br J Clin Pharmacol 2009;67:577-8.
14. Ansari MM, Gupta K, Bhandari S, Haleem S. Amoxicillin/clavulinic acid-induced anaphylaxis during anesthesia. J Anaesthesiol Clin Pharmacol 2012;28:531-2.

15. Awasthi S, Tripathi RK. Anaphylaxis following injection atracurium besylate: An uncommon but life threatening complication. Indian J Fundam Appl Life Sci 2013;3:211-3.
16. Babu TA, Sharmila V. Cefotaxime-induced near-fatal anaphylaxis in a neonate: A case report and review of literature. Indian J Pharmacol 2011;43:611-2.
17. Basu R, Rajkumar A, Datta NR. Anaphylaxis to cisplatin following nine previous uncomplicated cycles. Int J Clin Oncol 2002;7:365-7.
18. Bhagwat AG, Saxena KN. Intraoperative anaphylaxis to inj ceftriaxone: Here we go again. Indian J Anaesth 2008;52:462.
19. Choudhury M, Malik M, Velayoudam D. Late and acute reaction to iohexol, refractory to treatment. Indian J Anaesth 2011;55:631-3.
20. Chowdhry V, Debasish G, Dharmajivan S. Anaphylaxis to vecuronium: A rare event. Indian J Anaesth 2012;56:314-5.
21. Das S, Mondal S. Tetanus toxoid induced anaphylaxis. J Vaccines Vaccin 2012;3:126.
22. Dube SK, Panda PS, Agrawal GR, Singh DK. Anaphylaxis to artesunate? Indian J Crit Care Med 2012;16:55-7.
23. Elangovan A, Chacko J, Chatterjee S, Kuntoji B. Woman with supposed anaphylactic reaction. Persistent left superior vena cava. Ann Emerg Med 2012;59:98, 114.
24. George C, Williams A. Anaphylaxis with midazolam - Our experience. Indian J Anaesth 2011;55:630-1.
25. Ghai B, Wig J, Gupta V. Intraoperative severe anaphylaxis due to gelofusine during a neurosurgical procedure. Anesth Analg 2007;104:238.
26. Gowrinath K, Balachandran C. Anaphylactic reaction due to paracetamol. J Indian Med Assoc 2004;102:223, 226.
27. Gupta A, Srivastava U, Saxena A, Mittal A, Dwivedi Y. Severe anaphylactic reaction to atracurium. Indian J Pharmacol 2012;44:144-5.
28. Gupta YK, Shanmugam SP, Padhy BM, Goyal A. Palonosetron induced anaphylaxis in an adult female. Br J Clin Pharmacol 2010;70:149-50.
29. Hiremath DA. Anaphylaxis to IV atropine: A case report. Indian J Clin Pract 2013;23:799-800.
30. Kalra S, Kale S, Wadhwa R. Anaesthetic management of a parturient with anaphylaxis to ranitidine. J Anaesth Clin Pharmacol 2010;26:410-2.
31. Kothur K, Singh M, Dayal D. Ciprofloxacin-induced anaphylactoid reaction. Eur J Pediatr 2006;165:573-4.
32. Koul A, Jain R, Sood J. A critical incident report: Propofol triggered anaphylaxis. Indian J Anaesth 2011;55:530-3.
33. Kumar P, Girdhar KK, Anand R, Khera G. Life claiming anaphylaxis to intravenous ceftriaxone after negative skin test. Indian Anaesthetists' Forum 2005;6:1-6.
34. Mallick S, Chatterjee A, Basunia SR, Bisui B. Successful resuscitation in a case of sudden cardiac arrest in an epileptic patient posted for spinal surgery. Anesth Essays Res 2013;7:123-6.
35. Miraj A, Foaud A, Seth B. Cardiac arrest following an anaphylactic reaction to atracurium. BMJ Case Rep 2010;2010.
36. Mishra A, Dave N, Viradiya K. Fatal anaphylactic reaction to iron sucrose in pregnancy. Indian J Pharmacol 2013;45:93-4.
