Original Article

Causality, Severity and Preventability Assessment of Cutaneous Adverse Drug Reactions: A Prospective Observational Study in a Tertiary Care Hospital

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Abstract

Background: One major contributor to morbidity and death is adverse drug reactions, or ADRs. Among ADRs, CADR is the most common. Pharmacovigilance and ADR monitoring systems both depend on the efficient monitoring of CADRs. The purpose of this study is to evaluate the causality, severity, and preventability of different cutaneous adverse drug reactions at a tertiary care hospital. **Material and Methods:** From January 2019 to June 2020, 120 patients with CADRs who were hospitalized at K R Hospital or attended the Dermatology OPD participated in this prospective, observational research. A systematic questionnaire was used to gather and evaluate the data. **Results:** The WHO-UMC causality evaluation criteria were used to determine the likelihood of responses. Of the 120 instances examined, 16 were deemed Certain, 59 were deemed Probable, and 45 were deemed Possible responses. Using the Modified Hartwig and Siegel scale, the severity was classified as mild (55 instances), moderate (41 cases), and severe (24 cases). According to Schumock and Thornton's criteria, responses were classified as Definitely preventable (18 instances), probably preventable (19 cases), and not preventable (83 cases). **Conclusion:** Improving pharmacovigilance training programs is necessary to bridge knowledge and ADR-reporting gaps among healthcare professionals.

Keywords: Pharmacovigilance, Causality, Severity, Preventability, and Cutaneous Adverse Drug Reactions.

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Introduction

According to estimates, the fourth to sixth most common cause of mortality for hospitalized patients is adverse drug reactions (ADR).[1] Cutaneous ADRs (CADR) is any undesirable change in the structure or function of the skin, its appendages or mucous membrane and encompasses all adverse events related to drug eruption, regardless of the etiology. The Pharmacovigilance Programme of India was introduced in 2010 and uses a spontaneous reporting method to track adverse drug reactions.[2-4]

Effective monitoring of CADRs, both hospital-based and population-based, is an integral part of ADR monitoring programmes and Pharmacovigilance, not only to generate valid data but also to identify and assess predisposing/underlying risk factors and to evaluate treatment outcomes.[5]

However, rigorous epidemiological investigations seem to be insufficient, and reporting and recording of CADRs are not being coordinated and executed efficiently in the Indian community. Therefore, the goal of the current research is to gather data on the causes, severity, and preventability of drug-induced CADRs in our setting.[6]

Objectives

To evaluate the causality, severity and preventability of various cutaneous adverse drug reactions.

Materials and Methods

After obtaining written informed consent from the patients and approval from the Institutional Ethics Committee, a prospective, observational, questionnaire-based study was carried out on patients with drug-induced cutaneous adverse drug reactions who were admitted to the ward or attended the Dermatology OPD at K.R. Hospital, which is part of Mysore Medical College and Research Institute, Mysore, from January 2019 to June 2020. The Central Drugs Standard Control Organization's (CDSCO) ADR form contains information on cutaneous adverse drug reactions. The WHO

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scale is used to evaluate causality, the Modified Hartwig and Siegel scale to evaluate severity, and the Schumock and Thornton scale to evaluate preventability.

Study design: Observational study

Study period: 18 months (January 2019 – June 2020)

Sample design: Purposive sampling

Sample size: Sample size (s) is calculated to be 120 using an estimation technique with an α error of 5% and a prevalence (p) of 5% in drug-induced adverse cutaneous reactions in India.

$s = Z^2pq/d^2$ (z = 2.51)

p = prevalence (5%)

q = (100-p) = (100-5) = 95

s = 2.51 x 2.51 x.05 x.95/.05 x.05 = 119.3 = approximately 120

Inclusion Criteria

Patients who follow the criteria below will be included in the study

1. Those in which the diagnosis of the cutaneous adverse reaction was in accordance with the definition of ADRs, which the WHO provided.
2. Cutaneous drug reactions from any drug/drug group in any age and gender.
3. Those in which there was a plausible time relationship between the introduction of the drug and the onset of a reaction.

