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Prevalence of piperacillin-tazobactam induced hypersensitivity reaction in workers of Stallion's Pharmaceutical factory at Lahore

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ABSTRACT

BACKGROUND & OBJECTIVE: Piperacillin is an antibiotic that belongs to the ureidopenicillin family. Piperacillin-tazobactam provides cover against gram-positive, gram-negative bacteria and some bacteria of anaerobic nature. It is an extended-spectrum antibiotic and is used along with tazobactam which is an inhibitor of beta-lactamase. The main objective of our research was to identify the hypersensitivity reactions of piperacillin-tazobactam in pharmaceuticals factory and office workers.

METHODOLOGY: A Cross-sectional study was conducted at Stallion Pharmaceuticals (Pvt) Ltd located at Sundar Industrial Estate Lahore, Pakistan, from March to April 2018, after approval from the institutional research committee. All the workers, including factory workers and office workers at Stallion Pharmaceuticals (Pvt) Ltd were included in this study. Data was collected from each respondent by immediate-type skin testing. Data analysis was done by SPSS version 25, the demographic data was evaluated by descriptive statistics, Fisher Exact test was used for comparison and $p \leq 0.05$ was taken as significant.

RESULTS: The results of the study presented that hypersensitivity reaction was present in (7.5%) of males and (3.8%) of females. It was also observed that (8.8%) of factory workers had hypersensitivity reactions when they are gone through skin tests, and only (2.5%) of office workers were skin test positive. From the above results (11.2%) of all the respondents developed hypersensitivity reactions and (88.8%) showed no reaction when they were gone through skin tests, which contain 0.1 ml of piperacillin and tazobactam. Fisher exact test was applied, and results showed no significant difference between hypersensitivity reactions among factory and office workers as the p-value was .

CONCLUSION: Hypersensitivity reaction to piperacillin-tazobactam was minimal in the factory & office workers, and this was not significant.

KEYWORDS: Piperacillin, Factory workers, Office workers, Hypersensitivity reaction, Skin test.

INTRODUCTION

Piperacillin is an antibiotic that belongs to the ureidopenicillin family. It is an extended-spectrum antibiotic and is used along with tazobactam which is an inhibitor of beta-lactamase. Piperacillin-tazobactam provides cover against gram-positive, gram-negative bacteria and some bacteria of anaerobic nature. Piperacillin specifically provides cover against Pseudomonas aeruginosa which is a gram-negative bacterium and is resistant to many drugs. Because of its less side effects and action against Pseudomonas aeruginosaits, appropriate use is essential to decrease resistant development in many patients[1].

Unwanted side effects are described as transient mild to moderate include insomnia, nausea, vomiting, pruritus, rash, diarrhea, dyspepsia, allergic reactions, urticaria, superinfection, erythema, phlebitis and thrombophlebitis.

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In nosocomial (hospital acquired infections) trials of pneumonia, due to unwanted side effects, this drug was discontinued in 11% of patients. In clinical trials, due to dermatologic effects (rash, pruritus) and GIT effects (nausea, vomiting, diarrhea) this drug was discontinued in 3.2% of patients [2]. It is reported that some penicillin's causes occupational diseases like asthma, contact urticaria, contact dermatitis, anaphylaxis, and 6hypersensitive pneumonitis in healthcare professionals and pharmaceutical workers [3].

A hypersensitivity reaction refers to altered reactivity in which the body mounts an amplified immune response to a substance stated by Marc and Olson [4]. GellandCoombs[5] classified hypersensitivities into four different groups (types I, II, III, and IV), which depend upon the severity and potency of a reaction [5]. Type I is an immune reaction to an antigen mediated by IgE antibodies. Hypersensitivity reactions of Type II is also called cytotoxic hypersensitivities.

These reactions are caused by IgM antibodies and IgG antibodies. Hypersensitivity reactions of Type III are mediated by IgM antibodies and IgG antibodies. Type III hypersensitivities can cause inflammatory responses through a process in which the soluble antigens are combined with antibodies in the blood but not with host tissues. On the other hand, in Type II antigens are combined with host tissues to immediate a response. Hypersensitivity reactions of Type IV (delayed-type hypersensitivities) depend on T-cell interactions by recruiting other cells to the site of exposure which can take 12 or more hours to develop [6].

Type I hypersensitivity reactions can be determined by immediate-type skin testing, provocation testing, or radioallergosorbent tests (RASTs); Type II can be determined by measuring the IgGantibodieslevel to specific host proteins; Type III can be detected by testing serum IgG antibodies to specific antigens; TypeIV hypersensitivity reactions can be determined by delayed skin testing or memory lymphocyte immuno-stimulation assay. (MELISA). Continuous exposure to antigens may cause chronic conditions such as irritable bowel syndrome, asthma, autoimmune diseases, or even psychiatric illnesses [4].

The objective of this study was to:

- Identify the hypersensitivity reactions of piperacillin-tazobactam among pharmaceuticals factory and office workers.