37. Mishra DK, Sathyamurthy I, Subramanyan K, Girinath MR. Life threatening protamine reaction during bypass surgery – a case report. Indian Heart J 2009;61:216-7.
38. Mohapatra MK, Srinivas D, Kar AK, Murmu M. Anaphylactic reaction to intravenous artesunate. J Assoc Physicians India 2009;57:183-4.
39. Mukherjee S, Bhattacharya P. Severe anaphylactic reaction in IgA deficient patient following transfusion of whole blood. Asian J Transfus Sci 2011;5:177.
40. Murthy TV, Goyal R, Bhatia P, Singh VP, Prabhakar T. Compounded hypotension following spinal anaesthesia and anaphylaxis to 3.5% gelatin-a case report. Indian J Anaesth 2004;48:493-5.
41. Neki NS, Sharma R, Gupta SN, Gupta H, Maniea T. Anaphylactic reaction to intramuscular diclofenac. Case Rep Trop 2013;1:1-2.
42. Pant D, Vohra VK, Pandey SS, Sood J. Pulseless electrical activity during caesarean delivery under spinal anaesthesia: A case report of severe anaphylactic reaction to Syntocinon. Int J Obstet Anesth 2009;18:85-8.
43. Parikh G, Shah V, Singh D, Kadam P, Kharadi N. An unusual cause of anaphylaxis during surgery. Indian J Crit Care Med 2013;17:396-7.
44. Pattnaik SK, Peddinti KC, Samala KB. Adverse reactions to 6% hydroxyethyl starch in the operating room. J Clin Diagn Res 2013;7:2656.
45. Ravi PR, Vijay MN, Shouche S. Two cases of anaphylaxis under anaesthesia with vecuronium. Med J Armed Forces India 2013. [In Press]. Available from: http://www.mjafi.net/article/S0377-1237(13)00183-4/pdf. [Last accessed on 2014 Aug 10].
46. Ray M, Mitra S, Parmar V. Diclofenac induced fatal anaphylactic reaction. Indian Pediatr 1999;36:1067-9.
47. Samanta S, Paul M, Samanta S. Mephentermine triggered anaphylaxis in the peri-operative period: An unusual occurrence. Saudi J Anaesth 2013;7:219-20.
48. Samanta SK, Mahapatra NC, Fariduddin K, Mazumdar DB, Mandal K. Cortical blindness and paraplegia following hypoxic ischemic encephalopathy as a complication of common krait bite. Nepal J Ophthalmol 2011;3:206-9.
49. Sen I, Mitra S, Gombar KK. Fatal anaphylactic reaction to oral diclofenac sodium. Can J Anaesth 2001;48:421.
50. Sengupta A, Kohli JK. Antibiotic prophylaxis in cesarean section causing anaphylaxis and intrauterine fetal death. J Obstet Gynaecol Res 2008;34:252-4.
51. Shah N, Sangani S, Parikh S, Chahar K. A case report: Anaphylactic reaction to intravenous radiocontrast agent. B J Kines 2012;4:19-21. Available from: http://www.medadmbjmc.in/bjmc/docs/BJ_Kines_October_2012.pdf#page=21. [Last accessed on 2014 Aug 10].
52. Shankar AK, Puri R, Singh Y. Cardiovascular collapse under spinalanesthesia. J South Asian Fed Obstet Gynecol 2009;1:67-9.
53. Shanthi B, Bhavanadhar, Chandran P, Prasad AK. IgE- and IgG mediated severe anaphylactic platelet transfusion reaction in a known case of cerebral malaria. Asian J Transfus Sci 2013;7:81-3.
54. Shrivastava S. An experience with midazolam anaphylactoid reaction. J Anesth 2012;26:642-3.
55. Singbal SS, Rataboli PV. Anaphylaxis and hypersensitivity syndrome reactions in increasing severity following repeated exposure to tinidazole. J Postgrad Med 2005;51:243-4.
56. Singh R, Bansal D, Baduni N, Vajifdar H. Anaphylactic reaction to intravenous diclofenac. Indian J Crit Care Med 2011;15:37-9.
