Section: Pharmacology

Original Research Article

ANALYSIS OF SPONTANEOUS REPORTS OF TOXIDERMIA AT ADVERSE DRUG REACTION MONITORING CENTER IN TIRUPATI

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Abstract

Background: Cutaneous adverse drug reactions (CADRs) are significant concerns that impact patient safety and healthcare practices. This study aims to analyze the patterns, causality, severity, and preventability of CADRs at ADR monitoring center (AMC) in Tirupati. **Material and Methods:** A retrospective analysis was conducted on 190 spontaneous toxidermia reports. Drugs implicated, types of reactions, causality (WHO scale), severity (modified Hartwig and Siegel scale), and preventability (Schumock and Thornton scale) were assessed. **Results:** Capecitabine (15.8%), Doxorubicin (13.2%), and the combination of Tenofovir, Lamivudine, and Dolutegravir (10.5%) were identified as the most frequently implicated in CADR reports. Other notable drugs included Imatinib (9.5%), Ribavirin (7.9%), Sofosbuvir (6.9%), Zidovudine (5.3%), and Acyclovir (4.2%), Others 26.8%,completing the list of top implicated drugs in the study. Hyperpigmentation emerged as the most prevalent type of CADR, accounting for 26.3% of the reports, followed by rash (21.1%) and itching (18.4%) others 34.2%. The causality assessment of these reactions predominantly fell into 'probable/likely' (60%) and 'possible' (38%) categories, with a small fraction being 'certain' (2%).The severity of the reported adverse drug reactions was mostly mild, comprising 80% of the cases. The preventability assessment highlighted that 20% of the reactions were 'definitely preventable', with an additional 10% classified as 'probably preventable'. Departmental analysis showed that the Oncology department reported the highest number of ADRs (42.1%), closely followed by the ART Centre (21.1%). In terms of drug classes implicated in the reports, antineoplastics were the most common (36.8%), followed by antiretrovirals (31.6%), and antibiotics (21.1%). **Conclusion:** The study highlights the necessity for vigilant ADR monitoring and prevention strategies, especially for high-risk drugs. These findings contribute to enhancing drug safety and guiding clinicians in minimizing the risk of CADRs.

INTRODUCTION

Cutaneous adverse drug reactions (CADRs), also referred to as toxidermia, represent a significant area of concern in contemporary healthcare. They negatively impact patient well-being, elevate healthcare costs, and detrimentally affect overall quality of life.[1] These reactions manifest in a broad spectrum ranging from mild, transient rashes to severe, potentially fatal conditions such as Stevens-Johnson syndrome or toxic epidermal necrolysis.[2] The prompt identification and thorough assessment of CADRs are essential not only for effective patient management but also for enhancing drug safety and optimizing therapeutic outcomes.[3,4]

In the context of global health, the incidence and nature of CADRs can vary significantly, influenced by regional differences in genetic predispositions, prescribing patterns, and the prevalence of specific diseases.[5,6] Tirupati, a city renowned for its comprehensive healthcare facilities, is an exemplary location for the study of drug-related complications due to its extensive use of a wide range of

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pharmacological treatments. The Adverse Drug Reaction Monitoring Center in Tirupati, therefore, presents a unique vantage point to systematically analyze and understand the patterns, causality, severity, and preventability of CADRs in a specific regional healthcare setting.

The goal of this study is to meticulously evaluate the incidence and characteristics of CADRs that have been reported at this center. This evaluation involves an in-depth examination of the drugs most frequently associated with these adverse reactions, the specific types of reactions that patients experience, and a rigorous assessment of their causality and severity. To achieve this, the study employs well-established and globally recognized methodologies and scales, including the World Health Organization (WHO) and Naranjo causality assessment scales. These scales are instrumental in determining the likelihood of a drug causing an adverse reaction. Additionally, the severity of these reactions is quantified using the modified Hartwig and Siegel severity scale, which classifies the adverse reactions based on their impact on the patient's treatment and daily life.[7] Furthermore, the Schumock and Thornton preventability scale is utilized to evaluate the preventability of these reactions, which is crucial for developing strategies to mitigate these risks in clinical practice.

By providing a comprehensive analysis of CADRs in Tirupati, this study aims to contribute valuable knowledge into the regional patterns and risk factors associated with drug-induced skin reactions. The findings are anticipated to have significant implications for clinical practice, informing healthcare professionals about potential risks associated with certain medications and guiding them in making more informed prescribing decisions. Additionally, the study aims to influence policy-making by providing evidence-based recommendations for drug safety and pharmacovigilance programs, ultimately enhancing patient care and safety in the region.

