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Complications of intradermal drug allergy test- A retrospective analysis

[1]Dr. Binu Krishnan, MD, FCCP, FAPSR, Senior Consultant Pulmonologist, Department of Pulmonary and Sleep Medicine, PRS Hospital, India.

[2]Dr. Priya Shanmugharaj, Junior Medical Officer, Department of Pulmonary and Sleep Medicine, PRS Hospital, India.

[3]Dr. Thansiya Pookunju, Clinical Pharmacologist, Department of Pulmonary and Sleep Medicine, PRS Hospital, India.

Corresponding Author: Dr. Binu Krishnan, MD, FCCP, FAPSR, Senior Consultant Pulmonologist, Department of Pulmonary and Sleep Medicine, PRS Hospital, India.

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Abstract

Background and objective: Intradermal drug allergy test is a highly specific and reliable method of identifying drug allergy. Limited studies are available regarding the complications during this procedure. Primary objective was to assess the occurrence of complications during intradermal allergy test, there by assessing the safety of procedure.

Methodology: Retrospective data analysis of all consecutive adult patients who completed drug allergy test procedure at a tertiary care Centre in India for a period of 12 months. Test dose of medications were introduced intradermally and results obtained as per standard protocol. Both immediate (less than or equal to one hour) and delayed (more than one hour) complications were analysed.

Results: 325 patients were included in the study with mean age of 38.9 ± 14.3 years. Most of the patients were allergic to piroxicam (84%), followed by diclofenac, ketorolac (74.5%) and paracetamol (38.5%). 112 patients (34.5%) had allergy to more than five drugs. Only twenty-six patients (8%) developed complications during the procedure. Immediate complications included localized itching in 11 (3.4%), generalized itching in 3 (0.9%) patients. Delayed complications included localized itching 3 (0.9%) and generalized itching in 2(0.6%) patients. The presence of atopy, asthma and allergy to multiple drugs (more than five) were associated with the occurrence of complications (p value <0.01).

Conclusions: Intradermal drug allergy test was a rather safe procedure with minimal complications. Presence of asthma, atopy and allergy to multiple drugs were associated with occurrence of complications.

Keywords: complications, intradermal test, drug allergy, atopic hypersensitivity, asthma.

Introduction

The clinical picture of drug allergy is highly ambivalent in nature involving complex pathophysiologic mechanisms. Most of the allergic reactions may be either due to IgE mediated immediate hypersensitivity or T cell mediated delayed response. Some of these reactions may not have any immunologic basis at all. In some patients, even though a relevant history might be there, no obvious

allergy could be elucidated [1-5]. This may be due to various factors like improper concentration of various drugs used for the procedure or faulty technique during the procedure [6].

Different complications are likely to occur as a result of performing intradermal drug allergy test. Some of them occur during or immediately after the procedure. Also, these events can happen in a delayed manner (up to some hours after the procedure). Limited data is available regarding the potential complications of intradermal drug allergy test. The incidence of serious or near-fatal reactions during intradermal procedure is largely unheard off. Drug allergy test tests are conducted only in very few centres probably due to lack of expertise or fear of complications [7, 8].

In the present study, we made an attempt to understand the immediate and delayed complications of intradermal drug allergy test.

Objectives

Primary objective

To assess the rate of complications during intradermal allergy test, thereby assessing the safety of procedure.

Secondary objectives

To assess the relation between baseline variables and occurrence of complications.

To assess whether the rate of complication was more when individual patient was allergic to more number of drugs.

Materials and methods

This was a retrospective data analysis done in Department of Pulmonology and Sleep Medicine, PRS hospital, which is a tertiary care centre in Kerala, India. Our department had a dedicated Allergy Division, where intradermal drug allergy tests are performed. All consecutive drug allergy tests done between January and December 2016 (12 months) were analysed. Only patients with history of drug sensitivity were included for testing. Patients with history of recent anti-histamine usage were advised to refrain for a minimum period of 6 days from the drug. Similarly, corticosteroids were withheld for a period of 7 days prior to testing. This study was performed in accordance with the Declaration of Helsinki. This human study was approved by Institutional Ethics Committee- PRS Hospital.

As per the hospital protocol, drug allergy tests were not performed in a patient with no prior history of drug hypersensitivity. As part of studying the adult patients, those below the age of 18 years were excluded from the analysis.

Those patients with history of drug hypersensitivity in the preceding two weeks and pregnant females were not considered for the procedure.

Intradermal allergy tests were done in our Centre as per the standard panels of drugs. The drugs were broadly categorised as antibiotics, analgesics (NSAIDS and opioids), local anesthetics, general anaesthetic and others. The same panel was used in all patients (with additional drugs used as per the patient's allergy history). Antibiotic drugs were diluted for usage as per the Updated practice parameter 2008 recommendations [9]. All other drugs were diluted in 1:10 concentration. Normal saline (0.9%) was used as the control for the entire test. Informed consent was obtained from all patients prior to the procedure. The whole procedure was done in the clinic by Pulmonologist. Both pulse rate and oxygen saturation were monitored throughout the procedure using pulse oxymeter. Basic resuscitatory measures including crash-cart were available in the clinic itself to address any medical emergency.