57. Sinha M, Sinha R. Anaphylactic shock following intraurethral lidocaine administration during transurethral resection of the prostate. Indian J Urol 2008;24:114-5.
58. Sripriya R, Kumar VR, Prabhu R, Ravishankar M. Intraoperative anaphylaxis to ranitidine during cesarean section. J Nat Sci Biol Med 2013;4:257-9.
59. Swamy NM, Manjula BG, Sunitha, Lakshmi. Near fatal anaphylactic shock following iron sucrose injection for the treatment of anaemia. Int J Med Appl Sci 2013;2:28-31.
60. Tiwari AK, Tomar GS, Ganguly CS, Kapoor MC. Kounis syndrome resulting from anaphylaxis to diclofenac. Indian J Anaesth 2013;57:282-4.
61. Tomar GS, Tiwari AK, Chawla S, Mukherjee A, Ganguly S. Anaphylaxis related to fentanyl citrate. J Emerg Trauma Shock 2012;5:257-61.
62. Tummala K, Maniyal VK, Chandrashekaran R, Mathew N, Ganeshwala G. Cardiac anaphylaxis: A case of acute ST-segment elevation myocardial infarction after IM epinephrine for anaphylactic shock. Am J Emerg Med 2013;31:1157.e1-3.
63. Vaidya M, Ghike S, Jain S. Anaphylactoid reaction after use of intracervical dinoprostone gel. J Obstet Gynaecol Res 2014;40:833-5.
64. Vyas VH, Mohite SN, Khatavkar SS, Jagtap SR. Ranitidine anaphylaxis: A rare occurrence. Indian J Anaesth 2011;55:425-6.
65. An epidemiologic study of severe anaphylactic and anaphylactoid reactions among hospital patients: Methods and overall risks. The International Collaborative Study of Severe Anaphylaxis. Epidemiology 1998;9:141-6.
66. International Collaborative Study of Severe Anaphylaxis. Risk of anaphylaxis in a hospital population in relation to the use of various drugs: An international study. Pharmacoepidemiol Drug Saf 2003;12:195-202.

67. Laxenaire MC, Mertes PM, Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques. Anaphylaxis during anaesthesia. Results of a two-year survey in France. Br J Anaesth 2001;87:549-58.
68. van Puijenbroek EP, Egberts AC, Meyboom RH, Leufkens HG. Different risks for NSAID-induced anaphylaxis. Ann Pharmacother 2002;36:24-9.
69. Faria E, Rodrigues-Cernadas J, Gaspar A, Botelho C, Castro E, Lopes A, *et al.* Drug-induced anaphylaxis survey in Portuguese Allergy Departments. J Investig Allergol Clin Immunol 2014;24:40-8.
70. Mertes PM, Laxenaire MC, Alla F, Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999-2000. Anesthesiology 2003;99:536-45.
71. Ribeiro-Vaz I, Marques J, Demoly P, Polónia J, Gomes ER. Drug-induced anaphylaxis: A decade review of reporting to the Portuguese Pharmacovigilance Authority. Eur J Clin Pharmacol 2013;69:673-81.
72. van der Klauw MM, Stricker BH, Herings RM, Cost WS, Valkenburg HA, Wilson JH. A population based case-cohort study of drug-induced anaphylaxis. Br J Clin Pharmacol 1993;35:400-8.
73. de Silva IL, Mehr SS, Tey D, Tang ML. Paediatric anaphylaxis: A 5 year retrospective review. Allergy 2008;63:1071-6.
74. Moro Moro M, Tejedor Alonso MA, Esteban Hernández J, Múgica García MV, Rosado Ingelmo A, Vila Albelda C. Incidence of anaphylaxis and subtypes of anaphylaxis in a general hospital emergency department. J Investig Allergol Clin Immunol 2011;21:142-9.
75. Lenler-Petersen P, Hansen D, Andersen M, Sørensen HT, Bille H. Drug-related fatal anaphylactic shock in Denmark 1968-1990. A study based on notifications to the Committee on Adverse Drug Reactions. J Clin Epidemiol 1995;48:1185-8.
