A Study of Cutaneous Adverse Drug Reactions; Clinical/Morphological Pattern & Causative Agents Reported in an ADR Monitoring Centre in a Tertiary Care Hospital of North Karnataka

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Cutaneous adverse drug reactions (CADRs) are common, comprise approximately 2-3% of all the ADRs. Most of them are mild, self-limiting. Severe and potentially life-threatening eruptions occur in approximately 1 in 1000 hospitalised patients. Which carry a high degree of morbidity & mortality. Hence early detection, evaluation and monitoring of ADRs in particular CADRs are essential. As the pattern of CADRs is changing every year with the introduction of new medications & evolving prescription practices. To determine the pattern of various types of CADRs & to identify causative drug implicated in our setup, this study was carried out. A retrospective analysis of the CADRs retrieved from the Pharmacovigilance centre database, reported spontaneously between 25thAug 2015 to 31stOct 2019. The CADRs obtained were categorized according to their morphology & the suspected drugs were grouped according to ATC classification. Causality, severity & preventability assessment was done by using pretested scales. 70 patients had CADRs with male to female ratio of 1:2. Urticaria (37.14%) was the most common CADR & 5.7% of the CADRs were severe. Anti-infectives for systemic use (48.6%) was predominantly involved in the causation of CADRs. Most of the CADRs belong to a possible category, 75% of them were either recovered or recovering at the time of reporting & only 25% of the CADRs are preventable. Pattern of ACDRs & the drugs causing them are slightly different in our population as compared to other previous studies. Which emphasizes the need for robust ADR monitoring system in our setup.

Keywords: Cutaneous adverse drug reactions, Pharmacovigilance, Urticaria.

Cutaneous Adverse Drug Reaction (CADR) is any undesirable change in the structure or function of the skin, its appendages or mucous membrane & encompasses all adverse events related to drug eruption, regardless of the aetiology. The prevalence of CADRs is about 0.16 to 1.35%, as most of the reactions are underreported. A study in Germany showed that up to 68.2% of physician who suspected an adverse drug reaction (ADR), did not actually report these events to the appropriate authorities. This may be due to the tendency to report only severe ADR cases. Cutaneous reactions are common, comprise approximately 2-3% of all the ADRs. Most of the CADRs are mild, self-limiting and usually resolve after the offending agent has
been discontinued. Severe and potentially life-threatening eruptions occur in approximately 1 in 1000 hospitalized patients & the mortality rates for Stevens-Johnson syndrome (SJS), Stevens-Johnson syndrome - Toxic Epidermal Necrolysis (SJS TEN) overlap, toxic epidermal necrolysis (TEN) & drug induced hypersensitivity syndrome (DIHS) are approximately 5–10%, 30%, 50% and 10% respectively.

Atopy, genetic variations in drug metabolism, HLA variation, comorbidities, underlying disease, active viral infection, immune status of the patient, and concomitant intake of other drugs can alter the rate, presentation, course, and the outcome of CADRs. Along with that, only about 50% of drug reactions can be detected in the premarketing trials. Hence early detection, evaluation and monitoring of ADRs, in particular, CADRs is essential in order to prevent the morbidity & mortality due to severe CADRs.

As the pattern of CADRs is changing every year with the introduction of new medications & evolving prescription practices, understanding its precise nature may help narrow down the search for the offending drug. To determine the pattern of various types of CADRs & to find out the causative drug(s) implicated or suspected in the causation of CADRs in our setup, this study was carried out.

MATERIALS AND METHODS

A retrospective analysis of the CADRs retrieved from the Pharmacovigilance centre (BMPMC) database, reported spontaneously by the Health Care Professional’s working in BLDE(DU)’s SBM Patil Medical College Hospital in Vijayapura. The suspected CADRs were diagnosed by either treating consultants or the dermatologist & the relevant details of each CADRs were collected in the spontaneous ADR reporting form designed by NCC (National Coordinating Center). After due completion, CADR details were entered into the Vigiflow. The PDF (Portable Document Format) of ICSR (Individual Case Safety Report) generated was also utilized for data entry. The data pertains to the period extending from 25th Aug 2015 to 31st Oct 2019, an Institutional Ethical Clearance was obtained before starting the study.

