

## Evaluation Of Immunoglobulin E And Histamine Levels In Patients With And Without Drug Allergy.

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### Abstract

#### Objectives:

1. To estimate IgE and histamine levels in patients with drug allergy and with past history of drug allergy.
2. Compare these levels with that of normal individuals
3. Assess the association of demographic factors, nature of drugs and clinical presentation with IgE and histamine levels.

**Methodology:** 113 potential participants were totally interviewed. 66 selected based on selection criteria. 22 had current allergy (CA), 22 past history of allergy (PA) and 22 without any allergy (NA). Study was initiated after getting IHEC approval and informed consent from each participant. Estimation of serum IgE and histamine was done using ELISA kits.

Demographic details, details of drugs and clinical presentation were recorded. Time interval between onset of allergy and estimation of IgE and histamine was recorded for patients with PA. Results were analyzed using ANOVA and student t test.  $p < 0.05$  was considered significant.

**Results:** IgE and histamine levels were significantly higher in CA compared to NA and PA subjects.

Normal mean level IgE was 72.6 IU/ml and histamine 42.53 ng/ml. In PA levels were higher than that of NA but lower than CA. Males and civil workers had a higher level than females. Age related difference in the levels was not observed. NSAIDs induced allergy resulted in maximum elevation of IgE (538.74

IU/ml) and histamine (158.32 ng/ml) followed by antimicrobials (IgE 395.97 IU/ml) and histamine

(133.42 ng/ml). Patients who developed maculopapular rashes had maximum level of IgE (627.87 IU/ml) and histamine (182.25 ng/ml). The time dependent decline in both the levels was observed in PA.

Higher IgE level was associated with higher level of histamine in all the groups.

**Conclusion:** In CA, NSAIDs and maculopapular rashes resulted in maximum elevation of IgE and histamine. In PA, IgE level was higher than NA group. Whether estimation of IgE would indicate past allergy or the tendency to develop allergy has to be assessed by further studies with large samples.

**Keywords:** Immunoglobulin E, Histamine, Drug allergy, Rashes, Urticaria.

## INTRODUCTION

Drug allergy is a type of unpredictable adverse drug reaction. It refers to the reproducible allergic reaction initiated by exposure to a drug at a dose usually tolerated by non-allergic individuals. Adverse drug reaction has been defined by the World Health Organization as "Any noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment" <sup>(1)</sup>. The causative factors for drug allergy can be either drug related or the patient related. These factors include,

Drug associated factors: The drug's chemical nature, the dose of the drug, its duration and frequency of therapy, route of administration, co-administered drugs which can influence the reaction, nature of inactive ingredients, Cross-sensitization to related drugs

Host associated factors: The gender and age of the patient, genetic influences (HLA type, Drug metabolizing enzyme status), concomitant medical illness, and previous history of drug allergy, organ dysfunction like liver or renal disease.

Adverse drug reactions (ADRs) are classified into two broad categories:

- 1.) Type A reactions are "Predictable, common, and related to the pharmacologic actions of the drug".

2.) Type B reactions are “unpredictable, uncommon, and usually not related to the pharmacological actions of the drug<sup>(2)</sup>”.

About 80% of ADRs belong to the first category. For example, drug-induced toxicity like nephrotoxicity by anticancer drugs, hepatotoxicity by rifampicin, side effects like urinary retention by anti-cholinergic and drug interactions between ACE inhibitors and potassium sparing diuretics are of type A reaction.

Immune mediated or allergic drug reactions belong to the second category. These reactions are comparatively less common, and are mediated by the immunological mechanisms involving the release of IgE and histamine<sup>(3)</sup>.

Coombs and Gell<sup>(4)</sup> classified allergic reactions into,

- A.) “Immediate-type hypersensitivity reactions” (mediated by drug-specific IgE antibodies),
- B.) “Cytotoxic mediated reactions” (mediated by T lymphocytes)
- C.) “Immune complex reactions” (mediated by drug-specific IgG or IgM antibodies),
- D.) “Delayed-type hypersensitivity reactions” (mediated by drug-specific T lymphocytes).

The mast cells release varied inflammatory mediators in addition to histamine, each contributing to the major symptoms of the allergic response.

### **IgE**

The key components of immediate-allergic response are “Immunoglobulin (Ig) E” and its cell surface receptors, the high affinity receptor FcεRI and the low affinity receptor FcεRII (CD23)<sup>(5,6)</sup>. IgE stimulates the allergic mechanism through the FcεRI, (high affinity receptor), on blood cells and tissues.

