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Influence of Diet and NSAIDs in Allergic Skin Reactions

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ABSTRACT

Background: Vegetarian or non-vegetarian food and Non- Steroidal Anti-Inflammatory Medications (NSAIDs) also known as NSAIDs are separate factors in causing skin allergic reactions. The study aims to investigate whether there is a change in the incidence of allergies, associated with the concurrent exposure to both factors.

Methods: Patients were randomly allocated to four groups, two of each were control, one non-vegetarian and one vegetarian group with no medicines for the last three months. Group – I were non-vegetarians taking NSAIDs while group – II were vegetarians taking NSAIDs. Odds Ratio (*OR*) was calculated to find out the risk factor in developing skin reactions. Chi – square test was done to measure the significance of the *OR*.

Results/Discussion: Skin allergic reactions in the test group of non-vegetarians who consume NSAIDs were 38(9.3%). Control group of 400 non-vegetarians in the same community showed skin reactions in 13(3.3%) people. The *OR* was found to be 3. Chi – square value have shown high significance with a *P* – value less than 0.01. Allergic skin reactions in the test group of vegetarians who consume NSAIDs were 21 (5.6%). Control group of 400 vegetarians (without any drugs for last three months) in the same community showed skin reactions in 9 (2.3%) people. The *OR* was found to be 2.5. Chi – square value have shown significance with a *P* – value less than 0.05 in increasing allergic skin reactions.

Conclusion: Non-vegetarian patients who take NSAIDs have shown three times higher rates in allergic skin reactions, while vegetarian diet produces more or less additive effect with NSAIDs. Non-vegetarian food is a highly significant factor in increasing allergic skin reactions for the patients who take NSAIDs.

Keywords: Skin, NSAIDs, vegetarian, non-vegetarian

Short Title: NSAIDs & diet induced allergy

Introduction

Non-Steroidal Anti-Inflammatory Medications (NSAIMs) also known as NSAIDs are responsible for 21 to 25% of all adverse reactions to drugs.¹ Adverse drug reactions (ADRs) constitute a major clinical problem and increased healthcare costs. Skin adverse drug reactions are responsible for the majority of ADRs in hospitalized patients. Many of the commonly used drugs can produce cutaneous ADRs².

Skin adverse drug reactions can be caused by a wide variety of agents. They are responsible for approximately 3% of all disabling injuries during hospitalization and complications of drug therapy are the most common type of adverse event in hospitalized patients. Many of the commonly used drugs have reaction rates above one percent³. It is not significantly alarming issue on use of the medicines, but it explains that any drug may produce skin reactions.

One of the North-Indian studies in Chandigarh showed that the drugs are most often incriminated for the various skin ADRs were antimicrobials (42.6%), anticonvulsants (22.2%) and NSAIMs (18%). A total of 500 patients with skin ADR were enrolled during the study period. There were 298 (59.6%) males and 202 (40.4%) females, with an age range of 4 months to 76 years (mean 34.5 years). Maximum number of patients 252 (50.4%) were in the age group of 21-40 years, 126 (25.2%) below 20 years and 72 (14.4%) above 60 years. The incubation period for maculopapular rash and urticaria varied from 30 minutes to 3 weeks. Fixed drug eruption (FDE) had an incubation period ranging from two days to two months. The incubation period for serious drug reactions viz. Steven Johnson syndrome (SJS) and Toxic Epidermal Necrosis (TEN) varied from a few hours to one week⁴⁻⁵. Drugs (20%) were the second

most recognizable cause of anaphylactic reactions, with NSAIMs responsible for half of them⁶.