The CADRs gathered were categorized according to their morphology & the suspected drugs were grouped according to the Anatomical Therapeutic Chemical (ATC) classification of drugs. Causality assessment was done by using World Health Organization- Uppsala Monitoring Centre (WHO-UMC) causality assessment system, the severity was assessed by using the criterion developed by Hartwig et.al & the preventability was assessed by using Schumock-Thornton criteria. The data collected was analysed & inferences were drawn by using various statistical methods. SPSS Version 20 has been used for data entry & analysis.

RESULTS

A total of 70 patients had CADRs, out of
which 23 were males & 47 were females (Male to female ratio was 1:2). The mean age of patients suffering from CADRs was 35.71±19.87 years, minimum age of the patient who had CADR was 14 months & maximum was 95 years. The age range in which maximum CADRs were seen between 21-40 years.

**Table 1.** Showing distribution of various CADRs

| Type of CADR            | Frequency |
|-------------------------|-----------|
| Urticaria               | 26 (37.14%) |
| Maculopapular eruptions | 20 (28.57%) |
| SJS-TEN overlap         | 07 (10%)  |
| SJS                     | 05 (7.14%) |
| TEN                     | 03 (4.28%) |
| Alopecia                | 02 (2.85%) |
| Bullous Fixed Drug Eruptions (FDE) | 02 (2.85%) |
| Acute generalized exanthematous pustulosis (AGEP) | 01 (1.42%) |
| Lichenoid drug eruptions | 01 (1.42%) |
| Acneiform eruptions     | 01 (1.42%) |
| Petechial haemorrhages  | 01 (1.42%) |
| Skin atrophy            | 01 (1.42%) |

**Clinical/morphological presentation of CADRs**

The proportions of various CADRs are shown in Table 1. The most common CADR was urticaria, followed by maculopapular eruptions & the remaining morphological pattern were as shown in Table no.1.

15 patients had severe CADRs in the form of SJS, SJS-TEN overlap & TEN variants of epidermal necrolysis. Few representative cases are as shown below. Figure 1. Showing the lesions of a patient who had SJS-TEN overlap, following the ingestion of Tab. Ofloxacin 200 mg + Ornidazole 500 mg Injectable form of this fixed-dose combination (FDC) has been banned in India since 2017. Incidentally, the patient had similar complaints 2 years back, the details of the drug or the condition was not available with the patient. Figure 2, showing the Bullous fixed drug eruption following the ingestion of Tab. Amoxicillin 500 mg + Clavulanic acid 125 mg (Tab. Erox CV 625) & Figure 3, showing the urticarial rashes over the abdomen following infusion of Linezolid in a 13-year-old girl.

**Fig. 2.** Showing the dark coloured skin lesions with bullae over the right foot (Dorsum)

**Fig. 3.** Showing classical wheals of urticaria

**Causative drugs**

Nature of the drugs implicated in causing CADRs have been shown in Table no.2. According to that, Anti-infectives for systemic use was the predominant group involved in causation of CADRs as per the ATC classification.

Among the Anti-infectives for systemic use- 3rd generation cephalosporins (J01DD-4th level) mainly Ceftriaxone & Fluoroquinolones (J01MA), mainly Levofloxacin & FDC of Ofloxacin with Ornidazole were the most common culprits.

[14] 2 Patients also had CADR following ingestion...
Table 2. Showing different anatomical groups (Level 1 as per ATC) involved in causing CADRs

| ATC main group (1st level) | Frequency |
|----------------------------|-----------|
| Alimentary tract and metabolism | 8 (11.4%) |
| Blood and blood-forming organs | 4 (5.7%) |
| Cardiovascular system | 1 (1.4%) |
| Systemic hormonal preparations, excluding. | 1 (1.4%) |
| Sex hormones & Insulins | 1 (1.4%) |
| Anti-infectives for systemic use | 34 (48.6%) |
| Musculoskeletal system | 6 (8.6%) |
| Nervous system | 13 (18.6%) |
| Respiratory system | 01 (1.4%) |
| Various | 02 (2.9%) |

Causality assessment

According to the WHO-UMC causality assessment system, 48 (68.6%) CADRs were categorised as possible with regarding the suspected drugs & 21 (30%) were categorised as probable & only one was fulfilling the criteria of “Certain”.

