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

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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

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.[3]

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
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.\[9\]

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 the 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 publication: 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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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%). $\beta$-lactams (5.96%) were the most commonly incriminated antimicrobials. The most common causative drug was

\begin{figure}[h]
\centering
\includegraphics[scale=0.8]{study_selection_flow_diagram.png}
\caption{Study selection flow diagram}
\end{figure}
diclofenac (11.11%). Other commonly implicated drugs were atracurium (7.41%), vecuronium (5.56%), ranitidine

### Table 1: Characteristic of included studies in systemic review

| Article name | Type of study | Age (years) | Gender | Set up |
|--------------|---------------|-------------|--------|--------|
| Afonso et al. | Letter to editor | 30 | Female | Home |
| Anvari et al. | Letter to editor | 55 | Female | Perioperative |
| Awasthi and Tripathi | Case report | 38 | Female | Perioperative |
| Babu and Sharmila | Case report | 7 days | Male | Ward |
| Basu et al. | Case report | 57 | Female | Ward |
| Bhagyam and Saxena | Case report | 52 | Male | Perioperative |
| Choudhury et al. | Letter to editor | 35 | Male | Procedure room |
| Chowdhry et al. | Letter to editor | 48 | Female | Perioperative |
| Das and Mondal | Case report | 06 | Female | OPD |
| Dube et al. | Case report | 30 | Female | Perioperative |
| Elango et al. | Image in medicine | 30 | Female | Not stated |
| George and Williams | Letter to editor | 26 | Male | OPD |
| Ghae et al. | Letter to editor | 48 | Female | Perioperative |
| Govinath and | Case report | 58 | Female | Ward |
| Balachandran | Case report | 26 | Female | Home |
| Gupta et al. | Letter to editor | 18 | Female | Perioperative |
| Gupta et al. | Letter to editor | 40 | Female | Ward |
| Hirenmani | Case report | 35 | Female | Perioperative |
| Kalra et al. | Case report | 28 | Female | Perioperative |
| Kotmur et al. | Case report | 15 | Female | Home |
| Koul et al. | Case report | 56 | Male | Perioperative |
| Kumar et al. | Case report | 52 | Male | Perioperative |
| Mallick et al. | Case report | 18 | Female | Perioperative |
| Miraj et al. | Case report | 58 | Female | Perioperative |
| Mishra et al. | Case report | 20 | Female | PHC |
| Mishra et al. | Case report | 63 | Male | Perioperative |
| Mohapatra et al. | Correspondence | 20 | Male | Ward |
| Mukherjee and | Letter to editor | 56 | Female | Ward |
| Bhattacharya | Case report | 70 | Male | Perioperative |
| Murthy et al. | Case report | 40 | Female | OPD |
| Nekhi et al. | Case report | 34 | Female | Perioperative |
| Pant et al. | Case report | 40 | Female | Perioperative |
| Parikh et al. | Correspondence | 40 | Female | Perioperative |
| Pattnaik et al. | Letter to editor | 18 | Male | Perioperative |
| Ravi et al. | Case report | 43 | Female | Perioperative |
| Ravi et al. | Case report | 24 | Female | Perioperative |
| Ray et al. | Case report | 09 | Female | Home |
| Samanta et al. | Letter to editor | 32 | Male | Perioperative |
| Samanta et al. | Case report | 15 | Male | Ward |
| Sen et al. | Case report | 09 | Female | Home |
| Sengupta and Kohli | Case report | 35 | Female | Perioperative |
| Shah et al. | Case report | 30 | Male | Procedure room |
| Shankar et al. | Case report | 20 | Female | Perioperative |
| Shanti et al. | Case report | 18 | Male | Ward |
| Shrivastava | Case report | 37 | Male | Perioperative |
| Singal and Rataboli | Correspondence | 30 | Male | Home |
| Singh et al. | Case report | 25 | Female | ICU |
| Sinha and Sinha | Case report | 65 | Male | Perioperative |
| Sripriya et al. | Case report | 25 | Female | Perioperative |
| Swamy et al. | Case report | 28 | Female | Ward |
| Tiwari et al. | Case report | 64 | Male | Ward |
| Tomar et al. | Case report | 31 | Female | Perioperative |
| Tomar et al. | Case report | 26 | Male | Ward |
| Tummal et al. | Case report | 62 | Male | Home |
| Vaidya et al. | Case report | 20 | Female | Ward |
| Vyas et al. | Letter to editor | 65 | Male | Perioperative |

