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Review Article

Anaesthesia Section

Adverse Drug Reactions and Anaesthesia: A Narrative Review

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ABSTRACT

Adverse drug reactions are defined as the effects created by drugs producing unintended or noxious response in doses normally used for prophylaxis, diagnosis or therapy of diseases. Adverse drug reactions under anaesthesia occur by a number of mechanisms and several risk factors are often involved. The overall incidence of adverse drug reactions to anaesthetic drugs ranges between 1 in 10,000 and 1 in 20,000. Electronic databases were searched to obtain the relevant literature with keywords related to adverse drug reactions and anaesthesia. Total 110 articles were reviewed, bibliography cross-checked and relevant literature was included. This article discusses about the adverse drug reactions to various anaesthetic as well as non anaesthetic drugs used intraoperatively. Anaphylaxis under anaesthesia, its pathophysiology, clinical and laboratory diagnosis, management and prevention has also been discussed in detail. Allergic drug reactions and anaphylaxis in the operating room often presents unique diagnostic concerns as the early signs of anaphylaxis are often masked under general anaesthesia. The use of surgical drapes and use of multiple potential allergen drugs under anaesthesia also make the diagnostic process difficult. Thus, an adequate knowledge, understanding, vigilance and proper documentation with reporting in case of an event is warranted by the attending anaesthesiologist for a good perioperative outcome with decreased morbidity and mortality.

Keywords: Allergen drugs, Allergic reactions, Drug events, Operating room

INTRODUCTION

Anaesthetists are the medical specialists more likely to witness Adverse Drug Reactions (ADRs) in their practice. This is due, in part to the nature of the perioperative period, in which patients are exposed to a large variety of potential allergens including anaesthetic drugs as well as other miscellaneous agents like antiseptics, dyes, contrast, latex and antibiotics. The incidence of adverse drug reactions to anaesthetic drugs ranges between 1 in 10,000 to 1 in 20,000 with mortality in the order of around 10% [1,2]. Hence, it is essential that, anaesthesiologists, as perioperative specialists remain vigilant to the possibility of ADRs and be well informed about their recognition, immediate treatment and follow-up.

LITERATURE SEARCH

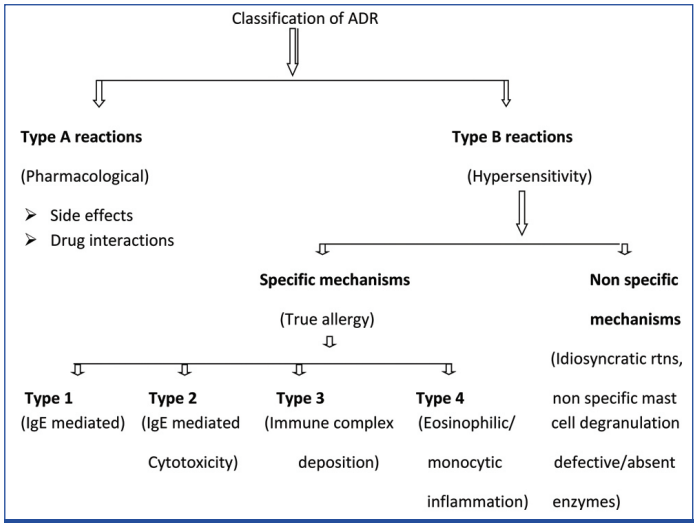
A literature search was undertaken using several electronic databases, (PubMed, Cochrane databases and specific journals), which pertain to adverse drug reactions in medicine and anaesthesia. The searches were conducted by the first author. The evidence and data cited consists of findings from either individual studies/case reports/series/meta-analysis or narrative/clinical reviews related to the topic. The aim of this article is to provide a comprehensive review on the adverse drug reactions in the field of anaesthesia. The review has also dealt in detail with anaphylaxis, pathophysiology, its diagnosis, management and reporting.

DEFINITIONS AND CLASSIFICATIONS

Adverse drug reaction is defined as any drug response that is not of prophylactic, diagnostic or therapeutic benefit to the patient. It can range from mild skin rashes to severe clinical presentation which accounts to about 10% and result in 0.02-0.04% of morbidity and mortality [3].

Classification of ADR: They can be classified as:

- **Type A (Augmented):** About 85-90% reaction which are relatively common and related to the main pharmacological effects of the drug. They are dose temporal and associated with drug administration such as medication overdose, exaggeration of drug's normal pharmacological actions, interactions with other drugs [4].
- **Type B (Bizzare):** About 10-15% reaction occurs due to some sort of genetic predisposition. They are called true allergy and are immunologically mediated. The event of sensitisation is followed by generation of specific antibodies. Upon renewed exposure, specific T-cells and/or Abs may mediate allergic reactions (Type 1-4 reactions according to Gell and Coombs) [Table/Fig-1] [5].



[Table/Fig-1]: Classification of adverse drug reactions.

ADVERSE DRUG REACTIONS UNDER ANAESTHESIA

Adverse drug reactions under anaesthesia occur by a number of mechanisms and several risk factors are often involved [6]. Though, a majority of reactions occur during induction and are non fatal, 9% of them can be fatal and represent a significant cause of morbidity and mortality [2].

In 60-80% cases, the observed manifestation of ADRs during General Anaesthesia (GA) is cardiovascular collapse, a relatively late event [7]. The early manifestations are masked during GA. Adverse drug reactions that happen during general anaesthesia can be due to drug overdose, secondary adverse effects, idiosyncratic reactions, drug intolerance, drug interactions and allergic reactions/hypersensitivity or anaphylaxis (immunological) [8].

ADR to Intravenous Induction Agents

The reactions to intravenous induction agents can vary from mild induction complications {excitatory phenomenon, respiratory depression, Cardiovascular System (CVS) changes} to severe hypersensitivity or idiosyncratic reactions (immune mediated/ anaphylaxis) [9].

