Assessment of Causality, Preventability and Severity of Cutaneous Adverse Drug Reactions: A Prospective Observational Study

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Authors’ contributions

This work was carried out in collaboration between all authors. Author RH designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SB and DJ managed the analyses of the study. Author TR managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: All drug regulatory authorities have to ensure the safety, efficacy and quality of all the marketed products. Quality and efficacy can be determined by the data from preclinical and clinical trials. In clinical trials at the pre-marketing stage, it is challenging to identify rare Adverse reactions (ADR) and delayed side effects or effects due to long-term exposure because of lack of follow-up. In this case, pharmacovigilance comes into picture where it plays a significant role in marketed drugs safety profile establishment.  
Aim: This study helps in safety profile establishment for drugs.  
Methodology: It was conducted by the Department of pharmacy practice at drug information Centre in collaboration with Department of pharmacology at private multi-specialty Hospital. ADR reporting forms of the Central Drug Standard Control Organization has been used for collecting the data, and this form includes patient demographic details like clinical history, co-morbid conditions

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like Diabetes mellitus, Hypertension, Asthma, history of any drug allergies etc. were collected. The chance of preventability modified Schumock and Thornton criteria was found to be very less, and it was evident that most of them were not. By using Hartwig et al., scale, the severity of ADRs were of moderate severity. The reason behind this moderate severity was a history of allergy and multiple drug therapy.

**Result:** It was observed that preventability 86% were not preventable whereas 14% were preventable as per Schumock and Thornton scale. In these cases of definitely preventable cases were due to history of reaction upon administration of the same drug. It is advised that in such cases usage of drug alert card is preferred.

**Conclusion:** The major risk factor for the development of ACDR includes self-medication, patients’ lack of awareness regarding the dose and frequency of administration, polypharmacy. This can be avoided by prescribing the required drugs only and by educating the patients regarding the drugs.

**Keywords:** Cutaneous adverse drug reaction; side effects; antimicrobial agents s.

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### 1. INTRODUCTION

Fitzgerald explained that the safety of drugs is essential to the patients and healthcare professionals as well. So many drugs were successful and shown benefits to the patients, but those drugs, later on, have shown some serious side effects which are termed as delayed side effects and thereby it resulted in their withdrawal [1]. Olsson S. stated that the main burden on health care systems globally is mainly due to drug-related disease. There is a lack of awareness among the patients regarding the drug-related problems, and these problems are not always certain, immediate and visible. They are often manifested as symptoms for common diseases [2]. All drug regulatory authorities have to ensure the safety, efficacy and quality of all the marketed products. Quality and efficacy can be determined by the data from preclinical and clinical trials. In clinical trials at the pre-marketing stage, it is challenging to identify rare Adverse reactions (ADR) and delayed side effects or effects due to long-term exposure because of lack of follow-up. In this case, pharmacovigilance comes into the picture where it plays a significant role in marketed drugs safety profile establishment [3]. The most commonly reported ADR is Adverse Cutaneous drug Reaction [4]. Though these kinds of cutaneous reactions are common, they are not reported, and therefore, there is a lack of information regarding incidence, the severity of this ADR [5]. Throughout the world, ADR is the leading cause of morbidity and mortality [6]. 28% of these ADRs are preventable [7]. Identification of these ADRs and reporting is crucial, and it will help the physicians to be on vigilant while prescribing such drugs and thereby reducing the healthcare cost [8]. Because of spontaneous reporting systems, marketed many medicines are being withdrawn because of safety concerns [9,10]. In India, ADR reporting is very less because of so many reasons like lack of time, underestimation of its importance and lack of awareness of filling ADR forms etc. [11]. This study aims to diagnose the ADR at early stages and for reducing the morbidity and mortality due to Cutaneous ADRs thereby ensuring the safety of the patients.

### 2. METHODOLOGY

This a prospective observational study conducted by the Department of pharmacy practice at drug information Centre in collaboration with Department of pharmacology at private multispecialty hospital in a period of 1 year (January 2019 to January 2020). As per study inclusion criteria only in-patients from dermatology department were included. Patients of all age groups who developed a subcutaneous reaction after consuming any drugs. As per exclusion criteria of our study patient are having no subcutaneous reaction while on therapy.

#### 2.1 Study Instrument

ADR reporting forms of the Central Drug Standard Control Organization has been used for collecting the data, and this form includes patient demographic details like clinical history, co-morbid conditions like Diabetes mellitus, Hypertension, Asthma, history of any drug allergies etc. were collected. Drug history like any drugs administered before the adverse reaction, dosage, route of administration, frequency of drug administration, including herbal medicines, whether the drug is over the counter or prescribed drug, was collected. Drug reaction history includes the type of reaction, the onset of
reaction, duration, the morphological pattern of the adverse reaction, name of the drug, brand name, manufacturing company and batch number, the seriousness of reaction etc. were collected.

2.1.1 Causality assessment by WHO scale

For Causality assessment WHO Uppsala Monitoring Centre (UMC) scale was used which includes certain, probable, possible, unlikely, unclassified, unclassifiable.