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

### 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 |
| Aminoglycosides | 1 |
| Other antibiotics | 5 (9.26)  |
| Artesunate | 2 |
| Co-trimoxazole | 1 |
| Ciprofloxacin | 1 |
| Tsidazole | 1 |
| NSAIDs | 7 (12.96)  |
| Diclofenac | 6 |
| Paracetamol | 1 |
| Neumuscular 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 |
| H2 receptor antagonists | 3 (5.56)  |
| Ranitidine | 3 |
| Local anesthetics | 2 (3.70)  |
| Bupivacaine | 1 |
| Lidocaine | 1 |
| Hematinics | 2 (3.70)  |
| Iron sucrose | 2 |
| Oxytocics | 2 (3.70)  |
| Oxytocin | 1 |
| Dinoprostone | 1 |
| Contrast media | 2 (3.70)  |
| Ioheol | 1 |
| Diatrizate | 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 |
| Mephenemidine | 1 |
| Palonosetron | 1 |
| Proamine sulfate | 1 |
| Cetirizine | 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%), vecuronium (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%), idiopathic urticaria (1.85%), household dermatological allergy (1.85%) and latex allergy (1.85%). History of anaphylaxis with same drugs (ranitidine and tinidazole) was positive in two cases.

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. Previous hypersensitivity reaction to the same group of drug was observed in one case and to the different group of drug was observed in two cases. 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%). 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%), diabetes mellitus (3.70%), obstructive pulmonary disease (1.85%), epilepsy (1.85%) and cerebral malaria (1.85%).

**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 + cutaneous     | 28 (51.85) |
| CVS + RS                 | 11 (20.37) |
| CVS + cutaneous          | 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 + cutaneous           | 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) |
| Dysrhythmia                  | 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) |
| Morbilliform 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) |
| Methylhistamine 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).[35] 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, H2 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.[19,33,36,37,49,53] 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.[35] 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)[26,53,64] 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]

**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.
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.\[7,67,68\] The observed rate of anaphylaxis in female gender is ranged from 61.9% to 72.7%.\[6,7,67,70,72,73\] 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.\[66\] 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.\[6,7,67,70,72,73\] In the international collaborative study, incidence of β-lactams-induced anaphylaxis was 5.7–32/100000 exposed patients.\[66\] Amoxicillin,\[7,73\] amoxicillin + clavulanic acid,\[74\] cefalosporins\[73\] 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), cefalosporins 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).\[66\] As per van Puijenbrook 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 NSAID.\[68\] 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 arypropionic 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.\[71\] 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 2.8/1,000 administrations, respectively.\[70\] 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.\[70\] This study supports it for neuromuscular blockers and anaesthetic agents. High

| 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
frequency of cross-reactivity (63.4–82.6%) is reported among neuromuscular blockers. Rocuronium and vecuronium in Laxenaire et al. and vecuronium, atracurium and pancuronium in Karila et al. 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. 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. NSAIDs-induced reactions can be immune or nonimmunne 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. In our study, allergen testing was performed in only one diclofenac 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.

Both intravenous and oral medications are commonly incriminated in the literature. More frequent reporting among inpatients than outpatients are in accordance with previous studies. 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. In contrast with our findings, de Silva et al. and Moro Moro et al. 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. In line with our findings, cardiovascular symptoms were predominant than cutaneous and respiratory in a study of perioperative anaphylaxis cases by Laxenaire et al. Overall grading for the severity of reactions (grade III > II > IV) are in accordance with the literature. Allergic conditions are less frequently observed than previous study. Bronchial asthma was associated with fatal outcome as reported in literature.

The adrenaline was used in 83.33% patients as against 57.6% in Renaudin et al. and 76% in de Silva et al. 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. 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. Optimum site of intramuscular injection is vastus lateralis muscle. Use of subcutaneous route for adrenaline is lower than previous study. 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. A recent systematic review did not identify any suitable randomized control trials (RCTs) or quasi-RCTs for the steroids and antihistamines in the management of anaphylaxis. Because of anti-allergic mechanisms, steroids are routinely incorporated in management. 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. However, they can prevent biphasic reaction. H1 antihistamines should be used as a second line treatment because of slow action and little effect on blood pressure and respiratory symptoms. The combination of H1 and H2 receptor antagonists are superior to H1 antihistamines alone for urticaria but not for the angioedema and pruritus. Vasopressors should be given if adrenaline and fluid resuscitation are not able to maintain systolic blood pressure >90 mm Hg. Inhaled β2-agonist should be used for the bronchospasm resistant to adequate doses of adrenaline.

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. 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. 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. 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. 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. Adrenalin 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. Fatalities can occur even if adrenaline is used correctly. 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. 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 Thornt criterion that is similar with the previous study showing 15% of preventable cutaneous allergic reactions. One Swedish study observed one fourth of the fatal ADRs could be prevented. 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%). 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. Kanjanarat et al. had observed prescribing of antimicrobials despite a history of allergy is one of the common reasons for the preventable adverse events. Recurrent anaphylaxis can be prevented by identification of risk factors, avoidance of allergen, with caution and constant supervision.

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’s back.

**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.

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