Estimation of “serum IgE” is an important parameter in the diagnosis and relationship with the severity of hypersensitive reactions<sup>(7)</sup>. IgE is normally present in small quantity; but its concentration increases to several hundred folds in “drug allergy, food allergy, allergic rhinitis, allergic bronchial asthma and atopic dermatitis or urticaria”. The normal serum IgE levels is reported as, <180 IU/mL for adult allergy free population<sup>(8)</sup>. Quite often IgE is estimated in drug allergy but not histamine.

### **Histamine**

“Histamine” is a biologically active amine compound, produced via decarboxylation of histidine by the pyridoxal phosphate-dependent enzyme L-histidine decarboxylase which is stored in mast cells. In the blood, it is stored in basophils<sup>(9)</sup>. In allergic reactions these cells are expressed abundantly in the organs such as “skin, upper and lower respiratory tracts, and gastrointestinal tract, as well as the reproductive mucosa”. These cells synthesize histamine and store in the secretory granules. Following interaction of antigen with IgE antibodies on the cell surface of mast cell, the histamine is released from the storage granules and it plays a major role in the immediate hypersensitivity responses. After the release of histamine from basophils and tissue mast cells, its biological effects such as vasodilatation, increased vascular permeability of small venules, arterioles, contraction of bronchial and other smooth muscle; increased gastric acid, increased nasal and lacrimal secretions.

**Actions of histamine:** The actions of histamine are mediated through four distinct receptors H1 to H4. All the four receptors are G-protein coupled receptors.

**Drug induced hypersensitivity:** Drug induced allergic reactions may be immune or non-immune related reaction. Immune mediated reactions include urticarial angioedema and anaphylaxis which are IgE mediated and reactions like exanthematous drug eruptions (T lymphocyte mediated), allergic contact dermatitis and drug hypersensitivity syndrome are T lymphocyte and eosinophil mediated. IgE mediated reactions are type 1 reactions and T cell mediated reactions are type 4 reactions. Drugs like penicillin can be directly chemically reactive due to the instability of its molecular structure and stimulate mast cells. Other drugs however, must be metabolized, or bio activated, to a reactive compound before an immune response is initiated <sup>(10, 11)</sup>. Bio activation is mainly mediated by cytochrome P450 enzymes in liver, but it can also occur at other sites, such as skin keratinocytes. <sup>(12)</sup>

Diagnosis of drug allergy is important because of its unpredictable nature. The diagnosis is mainly based on history and clinical features. The treatment is stopping the offending drug and providing symptomatic relief. Drug allergy not only affects the treatment but also the quality of life. If drug allergy is predictable and preventable it would avoid drug related morbidity and mortality. The clinical manifestations of drug allergy include urticaria, angioedema and intense pruritus. Urticaria is characterized by raised, pruritic and transient erythematous plaques that blanch on pressure (a sign indicative of venous dilatation and edema). Angioedema of the larynx can be fatal. Drug allergy can also cause dizziness, difficult breathing, confusion, fainting and anaphylactic shock.

Antibiotics belonging to the group of Beta lactams frequently induce allergic reactions. In addition, many other drugs are reported to cause immediate reactions such as quinolones, Cephalosporins and NSAIDs. Among them the most common drug group to generate such reactions can be NSAIDs.

30% of the subjects can develop reactions such as angioedema or urticaria or anaphylaxis due to drugs like peptide hormones which are intrinsically immunogenic. Some drugs are more liable to elicit clinically relevant immune responses than are others. Drugs in this category are given in Table [2].

**Table 2 Drugs frequently implicated in allergic reactions:**

Aspirin (other analgesics and antipyretics)	Sedative hypnotics Anticonvulsants	Iodinated contrast media Antisera and vaccines
Penicillins, Cephalosporins	Anesthetics (local & general) Phenolphthalein	Heavy metals Allopurinol
Sulfonamides Antituberculous drugs	Antipsychotics Tranquilizers	Penicillamine Antithyroid drugs
Nitrofurantoin  Antimalarials Griseofulvin	Antihypertensive drugs Antiarrhythmic agents	

Once a drug to allergy connection is established, it must be investigated whether the reaction was immunologically mediated. Subsequently, confirmatory tests, if available, should be used to determine the allergic status of the patient. A desensitization or graded challenge may be considered if the confirmatory tests are not available. Depending on the type of clinical reaction previously demonstrated, the need for drug re-administration is considered. Education and the compliance of the patient and primary care physician is an important element of patient management.

The list of allergic illnesses includes eczema, urticaria, angioedema, drug allergy, food allergy, and insect allergies, as well as asthma, rhinitis, and anaphylaxis.