The [Table/Fig-2] summarises the various system wise adverse drug reaction of intravenous induction agents based on various reports and reviews from the literature. Though, a majority of adverse reactions to induction agents are mild/transient and might not require active intervention in normal subjects, a constant vigilant anaesthesiologist is warranted to diagnose or manage severe life threatening reactions in those who are intolerant to the drug and thus might have exaggerated responses [10-16].

ADR to Opioids and Benzodiazepines

Though, benzodiazepines are considered to be cardiostable with transient side effects, cases of cardiac arrest have been reported in the literature following rapid intravenous injection of diazepam or midazolam [17]. There has also been a recent shift towards non opioid based anaesthesia practice in view of adverse effects of opioids mainly on the respiratory system [Table/Fig-3] [18-22].

ADR to Muscle Relaxants

Evidence states Neuromuscular Blocking Agents (NMBA) to be the first cause of perioperative reactions during general anaesthesia [23]. Though, administration of muscle relaxant may cause immunologically mediated Type 1 hypersensitivity response and/or complement activation, it is more commonly due to the release of histamine from tissue mast cells that causes clinical manifestations [Table/Fig-4] [24-27].

ADR to Inhalational Agents

The most common adverse effect of inhaled anaesthetic agents is Postoperative Nausea and Vomiting (PONV) [28]. A few inhalation agents are known to irritate the airways of patients with severe asthma and induce bronchospasm due to the pungent smell on induction, primarily with desflurane and isoflurane. Sevoflurane, desflurane and isoflurane decrease systemic vascular resistance leading to a drop in systemic blood pressure. These changes are transient and mild in normal subjects, however, are more profound in hypovolemic patients. Malignant Hyperthermia (MH) is also an adverse effect that can occur with the administration of inhaled anaesthetics, most commonly seen with the inhaled gas halothane. Patients susceptible to this adverse effect have heritable alterations between their proteins and muscular cytosolic concentrations of Ca^{2+} [29]. Nitrous oxide can cause diffusion hypoxia quickly following discontinuation of the agent. It is recommended that 100% FiO_2 be used to counteract the rapid dilution of O_2 in the alveoli [Table/Fig-5] [30-33].

Intravenous induction agents	Cardiovascular effects	Respiratory effects	Central nervous system effects	Gastrointestinal/Genitourinary effects/ others
Thiopentone/ Propofol	• Myocardial depression. • Decrease in arterial blood pressure due to vasodilating effects. • Treatment resistant bradycardia with junctional rhythm with thiopentone has been reported.	• Central respiratory depression/ apnea • Ventilator response to CO_2 abolished.	• Decrease in cerebral metabolism with an increase in cerebral blood flow and Intracranial Pressure (ICP). • Several cases of seizures including tonic clonic activity and opisthotonus have been reported with propofol (1 in 50000 cases).	• Severe anaphylactic reactions. • Postoperative Nausea Vomiting (PONV), rare case of pancreatitis. • Propofol causes pain on injection in 40 to 70% of patients. - Immune haemolytic anaemia and porphyrias with thiopentone.
Ketamine	• Increase in heart rate with a 20-30% increase in Blood Pressure (BP), systemic and pulmonary vascular resistance. • Direct myocardial depressant.	Increase in salivary, tracheal and bronchial secretions.	• Increase in intracranial and intraocular pressures. • Emergence reactions (vivid dreaming, hallucinations, sense of floating) reported in about 50%.	Blurred vision, nystagmus, diplopia.
Etomidate	Minimal effects on the cardiovascular system.	• Involuntary muscle movement. • Seizuires/epileptiform activity.	• Ventilatory responses to CO_2 is depressed by etomidate with 15-20% incidence of apnea.	A transient adrenal suppression unresponsive to Adrenocorticotropic Hormone (ACTH) stimulation occurs.

[Table/Fig-2]: The adverse drug reactions to intravenous induction agents under anaesthesia [11-16].

Opioids/ Benzodiazepines	Cardiovascular effects	Respiratory effects	Central nervous system effects	Gastrointestinal/Genitourinary effects/ others
Fentanyl, morphine, pethidine.	• Peripheral vasodilation with a significant hypotension. • Incidence of opioid induced bradycardia progressing to asystole have been reported.	• Depression of cough reflex. • Central respiratory depression with decreased ventilator response to CO_2. • Biphasic respiratory depression with fentanyl. • Rigidity of thoracic muscles often called wooden chest syndrome, seen with opioid induction.	• Norpethidine, a metabolite of pethidine associated with myoclonus and seizures. • Postoperative sedation, amnesia, psychomotor impairment, euphoria.	• Decrease in cortisol secretion in humans. • Reports of significant decrease in glucose and insulin along with an increase in serum levels of growth hormone. • PONV, Increase in intrabiliary pressures, prolongs the mean gastric emptying half time, risk of regurgitation. • Neonatal depression, urinary retention.

[Table/Fig-3]: The adverse drug reactions to opioids and benzodiazepines under anaesthesia [19-22].

Muscle relaxants	Cardiovascular adverse effects	Respiratory adverse effects	Central nervous system adverse effects	Gastrointestinal/Genitourinary effects/others
Atracurium/ Vecuronium	• Type 1 hypersensitivity/histamine release- erythema, transient decrease in BP and tachycardia, rarely circulatory collapse. • Bradycardia when given with fentanyl anaesthesia.	Histamine release/ hypersensitivity reactions/ bronchospasm.	Laudanosine, a metabolite of atracurium has a stimulant effect on the Central Nervous System (CNS) and can cause seizures.	-
Succinylcholine (Sch)	May vary from tachycardia and a rise in blood pressure due to stimulation of sympathetic ganglia in adults to bradycardia observed in infants and children.	Respiratory manifestations during anaphylaxis with Sch.	Associated with increase in intra ocular, intracranial and intragastric pressures.	• Fasciculations may result in muscle pain especially in the neck, back and shoulders. • Incidence of malignant hyperthermia. • Serious hyperkalemia in upper and motor neuron lesions, trauma or abdominal infections.