MATERIALS AND METHODS

Study Design and Setting: The research was designed as a retrospective, observational study aimed at evaluating and analyzing Cutaneous Adverse Drug Reactions (CADRs) reported to the Adverse Drug Reaction (ADR) Monitoring Center. This comprehensive analysis took place at the ADR Monitoring Centre (AMC), which is an integral part of Sri Venkateswara Medical College (SVMC). Located in Tirupati, this center is affiliated with the Department of Pharmacology and extends its association to the Sri Venkateswara Ramnarain Ruia Government General Hospital. The study's design allows for a detailed examination of the incidence, nature, and implications of CADRs within this specific healthcare setting, offering valuable knowledge into the patterns and trends of drug-related cutaneous reactions.

Study Subjects and Period: The study inclusively covered all suspected adverse drug reaction forms that reported instances of toxidermia, received by the AMC at SVMC from December 2022 to November 2023. This period marks the duration of the study, retrospectively encompassing a full year to ensure a comprehensive collection of data. Requisite approvals were obtained from the institutional scientific and ethics committee, ensuring adherence to ethical standards and research protocols. The focus on a clearly defined timeframe and subject group allows for a precise and methodical approach to understanding the CADRs, thereby facilitating a thorough investigation into various aspects such as causality, severity, and preventability of these reactions.

Inclusion Criteria

The study included all suspected CADR reporting forms received at the ADR monitoring centre (AMC), SVMC, within the specified study period.

Exclusion Criteria

The study excluded ADRs that were not categorized as CADRs. Specifically, CADR forms that lacked mandatory fields as required by the Pharmacovigilance Programme of India (PvPI) – such as patient initials, age at onset of reaction, reaction term(s), date of onset of reaction, suspected medications, and reporter information – were not included in the study.

Study Methods

This retrospective observational study evaluated all CADRs reported spontaneously by healthcare professionals to the AMC at SVMC/SVRRGGH, as part of the Pharmacovigilance Programme of India. This included reports from peripheral hospitals. The ADRs were recorded in a pre-designed Suspected Adverse Drug Reaction Reporting form and were sent as Individual Case Safety Reports (ICSR) to the Indian database (Vigiflow®).

Evaluation of Data

A retrospective analysis was conducted on 190 spontaneous toxidermia reports. The reported ADR data were evaluated to understand the pattern of ADRs concerning patient demographics, the nature of reactions, and outcomes. Analyses of causality, severity, and preventability were conducted.

Analysis of ADRs

Causality: The causality of each ADR with the suspected drug was assessed using the WHO causality assessment scale.

Preventability: The modified Schumock and Thornton Criteria were utilized to categorize ADRs as definitely preventable, probably preventable, and not preventable.

Severity: The severity of ADRs was determined using the Modified Hartwig and Siegel Scale, which assists in classifying the severity of an ADR as mild (level 1, 2), moderate (level 3, 4a, 4b), or severe (level 5, 6, 7).

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Statistical Analysis

Descriptive analysis of the data was performed using Microsoft Excel. The results were expressed in numerical values and percentages, facilitating a comprehensive understanding of the patterns and implications of CADRs in the study population.

RESULTS

The comprehensive analysis at the Adverse Drug Reaction Monitoring Center in Tirupati focused on spontaneous reports of toxidermia attributed to various medications. This analysis spanned across different drug categories, with a particular emphasis on anticancer and antiretroviral medications due to their significant representation among the reports.

Distribution of CADR Reports by Various Drugs

The distribution of Chemotherapy-Associated Drug Reactions (CADRs) was extensively catalogued in Table No. 1. Capecitabine led the list with 30 instances (15.8%), followed closely by Doxorubicin with 25 reports (13.2%), and a combination therapy of Tenofovir, Lamivudine, and Dolutegravir with 20 instances (10.5%). Other notable medications included Imatinib (18 reports, 9.5%), Ribavirin (15 reports, 7.9%), Sofosbuvir (13 reports, 6.9%), Zidovudine (10 reports, 5.3%), and Acyclovir (8 reports, 4.2%)Others(51 reports,26.8%).

Types of Cutaneous Adverse Drug Reactions

Table No. 2 outlines the prevalence of specific types of cutaneous ADRs, with hyperpigmentation (50 reports, 26.3%) being the most frequently documented reaction, followed by rash (40 reports, 21.1%), and itching (35 reports, 18.4%).Others (65 reports, 34.2%).

Causality Assessment of ADRs

The causality assessment, detailed in Table No. 3, revealed that the majority of ADRs were classified as "Probable/Likely" (114 reactions, 60%), followed by "Possible" (72 reactions, 38%). A minimal fraction was identified as "Certain" (4 reactions, 2%).

Severity Assessment of ADRs

As depicted in Table No. 4, the severity of ADRs was predominantly mild (152 ADRs, 80%), with moderate (29 ADRs, 15%) and severe reactions (9 ADRs, 5%) being less common.