In India, 20% to 30% of the whole population has at least one of these allergy illnesses. Currently, ADRs account for 3% to 6% of all hospital admissions. Drug allergy accounts for about 10% of all ADRs, but the true incidence of drug allergy in the community among children and adults, is unknown. Many children are misdiagnosed as being “allergic” to various medications, particularly antibiotics and result in carrying this label into adulthood. These patients are often treated with alternate medication that may be harmful, less effective and more expensive. This in turn may result in increased morbidity, mortality and expenditure of treatment.<sup>(13,14)</sup> The allergic reactions may impair the person's ability to function because of itching, irritability, and ulceration due to scratching, secondary bacterial infection, scar formation and the side effects of anti-histamine therapy. Thus drug allergy can adversely affect the quality of life and psychological wellbeing of the individual.

If strategies are planned for early identification of drug allergy and followed by appropriate interventions, the consequences of allergic disorders can be minimized.

The diagnosis of ADRs has to rely on circumstantial evidence, based on the time of onset to the introduction of the drug or change in dose or drug discontinuation. The type of investigation for diagnosis of drug allergy depends on whether the initial reaction was IgE or non-IgE mediated. Diagnostic tests should be used as an adjunct to the clinical history and examination. In addition, there are often a few specific or sensitive *in vitro* and *in vivo* tests.

The *In vivo* test includes Skin tests, Patch tests, Skin biopsy and Drug provocation (challenge) tests (DPTs).

The *in-vitro* test includes measurement of mediators (histamine, tryptase, leukotrienes), Allergen-specific IgE levels, Flow cytometry–based basophil activation assays, the enzyme-linked immunosorbent assay (ELISA)<sup>(15)</sup>.

It is known that IgE and histamine are elevated in allergic reactions. But it is not known to what extent the rise occurs during allergy, how long the levels remain elevated and what is the normal level of IgE and histamine in Indian population. A few researchers have investigated histamine levels in blood, plasma and in urine for the patients currently having drug allergy. But histamine levels in remission state of drug allergy and normal have not been adequately evaluated. Correlation between IgE and histamine has also not been studied.

The difference in the levels among the normal, drug exposed non allergic and individuals with drug allergy if studied it might help to identify allergy prone patients. Hence the current study was undertaken to assess IgE and histamine levels in patients reporting with current drug allergy, who report with the history of past drug allergy and compare these levels with

normal, healthy individuals as well as assess the trend in the levels of IgE and histamine in the clinical course of drug allergy.

### **AIMS AND OBJECTIVES**

1. To estimate IgE and histamine levels in patients with drug allergy and with past history of drug allergy.
2. Compare these levels with that of normal individuals
3. Assess the association of demographic factors, nature of drugs and clinical presentation with IgE and histamine levels.

### **Methodology**

The approval for the conduct of the study was obtained from Institute Human Ethics Committee, Approval Letter No: 271/IHEC/8-17 dated 12-09-2017.

**Study setting:** The study was conducted in Chettinad Hospital and Research Institute.

**Study design:** A Prospective observational clinical study.

**Study period:** One year from (September 2017 to August 2018)

**Study participants:**

#### **Inclusion criteria:**

- Age: 18-65yrs.
- Gender: Male and Female.
- Patients who were willing to give consent.
- Patients who had taken drugs but not developed drug allergy,
- Patients with past history of drug allergy,
- Patients currently having drug allergy.

#### **Exclusion criteria:**

- Patients with diabetes, bronchial asthma, peptic ulcer, Cardio vascular disease and autoimmune disorders.
- Immuno-compromised individuals –HIV, Hepatitis B.
- Patients on drugs that could influence the immune response such as steroids and other immune-modulators and drugs influencing histamine such as antihistamines.
- Patients with food allergy, allergic rhinitis and seasonal rhinitis, other chemical allergies.

- Pregnant and nursing mothers.

### Sample size:

Sample size was calculated based on the prevalence of drug allergy.

Cochran's formula for calculating sample size:

$$n = \frac{(Z_{1-\alpha/2})^2 p (1-p)}{d^2}$$

Z= Statistic level of confidence

P= Expected prevalence or proportion (prevalence 6%)

d= Precision

$$n = 44.12$$

N=44 subjects, however 66 participants were included and divided into the following 3 groups:

Group1: Patients reported with drug allergy, having clinical manifestations of urticaria, angioedema, maculopapular rashes and pruritus-22.