Exclusion Criteria

Patients who follow the criteria below will be excluded from the study

1. Individuals without obvious skin lesions who reported symptoms (such as itching).
2. Individuals who were unable to remember the name of the suspected medications they had taken, as well as those whose lesions, upon closer inspection, were shown to be illness-related (such as viral exanthems, rickettsial infection rash, and collagen vascular disease).
3. Individuals who claimed to have used homeopathic and ayurvedic medications were also disqualified since they were unable to identify the herbal components in their cases.

Results

In this study, the Causality, Severity, and Preventability of various Cutaneous ADRs were assessed in 120 study subjects.

Table 1: Causality of cutaneous adverse drug reactions

Sl.no.	Causality	No. of cases	Percentage
1	Certain	16	13.33%
2	Probable	59	49.17%
3	Possible	45	37.50%
Total		120	100%

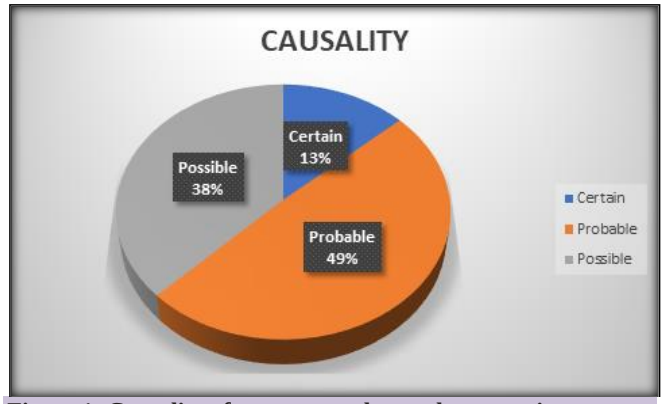

Figure 1: Causality of cutaneous adverse drug reactions

The WHO-UMC causality evaluation criteria were used to evaluate the likelihood of responses as Certain, Probable and Possible. Only sixteen instances were deemed Certain because there was a clear temporal correlation between drug consumption and the occurrence, which was pharmacologically conclusive, could not be clarified through other illnesses or medications, and had a clear withdrawal reaction. For ethical reasons, there was no effort to perform drug rechallenge. 59 instances (49.17%) were deemed Probable because there was an acceptable temporal association between drug consumption and the occurrence of the event, which couldn't have been explained by illness or other substances, and there was a reasonable reaction to withdrawal. Due to the events' plausible temporal association to drug consumption, which may potentially be explained by illness or other substances, and the lack of clear information about drug withdrawal, 45 instances (37.5%) were considered Possible responses. [Table 1 & Figure 1].

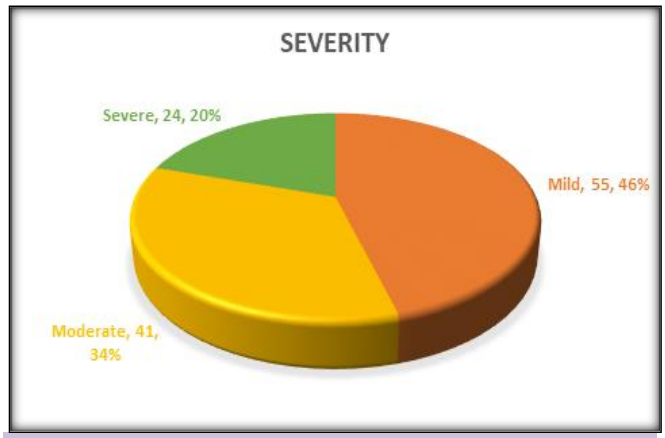

Figure 2: Severity of Cutaneous Adverse Drug Reactions

The Modified Hartwig and Siegel scale was used to classify cutaneous adverse drug reactions into three categories: mild, moderate, and severe. Majority of cutaneous ADRs were mild(45.83%). This consisted of 14 cases of urticaria, 29 cases of fixed drug eruptions, 3 cases of photosensitivity,