Preventability Assessment of ADRs

The preventability of ADRs, catalogued in Table No. 5, indicated that a portion of ADRs could be definitely (38 ADRs, 20%) or probably (19 ADRs, 10%) preventable, whereas the majority were deemed unpreventable (133 ADRs, 70%).

Actions Taken in Response to ADRs

In response to ADRs, the actions taken varied significantly, as reported in Table No. 6. Drug withdrawal was the most frequent action (95 cases, 50%), followed by the continuation of treatment without changes (66 cases, 35%), and dose reduction (29 cases, 15%).

Departmental and Drug Class Analysis

The departmental and drug class analyses, presented in Table No. 7, highlighted the primary sources of ADR reports. The Oncology department of a peripheral hospital was the largest contributor (80 reports, 42.1%), followed by the ART Centre (40 reports, 21.1%) and other departments. In terms of drug classes, antineoplastics (70 reports, 36.8%) and antiretrovirals (60 reports, 31.6%) were the most implicated, followed by antibiotics (40 reports, 21.1%) and analgesics (10 reports, 5.3%).

This comprehensive evaluation of toxidermia cases highlights the need for ongoing monitoring and the development of preventive strategies, particularly for drugs with a higher incidence of CADRs.

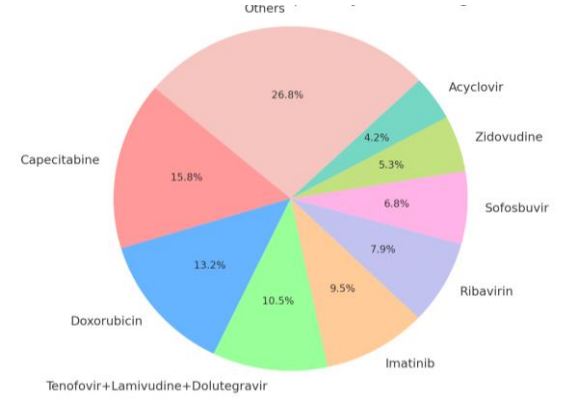

Figure 1: Distribution of CADR Reports by Various Drugs

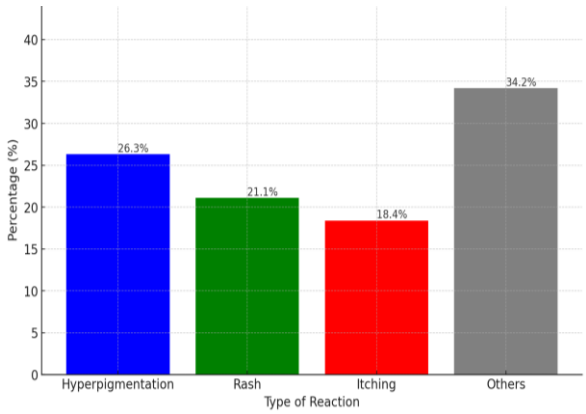

Figure 2: Types of Cutaneous Adverse Drug Reactions

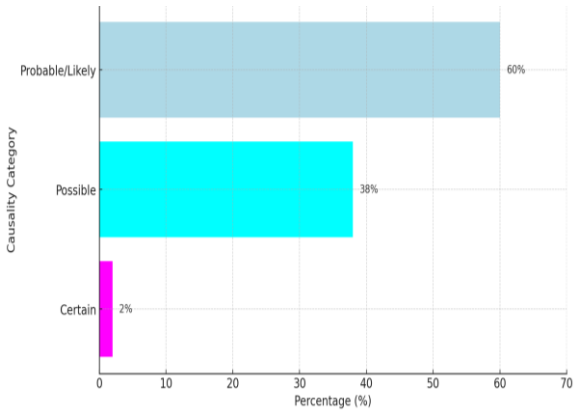

Figure 3: Causality Assessment of ADRs

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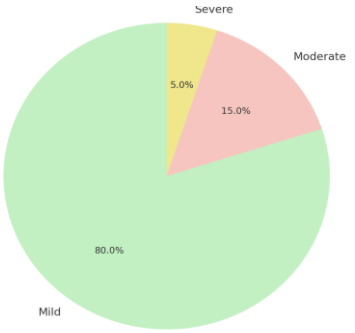

Figure 4: Severity Assessment of ADRs

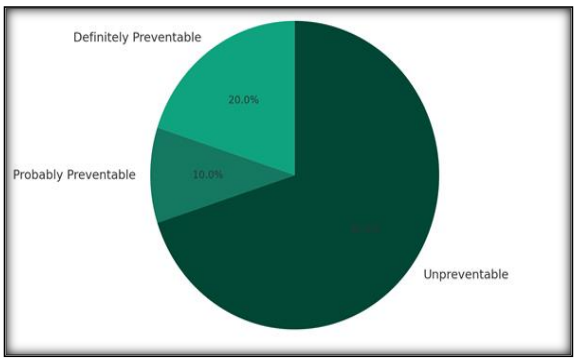

Figure 5: Preventability Assessment of ADRs

Table 1: Distribution of CADR Reports by Various Drugs

Drug	Number of Instances	Percentage of Total Reports
Capecitabine	30	15.8%
Doxorubicin	25	13.2%
Tenofovir+Lamivudine+Dolutegravir	20	10.5%
Imatinib	18	9.5%
Ribavirin	15	7.9%
Sofosbuvir	13	6.9%
Zidovudine	10	5.3%
Acyclovir	8	4.2%
Others	51	26.8%