Group2: Patients with past history of drug allergy –22

Group3: Control participants without history of drug allergy-22

### Study Procedure:

All the participants who fulfilled the eligibility criteria were included in the study. Data collection was done after obtaining informed written consent from each individual. Each participant was interviewed in the outpatient department of CHRI using semi-structured questionnaire. The questionnaire included demographic details, history and nature of drug allergy, details of drugs and clinical presentation. Following the interview, 5ml of blood was collected from all the participants under aseptic condition and samples were stored under -20°C. Once all the samples were collected serum IgE and histamine levels were estimated using the respective ELISA kit.

**Data entry and statistical analysis:** Data were entered into Microsoft excel and analysis was done using SPSS version 19.0. Difference between level of Histamine and IgE among the three groups was assessed using Analysis of Variance (ANOVA) test. Correlation of IgE and histamine with the following parameters was assessed a) Gender, b) Current, past and no allergy, c) Difference among the drug groups d) Clinical presentation and e) Occupation.

P value less than 0.05 was considered statistically significant.

## RESULTS

A total of 113 potential participants were interviewed. Among them 66 were included in the study based on selection criteria. 22 participants (Group 1) did not have any drug allergy, 22 (Group 2) had history of drug allergy and 22 in Group (3) had current drug allergy. The time interval between the allergic episode and the recruitment to the study in group 2 ranged from 26 days to more than 5 years. There were no drop outs. All of them completed the study.

There were totally 41 males and 25 females and their distribution is given below:

**Table 3: Gender distribution**

Category	Male	Female	Total
GP1-CA	12	10	22
GP2-PA	11	11	22
GP3-NA	18	4	22

GP- Group; CA-Current allergy; PA- past allergy; NA- No allergy

The age of the participants ranged from 21-58 as given in the table:

**Table 4: Age distribution**

Category	Age in years			
	18-30	31-40	41-50	>50
CA	10	5	4	3
PA	12	5	4	1
NA	14	8	-	-

The occupation of the participants included the following: Student, professionals in Information technology, Business, Other officials, Construction workers, Home makers. The details of serum IgE, Histamine levels and the significance of difference among the 3 groups are provided in table 1 & 2.

**Table 5: Serum IgE level (3 groups)**

S.No	Groups	Serum IgE(IU/ml)	Min	Max	95% confidence Interval
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		Mean±SEM			Lower bound	Upper bound
1	CA	431.86±34.91***	185.22	695.27	347.2609	492.4644
2	PA	152.82±6.48*	109.69	217.92	141.3338	168.3161
3	NA	72.60±6.48	10.93	119.70	59.1184	86.0909

All values are expressed as Mean±SEM, \*p<0.05 compared with NA, \*\*\*p<0.001 compared with PA and NA.

**Table 6: Serum Histamine level (3 groups)**

S.No	Groups	Serum Histamine (ng/ml) Mean±SEM	Min	Max	95% confidence Interval	
					Lower bound	Upper bound
1	CA	143.47 ±11.78***	85.43	293.31	115.97	164.98
2	PA	65.51 ±4.10*	35.74	98.55	59.51	76.60
3	NA	42.53 ±3.30	15.17	65.27	35.67	49.40

All values are expressed as Mean±SEM, \*p<0.05 compared with NA, \*\*\*p<0.001 compared with PA and NA. In both the tests, Group 1 was compared with group 2 & 3 and Group 2 was compared with group 3. Both IgE and histamine levels were found to be significantly high in CA group. Participants with history of past allergy had levels between group 1 and 3. The difference in Serum IgE and histamine levels between group 1 and 2 was highly significant (p<0.001) and when group 2 was compared with group 3 it was also found to be significant (P<0.05).

**Table 7: Gender and IgE, histamine level in all the three groups**

Gender	CA		PA		NA	
	IgE IU/ml	Histamine ng/ml	IgE IU/ml	Histamine ng/ml	IgE IU/ml	Histamine ng/ml
Male	466.17	160.98	159.43	54.14	77.84	47.80
Female	390.55	115.87	151.54	49.95	49.00	35.00

It was found that males had higher level of IgE and histamine than females in all three groups.

### Details of drugs taken by the participants

The details of the drug taken by the patients were collected from the prescriptions as well as the details provided by the patients about OTC drugs. Those who could not provide the information were grouped as unknown. The data obtained from participants with CA revealed that the drugs taken by them included the following: Ibuprofen, Paracetamol, Tramadol, Dicyclomine, Pseudo ephedrine, Caffeine, Loratidine, Codeine, Ciprofloxacin, Cefixime, Metronidazole, Lactobacillus, Azithromycin, Tinidazole, Erythromycin, Amoxicillin with clavulanic acid, Cefixime, Esomeprazole, Pantoprazole, Ambroxol, Bifilac and Multivitamin. Four participants did not know the details of the drugs. The drugs taken by the participants with PA included the following: Paracetamol, Diclofenac, Linezolid, Aceclofenac, Ibuprofen, Serratiopeptidase, Amoxicillin with clavulanic acid, Erythromycin, Cefixime, Ciprofloxacin, Metronidazole, Azithromycin, Sulfonamide drugs, Lactobacillus, Pantoprazole, Otilonium bromide, fungal diastase, Amitriptyline. Eight participants did not know the details of the drugs.