[Table/Fig-4]: Adverse drug reactions to non depolarising and depolarising muscle relaxants under anaesthesia [24-27].

Inhalational agents	Cardiovascular adverse effects	Respiratory adverse effects	Central nervous system adverse effects	Gastrointestinal/Genitourinary effects/others
Nitrous oxide/ halogenated inhalational agents.	• Depress myocardial contractility by a direct effect and decrease blood pressure in a dose dependent manner {↓ in cardiac output and Systemic Vascular Resistance (SVR)}. • Halothane sensitises the myocardium to catecholamines, dysarrythmias are common. • Dose dependent decrease in myocardial blood flow.	• Profound respiratory depressants. • Depress the CO_2 response curve. • Isoflurane, enflurane and desflurane have been reported to induce cough, bronchospasm and breath holding.	• Decrease cerebral metabolic rate and increase ICP in a dose related manner. Cerebral blood flow is increased to a greater extent and autoregulation lost to a greater extent with halothane than with enflurane or isoflurane	• There is an ↑ incidence of PONV. • Hepatic dysfunction(mild hepatitis to necrosis) • ↓in renal blood flow and Glomerular Filtration Rate (GFR), • Sevoflurane react with CO_2 absorbants to form vinyl ether/compound A (probable nephrotoxicity). • Malignant hyperthermia.

[Table/Fig-5]: The adverse drug reactions to inhalational induction agents under anaesthesia [30-33].

ADR to Local Anaesthetics

Systemic and localised adverse effects of local anaesthetic drugs usually occur because of excessive dosage, rapid absorption or inadvertent intravenous injection. The incidence of true allergy is not known, but has been widely quoted that <1% of all reactions to local anaesthetics are allergic in nature [Table/Fig-6] [34-37].

ADR to Neuraxial/Regional Anaesthesia

The adverse complications of regional anaesthesia range from bothersome to crippling and life threatening complications [38]. The adverse effects can be classified as that resulting from physiological excessive side-effects, placement of the needle (or catheter) and drug toxicity [Table/Fig-7].

Drug	Cardiovascular adverse effects	Respiratory adverse effects	Central nervous system adverse effects	Gastrointestinal/Genitourinary effects/others
Local anaesthetics	• Generally begin after signs of CNS toxicity have occurred. • Bupivacaine appear to be more cardiotoxic. • Higher concentrations decrease myocardial contractility, decrease conduction velocity in the heart, may progress to sinus bradycardia, dysarrythmias {torsades, Ventricular Tachycardia (VT), Ventricular Fibrillation (VF) and/or refractory asystole}.	Respiratory complications like bronchospasm and respiratory arrest have been reported following inadvertent intravenous or intrathecal injections.	Excitation of CNS (numbness of tongue, perioral area, tinnitus, muscle twitching, tremors and restlessness), may progress to seizure, respiratory failure and coma (CNS depression)	• Ester derivatives of p-Aminobenzoic Acid (PABA) (Benzocaine, procaine, tetracaine) cause most of the allergic reactions. • Allergic reactions to amide local anaesthetics are unusual and may be related to the preservatives used.

[Table/Fig-6]: The adverse drug reactions to use of local anaesthetics [34-37].

Adverse or exaggerated physiological responses	Complications related to needle/catheter placement	Complications due to drug toxicity
• High block • Total spinal anaesthesia • Cardiac arrest • Anterior spinal artery syndrome • Urinary retention	• Post dural puncture headache • Neural injury • Intraspinal/Epidural hematoma • Arachnoiditis/meningitis • Epidural abscess	• Systemic local anaesthetic toxicity • Transient neurological symptoms • Cauda equine syndrome

[Table/Fig-7]: Complications of neuraxial anaesthesia.

The incidence of neurologic Central Neuraxial Blockade (CNB) complications is estimated to be between 1/1000 and 1/1,000,000 [39]. A very large survey of regional anaesthesia from France showed relatively low incidence of serious complications from regional anaesthesia [40]. The incidence of complications were higher with spinal than with epidural anaesthesia. Though fatal cardiac arrest events were encountered, they could not be directly attributed to spinal anaesthesia. About 80% of patients with neurological deficits had complete recovery within three months.

NON ANAESTHESIA DRUG RELATED ADVERSE REACTIONS

Non anaesthesia drugs causing adverse drug reactions (Latex, antibiotics, plasma volume expanders, blood) have been studied extensively [41-43].

Latex Allergy

There is evidence that about 20% of perioperative anaphylaxis is attributed to latex and it is the second cause of adverse reactions during the perioperative period [44]. Patients undergoing multiple surgical procedure or patients who need chronic bladder care (urogenital malformations, spinal cord trauma), professional exposure in healthcare workers [41]. Obstetric population are associated with an increased frequency of latex allergy. Sensitised individuals may develop urticaria, angioedema, allergic rhinitis, asthma or anaphylaxis [45]. Prevention can be done by either avoidance of sensitisation in high risk population or by establishing a latex free environment in Operation Theatre (OT) and recovery rooms.

Antibiotic Allergy

About 15% of anaesthesia related anaphylaxis perioperatively are due to antibiotics [46]. Anaphylaxis to antibiotics are more common with penicillins and cephalosporins constituting to 70% of perioperative anaphylactic reactions induced by antibiotics [42].

Beta lactam antibiotics, vancomycin and quinolones are also frequently implicated. Vancomycin, is typically associated with "red man syndrome" characterised by flushing, pruritis and an erythematous rash of the head and upper torso and arterial hypotension [47].

