INTRODUCTION

Anaphylaxis is an immediate immunological mediated severe allergic reaction to an administered substance. That result in respiratory and/or cardiovascular compromise often associated with urticaria and/or angioedema, these symptoms result from the release of inflammatory mediators from mast cells and can be triggered by allergen interaction with specific IgE on the mast cell surface or can be non-IgE mediated (pseudoallergic or anaphylactoid reactions) ***(Elliott, 2015)***.

In anaphylaxis, mast cell degranulation leads to markedly increased blood tryptase concentrations which can be useful for the investigation of suspected cases. Tryptase concentration in the blood may not increase significantly until 30 minutes or more after the onset of symptoms and peak 1-2 hours after onset, there are some reactions that cause similar symptoms, but are not due to production of IgE, it can be more difficult to identify the exact cause of these reactions ***(Ebo et al., 2007)***.

Some anesthetic drugs administered during surgery have side effects that are similar to those induced by immunologic mechanisms ***(Lobera, 2008)***.

The immune system is an integral part of human protection against disease, but the normally protective immune mechanisms can sometimes cause detrimental reactions in the

host. Such reactions are known as hypersensitivity reactions, and the study of these is termed immunopathology. The traditional classification for hypersensitivity reactions is that of Gell and Coombs and is currently the most commonly known classification system Gell ***(Ariza et al., 2014).***

It divides the hypersensitivity reactions into the following 4 types:

* Type I reactions (ie, immediate hypersensitivity reactions) involve immunoglobulin E (IgE)–mediated release of histamine and other mediators from mast cells and basophils. Examples include anaphylaxis and allergic rhinoconjunctivitis ***(Ariza et al., 2014).***

* Type II reactions (ie, cytotoxic hypersensitivity reactions) involve immunoglobulin G or immunoglobulin M antibodies bound to cell surface antigens, with subsequent complement fixation. An example is drug-induced hemolytic anemia.

* Type III reactions (ie, immune-complex reactions) involve circulating antigen-antibody immune complexes that deposit in postcapillary venules, with subsequent complement fixation. An example is serum sickness.

* Type IV reactions (ie, delayed hypersensitivity reactions, cell-mediated immunity) are mediated by T cells rather than

by antibodies. An example is contact dermatitis from poison ivy or nickel allergy ***(Ariza et al., 2014)***.

This system divides immunopathologic responses into the following 7 categories:

* Inactivation/activation antibody reactions
* Cytotoxic or cytolytic antibody reactions
* Immune-complex reactions
* Allergic reactions
* T-cell cytotoxic reactions
* Delayed hypersensitivity reactions
* Granulomatous reactions

This system accounts for the fact that multiple components of the immune system can be involved in various types of hypersensitivity reactions. For example, T cells play an important role in the pathophysiology of allergic reactions ***(*Koppert*,et al., 2001).***

Aim of the Work

The aim of this work was to review the effects of anesthetic drugs that cause anaphylaxis in perioperative period and to give an idea about new modalities of management of anaphylaxis during anesthesia.

Chapter 1

PATHOPHYSIOLOGY

Anaphylaxis is an immediate immunologically mediated severe allergic reaction to an administered substance.It is due to the release of inflammatory mediators and cytokines from mast cells and basophils, typically due to an immunologic reaction but sometimes non-immunologic mechanism ***(Khan et al., 2011).***

Thus classified as a type I hypersensitivity reaction, it was recognised that the reaction may be IgE-mediated or non IgE-mediated ***(Sampson et al., 2006).***

1) Immunologic

In the immunologic mechanism, immunoglobulin E (IgE) binds to the antigen (the foreign material that provokes the allergic reaction). Antigen-bound IgE then activates FceRI receptors on mast cells and basophils. This leads to the release of inflammatory mediators such as histamine. These mediators subsequently increase the contraction of bronchial smooth muscles, trigger vasodilation, increase the leakage of fluid from blood vessels, and cause heart muscle depression. There is also an immunologic mechanism that does not rely on IgE ***(Dewachter et al., 2011).***

2) Non-immunologic

Non-immunologic mechanisms involve substances that directly cause the degranulation of mast cells and basophils. These include agents such as contrast medium, opioids, temperature (hot or cold), and vibration. Sulfites may cause reactions by both immunologic and non-immunologic mechanisms ***(Parker, et al., 2011).***

Initial sensitisation occurs when the T lymphocytes in susceptible patients are presented with an allergen, and in response produce IgE antibodies. The IgE antibodies bind to high affinity to receptors on mast cells and basophils, and to low affinity to receptors of leucocytes, platelets and eosinphils. Re-exposure to the same allergen results in multivalent cross-linking of the IgE antibodies bound to the high affinity receptors, activating intracellular transduction cascades with release of preformed mediators (histamine, tryptase, chymase, and heparin) from mast cells and basophils ***(Pradeu, et al., 2006).***