Serial numbers were marked in the anterior aspect of both right and left arms and forearms of patients with at least one inch separation in between. Region around the

cubital fossa is spared due to anticipated blood vessel prick during the procedure. Drugs were given in the dose of 0.1 ml intradermally with 26 size ½ inch needle. A wheal of 5mm diameter was introduced with all drugs. After 20 to 40 minutes, the reactions were measured. A wheal and flare of 10mm or more (more than or equal to double the initial size) was taken as positive result. Once the procedure is over, patients were made to wait for at least 3 hours to look for any delayed reaction. All patients were sent out of the clinic with advice to report to Emergency Room in case of any symptom of delayed reaction.

In the present study, complications were broadly divided into two groups based on the following arbitrary definitions:

Immediate

Those occurring less than or equal to one hour after the onset of procedure.

Delayed

Those occurring more than one hour after the onset of procedure.

These were subdivided into

- minor, and
- major (life threatening) complications

All those which were localised or did not involve more than one system were considered to be minor in nature.

Statistical tests used

Categorical and quantitative variables were expressed as frequency (percentage) and mean ± SD respectively. Chi-square test was used to find association between categorical variables. For all statistical interpretations, $p<0.05$ was considered the threshold for statistical significance. The data were entered into Microsoft Excel 2013 and statistical analyses was performed by using statistical software package SPSS, version 20.0.

Results

A total of 325 patients were included in the study during that study-period of 12 months. Mean age was 38.9 ± 14.3 years. 57.8% of patients were in the less than forty age- group category. Males constituted only 16 percent of the total study population. Thirty-five patients (10.8%) had history of atopy while 31 (9.5%) had documented evidence of asthma (Table 1).

Most of the patients were allergic to non-steroidal anti-inflammatory drugs. Occurrence of hypersensitivity was highest with piroxicam (84%), followed by diclofenac and ketorolac (74.5%). Paracetamol allergy was detected in 38.5% of patients. Benzyl penicillin and ampicillin allergy was reported in 39.7% and 44.6% respectively. Fluoroquinolone (ciprofloxacin) allergy was noted in 42.8% of patients. Out of 325 people, no allergy was reported in 23 (7.1%). One hundred and twelve patients (34.5%) had allergy to more than five drugs (Table 2, Table S1).

Only twenty-six patients (8%) developed complications during the procedure (Table 3). All of them had only minor complications. Itching was the most common complication to occur during and after the procedure. Immediate complications included localized itching in 11 (3.4%), generalized itching in 3 (0.9%) patients. Other immediate complications were swelling 3 (0.9%), tiredness 2(0.6%) and headache in 2(0.6%) of them. Delayed complications included localized itching 3 (0.9%) and generalized itching in 2(0.6%) patients. No major life-threatening complication was recorded in any of these subjects (Table 4).

Selected baseline variables were evaluated to assess the association with complications (Table 5, 6). It was found that the presence of atopy and asthma were associated with the occurrence of complications (p value <0.01).

The relationship between multiple drug allergy and rate of complications was analysed. It was concluded that allergy to multiple drugs (more than five) in a patient were associated with the occurrence of complications (p value <0.01).

Discussion

The mean age of study subjects was 38.9 ± 14.3 years signifying a younger age-group preponderance. Also, vast majority (84%) of them were females. According to De Martinis M et al, female propensity to drug allergy may be due to several possible mechanisms like genetic factors, epigenetic changes, difference in health care utilization, exposition to medications and hormonal influences on immune cells [10]. Asthma (9.5%) and atopy (10.8%) were the most common co-morbidities in these patients. Blanca-Lopez N et al stated that drug allergy may be more in patients with atopy but concrete evidence is still lacking [11].

In their study, Thong B Y et al estimated that the most common causative NSAIDs were diclofenac, mefenamic acid or paracetamol [12]. In the present study also, NSAIDs were found to be the common causative factor for drug allergy. The occurrence of allergic reactions was highest with piroxicam (84%), followed by diclofenac and ketorolac (74.5%) and paracetamol allergy was noted in 38.5% of patients.

Al-Ahmad M et al found that anti-inflammatory drugs and analgesics contributed to 39.22% of all confirmed drug allergies, followed by antibiotics 38.1% (Beta-lactam antibiotics constituted 73.98% of all antibiotics [6]. In our study, it was found that benzyl penicillin and ampicillin allergy was reported in 39.7% and 44.6% respectively. Fluoroquinolone (ciprofloxacin) allergy was reported in 42.8% of patients.

According to Al-Ahmad et al, the concentration of drugs used and the technique might vary between different centres, thereby affecting the sensitivity and specificity of the procedure. The interpretation of positivity might also be different in various places. Almost 20 million people are estimated to be labelled as allergic to penicillin. But the shortage of allergists who are trained in drug allergy test is a concern to be addressed globally.