Colloids

Adverse drug reaction to colloids have been discussed widely in the literature [48]. Anaphylactic reactions to gelofusine and other gelatine based plasma volume expanders carries an incidence of 0.07-0.15% [43]. They are three times more likely to cause anaphylaxis than crystalloids and albumin [49]. There has also been higher incidence of allergic reaction to first and second generation starches.

These reactions are normally type 1, IgE mediated anaphylaxis reaction, though rarely anaphylactoid reactions have also been reported. Cutaneous signs followed by hypotension is the most common presenting sign perioperatively, with reactions most commonly occurring within ten minutes of starting the infusion [50].

Chlorhexidine

The incidence of anaphylaxis to chlorhexidine is about 0.78 per 1,00,000 exposures [51]. Patients may often become sensitised to chlorhexidine before a surgical procedure as it is widely used all over the world as a common skin disinfectant in minor skin scratches and as a mouth wash [52]. Reported symptoms in the literature vary from mild cutaneous reactions to severe life threatening anaphylaxis [53]. Povidone Iodine (betadine), another commonly used topical antiseptic solution has been found to be associated with allergic contact dermatitis.

Non Steroidal Anti-inflammatory Drugs (NSAIDS)

Multiple studies have identified aspirin and NSAIDS as one of the commonest causes of drug induced anaphylaxis [54,55]. Inhibition of Prostaglandin E2 (PGE 2) pathway (cyclooxygenase) leads to

excessive leukotriene production and subsequent mediator release. The route of administration is usually oral, rectal or intravenous with onset of reaction upto 10 minutes, 15-30 minutes and upto 60 minutes after the administration.

Blood and Blood Products

There is consensus that blood transfusion has been associated with both acute non immune mediated and acute immune mediated reaction with a reported incidence of 3% [56]. Multiple studies have identified allergic reactions like urticaria with erythema and pruritis, that occur within seconds or minutes of the start of transfusion or may take several hours to develop [57].

Anaphylaxis is a more severe form of an allergic reaction with an incidence of 1:20000 to 1:50000 transfusions [58]. Though, it is easy to identify adverse transfusion reactions in awake patients, it often becomes difficult to identify adverse transfusion reaction under anaesthesia. In these situations, signs like arrhythmias, tachycardia, localised or cutaneous reactions, hypotension or increased airway resistance due to laryngo or bronchospasm may serve as an indicator of underlying adverse transfusion reaction [56,58]. In one of the case reports by Rudingwa P et al., the presence of acute intraoperative hematuria was the only clue that led to the suspicion of mismatch transfusion and thereby initiated further evaluation and treatment [59]. It is mandatory to record the type of transfusion reaction suspected, length of time of reaction after starting, volume, type and pack numbers of blood products transfused in the patient's notes [56].

OTHER MISCELLANEOUS AGENTS

Many other non specific agents used during anaesthesia may be associated with anaphylaxis, including apoprotinin, protamine, ondansetron, radiological contrast dyes, oxytocin [60-62]. When a trigger is not identified following standard investigation with routine suspected agents, the possibility of other less common or "hidden" allergens should be considered.

ANAPHYLAXIS UNDER ANAESTHESIA

Incidence: The incidence of anaphylaxis is estimated between 1 in 4,000 and 1 in 20,000 anaesthetic procedures, as reported by Mali S, in a review article [63]. However, anaphylactic reactions (immune IgE mediated) cannot be clinically distinguished from non immune mediated mast cell reactions (account for 30-40% of hypersensitivity reactions) [44]. In one of the recent studies on anaphylaxis during general anaesthesia, an IgE mediated cause was identified in 64% of cases with NMBA constituting the leading cause of anaphylaxis (38%).

Aetiological factors: Multiple studies in the literature have identified neuromuscular blocking agents to represent the first cause of perioperative anaphylaxis followed by latex (12.1%), antibiotics (8%), induction agents (3.7%), opioids (1.4%), colloids (2.7%) and others like dyes and antiseptics (2.9%) [64,65].

Pathophysiology: The clinical features in anaphylaxis are due to ongoing release of mediators from mast cells and basophils, mediated by Type E immunoglobulins [66].

The mechanism involves production of IgE antibodies on initial exposure to an allergen in susceptible individuals [67]. On re-exposure, multicentric allergen cross links two specific IgE receptors which then induce a signal transduction cascade releasing systemically preformed mediators (histamine, tryptase and chymase) and proteoglycans from cells within tissues and blood. The involved target organs include skin, mucus membrane, cardiovascular, respiratory and gastrointestinal systems [66].

Recognition of anaphylaxis under anaesthesia: In event of an anaphylactic reaction, numerous factors make assessment and establishing a temporal relationship difficult. As with anaesthesia practice, several medications are usually administered and in quick succession, there may be difficulty in distinguishing the haemodynamic effects of anaesthetic drugs from anaphylaxis [63]. Cutaneous features of anaphylaxis may go undetected in a fully draped patient, the clinical features may be delayed or confused with other causes of hypotension like myocardial infarction, cardiac arrhythmias, drug overdose or pulmonary embolus [68,69].

Clinical feature: A survey of anaphylaxis as reported in the National Audit Project (NAPS 6), during anaesthesia demonstrated that CVS symptoms (73.6%), cutaneous symptoms (69.9%) and bronchospasm (44.2%) were the most common clinical features [70].