6 cases of acneform eruptions, 1 case of eczema, and 2 cases of hyperpigmentation. This was followed by 41 cases (34.17%) of moderate severity, comprising 28 cases of maculopapular rash, 5 cases of erythema multiforme, and 8 cases of Drug hypersensitivity syndrome. The fewest cases were severe, comprising 24 cases (20%), including 12 cases of Stevens-Johnson Syndrome, 9 cases of Toxic Epidermal Necrolysis, and 3 cases of angioedema. [Table 2 & Figure 2]

Table 2: Severity of Cutaneous Adverse Drug Reactions

Sl.no.	Severity	No. Of cases	Percentage
1	Mild	55	45.83%
2	Moderate	41	34.17%
3	Severe	24	20%
Total		120	100%

Table 3: Preventability of cutaneous adverse drug reactions

Sl.no.	Preventability	No. Of cases	Percentage
1	Definitely preventable	18	15%
2	Probably preventable	19	15.83%
3	Not preventable	83	69.17%

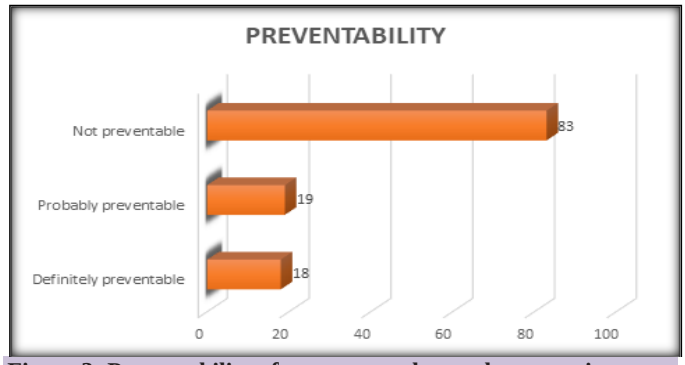

Figure 3: Preventability of cutaneous adverse drug reactions

Reactions were categorizedas Definitely preventable, Probably preventable and Not preventable using the Schumock and Thornton criterion. 69.17% (83 cases) were not preventable, 15.83% (19 cases) were probably preventable, and 15% (18 cases) were definitely preventable. [Table 3 & Figure 3]

Discussion

In both inpatient and outpatient settings, cutaneous adverse drug reactions are a significant and prevalent issue. CADRs are distressing to both the patients and physicians.

Table 4: Comparison of Causality

Causality	Present study	Modi et al,[7]	Kumar et al,[8]	Thakkar et al,[6]
Certain	18.33%	1.45%	13.01%	2.92%
Probable	45%	32.99%	56.10%	35.08%
Possible	36.67%	65.56%	30.70%	38.01%
Unclassifiable	0%	0%	0%	24.56%

Causality was assessed according to the WHO-UMC causality assessment criteria as certain, probable, and possible in the present study. All the above studies have used a similar algorithm for causality assessment. This assessment tool, which is easy to apply, can be widely used across diverse study populations with varying genetic backgrounds.

The largest number of cases were probable, followed by possible. The least number of cases was certain. A study done by Kumar et al,[8] showed similar findings. Whereas studies by Modi et al,[7] and Thakkar et al,[6] showed the highest number of cases in the possible category. Most of the cases were probable, which may be due to concurrent use of multiple medications and possible drug interactions. [Table 4]

Table 5: Comparison of Severity

Severity	Present study	Modi et al,[7]	Kumar et al,[8]	Agrawal et al,[3]
Mild	45.83%	16.50%	72.30%	70.60%
Moderate	34.17%	81.20%	25%	16.90%
Severe	20%	2.30%	2.60%	12.50%

In the present study, severity was assessed using the Modified Hartwig and Siegel scale: mild, moderate, and severe. The largest number of cases were mild, followed by moderate severity. This was similar to the study done by Kumar et al,[8] and Agrawal et al[3].In contrast to above studies, majority of the cases belonged to moderate severity in the study done by Modi et al.[7] Severe cases comprised 20% of the cases in the present study, which was comparable with the study done by Agrawal et al,[3] but higher than the studies done by Modi et al,[7] and Kumar et al[8].Mild CADRs were more (45.83%) which could be a result of easy and free accessibility of dermatologist in the present setup.