Few patients (8%) had complications during intradermal drug allergy test in the present study. Most of them were immediate in nature. Common immediate complications included localised itching, generalised itching, swelling, tiredness and headache. Localised itching was more common with ciprofloxacin, diclofenac, ketorolac and piroxicam (11 each in number). Generalized itching was more seen in diclofenac, ketorolac and piroxicam (3 each in number). Swelling, tiredness and headache were present only in a few numbers of procedures (0.9%, 0.6% and 0.6% respectively). The occurrence of delayed complications was equally limited in number (localized itching in 0.9% and generalized itching in 0.9%). No life-threatening adverse event were noted during the procedures, which indicated the safety of intradermal test procedure. In the retrospective analysis by Yee Kiat Heng et al on Beta- Lactam allergy testing, it was found that none of the reactions were life-threatening nor severe requiring admission or subcutaneous adrenaline [13].

Another method of identifying drug allergy is by drug provocation test. Ozge Soyer et al studied about the various pros and cons of provocation tests for drug hypersensitivity [14]. They noted that drug provocation tests represented a potential risk to the patient and were time consuming. These findings should be an added advantage for intradermal tests which had a higher safety profile.

Patients who had a history of atopy, including asthma, eczema, or allergic rhinitis, might be at increased risk for more severe adverse drug reactions [15, 16]. Presence of

asthma, atopy and allergy to multiple drugs (more than five per patient) were found to be associated with occurrence of complications in the present study ($p<0.01$). To the best of our knowledge, the association between complications during intradermal allergy test and any of those host factors were not previously studied. Our study had certain limitations. It was a retrospective analysis done in a tertiary care setting. A prospective multi-Centre study would further help to narrow the knowledge-gap in that regard.

Conclusion

Intradermal drug allergy test was a safe procedure with minimal complications. Presence of host factors such as asthma, atopy and allergy to multiple drugs were associated with occurrence of complications. The low rate of complications should enhance the confidence of clinicians to start more intradermal allergy test programmes.

Abbreviations

IgE: Immunoglobulin E

NSAID: Non-Steroidal Anti-Inflammatory Drug

SD: Standard Deviation.

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Legend Figures

Table 1. Baseline characteristics of patients.

	Count	Percent
Age : < 40 years	188	57.8
Mean ± SD	38.9 ± 14.3	
Gender : Male	52	16.0
BMI: > 30	35	10.8
Saturation: < 95%	5	1.5
Pulse > 100/ minute	5	1.5
Diabetes	14	4.3
Hypertension	17	5.2
Atopy	35	10.8
Asthma	31	9.5

Table 2. Percentage distribution of the sample according to Allergy

Allergy	Count	Percent
benzyl penicillin	129	39.7
ampicillin	145	44.6
ciprofloxacin	139	42.8
cefotaxime	78	24.0
ceftriaxone	106	32.6
paracetamol	125	38.5
diclofenac	242	74.5
ketorolac	242	74.5
piroxicam	273	84.0
thiiopentone	23	7.1
ketamine	32	9.8
Ranitidine	5	1.5
Pethdine	3	0.9
Morphine	4	1.2
Ondansetron	1	0.3
Succinylcholine	1	0.3
Promethazine	1	0.3
Azithouromycin	1	0.3
Buprenorphine	2	0.6
Tramadol	8	2.5

Ranitidine, Morphine	1	0.3
Pethdine, Morphine	1	0.3
Diazepam, Buprenorphine	1	0.3

Table 3. Percentage distribution of the sample according to complications

Complications	Count	Percent
Present	26	8.0
Absent	299	92.0

Table 4. Percentage distribution of the sample according to type of complication

Complication	Count	Percent
Localised Itching (Immediate Complication)	11	3.4
Generalized Itch (Immediate Complication)	3	0.9
Swelling (Immediate Complication)	3	0.9
Tiredness (Immediate Complication)	2	0.6
Headache (Immediate Complication)	2	0.6
Localised Itching (Delayed Complication[after 1hour])	3	0.9
Generalized Itch Delayed Complication [after 1hour])	2	0.6

Table 5. Percentage distribution of the sample according to number of drug allergy

Number of drug allergy	Count	Percent
Number of drugs	23	7.1
1 - 5	190	58.5
> 5	112	34.5

Table 6. Association of Complication with selected background variables

		complication				χ^2	p
		Present		Absent			
		Count	Percent	Count	Percent		
Age	< 40	14	7.4	174	92.6	0.19	0.667
	>= 40	12	8.8	125	91.2		
Sex	Male	3	5.8	49	94.2	0.42	0.518
	Female	23	8.4	250	91.6		
BMI	> 30	2	5.7	33	94.3	0.28	0.598

	< 30	24	8.3	266	91.7		
Diabetes	Present	2	14.3	12	85.7	0.79	0.375
	Absent	24	7.7	287	92.3		
Hypertension	Present	0	0.0	17	100.0	1.56	0.212
	Absent	26	8.4	282	91.6		
Atopy	Present	12	34.3	23	65.7	36.82**	p<0.01
	Absent	14	4.8	276	95.2		
Asthma	Present	14	45.2	17	54.8	64.29**	p<0.01
	Absent	12	4.1	282	95.9		
number of drug allergy	<= 5	3	1.4	210	98.6	36.49**	p<0.01
	> 5	23	20.5	89	79.5		