METHODOLOGY

It was a cross-sectional study, and the research was conducted at Stallion Pharmaceuticals (Pvt) Ltd located at Sundar Industrial Estate, Lahore Pakistan, from March to April 2018 after approval from the institutional research committee with IEC/36-20.

The research population of the study considered was all (80) workers, including factory workers and office workers at Stallion Pharmaceuticals (Pvt) Ltd. The research tools used in data collection were observations by immediate-type skin testing.

The data was collected from each respondent by skin testing after injecting 0.1ml of piperacillin and tazobactam to detect hypersensitivity. This skin testing was done by pricking the skin with a needle or pin, which contains a small amount of antigen. The patient is considered allergic to that antigen if there is an induration of 5mm at the prick site. Informed consent was taken from each participant on written Performa. Data analysis was done by SPSS version 25, the demographic data was evaluated by descriptive statistics, Fisher Exact test was used for comparison, and p-value of ≤ 0.05 was taken as significant.

RESULTS

The main objective of our research was to identify the hypersensitivity reactions of piperacillin-tazobactam in pharmaceutical workers. The research was conducted at Stallion Pharmaceuticals (Pvt) Ltd located at Sundar Industrial Estate, Lahore Pakistan. Total of 80 respondents were studied from March to April 2018. The test was done on both males and females of different age groups, which included factory and office workers. Total males 56 (70%) and females 24 (30%) were included in this study. Major participants were from the age group 26-35 (31.25%) years, 61(76.25%) factory and 19(23.75%) office workers were included in this study.

Table-I: Distribution of respondents according to Gender.

Gender	n(%)
Male	56(70%)
Female	24(30%)
Total	80(100%)

The data in Table-I showed that out of 80 participants, (70%) were males, and (30%) were females.

Table-II: Distribution of respondents according to their age.

Age	n(%)
15-25	23(28.75%)
26-35	25(31.25%)
36-45	19(23.75%)
Above 45	13(16.25%)
Total	80(100%)

Table-II showed that 23(28.75%) were of the age group 15-25 years, 25(31.25%) belong to age group of 26-35 years, and 19(23.75%) were of 26-45years, while 13(16.25%) were above 45 years.

Table-III: Distribution of respondents according to their job description.

Occupation	n(%)
Factory worker	61(76.25%)
Office worker	19(23.75%)
Total	80

Table-III showed that 61(76.25%) were factory workers while 19(23.75%) were office workers of the factory were participated in this study.

Table-IV: Hypersensitivity reaction among male and female participants.

Gender	Yes	No	Total	p-value
Male	6(7.5%)	50(62.5%)	56(70%)	
Female	3(3.75%)	21(26.25%)	24(30%)	1.00
Total	9(11.25%)	71(88.75%)	80(100%)	

Table-IV showed that among males and females, 6 (7.5%) males and 3(3.75%) females showed a positive hypersensitive reaction and 50(62.5%) males and 21(26.25%) females show negative hypersensitive reaction with a p-value of 1.00, which is insignificant.

Table-V: Hypersensitivity reaction among all respondents.

Reaction	n(%)
Present	9(11.25%)
Absent	71(88.75%)
Total	80(100%)

Table-V showed that out of 80 participants, hypersensitivity reaction was present only in 9(11.25%) while 71(88.75%) did not show any hypersensitivity reaction.

Table-VI: Association of hypersensitivity reaction among factory workers and office workers.

Workers	Drug Effect		Total	p-value
	Yes	No		
Factory Workers	7 (8.75%)	54 (67.5%)	61(76.25%)	1.00
Office Workers	2 (2.5%)	17(21.25%)	19(23.75%)	
Total	9(11.25%)	71(88.75%)	80(100%)	

Table-VI showed that among Factory workers and office workers, 7 (8.75%) factory workers and 2 (2.5%) office workers showed a positive hypersensitive reaction. 54(67.5%) factory workers and 17(21.25%) office workers shows negative hypersensitive reaction. Chi-square analysis results showed that no significant difference in hypersensitivity reaction was seen between factory and office workers as the p-value is 1.00

DISCUSSION

The main objective of our research was to identify the hypersensitivity reactions of piperacillin-tazobactam among pharmaceuticals office and factory workers. The research was conducted at Stallion Pharmaceuticals (Pvt) Ltd, located at Sundar Industrial Estate, Lahore, Pakistan. The results of our study presented that hypersensitivity reaction was present in (7.5%) of males and (3.8%) of females. From the above results (11.2%) of all the respondents developed a hypersensitivity reaction, and (88.8%) did not show a reaction when they were gone through a skin test, which contain 0.1 ml of piperacillin and tazobactam.

Other research studies that reported adverse effects with piperacillin/tazobactam therapy were; type-I hypersensitivity, acute delirium, neutropenia, rash delayed type hypersensitivity reaction, and paresthesia. So, the results of our study regarding hypersensitivity are consistent with these studies. It shows that this drug has proven side effects of hypersensitivity to some exposed persons.