This induces the release of pro-inflammatory phospholipid derived mediators (prostaglandin D2, leukotrienes, platelet activating factor (PAF), thromboxane A2,) which in turn cause the release of chemokines and cytokines, with recruitment of inflammatory cells.A very small amount of antigen is required for this mechanism ***(***Yuan, ***et al., 2009).***

Non IgE-mediated immunologic type I reactions are clinically indistinguishable from the IgE-mediated response, and can occur on first exposure to an allergen. IgG-mediated reactions are less frequent and less serious than IgE-mediated reactions ***(Mertes et al., 2011).***

Histamine release may be idiopathic, it may be triggered directly (with physical factors such as cold or heat, morphine and vancomycin), or may be released in response to bradykinin or complement activation ***(Lieberman,et al., 2010).***

IgG binding to certain antigens may produce a similar effect.IgG-antigen complexes bind to receptors on macrophages and/or basophils mediating the release of PAF (but not histamine) ***(Vadas et al., 2003).***

PAF mediates smooth muscle relaxation and enhances vascular permeability. This mechanism requires a much larger IgG-antibody interaction than the IgE-mediated response. IgG also functions as a negative feedback mechanism on the IgE-mediated pathway, inhibiting IgE-mediated histamine release ***(Mclntyre, et al., 2009).***

Pathophysiologic Process

Types of Allergic Reactions.

Type I allergic hypersensitivity reactions resulting in anaphylaxis are now defined as immunoglobulin E (IgE)-triggered and non–IgE triggered (previously known as anaphylactoid) reactions ***(Lieberman,et al., 2011).***

Types II, III, and IV reactions do not result in anaphylaxis. Type I IgE-mediated anaphylaxis occurs on subsequent exposure after a patient is sensitized to an antigen. The production of an antigen-specific IgE is critical to eliciting an anaphylactic response. On reexposure, the antigenic protein binds to IgE antibodies on the high-affinity receptor for IgE on the cell walls of mast cells and basophils. Multivalent allergens need to cross-link with at least 2 IgE receptor sites on the surface of the cell membrane to induce the release of inflammatory mediators ***(Stone et al., 2010).***

Allergen activation causes the eruption of potent preformed and newly generated inflammatory mediators from mast cells and basophils. Type I non-IgE immunologic reactions can occur with the first exposure to the antigen and can be indistinguishable from IgE-mediated responses ***(Peavy et al., 2008).***

Non-immunologic mechanisms may be idiopathic or may result from a combination of mechanisms. Non-IgE reactions

may directly trigger the release of histamine, may occur in response to complement or bradykinin activation, or can be mediated by an IgG antigen. In an 8-year survey of surgical patients who experienced anaphylaxis, IgE-mediated reactions were more frequent (n = 1,816 [72.2%]) and severe (grade 3; n = 1,092; [60%]) than non-IgE reactions, which occurred less frequently (n = 700; [27.8%]) and were milder (grade 1; n = 372; [53%]) ***(Mertes et al., 2011).***

Although mast cells are present in all tissues, basophils circulate in the vasculature. Mast cells are found within most organs and tissues, especially in the heart, vasculature, respiratory and gastrointestinal tracts, and integument. The release of cell mediators is controlled by calcium channel receptors. Mast cells and basophils have similar receptors and functions: to respond to signals of innate and adaptive immunity and to release inflammatory mediators ***(Stone et al., 2010).***

The early phase of an allergic reaction that induces mast cell degranulation may be followed by a late phase reaction with the release of cytokines that can interact with T-helper type 2 cells. In turn, cytokines such as interleukin 4 (IL-4) stimulate B cells to generate IgE and further stimulate mast cells and eosinophils ***(Mirotti et al., 2011).***

Lipids, free radicals, and/or inflammatory proteins and enzymes also regulate the innate immune response. The cascading complement system (C3a-C5a) directly activates the

release of mediators through non-IgE mechanisms ***(Laroche et al., 2011).***

Allergic sensitization occurs when T lymphocytes are signaled by an antigen-presenting cell such as dendritic cells in the lymphatic system and then interact with B cells to induce IgE production. The B lymphocytes develop into plasma cells that secrete immunoglobulin antibodies such as IgG or IgE or memory cells with receptors that remember antigens. Because gene segments encode the formation of hundreds of allergen-specific B and T cells, millions of different receptors can develop with long lasting memory ***(Ben-Shoshan et al., 2011).***