76. Mertes PM, Laxenaire MC, GERAP. Anaphylactic and anaphylactoid reactions occurring during anaesthesia in France. Seventh epidemiologic survey (January 2001-December 2002). Ann Fr Anesth Reanim 2004;23:1133-43.
77. Mertes PM, Alla F, Tréchot P, Auroy Y, Jougla E, Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques. Anaphylaxis during anesthesia in France: An 8-year national survey. J Allergy Clin Immunol 2011;128:366-73.
78. Karila C, Brunet-Langot D, Labbez F, Jacqmarcq O, Ponvert C, Paupe J, *et al.* Anaphylaxis during anesthesia: Results of a 12-year survey at a French pediatric center. Allergy 2005;60:828-34.
79. Sadleir PH, Clarke RC, Bunning DL, Platt PR. Anaphylaxis to neuromuscular blocking drugs: Incidence and cross-reactivity in Western Australia from 2002 to 2011. Br J Anaesth 2013;110:981-7.
80. Lobera T, Audicana MT, Pozo MD, Blasco A, Fernández E, Cañada P, *et al.* Study of hypersensitivity reactions and anaphylaxis during anesthesia in Spain. J Investig Allergol Clin Immunol 2008;18:350-6.
81. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000;30:1144-50.
82. Dhami S, Panesar SS, Roberts G, Muraro A, Worm M, Bilo MB, *et al.* Food Allergy and Anaphylaxis Guidelines Group. Management of anaphylaxis: A systematic review. Allergy 2014;69:168-75.
83. Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: Intramuscular versus subcutaneous injection. J Allergy Clin Immunol 2001;108:871-3.
84. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, *et al.* The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol 2010;126:477-80.e1.
85. Simons FE, Ardusso LR, Dimov V, Ebisawa M, El-Gamal YM, Lockey RF, *et al.* World Allergy Organization Anaphylaxis Guidelines: 2013 update of the evidence base. Int Arch Allergy Immunol 2013;162:193-204.
86. Simons FE, Schatz M. Anaphylaxis during pregnancy. J Allergy Clin Immunol 2012;130:597-606.
87. Adriaensens I, Vereauteren M, Soetens F, Janssen L, Leysen J, Ebo D. Allergic reactions during labour analgesia and caesarean section anaesthesia. Int J Obstet Anesth 2013;22:231-42.
88. Ding YJ, Song H, Liu JH, Wang GH. Brain injury due to anaphylactic shock as a result of formocresol used during root canal treatment. Int Endod J 2013;46:999-1005.
89. Schäbitz WR, Berger C, Knauth M, Meinck HM, Steiner T. Hypoxic brain damage after intramuscular self-injection of diclofenac for acute back pain. Eur J Anaesthesiol 2001;18:763-5.
90. Reitter M, Petitpain N, Latarche C, Cottin J, Massy N, Demoly P, *et al.* Fatal anaphylaxis with neuromuscular blocking agents: A risk factor and management analysis. Allergy 2014;69:954-9.
91. Fiszenson-Albala F, Auzerie V, Mahe E, Farinotti R, Durand-Stocco C, Crickx B, *et al.* A 6-month prospective survey of cutaneous drug reactions in a hospital setting. Br J Dermatol 2003;149:1018-22.
92. Jönsson AK, Hakkarainen KM, Spigset O, Druid H, Hiselius A, Hägg S. Preventable drug related mortality in a Swedish population. Pharmacoepidemiol Drug Saf 2010;19:211-5.
93. Hakkarainen KM, Hedna K, Petzold M, Hägg S. Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions: A meta-analysis. PLoS One 2012;7:e33236.
94. Kanjanarat P, Winterstein AG, Johns TE, Hatton RC, Gonzalez-Rothi R, Segal R. Nature of preventable adverse drug events in hospitals: A literature review. Am J Health Syst Pharm 2003;60:1750-9.

How to cite this article: Patel TK, Patel PB, Barvaliya MJ, Tripathi CB. Drug-induced anaphylactic reactions in Indian population: A systematic review. Indian J Crit Care Med 2014;18:796-806.

Source of Support: Nil, **Conflict of Interest:** None declared.