2.1.2 Preventability assessment by Schumock and Thornton scale

Preventability of ADRs was assessed by using modified Schumock and Thornton criteria in which ADRs are classified into definitely preventable, probably preventable and not preventable [12]

2.1.3 Severity Assessment by Hartwig and Siegel scale

Whereas severity of ADRs was assessed by using Hartwig and Siegel scale, and in this scale, ADRs are classified into mild, moderate and severe [13].

2.2 Statistical Analysis

The demographic data like age, group, gender, drug, the causative agent of ACDR were assessed by descriptive analysis in Microsoft Excel and SAS 9.2 version was used for the statistical analysis. By using the chi-square test, binary outcomes were compared between the groups for assessing the significant by keeping P-value at 0.05.

3. RESULT

During the study period, 12895 patients were attended in Dermatology department of the multispecialty hospital among which 48 subjects (1.5%) have ACDR including both the patients with developed ACDR or ACDR which was developed at the time of hospital stay. Only 38 patients were inpatients of the total subjects. The patients with cutaneous drug reaction have a median age of 38 years, and the minimum age is eight years and maximum ranges to 79 years. Antimicrobials were most commonly associated with a cutaneous drug reaction. Out of 38 patients, 28 patients developed ACDR due to antimalarial drugs, and eight patients developed ADR because of NSAIDs. In 2 patients, the cause of ACDR was unknown.

Table 1. Type of ACDR with cause

| Type of ACDR | Cause and percentage |
|--------------|----------------------|
| Fixed Drug Eruption | Paracetamol (44.5%) |
| Maculopapular rash | Artemether (22.8%) |
| Urticaria | Amoxycillin (11.6%) |
| Flagellate hyperpigmentation | Bleomycin (4.5%) |
| Photosensitivity | Chloroquine (2.8%) |
| Bullous eruptions | Ofloxacin (1%) |
| Pruritis | Unknown (12.8%) |
| Dermatitis | Exfoliative dermatitis |

3.1 Causality Assessment

As mentioned above, causality of ADRs were analyzed by using the WHO scale in which certain, possible, probable, unlikely, unclassified, unclassifiable types will be seen.

Table 2. Causality assessment using the WHO scale

| Types | Percentage |
|-------|------------|
| Certain | 02% |
| Possible | 23% |
| Probable | 68% |
| Unlikely | 4% |
| Unclassified | 2% |
| Unclassifiable | 1% |
| Total | 100% |

3.2 Severity Assessment

The severity of ACDRs was identified using Hartwig scale in which ACDR developed is of moderate-severe 49% in this study, and 48% were mild, and 3% were severe. The chance of preventability modified Schumock and Thornton criteria was found to be very less, and it was evident that most of them were not preventable as described in Table 3.

Table 3. Preventability assessment using modified Schumock and Thornton criteria

| Types | Percentage |
|-------|------------|
| Preventable | 13.9% |
| Non-preventable | 86.1% |
| Total | 100 |
4. DISCUSSION

In this Prospective study, it was observed that Fixed Drug Eruptions were the most common reaction, and it was most commonly caused by paracetamol. Antimicrobials were the Second commonest cause of developing ACDR. In this study, we observed that this is mainly due to two risk factors like multiple drugs administration and allergic history are associated with a severe level of reaction. Most of the ACDRs are due to self-medication. There was no significant gender variation in the occurrence of ACDR, and most commonly, these ACDRs are seen in the geriatric population. As per the literature, it was found that penicillin was the most offending group [14]. In contrast, a study conducted by Jhaj R. et al. [15] beta lactam group of antibiotics were the most common cause of ACDR. But in our study, most of the ACDRs were due to paracetamol. And the reason behind this may be the frequent prescription of this drug and self-medication. This identification correlates with the study conducted by Pudukadan David et al. [16] in which they identified that paracetamol is the primary cause of FDE. In contrast, most of the studies stated that FDE is primarily due to Co-trimoxazole. In this study, most of the ACDRs are due to self-medication which highlights the importance of creating awareness among the patients to prevent these ACDR. In the case of severity after performing the statistical analysis, it was observed that multiple drug therapy and history of allergy are the significant risk factors. Out of 38 cases, 28 were probable, and 10 were possible cases. As this is prospective study rechallenge was not done in all the subjects. By using Hartwig et al., scale, the severity of ADRs were of moderate severity. The reason behind this moderate severity was a history of allergy and multiple drug therapy. It was observed that preventability 86% were not preventable whereas 14% were preventable as per Schumock and Thornton scale. In these cases of definitely preventable cases were due to history of reaction upon administration of the same drug. It is advised that in such cases usage of drug alert card is preferred. The main drawback of this study is less sample size; we can’t extrapolate the data to a larger population.

CONCLUSION

In conclusion, the major risk factor for the development of ACDR includes self-medication, lack of awareness in patients regarding the dose and frequency of administration, polypharmacy. This can be avoided by prescribing the required drugs only and by educating the patients regarding the drugs.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

The study obtained approval from the Institutional Human Ethical Committee (IHEC). Patient informed consent was also obtained from individual patients who were enrolled in study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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