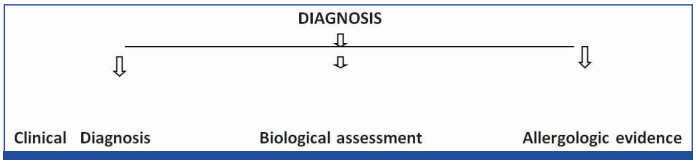
Ring and Messmer described a severity grading in clinical diagnosis of anaphylaxis, where, grades I and II reactions are not life-threatening and are more likely to be non allergic, although they may still be IgE-mediated. Grades III and IV are life-threatening conditions, also called 'anaphylaxis', which are usually IgE-mediated [Table/Fig-8] [71].

Grade	Signs
I	Cutaneous mucous signs
II	Cutaneous mucus signs Cardiovascular signs (hypotension, tachycardia) Respiratory signs
III	Cardiovascular collapse
IV	Bronchospasm

[Table/Fig-8]: Clinical severity grading of anaphylaxis by Ring and Messmer.

Diagnosis

The aetiological diagnosis of an immediate reaction occurring under anaesthesia depends on a triad including clinical, biological and allergologic evidence [Table/Fig-9] [72].



[Table/Fig-9]: The triad for diagnosis of anaphylaxis.

1) Clinical diagnosis: The first line of evidence for the diagnosis of anaphylaxis includes the features and severity of clinical signs. According to Ring and Messemer, grade III or IV symptoms are reported to be associated with severe anaphylaxis reaction. The symptoms often include bronchospasm, cutaneous mucus signs, pulmonary edema, desaturation and difficult lung inflation due to severe bronchospasm [42]. Cardiovascular symptoms often progress to arrhythmias and cardiovascular collapse. Acute coronary events associated with hypersensitivity reaction are referred to as Kounis syndrome (allergic angina) [71].

A number of factors have been explored in the literature, and it is found that patient's sensitivity level, allergen concentration and the route of administration are important in determining the onset and severity of symptoms [42].

2) Biological assessment: In-vitro and in-vivo biochemical tests such as an increase in serum histamine concentration and tryptase measurements are recommended for the diagnosis of immediate reaction [72]. Other in-vitro tools have been proposed like specific IgE assays for various drugs (thiopentone, propofol, antibiotics) [73].

3) Allergologic/skin tests: Multiple studies have been conducted and concluded skin tests to be the gold standard for detection of IgE mediated reaction. It is performed by exposing the mast cells of the skin to the suspected allergen in patients having experienced anaphylaxis [74]. The test help to identify the causative agent to definitely avoid it.

Treatment of Anaphylaxis

A number of protocols and management algorithms have been described in the literature for acute recognition and management of anaphylaxis [75,76].

1) Restoration of CVS haemostasis: Expansion of intravascular volume status with administration of iv epinephrine is the first priority [75].

Fluid therapy: Upto 73% of blood volume may extravasate into the interstitial space within 15 minutes after the onset of event. Recent consensus of the International Suspected Perioperative Allergic Reaction (ISPAR) group recommends that crystalloid boluses upto 20 mL/kg, repeated where the clinical response is inadequate and further choice tailored to the severity of anaphylaxis.

Adrenaline: Early administration of intravenous adrenaline is warranted [77]. Grade 3 may require titrated intravenous (i.v) bolus administration (100-200 µ) followed by continuous infusion (1-4 ug/min). Grade 4: Cardiac arrest requires CPR and high doses of epinephrine 1-3 mg i.v over three minutes followed by continuous infusion (4-10 µg/min) [78].

2) Restoration of airway and management of bronchospasm: If the event has occurred after administration of NMBAs, airway should be promptly secured if not done already. If during RA such as due to antibiotics, oxygen by face mask should suffice, followed by further management accordingly [78].

Bronchospasm is treated with inhaled beta 2 agonists via a nebulizer (salbutamol or albuterol). In case of persistent bronchospasm, iv injection of beta 2 agonist is recommended and a continuous infusion (5-25 µg/min) is considered. Intravenous glucocorticoids (like methylprednisolone) remain a key component of management, as their potential anti inflammatory effects decrease airway inflammation.

3) Other miscellaneous agents

a) A systemic review and meta analysis of 30 clinical trials, has stated corticosteroids and/or H1 receptor antagonists (anti histamines) to be of proven benefit especially for angioedema [79].

b) Sugammadex should be administered, in the setting of rocuronium related anaphylaxis.

4) Anaphylactic shock refractory to adrenaline:

Adrenaline sometimes fail to restore the profound disturbances of CVS haemostasis. This singular entity is called anaphylactic shock refractory to catecholamines (3-5%). It occurs because of [80]:

- Failure to discontinue the culprit agent or lower the anaesthetic depth.
- Underdosing or overdosing of adrenaline (leading to desensitisation)
- Delayed adrenaline administration
- Inadequate fluids

Arginine Vasopressin (AVP) may be used as an alternative rescue therapy in such scenarios, in a dose of 1-2 IU; followed by infusion at 2 IU/hr.

Nor adrenaline, metaraminol, glucagon.A review of case reports recommended the use of nor adrenaline, metaraminol and glucagon in this setting especially for patients on beta blocker therapy [80].

Extracorporeal Life Support (ECLS) has been successfully used in a few cases of refractory anaphylaxis.

Prevention of Anaphylaxis

1) In case of history of anaphylaxis to a particular drug, it should be avoided with planning of safe alternatives for the same.

2) When specific agent was not identified, it should be considered to replace all drugs administered before the onset of reaction with alternatives.

3) In case of susceptible individuals/history of atopy, it is advisable to avoid triggers like Latex, use alternatives to NMBAs like LA and inhalational agents if possible, and slow administration of histamine releasing drugs [81].

4) Premedication with steroids and/or anti histamines have been found to be useful, though controversial reports exists [82].

REPORTING OF ADR UNDER ANAESTHESIA

Critical incident reporting is the key component of patient safety [83]. This involves introduction of Incident Reporting Systems (IRS) which have been organised at variety of levels: within individual departments of anaesthesia, within individual hospitals at regional level and national level [84]. While immediate analysis and feedback are essential at local level, wide dissemination of safety lessons can improve patient care on a larger scale.