The majority of the drugs in both the groups include antimicrobials, NSAIDs, Anti-ulcer drugs, Probiotics, Vitamins and others.

Though the participants were taking more than one drug, based on the commonly implicated main classes of drugs the participants were divided into 4 groups as given below:

**Table 8: Number of participants in different drug groups in CA**

S.no	Category of drug	Name of the drugs	No of participants with allergy
1	NSAIDs	Diclofenac	3
		Ibuprofen	2
		Tramadol	2
		Paracetamol	1
2	Antibiotics along with vitamins and probiotics	Amoxicillin clavulanic acid	2
		Azithromycin	1
		Sulfonamides	1
		Erythromycin	1
		Ciprofloxacin	1
3	Combination of drugs along with vitamins and probiotics	Ciprofloxacin+ Metronidazole	1
		Ciprofloxacin-Tinidazole	1
		+Dicycloamine	
		Amoxicillin+ Pantoprazole	1
		Cefixime	+ 1

		Azithromycin	
4	Unknown		4
Total			22

**Table 9: Number of participants in different drug groups in PA**

S.no	Category of drug	Name of the drugs	No of participants with PA
1	NSAIDs	Diclofenac	2
		Ibuprofen	1
		Paracetamol	1
2	Antibiotics	Amoxicillin clavulanic acid	2
		Sulfonamides	2
		Erythromycin	2
3	Combination of drugs	Ciprofloxacin+Metronidazole	1
		Ciprofloxacin-Tinidazole+Dicycloamine	1
4	Unknown		10
Total			22

**Table 10: Drug Category and the level of Histamine and IgE in CA**

S.no	Category of drug induced allergy	Serum Histamine (ng/ml) Mean±SEM	ANOVA		Serum IgE(IU/ml) Mean±SEM	ANOVA	
			P value	F value		P value	F value
1	NSAIDs	158.32*	0.048	3.546	538.74*	0.036	2.762
2	Antibiotics	133.42			395.97*		
3	Combination of drugs	151.07*			385.10		
4	Unknown	101.07			318.36		

\*p<0.05 compared with unknown group

Both serum IgE and histamine levels were found to be higher in participants taking NSAIDs than the other drugs. The difference between NSAID group and unknown as well as combination was found to be significant.

**Table 11: Drug Category and the level of Histamine and IgE in PA**

S.no	Category of drug	No of participants	Serum Histamine (ng/ml) Mean±SEM	Serum IgE(IU/ml) Mean±SEM
1	NSAIDs	4	60.4	145.72
2	Antibiotics	6	43.64	164.79
3	Combination of drugs	2	75.12	194.19
4	Unknown	10	50.75	139.60

Both serum IgE and histamine levels in PA were found to be higher in combination of drugs while compared to antibiotics, NSAIDs and others. There was no statistically significant difference among the drug groups in PA. Patients with drug allergy had the clinical symptoms and signs like maculopapular rashes, urticaria, angioedema and pruritus. Depending upon the clinical presentation, the following grouping was done and their level of IgE and Histamine was separately analyzed.

**Table 12: Clinical manifestations and IgE and histamine levels.**

S.no	Clinical manifestations	Histamine ng/ml	IgE IU/ml
1	Maculopapular rashes	182.25±40.79	627.87±47.37
2	Urticaria	106.85±20.89	370.39±101.29
3	Angioedema	138.98±50.43	431.33±33.94
4	Pruritus	101.87±6.86	280.87±25.09

Serum IgE and histamine levels were higher in patients with maculopapular rashes followed by angioedema and others.