Although no deaths were recorded, severe CADRs (20%), such as SJS and TEN, necessitated extended hospital stays

and close observation. SJS is a severe, sometimes fatal, mucocutaneous response marked by widespread necrosis and skin-epidermis separation. Keratinocyte apoptosis results from a delayed type of hypersensitivity response involving CD8+ cytotoxic T lymphocytes. The pathophysiology of SJS/TEN is also influenced by the cytolytic molecules granulysin and FasL. According to this research, carbamazepine, diclofenac, and phenytoin are commonly linked to SJS. This result was consistent with research by Sasidharanpillai et al,[9] in Kerala, who similarly found that the most prevalent class of medications associated with SJS was anti-epileptics. [Table 5]

Table 6: Comparison of Preventability

Preventability	Present study	Thakkar et al,[6]	Kumar et al,[8]
Definitely preventable	15.00%	16.95%	69.10%
Probably preventable	15.83%	0%	17.10%
Not preventable	69.17%	83.05%	13.80%

The majority of the instances were not preventable, according to the Schumock and Thornton criteria. This was comparable to the research conducted by Thakkar et al[6].However, research by Kumar et al,[8] revealed that the majority of instances fell into definitely preventablecategory. 15% of CADRs weredefinitely preventable, with patient's incorrect self-medication choices and inaccurate documentation of their prior drug response histories being major causes. [Table 6] The current research demonstrates that the clinical spectrum of CADRs was almost identical to that observed in previous investigations, with little variation in the degree of response and the specific medications that elicited them. Antimicrobials, analgesics/NSAIDs, and anti-epileptics were significant contributing medications. The majority of the responses ranged in intensity from mild to moderate. When prescribing medications known to cause CADRs, such as β-lactam antibiotics, NSAIDs, and anti-epileptics, clinical practice can significantly reduce their incidence, frequency, severity, morbidity, and potential mortality through early detection, prompt withdrawal of the offending medication, and appropriate rescue measures. Giving the patient a warning card to prevent further exposure is also crucial. The overall incidence, prevalence, and pattern of CADRs, as well as the medicines that cause them, may be better understood through a comprehensive population-based prospective study. The pharmacovigilance program may benefit from this as well. Benefits of this research: This research has collected accurate prospective data on cutaneous adverse drug reactions in a large population, including both inpatients and outpatients. In most studies, case verification was based on retrospective analysis, whereas in our study, each case was prospectively evaluated by a consultant dermatologist. The database provides a potential source of information on causality, severity, and preventability of cutaneous adverse drug reactions.

Limitations of this study: This research had several limitations. In polypharmacy cases, causality evaluation was rather ambiguous, particularly because rechallenge was not undertaken for ethical reasons. Because the hospital primarily serves a lower socioeconomic class, our research population's exposure to newer pharmaceuticals was limited. As a result, their drug use patterns were mostly confined to the medications provided by the hospital pharmacy. As a result, the medication data produced by this trial could not be generalized. Patients did not show up after treatment, making long-term monitoring and follow-up impossible.

Conclusion

Adverse drug reactions have grown quite prevalent in recent years due to the rise in the number of medications. Among them, cutaneous adverse drug reactions are significant and have garnered attention. Improved training in pharmacovigilance and drug risk perceptions is necessary to close the gaps in health professionals' awareness and reporting of adverse medication reactions. Enhanced knowledge among the healthcare workers about ADR reporting will improve the overall patient health.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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