There are four basic steps in a successful critical incident reporting and analysis [85,86].

a) Data input: Should be independent and non punitive.

b) The data: The actual data reporting should have the freedom to narrate what actually happened.

c) Analysis: A good quality report should tend itself for detailed analysis of the chain of events that lead to the incident.

d) Feedback: To learn from mistakes and to ensure systems are improved for better patient safety in future and to encourage further reporting.

The main reasons for under reporting includes fear of punitive action, legal ramifications, lack of understanding as to what should be reported and lack of awareness as to how reported incidents will be analysed.

CONCLUSION(S)

The nature of anaesthetic practice is such that exposure to risk is inordinately high. Adequate knowledge and experience, proper perioperative assessment of the patient, labelling of syringes, checking of lines and cannulas, slow administration of drugs are necessary to decrease the incidence of ADRs in anaesthesia. Anaphylaxis is the most serious ADR and can be life threatening. Prevention, management, documenatation, appropriate labelling of the patient and critical incident reporting should be encouraged in anaesthesia practice to improve patient safety and decrease morbidity and mortality.

REFERENCES

[1] Zheng Z, Zhong H, Zhang Q, Huang Q, Wu H. HLA-B* 1502 is associated with aromatic anticonvulsant drug-induced cutaneous adverse drug reactions among the Hakka population in China. J Int Med Res. 2020;48(3):0300060520911276.
[2] Holdcroft A. UK drug analysis prints and anaesthetic adverse drug reactions. Pharmacoepidemiol Drug Saf. 2007;16(3):316-28.
[3] Coleman JJ, Pontefract SK. Adverse drug reactions. Clin Med (Lond). 2016;16(5):481.
[4] Iasella CJ, Johnson HJ, Dunn MA. Adverse drug reactions: Type A (intrinsic) or type B (idiosyncratic). Clin Liver Dis. 20171;21(1):73-87.
[5] Kaufman G. Adverse drug reactions: Classification, susceptibility and reporting. Nurs Stand. 201610;30(50).
[6] Patton K, Borshoff DC. Adverse drug reactions. Anaesthesia. 2018;73:76-84.
[7] Fisher MM, More DG. The epidemiology and clinical features of anaphylactic reactions in anaesthesia. Anaesth Intensive Care. 1981;9(3):226-34.
[8] Berthoud MC, Reilly CS. Adverse effects of general anaesthetics. Drug Saf. 1992;7(6):434-59.
[9] Khan KS, Hayes I, Buggy DJ. Pharmacology of anaesthetic agents I: Intravenous anaesthetic agents. Continuing Education in Anaesthesia, Critical Care & Pain. 20141;14(3):100-05.
[10] Djordjević B, Stojiljković MP, Loncar-Stojiljković D, Krivokapić D, Adamov A. Adverse effects reported after inductive doses of the intravenous anesthetics, thiopentone, etomidate and propofol. Vojnosanit Pregl. 19991;56(2):143-50.
[11] Sharma S, Nair PP, Murgai A, Selvaraj RJ. Transient bradycardia induced by thiopentone sodium: A unique challenge in the management of refractory status epilepticus. BMJ Case Rep. 2013;2013:bcr2013200484.
[12] Yanaru T, Sugi Y, Higa K, Shono S, Katori K, Nitahiara K. Propofol-induced generalized tonic-clonic seizure: A case report. Masui. 20101;59(8):1036-38.
[13] Briassoulis G, Hatzis T, Mammi P, Alikatora A. Persistent anaphylactic reaction after induction with thiopentone and cisatracurium. Paediatr Anaesth. 2000;10(4):429-34.
[14] Sim JY, Lee SH, Park DY, Jung JA, Ki KH, Lee DH, et al. Pain on injection with microemulsion propofol. Br J Clin Pharmacol. 2009;67(3):316-25.
[15] Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. Am J Emerg Med. 20081;26(9):985-1028.