**Table 13: Correlation between time interval from occurrence of allergy and estimation of IgE and histamine in PA group.**

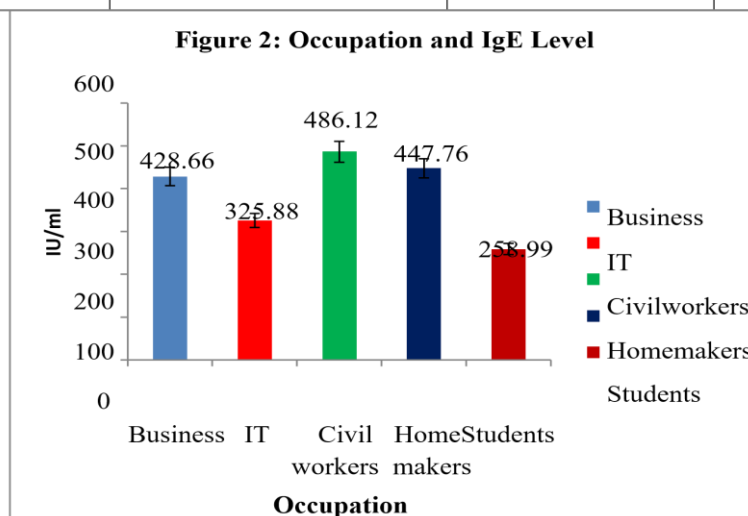
S.no	No of participants	Histamine ng/ml	IgE IU/ml
<1month	7	64.09	185.79
1month -6months	6	62.11	160.40
6months- 1year	2	48.06	137.61
1 year - 5years	3	33.07	130.57

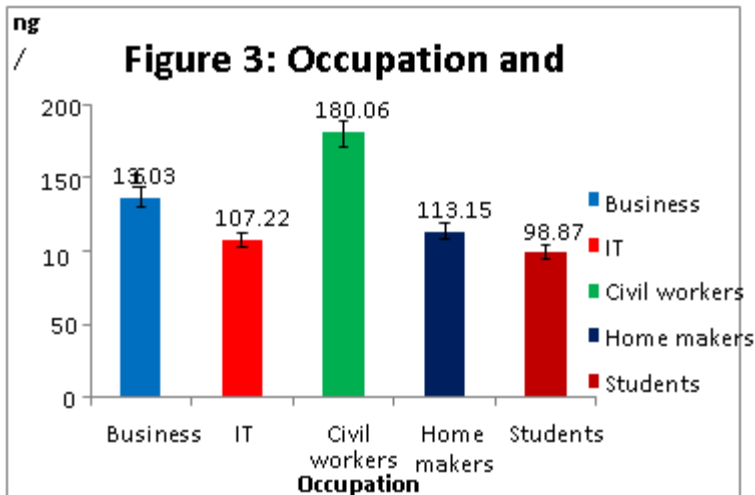
>5years	4	30.16	120.08
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In patients with past allergy the time interval between the occurrence of allergy and the study (blood sampling) ranged from less than a month to more than 5 years. Sub-grouping based on this time interval revealed that there is a progressive decline in both IgE and histamine levels, which reached the normal range within 6 months.

**Table 14: Occupation and the level of Histamine and IgE in CA**

S.no	Occupation	Serum IgE(IU/ml) Mean±SEM	Serum Histamine (ng/ml) Mean±SEM
1	Business	428.66	136.03
2	Information technology	325.88	113.15
3	Civil workers	486.12	180.06
4	Home makers	447.76	107
5	Students	258.9	98.87





Both IgE and histamine levels were found to be higher in civil workers, followed by those doing Business, Home makers, Information technology and Students. Based on the results, the following observations were made

- 1) Both IgE and histamine levels were significantly higher in CA group.
- 2) Patients with PA had a higher IgE and histamine levels than NA group.
- 3) Males had higher level of IgE and histamine than females.
- 4) Serum IgE and histamine levels were maximum in patients taking NSAIDs followed by antimicrobials.
- 5) Patients who developed maculopapular rashes had the highest IgE and histamine levels followed by those with angioedema.
- 6) Civil workers had a higher level of IgE and histamine level was observed in all the groups.
- 7) Correlation between IgE and histamine level was observed in all the groups.

Time dependent decline is seen in levels of IgE and histamine in PA group.

## DISCUSSION

Drug hypersensitivity reactions (DHRs) are the adverse effects of pharmaceutical formulations including (active ingredients and excipients) <sup>(16)</sup>. According to WHO, the DHRs belong to type B adverse drug reactions and defined as the dose-independent, unpredictable, <sup>(17,18)</sup> noxious, and unintended response to a drug taken at a dose normally used in humans. Type- A reactions are dose dependent and predictable which includes overdoses and pharmacological reactions. DHRs are one of the main cause of the post-marketing withdrawal of drugs. <sup>(19)</sup> The nature of DHRs may be allergic or non-allergic and is mediated immunologically, which are life-threatening, may require hospitalization, and changes in therapy. Both under diagnosis and over diagnosis of DHRs are common. <sup>(20, 21)</sup> Diagnosing DHR based on history without proper testing may affect treatment options, resulting in complications, and requirement of expensive or less-effective drugs, in contrast to patients who had undergone a complete drug allergy diagnosis. <sup>(22)</sup> Several guidelines are available to classify drug induced DHRs to support the treatment options. The systematic approach for the diagnosis and treatment of DHRs brings the potential to increase