Inflammatory Mediators Inflammatory mediators released from mast cells and basophils such as histamine, proteases (among which is tryptase), leukotrienes, and prostaglandins elicit immediate symptoms of an allergic reaction such as pruritis, wheezing, or hypotension, and can induce cardiovascular collapse. The inflammatory mediators released from cardiac mast cells such as cysteinyl leukotrienes and prostaglandins decrease myocardial perfusion and contractility. Platelet-activating factor can constrict the coronary arteries, decrease coronary perfusion and contractility, and can contribute to coronary plaque rupture. Furthermore, cardiac mast cells can release chymase and carboxypepidase, which activate the reninangiotensin system ***(Triggiani et al., 2008).***

Table (1): Major Mediator Actions of Mast Cells and Basophils Implicated in Anaphylaxis ***(Stone et al., 2010).***

Mediators	Pathophysiologic effects
Histamine	H1: Mucus secretion, edema, cardiac depression, coronary vasoconstriction, renin release; H2: gastric acid secretion, nitric oxide induction, vasodilatation, tachycardia; H3: decreased norepinephrine level; H4: chemotaxis, inflammation
Heparin	Anticoagulation, activates prekallikrein and contact systems, bradykinin
Tryptase	Activates prekallikrein and complement, bradykinin, anaphylatoxins
Chymase	Renin production, compensatory norepinephrine secretion, dysrhythmias
Carboxypeptidase	A Prostaglandin and leukotriene synthesis, inflammation
Platelet-activating factor	Bronchoconstriction, decreased coronary blood flow and contractility, nitric oxide induction, vasodilatation, hypotension, platelet aggregation, recruitment of neutrophils and eosinophils, biphasic late response, anticoagulation
Prostaglandin D2	Bronchoconstriction, pulmonary and coronary vasoconstriction, peripheral vasodilatation, vascular permeability, hypotension, flushing, urticaria
Leukotriene LTC4	Bronchoconstriction, airway remodeling, angioedema, nitric oxide induction, increased vascular permeability, hypotension
Kallikrein	Renin production, complement activation, fibrinolysis, clotting
Tumor necrosis factor	Neutrophil activation, chemokines, cytokines, effector cell recruitment

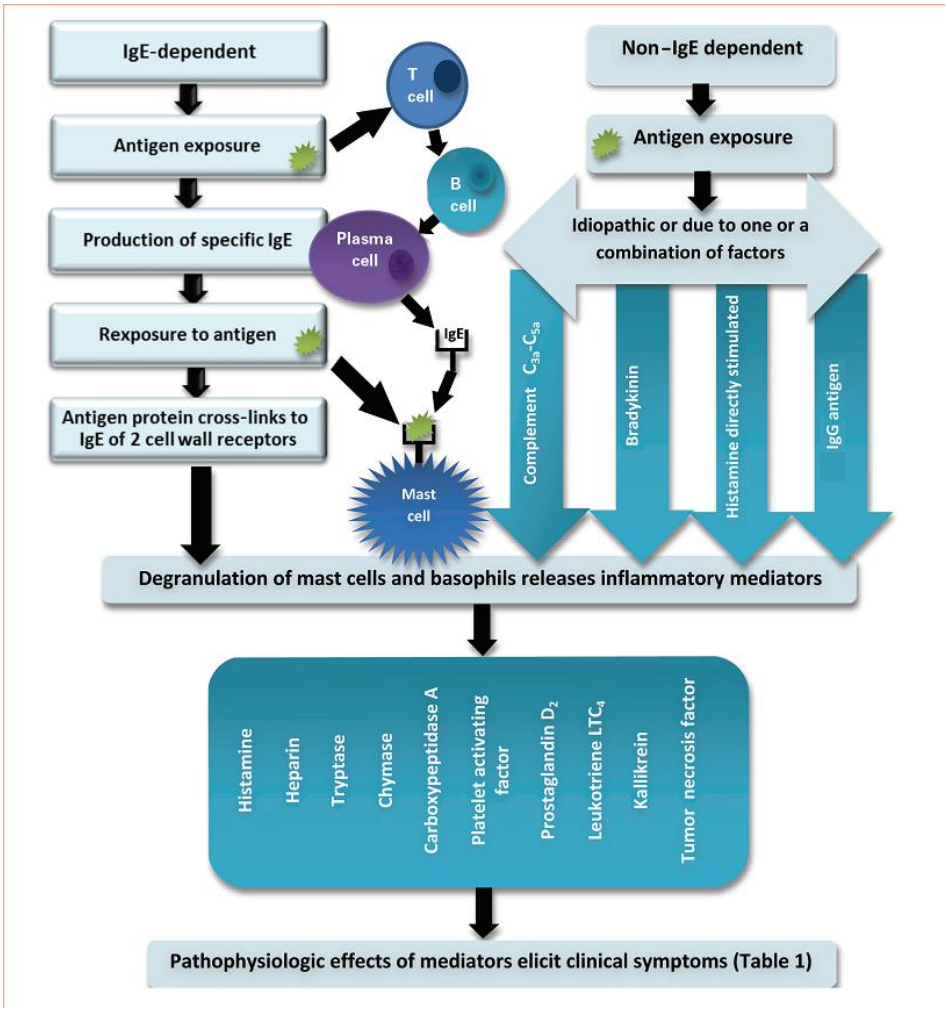

Figure (1): Physiologic Pathways to Type I Hypersensitivity Reactions. Abbreviations: Ig, immunoglobulin; PAF, platelet-activating factor ***(Bonilla and Oettgen, 2010).***