[16] Williams LM, Boyd KL, Fitzgerald BM. Etomidate. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 Jun 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK535364/.
[17] Duprey MS, Al-Qadheeb NS, O'Donnell N, Hoffman KB, Weinstock J, Madias C, et al. Serious cardiovascular adverse events reported with intravenous sedatives: A retrospective analysis of the MedWatch adverse event reporting system. Drugs Real World Outcomes. 2019;6(3):141-49.
[18] Frauenknecht J, Kirkham KR, Jacot Guillarmod A, Albrecht E. Analgesic impact of intra operative opioids vs. opioid free anaesthesia: A systematic review and meta analysis. Anaesthesia. 2019;74(5):651-62.
[19] Sudhakaran S, Surani SS, Surani SR. Prolonged ventricular asystole: A rare adverse effect of hydrocodone use. Am J Case Rep. 2014;15:450.
[20] Ramos-Matos CF, Bistas KG, Lopez-Ojeda W. Fentanyl. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 Jun 3]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK459275/.
[21] Phua CK, Wee A, Lim A, Abisheganaden J, Verma A. Fentanyl-induced chest wall rigidity syndrome in a routine bronchoscopy. Respir Med Case Rep. 2017;20:205-07.
[22] Suga Y, Uchida M, Suzuki S, Sugawara H, Torigoe K, Futamura A, et al. Current status of adverse events related with opioid analgesics in Japan: Assessment based on Japanese adverse drug event report database. Biol Pharm Bull. 2019;42(5):801-06.
[23] 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(1):123-26.
[24] Clarke RS, Mirakhur RK. Adverse effects of muscle relaxants. Adverse Drug React Toxicol Rev. 1994;13(1):23-41.
[25] Ritz ML, Derian A. Atracurium. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 Jun 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK499995/.
[26] Heier T. [Muscle relaxants]. Spine (Phila Pa 1976). 2010;130(4):398-401.
[27] Piotrowski AJ, Fendler WM. Hyperkalemia and cardiac arrest following succinylcholine administration in a 16-year-old boy with acute nonlymphoblastic leukemia and sepsis. Pediatr Crit Care Med. 2007;8(2):183-85.
[28] Scheiermann P, Herzog F, Siebenhofer A, Strametz R, Weberschock T. Intravenous versus inhalational anesthesia for pediatric inpatient surgery- A systematic review and meta-analysis. J Clin Anesth. 2018;49:19-25.
[29] Hopkins PM, Gupta PK, Bilmen JG. Malignant hyperthermia. Handb Clin Neurol. 2018;157:645-61.
[30] Kharasch ED. Adverse drug reactions with halogenated anesthetics. Clinical Pharmacology & Therapeutics. 2008;84(1):158-62.
[31] Stachnik J. Inhaled anesthetic agents. Am J Health Syst Pharm. 2006;63(7):623-34.
[32] Torri G. Inhalation anesthetics: A review. Minerva Anestesiol. 2010;76(3):215-28.
[33] Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: A review. Orphanet J Rare Dis. 2015;10. [cited 2021 Jun 8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4524368/.
[34] Fuzier R, Lapeyre-Mestre M, Mertes PM, Nicolas JF, Benoit Y, Didier A, et al. Immediate and delayed type allergic reactions to amide local anesthetics: Clinical features and skin testing. Pharmacoepidemiol Drug Saf. 2009;18(7):595-01.
[35] Liu W, Yang X, Li C, Mo A. Adverse drug reactions to local anesthetics: A systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol. 20131;115(3):319-27.
[36] Dillane D, Finucane BT. Local anesthetic systemic toxicity. Can J Anaesth. 2010;57(4):368-80.
[37] Bina B, Hersh EV, Hilario M, Alvarez K, McLaughlin B. True allergy to amide local anesthetics: A review and case presentation. Anesthesia progress. 2018;65(2):119-23.
[38] Agarwal A, Kishore K. Complications and controversies of regional anaesthesia: A review. Indian J Anaesth. 2009;53(5):543-53.
[39] Chiapparini L, Sghirlanzoni A, Pareyson D, Savoiardo M. Imaging and outcome in severe complications of lumbar epidural anaesthesia: Report of 16 cases. Neuroradiology. 2000;42(8):564-71.
[40] Auroy Y, Narchi P, Messiah A, Litt L, Rouvier B, Samii K. Serious complications related to regional anesthesia: Results of a prospective survey in France. Anesthesiology. 1997;87(3):479-86.
[41] Bigat Z, Kayacan N, Ertugrul F, Karsli B. Latex allergy on anaesthesiologist and anaesthesia managements: Are the health workers high risk patients? J Pak Med Assoc. 20141;64(4):453-56.
[42] Gandhi R, Sharma B, Sood J, Sehgal R, Chugh P. Anaphylaxis during anaesthesia: Indian scenario. Indian J Anaesth. 2017;61(5):387-92.
[43] Farooque S, Kenny M, Marshall SD. Anaphylaxis to intravenous gelatin-based solutions: A case series examining clinical features and severity. Anaesthesia. 2019;74(2):174-79.
[44] Di Leo E, Delle Donne P, Calogiuri GF, Macchia L, Nettis E. Focus on the agents most frequently responsible for perioperative anaphylaxis. Clinical and Molecular Allergy. 2018;16(1):01-06.
[45] Turillazzi E, Greco P, Neri M, Pomara C, Riezzo I, Fineschi V. Anaphylactic latex reaction during anaesthesia: The silent culprit in a fatal case. Forensic Science International. 2008;179(1):e5-8.
[46] Mertes PM, Laxenaire MC. Allergy and anaphylaxis in anaesthesia. Minerva anestesiologica. 2004;70(5):285-92.
[47] Martel TJ, Jamil RT, King KC. Red Man Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 Jun 3]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK482506/
[48] Hanžek I, Tonković D, Margaretić Piljek N, Palian M, Mihaljević D, Penavić A, et al. Allergic reactions to colloid fluids in anesthesia. Psychiatria Danubina. 2020;32(suppl. 4):429-31.
[49] Marrel J, Christ D, Spahn DR. Anaphylactic shock after sensitization to gelatin. Br J Anaesth. 2011;107(4):647-48.
[50] Vercauteren MP, Coppejans HC, Sermeus L. Anaphylactoid reaction to hydroxyethylstarch during cesarean delivery in a patient with HELLP syndrome. Anesth Analg. 2003;96(3):859-61.