outcomes.<sup>(23)</sup> Hence a proper diagnosis of DHRs is necessary to ensure adequate treatment and preventive measures. DHRs are usually IgE mediated. Estimation of IgE is usually done to confirm IgE mediated hypersensitivity reactions. The main mediator of allergic reactions that manifest clinically is histamine. However histamine is not routinely estimated in allergic patients. A basal level of IgE and histamine is usually present in the circulation and the normal level reported in previous studies is less than 180 IU/ml for IgE and for histamine ranges from 2565ng/ml.<sup>(24)</sup> The circulating basal histamine is reported to contribute to several functions such as regulation of blood pressure, neuronal function, cell proliferation (respiratory smooth muscle and chondrocytes), and regulation of blood sugar levels, control of sleep, wakefulness and body temperature. **Brewo and Sullivan**<sup>(25)</sup>

During allergic reactions histamine gets released in high quantity mainly from mast cells as well as basophils. The exact duration of action is not established. The half-life of histamine is reported to be 15 minutes to one hour.

The main role of IgE is mediating immediate hypersensitivity reaction. Emerging evidences indicate newer roles for IgE in rendering protection against parasitic infestations, controlling homeostasis of mast cells as well as regulation of IgE receptors. The half-life of IgE is reported to be 2-3 days. **Oliver Tburton**<sup>(26)</sup>. The serum level of IgE in normal individuals is reported to reach about 50ng/ml. Levels upto <180 IU/ml is also considered normal for IgE<sup>(22)</sup>. It is not well established to what extent IgE and histamine increase and whether the levels during allergic reactions will return to basal level once the allergic reaction subsides. Hence this study was conducted with the objectives of finding out

A: The average histamine and IgE level in patients who have not experienced any allergic reaction to drugs.

B: Levels of IgE and histamine in patients during allergic reaction to drugs.

C: IgE and histamine levels in patients recovered from allergic reactions to drugs and whether this level is equal to the level in non-allergic individuals.

66 participants were recruited to the study and they were in 3 different groups, current allergy, past allergy and no allergy, with 22 in each group. The average level in normal participants recruited was 72.60±6.48 IU/ml and 42.53±3.30 ng/ml for IgE and histamine respectively. The results of our study had shown that both IgE (431.86±34.91 IU/ml) and histamine (143.47±11.78ng/ml) levels were significantly elevated in patients suffering from current drug allergy (P<0.001). It was observed that IgE and histamine level did not reduce to the level equal to that of normal subjects in patients with past history of allergy. In patients with past allergy, histamine and IgE levels were found to be lower than the levels seen in current allergy 65.51±4.10 ng/ml and 152.82±6.48IU/ml respectively, but found to be higher than the level of control group. This difference was also found to be significant (P<0.05). But in subgroup analysis based on the interval between the time occurrence of allergy and estimation of IgE and histamine, a progressive time dependent decline was observed.

The studies conducted on IgE or histamine found to be very few and infrequently conducted. **Hua Huang et al.**,<sup>27</sup> studied molecular regulation of histamine synthesis. In this review, they focused on the molecular mechanisms involved in the regulation of

histamine synthesis in mammals. The authors reported that the regulation of transcription of Hdc gene is involved in the synthesis, accumulation and replenishment of histamine leading to exacerbation of allergy and anaphylaxis.

**Marraccini P et al.**,<sup>28</sup> evaluated the possibility of using basophil activation test as a surrogate tool for drug sensitivity testing. They evaluated the sensitivity and specificity of this test using the samples collected from 204 patients with drug hypersensitivity reactions to antibiotics and NSAIDs. Basophil activation test showed 100% specificity with NSAID challenge, 92% specificity to antibiotics and low sensitivity (40%) to antibiotics. **Demoly et al.**,<sup>29</sup> found the total histamine level in case of 4 patients with paracetamol induced anaphylactic shock was 140,89,63,112 ng/ml estimated after an interval of 2 to 3.5 months after the occurrence of anaphylactic shock. **Gasser P et al.**,<sup>30</sup> reviewed the role of IgE in allergic disease. In this review, they highlighted the mechanisms involved at molecular level with anti-IgE molecules and suggested the possibility of using new class of IgE inhibitors that could help in improving the treatment efficacy in allergic diseases in future. **Faridha agha et al.**,<sup>31</sup> evaluated specific IgE levels in adults in relationship to sex, age and environmental factors and reported that males had a higher IgE level than females at any given age.