Preventability & severity assessment

Among all the CADRs-only 25.71% of CADRs were preventable according to the Schumock-Thornton criteria & the remaining were not preventable.

According to the criterion developed by Hartwig et al., CADRs were classified as,

a) Mild – 30 cases (42.9%)

b) Moderate- 36 cases (51.4%)

c) Severe –4 cases (5.7%)

Although, SJS-TEN spectrum CADRs are considered as severe CADRs. But according to the criterion developed by Hartwig et al., only four patients required Intensive medical care. Hence, 11 cases here were categorically put into CADRs of moderate severity.

The outcome of CADRs

The outcome of CADRs were as shown in figure 4. 75% of the CADRs were either recovered or recovering at the time of reporting. Unfortunately, one patient had died because of Acute Myocardial Infarction, though it was a fatal outcome, not attributed to ADR.

DISCUSSION

The present study was carried to determine the pattern of CADRs in our setup; a total of 70
CADRs were reported during the study period. The mean age of patients suffering from CADRs was 35.71±19.87 years. The age range in which maximum CADRs were seen between 21-40 years. Which is in accordance with the study carried out by Pudukadan D et al15 & Dimri D et al16 In our study, there was female preponderance about the occurrence of CADRs. Which was similar to most of the previous studies, but opposite to the research carried out by Agrawal et al.

The most common CADR was Urticaria. Which accounted for 37.14% of all CADRs in our study. Which was in conformity with the survey by Al-Raaie et al17 & opposite to the study by Agrawal, et al. According to them, the most common CADR was FDE. The second most common CADR was Maculopapular rash or eruptions (28.57%), which was similar to the study carried out by Pudukadan D et al.& opposite to the research carried out by Janardhan B et al., according to them the Maculopapular eruptions were the most common CADR, followed by urticaria.18 This variation could be due to different patterns of drug usage and distinct ethnic group characteristics. Along with that, 15 (21.42%) patients had epidermal necrolysis variants. Which carry a high degree of morbidity, economic burden & mortality19

Anti-infectives for systemic use was the most common anatomical group, suspected to be involved in the causation of CADRs. Which was similar to the previous studies such as Jha N et al.& Sharma R et al.20 But, opposite to the research conducted by Al-Raaie et al. According to them nonsteroidal anti-inflammatory agents (NSAIDs)-M01A (3rd level, Pharmacological subgroup) OR Musculoskeletal system (Level 1, anatomical group-as per ATC classification), was predominantly involved in the causation of CADRs. Within Anti-infectives for systemic use, 3rd generation Cephalosporins (ATC code-J01DD) were incriminated in the causation of CADRs.21 Different patterns of drug usage in the populations studied can explain this variation. Also, we lack uniform quality of medications throughout India & availability of standard treatment guidelines.

The nervous system was the second most common group, incriminated in the causation of CADRs. Which was similar to a study carried out by Sharma VK et al.22 & opposite to the research carried out by Sharma S et al.23 & Modi A et al.24 According to the WHO-UMC causality assessment system, most of the CADRs were categorised as “Possible”, because the dechallenge was interrupted by the symptomatic treatment of CADRs. Rechallenge was not performed on the ethical ground; hence it was difficult to assign a category of “Certain”. Therefore, few of them were categorised as “Probable”. Among all the CADR’s -only ¼ (25.71%) of them were preventable, which was similar to the study carried out by Modi A et al. Most of the CADRs were mild to moderate in severity & only 4 (5.7%) patient had SCARs. Which was similar to the study carried out by Sharma R et al. 75% of the CADRs were either recovered or recovering at the time of reporting with or without symptomatic treatment & outcome was unknown in remaining patients. This was due to the lack of follow up. Limitation of this study was the sample size, maybe due to under-reporting & at times the patients will consult a general practitioner for an ADR, there is no way how we can track them

CONCLUSION

Pattern of ACDRs & the drugs causing them are slightly different in our population from others. May due to availability of even high-risk drugs without prescription & being an economically weak area, which makes them take medicines issued by the pharmacist or people working in a pharmacy. Which emphasises the need for more extensive ADR monitoring in our setup & it will be useful in generating our data. For physicians, it is always a challenge to weigh the benefits & risks of each therapeutic decision because there are no reliable tools for diagnosing ADRs. Further studies in this area are needed for early recognition & prevention of morbidity due to CADRs.

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