[51] Odedra KM, Farooque S. Chlorhexidine: An unrecognised cause of anaphylaxis. Postgrad Med J. 2014;90(1070):709-14.
[52] Rose MA, Garcez T, Savic S, Garvey LH. Chlorhexidine allergy in the perioperative setting: A narrative review. Br J Anaesth. 2019;123(1):e95-03.
[53] Sharp G, Green S, Rose M. Chlorhexidine-induced anaphylaxis in surgical patients: A review of the literature. ANZ Journal of Surgery. 2016;86(4):237-43.
[54] Wöhrl S. NSAID hypersensitivity–recommendations for diagnostic work up and patient management. Allergo J Int. 2018;27(4):114-21.
[55] Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs)–classification, diagnosis and management: Review of the EAACI/ENDA# and GA2LEN/HANNA. Allergy. 2011;66(7):818-29.
[56] Sahu S, Hemlata AV. Adverse events related to blood transfusion. Indian J Anaesth. 2014;58(5):543.
[57] Maxwell MJ, Wilson MJ. Complications of blood transfusion. Continuing Education in Anaesthesia, Critical Care & Pain. 2006;6(6):225-29.
[58] Murthy VVR, Kumar BJ, Chandrasekhar K, Srilakshmi T. "A case of anaphylaxis after blood transfusion"- An alarm to the anesthesiologist and surgeon. ARC J Anesthesiol. 2018;3(3):10-12.
[59] Rudingwa P, Senthilnathan M, Suganya S, Panneerselvam S. Intraoperative acute hematuria: Sole clue to mismatch transfusion. Asian J Transfus Sci. 2019;13(1):63-65.
[60] Peng CH, Tan PH, Lin CH, Lin HY, Kuo CH, Chung HC. Fatal anaphylactoid shock associated with protamine for heparin reversal during anesthesia. Acta Anaesthesiologica Sinica. 2000;38(2):97-102.
[61] Lin MC, Hsieh TK, Liu CA, Chu CC, Chen JY, Wang JJ, et al. Anaphylactoid shock induced by oxytocin administration- A case report. Acta Anaesthesiologica. 2007;45(4):233-36.
[62] Mehra KK, Gogtay NJ, Ainchwar R, Bichile LS. Hypersensitivity to intravenous ondansetron: A case report. J Med Case Rep. 2008;2(1):01-03.
[63] Mali S. Anaphylaxis during the perioperative period. Anesthesia, Essays and Researches. 2012;6(2):124.
[64] Sánchez Palacios A, Ortiz Ponce M, Rodríguez Pérez A. [Allergic reactions and pseudoallergies in surgical interventions with general anesthesia]. Allergol Immunopathol (Madr). 2000;28(1):24-36.
[65] Caffarelli C, Stringari G, Pajno GB, Peroni DG, Franceschini F, Iacono ID, et al. Perioperative allergy: Risk factors. Int J Immunopathol Pharmacol. 2011;24(3_suppl):27-34.
[66] Reber LL, Hernandez JD, Galli SJ. The pathophysiology of anaphylaxis. J Allergy Clin Immunol. 2017;140(2):335-48.
[67] Khan BQ, Kemp SF. Pathophysiology of anaphylaxis. Curr Opin Allergy Clin Immunol. 2011;11(4):319-25.
[68] Dewachter P, Savic L. Perioperative anaphylaxis: Pathophysiology, clinical presentation and management. BJA education. 2019;19(10):313-20.
[69] Lieberman P. Anaphylactic reactions during surgical and medical procedures. J Allergy Clin Immunol. 20021;110(2):S64-69.
[70] Harper NJ, Cook TM, Garcez T, Farmer L, Floss K, Marinho S, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). Br J Anaesth. 2018;121(1):159-71.
[71] Dewachter P, Mouton-Faivre C, Emala CW, Riou B. Anaphylaxis and anesthesia: Controversies and new insights. Anesthesiology. 2009;111(5):1141-50.
[72] Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: Diagnostic approach. Allergy. 2007;62(5):471-87.
[73] Dewachter P, Mouton-Faivre C. What investigation after an anaphylactic reaction during anaesthesia?. Curr Opin Anaesthesiol. 2008;21(3):363-68.
[74] Orihara M, Takazawa T, Nagumo K, Sakamoto S, Horiuchi T, Saito S. Interpreting the results of early skin tests after perioperative anaphylaxis requires special attention: A case report and review of literature. J Anesth. 2020;34(4):624-29.
[75] Garvey LH, Dewachter P, Hepner DL, Mertes PM, Voltolini S, Clarke R, et al. Management of suspected immediate perioperative allergic reactions: An international overview and consensus recommendations. Br J Anaesth. 2019;123(1):e50-64.
[76] Soetens FM. Anaphylaxis during anaesthesia: Diagnosis and treatment. Acta Anaesthesiologica Belgica. 2004;55:229-38.
[77] Garvey LH, Belhage B, Krøigaard M, Husum B, Malling HJ, Mosbech H. Treatment with epinephrine (adrenaline) in suspected anaphylaxis during anesthesia in Denmark. Anesthesiology. 2011;115(1):111-16.
[78] Ring J, Beyer K, Biedermann T, Bircher A, Duda D, Fischer J, et al. Guideline for acute therapy and management of anaphylaxis. Allergo J Int. 2014;23(3):96-12.
[79] Liyanage CK, Galappatthy P, Seneviratne SL. Corticosteroids in management of anaphylaxis; A systematic review of evidence. Eur Ann Allergy Clin Immunol. 2017;49(5):196-207.
[80] Francuzik W, Dölle S, Worm M. Risk factors and treatment of refractory anaphylaxis- A review of case reports. Expert Rev Clin Immunol. 2018;14(4):307-14.
[81] Fisher MM, Doig GS. Prevention of anaphylactic reactions to anaesthetic drugs. Drug Safety. 2004;27(6):393-10.
[82] Caffarelli C, Stringari G, Miraglia Del Giudice M, Crisafulli G, Cardinale F, Peroni DG, et al. Prevention of allergic reactions in anesthetized patients. Int J Immunopathol Pharmacol. 2011;24(3 Suppl):S91-99.

[83] Gupta S, Naithani U, Brajesh SK, Pathania VS, Gupta A. Critical incident reporting in anaesthesia: A prospective internal audit. Indian J Anaesth. 2009;53(4):425-33.
[84] Agbamu PO, Menkiti ID, Ohuoba EI, Desalu I. Critical incidents and near misses during anesthesia: A prospective audit. Journal of Clinical Sciences. 20171;14(1):18.
[85] Petschnig W, Haslinger-Baumann E. Critical Incident Reporting System (CIRS): A fundamental component of risk management in health care systems to enhance patient safety. Safety in Health. 2017;3(1):01-06.
[86] Mahajan RP. Critical incident reporting and learning. Br J Anaesth. 2010;105(1):69-75.

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