Vegetable proteins such as Soy, wheat, peanuts, tree nuts are found to cause skin allergic reactions.⁷ Reactions due to other uncommon foods like mustard, flavourings, and honey are comparatively rare, but it changes from country to county and people to people.⁸ Severe reactions to soy are rare compared to reactions to peanuts, tree nuts, *A. simplex* that infects fish and Shellfish.⁹ Swedish researchers recently concluded that soy have the potential to cause food anaphylaxis.¹⁰

Methods

This observational study was conducted on adult patients (18 to 65 years of old) taking any NSAIMs. The patients are grouped in to vegetarian and non-vegetarian. Those who consume meat, fish and egg for last 6 months were considered as non-vegetarian. Those who don't take meat, fish and egg for last 6 months were considered as vegetarian. Control groups were the public interviewed from the bus stop and shopping center near to pharmacy. Subjects in the control groups have not taken any drugs for the last 3 months. In the test and control group the sample population was a good representation of the public living in that area. Different social status, diet patterns, employees, workers, in both genders was visiting the urban area for their work, health care, education, and commercial needs. In all the groups, allergic skin reactions or pseudoallergic skin reactions were noted using causality assessment.

In both test and control group, the non-vegetarians were available more than the proportion of vegetarian. In this six month study data collection from non-vegetarians

were finished within five months. But due to less number of vegetarian test group (who also consume NSAIDs) the study was extended up to eight months only for the vegetarian test group. Still we could get only 372 patients than the expected 400 sample size. Other variables which could produce skin allergic reactions are expected to be randomly distributed in the groups under study.

Prescriptions through the community pharmacies in Kasaragod were evaluated for test groups. The Narinjo Scale of Causality assessment¹¹ and CIOMS Form for suspect adverse reaction report were used to assess the patients by recording their probable or definite ADRs. Diclofenac (24%) and Aceclofenac (14%) were the most commonly prescribed NSAID – monotherapy in Kasaragod district, South India. Odds Ratio (*OR*) is calculated to find out risk factor associated with test and control groups. In case control studies like this, odds are obtained for presence of a risk factor in cases and control. The ratio of these two odds is called odds ratio. *OR* is the measure of strength of association between the outcome and antecedent.¹² SPSS version 12.0 for windows software was used to find out the significance of the *OR* using 2x2 contingency table in Chi-square test with degrees of freedom (*df*) 1.0.

Results

Allergic skin rashes or urticaria scored five or above (probable or definite) in the narinjo scale of causality assessment was considered as skin allergic reactions for the study. In the patient interview, any skin reactions happened for the last 2 months were investigated. Many patients who could not produce their prescriptions or could not recognize all the medicines before the occurrence of adverse reactions were excluded from the study. Those

patients took NSAIDs without antimicrobials or anticonvulsants at least for a period of one month were entered in test groups. Test group-I was for non-vegetarian who consume NSAIDs and test group-II for vegetarian population who consume NSAIDs. In the control groups, allergic skin events were counted for vegetarian and non-vegetarian foods in absence of any medicines for the past 3 months.

Skin allergic reactions in the test group of non-vegetarians who consume NSAIDs were 38(9.3%). Control group of 400 non-vegetarians in the same community showed skin reactions in 13(3.3%) people. NSAIDs in non-vegetarians increased the occurrence of allergic skin reactions.

The odds ratio for the allergic skin reactions in the non-vegetarian population in the presence of NSAIDs was found to be 3.03. It was remarkably higher than the *OR* 1.0 which represent that the occurrence of allergic reactions are same in test or control groups. Chi-square test was done to find out the significance of the *OR*. The null hypothesis was that, NSAIDs do not increase adverse skin reactions. In 2x2 tables, the *P* – value 0.05 had the critical value 3.843 and for the *P* – value 0.01 had the critical value 6.637. Our study finding showed a chi-square value of 12.37 which is much higher than the required 6.637 critical value. Clearly the null hypothesis was rejected and the *OR* was proved to be highly significant.

Allergic skin reactions in the test group of vegetarians who consume NSAIDs were 21 (5.6%). Control group of 400 vegetarians (without any drugs for last three months) in the same community showed skin reactions in 9 (2.3%) people.