However, IgE and histamine levels have not been estimated in different drug groups previously. It was observed that in patients with NSAID induced allergy both the mediators level was high. When IgE and histamine levels were correlated with clinical presentations it was observed for the first time that patients who had maculopapular rashes and urticaria had a higher levels of IgE and histamine than patients with pruritus and angioedema. The reason for higher value could be due to the extensive nature of the allergic reactions. Such an observation has not been made previously.

It can be inferred from this study that

- a.) IgE and histamine levels were higher in patients with current allergy
- b.) Both the levels were within normal range in the non-allergic individuals but lower than the levels reported in other countries.
- c.) It was observe for the first time that patients with past allergy had a higher mean level of both IgE and histamine than the normal group indicating that the decline in the level might take a longer time to reach the level of normal subjects.
- d.) Time dependent decline in IgE and histamine was seen in subgroup analysis. However IgE was found to be higher than that of the control group even after an interval of 5years. This was a new observation in this study.
- e.) NSAIDs induced allergy causes higher elevation of IgE and histamine followed by antimicrobials
- f.) In patients with maculopapular rashes IgE and histamine levels are found to be higher than with angioedema, pruritus.



- g.) Whether an elevated IgE in an individual compared to the mean value observed in the normal population predict the risk of developing drug allergy in future has to analyzed in further studies.

## SUMMARY

The present study was conducted to estimate the level of serum IgE and histamine in patients with current drug allergy, those who had a past history of drug allergy and normal individuals who had not developed any allergy. The approval for the conduct of the study was obtained from Institute Human Ethics Committee. A total of 113 patients were interviewed and 66 participants were recruited in the study after getting informed consent. They were divided into 3 groups namely CA (Current allergy), PA (Past allergy) and NA (No allergy) each group comprising of 22 participants. 5ml venous blood was collected and serum samples was separated and stored at -20<sup>0</sup>c. Serum histamine and IgE level was measured using an ELISA kit according to the manufacturer's protocol. The results were analyzed based on the mean value of histamine and IgE in all three groups and correlated with age, gender, occupation, nature of drugs involved in allergy and the clinical presentation. Statistical analysis was done by student t-test followed by one way ANOVA.

Among the 66 participants, 41 were males and 25 females and they were aged between 18 and 59 years. The study participants consisted of college students, home makers, those who worked in private sectors, civil workers & public sector organizations and others had their own small scale occupation/business. The results of the study indicated that the levels of IgE and histamine in CA group was higher than PA and NA groups and the level in PA group was higher than NA group. Both the levels were within normal range in the NA but lower than the levels reported in previous studies. Patients with past allergy had a higher level of both IgE and histamine than the normal group even after an interval of 5 years from the onset of allergic reaction, indicating that the decline in the level might take a longer time to reach the level of normal subjects. NSAIDs induced allergy resulted in a higher elevation of IgE and histamine followed by antimicrobials. In patients with maculopapular rashes IgE and histamine levels are found to be higher than with angioedema, pruritus. Though the time dependent decline in the level of IgE and histamine was observed in PA group the samples in each subgroup was considerably small. Moreover the IgE level was higher than NA group even after 5 years.

Thus this study has given a probable diagnostic indicator that if IgE and histamine levels are higher in individuals, it can be predicted that they had past allergy to drugs or they might have a tendency to develop drug allergy in future. Hence whether estimation of IgE and histamine before administration of drugs that are known to cause allergic reactions can be used as a deciding factor for selection of drugs and prevention of drug allergy has to be studied further with larger samples.

## CONCLUSIONS

The following conclusions can be drawn from the study

1. All the participants had IgE and histamine in their serum samples. Both IgE and histamine levels were significantly higher in CA group.
2. Patients with PA had a higher IgE and histamine levels than NA group.
3. Males had higher level of IgE and histamine than females.

4. Serum IgE and histamine levels were maximum in patients taking NSAIDs followed by antimicrobials.
5. Patients who developed maculopapular rashes had the highest IgE and histamine levels followed by those with angioedema and pruritus.
6. Occurrence of time dependent decline is seen in levels of IgE and histamine in PA group.
7. IgE level remains higher than the average level in the normal population for a long time even after recovery from allergy.

**Limitations of the present study:** The patients in the current allergy group were not followed over a time period and the values of IgE and histamine estimated which would have indicated the changes that can occur in each individual.

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