Histaminergic System Four types of histamine (H) receptors are distributed throughout the body. The H4 receptors are found in the innervations of the vasculature and cells of the blood, lung, liver, spleen, and gut; stimulation of the H4 receptors precipitates inflammation. The central nervous system is regulated by H1, H2, and H3 receptors. The H3 neurons in the

tuberomamillary nucleus of the hypothalamus control neurotransmitters. The release of histamine is modulated by feedback from the H3 autoreceptors and from muscarinic, adrenergic, and peptidergic receptors ***(Mirotti et al., 2011).***

The tuberomamillary nucleus controls the release of acetylcholine and other neurotransmitters. This hypothalamic center is regulated by H3 autoreceptors that are inhibited by histamine. Inflammatory mediators released by tissues stimulate the afferent sensory fibers to the central nervous system, which causes the efferent vagus nerve release of acetylcholine. At the parasympathetic ganglion via autoinhibitory mechanisms of the postganglionic nerves, the nicotinic or muscarinic receptors release acetylcholine ***(Mirotti et al., 2011).***

Stimulation of the H3 receptors of the presynaptic terminals of sympathetic nerves inhibits epinephrine release from the adrenals, heart, and the peripheral vasculature ***(Hepner et al., 2003).***

The H2 receptors regulate cognitive brain function and the function of the gastric and immune systems. The H2 receptors in the gut stimulate proton pump secretion of gastric acid. The H1 receptors are distributed widely throughout the entire body and nervous system. The release of histamine stimulates the H1 receptors of smooth muscle, causing constriction of the bronchi and vasodilation ***(Liew et al., 2009).***

Activation of the H1 receptors in the coronary vasculature may precipitate dysrhythmias, myocardial ischemia, cardiac depression, hypotension, shock, and cardiac arrest ***(Triggiani et al., 2008).***

Anaphylaxis sever scale

Table (2): Severity Grades for Anaphylaxis Signs and Symptoms ***(Dewachter and Hepner, 2011).***

Grade I	Grade II	Grade III	Grade IV
Cutaneous	**Cutaneous**	**Cardiovascular**	**Cardiovascular**
Erythema	Grade I signs	Grade II signs plus	Pulseless electrical activity
Pruritis	**Cardiovascular**	Cardiovascular collapse	Cardiac arrest
Urticaria	Hypotension	Profound hypotension	Death
Angioedema	Tachycardia	Bradycardia	
	Presyncope	Dysrhythmia	
	Respiratory	**Respiratory**	
	Dyspnea	Bronchospasm	
	Wheezing	Hypoxia (Sao2 < 92%)	
	Gastrointestinal	**Gastrointestinal**	
	Nausea	Grade II signs plus	
	Grade II signs plus	Incontinence	
	Diarrhea	**Neurologic**	
	Abdominal pain	Confused	
		Unconscious	

Chapter 2

PHARMACOLOGY OF DRUGS CAUSING ANAPHYLAXIS DURING ANESTHESIA

There are drugs that cause severe adverse events during anesthesia, which exaggerated due to pharmacological effect, e.g., hypotension during extradural anesthesia or with propofol; bradycardia and hypotension after opiates. Anaphylaxis to one of the i.v. neuromuscular blocking agents (NMBAs) or anesthetic drugs. Adverse reaction to another administered drug e.g., drug with premedication; antibiotic with induction; analgesic, e.g., non-steroidal anti-inflammatory drugs (NSAID) rectally or opiate intraoperatively ***(Ewan et al., 2009).***

There are other substances causes allergic reactions or anaphylaxis, eg., Latex rubber allergy. Reaction to intravenous infusion, for example colloid, blood, plasma and chlorhexidine or a diagnostic dye ***(Ewan et al., 2009).***

A. Neuromuscular blocking agents:

The most common cause of anaphylaxis during during perioperative period is neuromuscular blocking agents (muscle relaxants), which are responsible for 60% to 70% of episodes of anaphylaxis occurring during anesthesia**.** All NMBAs can elicit anaphylaxis and there is an agreement that the short-acting