The odds ratio for the allergic skin reactions in the vegetarian population in the presence of NSAIDs was found to be 2.6. It was higher

than the *OR* 1.0 like in non-vegetarians. In 2x2 tables, the *P* – value 0.05 had the critical value 3.843 and for the *P* – value 0.01 had the critical value 6.637. The chi-square value for vegetarian population with NSAIDs was 5.95. Here null hypothesis could be rejected for 95% confidence interval as the result is higher than the critical value for *P* – value 0.05. But the result is lower and insignificant for 99% confidence interval.

Discussion

Many non-vegetarian foods and vegetarian foods have causal relationship with skin allergic reactions in the vulnerable population. NSAIDs are also shown to cause cutaneous allergic reactions of varying degree. It is interesting to know that what would be the occurrence of skin allergic reactions when these variables together could contribute.

The odds ratio suggests three times higher incidence of allergic skin reactions to the non-vegetarian by the use of NSAIDs. In other words, an additional 6.1% of the skin allergic reactions were seen by the use of NSAIDs. This is pretty higher than the 3.3 % incidence due to non-vegetarian food alone. The chi-square test value provides high level of significance for the increase in skin reactions. The *P* – value is coming under 0.01. The *OR* of approximately 3 states a three times higher risk factor in causing skin reactions.

There was an approximately two times increase in the (230%) incidence of allergic skin reactions to the vegetarian by the use of NSAIDs were found. In other words, an additional 3.3% of the skin allergic reactions were seen by the use of NSAIDs. This was pretty comparable to the 2.3% incidence due to vegetarian food alone. The chi-square test value provided significance for the increase in

skin reactions. The *P* – value was coming under 0.05. The *OR* of approximately 2.5 states a two and a half higher risk factor in causing skin reactions. At the same time it is interesting to note that the *OR* was not proved highly significant through chi – square test. Thus we were convinced to state that there a two time higher risk in causing skin reactions. This finding was influenced by the findings in the non-vegetarian groups.

Average occurrence of allergic skin reactions due to NSAIDs also could be evaluated. When adding the values in non-vegetarian and vegetarian test groups - I & II, there were a total of 59 incidences among 783 patients. Risks of developing skin reactions were calculated to be 7.5%. The control groups with no medicines for last three months have shown 2.8% allergic skin reactions. Gastrointestinal and skin allergic reactions are the common adverse reactions with NSAIDs along with cardiac, liver and renal toxicity.¹³⁻¹⁵

We had also discussed the studies mentioned in the introduction that, out of the skin reactions happened, 18 % was caused by NSAIDs and out of all adverse drug reactions NSAIDs contribute to 21-25%.

Conclusion

Non-vegetarian population using NSAIDs were found to be at high risk of developing skin allergic reactions. Use of NSAIDs in the non-vegetarian population was found to increase the incidence of allergic skin reactions for three times. Non-vegetarian food was shown to produce synergistic effect in the occurrence of allergic skin reactions. Meanwhile in the vegetarian food populations taking NSAIDs produce more or less additive effects.

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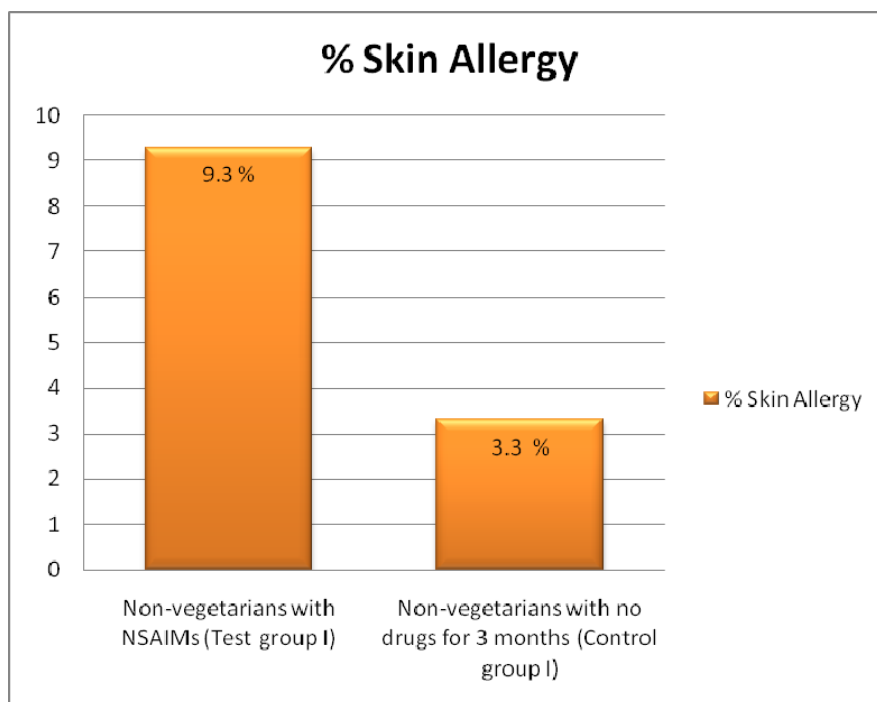
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Table 1: NSAIM induced skin allergic reactions in non-vegetarians