There are two categories of an allergic reaction related to beta lactam antibiotics. The IgE mediated and non-IgE mediated. An example of a 84 years old man who suddenly developed toxic epidermal necrolysis on 72% of his body surface in reaction to 3rd generation cephalosporin. After recovering from this reaction, the patient suffered from an IgE mediated allergy reaction to piperacillin-tazobactam. Later on, RAST revealed positive results for penicillins. With this case we came to know that hypersensitivity to penicillin was a predisposition to cephalosporin allergy [7].

A recent study conducted in the United Kingdom discussed piperacillin-tazobactam hypersensitivity. Among all (87) patients (48)55% patients showed hypersensitivity to piperacillin-tazobactam, of whom (26)54% patients presented with immediate and (22)45% non-immediate hypersensitivity. Patients with cystic fibrosis are more prone to develop hypersensitivity reactions [13]. Another study discussed a 31 year old patient with cystic fibrosis who developed FDE (Fixed Drug Eruption) to piperacillin-tazobactam. FDE is a drug reaction characterized by round well-circumscribed erythematous macules and plaques on cutaneous and mucosal surfaces [14].

Hays WB, discussed a case report which described a case of a female nurse who experienced recurrent hypersensitivity reactions in a few months only in a work environment. There was no apparent cause. Skin prick tests were positive to piperacillin and penicillin G. after the nurse was transferred to another department, no further hypersensitivity reactions occurred [15]. Another study was conducted in America which showed that only 1% of the participant showed hypersensitivity reaction[16].

Acute generalized exanthematous pustulosis is a rare disease caused by a hypersensitivity reaction of beta lactam drugs. Its diagnosis was confirmed by skin biopsy. This discovery leads him to discover other skin allergies due to antibiotic use i.e. (piperacillin-tazobactam) [10]. Another example of acute generalized exanthematous pustulosis was reported in a 78 years old lady who was being treated with piperacillin/tazobactam[12].

Serum IgE antibody to piperacillin-human serum albumin (HSA) conjugate was detected in a patient that developed anaphylaxis after her occupational exposure. A case of 24 year old nurse reported who had worked at University Hospital for 2 years. She had a history of atopic dermatitis. On injecting piperacillin, after 10mins, she experienced abdominal pain, dizziness, generalized urticaria, diarrhea, and chest tightness. A skin prick test was done for common inhalant allergens, which was negative, while her serum

total IgE was increased (283IU/mL). By doing (ELISA), a high level of piperacillin-specific IgE was detected in her serum after using piperacillin-HSA conjugate. These data suggest that the hapten of piperacillin after interacting with IgE mediated occupational anaphylaxis and urticaria in the workplace where piperacillin exposure is present [11].

In a previous study, 2 of 311 nurses of tertiary hospitals showed a positive skin prick test for piperacillin (0.6%) [8]. Two studies were attempted to measure specific IgE antibody levels of piperacillin in serum. Out of two cases, one case is of acute bronchitis patient who developed anaphylaxis, urticarial, and angioedema after intravenous injection of piperacillin, and the other was a case of pharmaceutical worker who developed occupational asthma, rhinitis, and urticaria induced by exposure to piperacillin powder. All the above studies show that the results of our studies are in line and consistent with the above studies. So, it is proved that the drug under study has hypersensitivity reactions to some exposed persons.

While treating someone with piperacillin-tazobactam the clinicians should keep in mind the possibility of thrombocytopenia because a severe case of thrombocytopenia reported on 12th day of hospitalization when 63-year-old women who had aspiration pneumonia when she was being treated with this drug. Parekh et al. discontinued piperacillin/tazobactam after the possible causes of thrombocytopenia has been ruled out. In a short time her platelet counts improved. This discontinuation proved to be life saving for her [9]. Another study evidenced that piperacillin-tazobactam hypersensitivity reactions were present in the study participants [17]. Another study also showed that there are long-term side effects of these drugs as well [18].

CONCLUSION

Hypersensitivity reaction to piperacillin-tazobactam was minimal in the factory & office workers, and this was not significant.

RECOMMENDATIONS:

After our study about the drug piperacillin/tazobactam's hypersensitivity reactions, we surprisingly found out that hypersensitivity reaction was present in factory workers as well as office workers. Hence, we recommend further studies should be done in this regard as we suspect that drug might have effects on surrounding areas. We also recommend that those working in pharmaceutical manufacturing units (office workers, factory workers) must use personal protective equipment. It is further recommended that this drug should be used in clinical patients after giving a test dose because it can have anaphylactic shock due to severe hypersensitivity reactions.

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Author's Contribution:

Ali Anwar Sulehri: Substantial contributions to the conception or design of the work
Hafiz Muhammad Hammad Yaqub: Interpretation of data for the work.
Humayun Suqrat Hassan Imam: Analysis, and interpretation of data for the work.
Uzma Sagheer: Drafting the work and revising it critically for important intellectual content.
Muhammad Abubakar: Interpreted the data, drafted the article and gave final approval.

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