Table 2: Types of Cutaneous Adverse Drug Reactions

Type of Reaction	Number of Reports	Percentage
Hyperpigmentation	50	26.3%
Rash	40	21.1%
Itching	35	18.4%
others	65	34.2%

Table 3: Causality Assessment of ADRs

Causality Category	Number of Reactions	Percentage
Probable/Likely	114	60%
Possible	72	38%
Certain	4	2%

Table 4: Severity Assessment of ADRs

Severity Level	Number of ADRs	Percentage
Mild	152	80%
Moderate	29	15%
Severe	9	5%

Table 5: Preventability Assessment of ADRs

Preventability	Number of ADRs	Percentage
Definitely Preventable	38	20%
Probably Preventable	19	10%
Unpreventable	133	70%

Table 6: Actions Taken in Response to ADRs

Action Taken	Number of Cases	Percentage
Drug Withdrawal	95	50%
Dose Reduced	29	15%
Treatment Continued	66	35%

Table 7: Departmental and Drug Class Analysis

Departmental Reporting

Department	Number of Reports	Percentage
Oncology (PERIPHERAL HOSPITAL)	80	42.1%
ART Centre	40	21.1%
Paediatrics	20	10.5%
General Medicine	15	7.9%
Others	35	18.4%

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Table 8: Drug Class Implication

Drug Class	Number of Reports	Percentage
Antineoplastics	70	36.8%
Antiretrovirals	60	31.6%
Antibiotics	40	21.1%
Analgesics	10	5.3%
Others	10	5.3%

DISCUSSION

The findings from this retrospective study on Cutaneous Adverse Drug Reactions (CADRs) at the Adverse Drug Reaction Monitoring Center in Tirupati provide critical knowledge into the patterns, causality, severity, and preventability of these reactions. The study identified capecitabine, doxorubicin, imitinab, ribavirin, sofosbuvir, zidovudin, acyclovir and the combination therapy of Tenofovir, Lamivudine, and Dolutegravir as the most frequently implicated drugs in CADRs. These findings are consistent with existing literature,[8,9,13] which indicates a higher incidence of CADRs with certain drug classes, particularly antineoplastics and antiretrovirals.

Hyperpigmentation, rash, and itching emerged as the most common manifestations of CADRs. This trend highlights the need for healthcare professionals to be vigilant about these symptoms, especially in patients undergoing treatment with the identified high-risk drugs.[10,11] The predominance of hyperpigmentation as a CADR could be indicative of regional or genetic factors influencing drug reactions, a hypothesis that warrants further investigation.

The causality assessment revealed that the majority of reactions were classified as 'probable/likely' or 'possible'. This highlights the challenges in establishing definitive causality in CADRs, a task compounded by factors such as polypharmacy, comorbidities, and individual patient factors. The application of WHO scales facilitated a structured approach to causality assessment, but the results also emphasize the inherent complexities in making these determinations.[12]

In terms of severity, most CADRs were found to be mild, with a smaller proportion being moderate or severe, and a few cases requiring hospitalization. This severity distribution is reassuring as it suggests that most CADRs can be managed effectively without leading to severe outcomes.[14] However, the instances requiring hospitalization remind us of the potential for serious health implications and the need for prompt recognition and management of CADRs.

The preventability assessment using the modified Schumock and Thornton Criteria indicated that a significant proportion of CADRs could have been prevented. This finding is critical for healthcare policy and practice, as it suggests that interventions to improve drug safety and prescribing practices could effectively reduce the incidence of CADRs.

The study's reliance on data from a single centre is both a strength and a limitation. While it provides an in-depth look at CADRs in a specific setting, the findings may not be generalizable to other regions or populations. Furthermore, the retrospective design limits the ability to establish temporal relationships and causality definitively.

CONCLUSION

This study contributes valuable information to the understanding of CADRs, highlighting key drugs and reaction types, and highlighting the importance of causality, severity, and preventability assessments. These findings should inform clinical practice, guiding healthcare professionals in monitoring for CADRs and implementing strategies to mitigate risk, especially in high-risk patient populations. Additionally, the study highlights the importance of ongoing pharmacovigilance and the need for robust systems to monitor, report, and analyze adverse drug reactions.

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