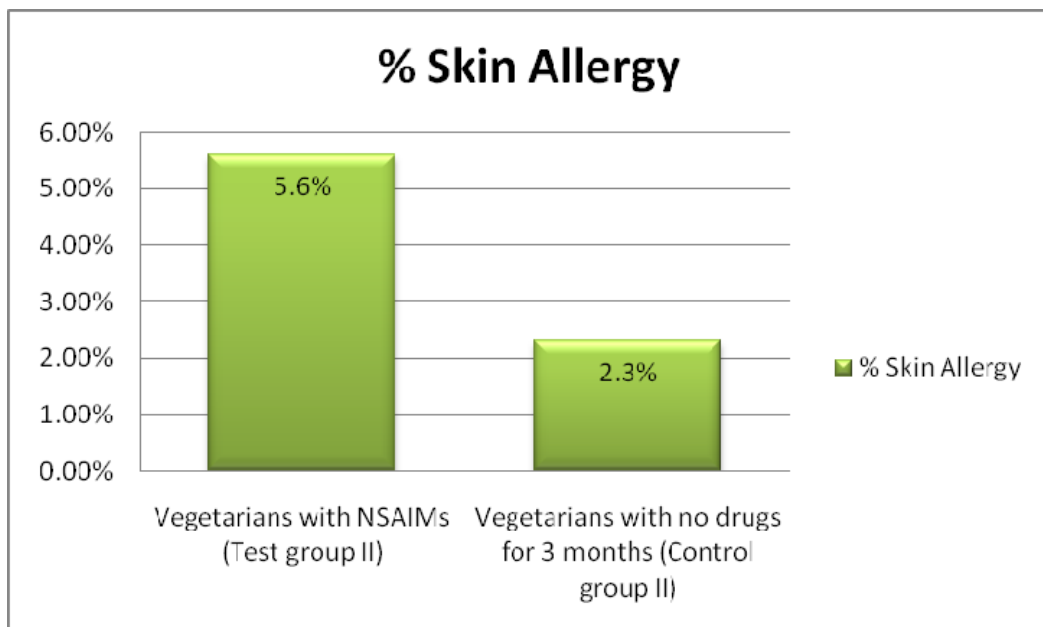
Groups	Skin Allergy	No skin Allergy	Total
Non-vegetarians with NSAIMs (Test group I)	38 (9.3%)	373	411
Non-vegetarians with no drugs for 3 months (Control group I)	13 (3.3%)	387	400



Graph 1: Allergic Skin reactions in Non-vegetarians

Table 2: NSAIM induced skin allergic reactions in vegetarians

Groups	Skin Allergy	No skin Allergy	Total
Vegetarians with NSAIMs (Test group II)	21 (5.6%)	351	372
Vegetarians with no drugs for 3 months (Control group II)	09 (2.3%)	391	400



Graph 2: Allergic Skin reactions in Vegetarians