RESEARCH ARTICLE

Retrospective study on cutaneous adverse drug reactions in a tertiary care center

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Received: October 02, 2022; Accepted: October 26, 2022

ABSTRACT

Background: Cutaneous adverse drug reactions (CADRs) range from mild-to-severe types and occasionally can become fatal. Hence, these incur additional financial burden both to patients and community. Aim and Objective: The aim of the study was to describe the characteristics of CADRs reported to ADR monitoring center (AMC) of a tertiary care center. Materials and Methods: CADRs reported to the AMC over a period of 2 ½ years were retrospectively studied. This study mainly focused on affected age group, gender, various pattern of CADRs, the group and name of drugs causing CADRs, and severity and causality assessment. Results: CADRs contributed 31.6% of the total ADRs reported to the AMC. Among these, 51.7% were females and 40% were of 51–60 years age group. About 37.9% of CADRs were pruritus. Antibacterial drugs were the most common cause of CADRs and beta-lactam antibiotics were responsible for 30% of CADRs. Stevens Johnson syndrome (SJS) constituted 4.9% of CADRs and 20% of this was due to Paracetamol. Drugs were withdrawn in 89% of cases and 85% cases recovered. On causality assessment, 94% were of probable category. Conclusion: Pruritus was the most commonly observed CADR and antibacterial drugs were the most common cause. Beta lactam antibiotic was the most frequent antibacterial drug to cause CADRs. The most common serious CADR was SJS and Paracetamol was the most frequent culprit drug.

KEYWORDS: Cutaneous Adverse Drug Reaction; Causality Assessment; Pharmacovigilance; Stevens Johnson Syndrome

INTRODUCTION

Any unintended/undesirable reactions occurring on skin or mucus membrane due to drug administration are called cutaneous adverse drug reactions (CADRs). They comprise 2–3% of all ADRs. Introduction of new drugs in the market, various comorbid conditions, polypharmacy and availability of over-the-counter drugs increase the risk of both ADRs and CADRs. The common drugs causing CADRs are beta-lactam antibiotics, sulfonamides, non-steroidal anti-inflammatory drugs (NSAIDs), anti-epileptics, etc. Most frequently observed patterns of CADRs are maculopapular rash, urticaria, angioedema, fixed drug eruption (FDE), and erythema multiforme. Although these reactions are mild in severity to begin with, they can progress to be lethal and contributes significantly to the economic burden shouldered by the patients and the community. Erythroderma, drug reaction with eosinophilia and systemic symptoms (DRESS), and Stevens–Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) spectrum are categorized as such serious CADRs. Hence, a detailed knowledge about various patterns of CADRs, their extent of progression, prognosis, and the common culprit drugs is very much essential. This helps to
diagnose such CADRs very early and to start appropriate treatment. However, the prevalence and pattern of CADRs differ from country to country and this suggests the need for local data. Objective of this study was to describe the pattern of CADRs reported to an ADR monitoring center (AMC) in a tertiary care center and to find out the most common drugs implicated.

**MATERIALS AND METHODS**

This descriptive study was conducted in the department of pharmacology of a tertiary care center at central zone of Kerala which is a registered AMC under Indian Pharmacopoeia Commission (IPC) since 2012. Study sample is selected from the suspected ADR reported to the AMC from January 2019 to August 2021. As this study was a retrospective analysis of ADRs routinely reported to the center, Institutional Review Board clearance was not obtained. Permission from IPC to conduct the study was obtained. During this period, a total of 642 ADRs were reported to the center. Among these suspected ADR forms, those ADRs which described reactions affecting skin and mucus membrane were included in the study and categorized as CADRs. Details in each form such as age, gender, pattern of CADR, drug causing the reaction and the group to which the drug belong, seriousness, action taken, outcome, and causality assessment were entered in a structured proforma. Causality assessment was done using the World Health Organization Uppsala Monitoring Centre (WHO-UMC) scale. All data were entered in MS Excel. Descriptive analysis was done using SPSS 16 software to estimate the result.

**RESULTS**

This study analyzed the CADRs reported to the AMC. The total ADRs reported to the center during the study period were 642. Out of these, 203 (31.6%) cases were CADRs. Among these, 51.7% (n = 105) were females. The maximally affected age group (n = 41, 40%) was 51–60 years and the least affected age group was 0–10 years (n = 7, 5%).

The patterns of reactions reported and their proportion were pruritus (37.9%), rashes (27%), erythema (21%), urticaria (5.4%), SJS (4.9%), angioedema (1.4%), mucositis (0.5%), hyperpigmented lesion (0.5%), mucocutaneous syndrome (0.5%), oral candidiasis (0.5%), and photosensitivity (0.5%).

Major drug groups causing CADRs were antibacterial drugs (56.65%), NSAIDs (11.3%), antiepileptics (8.4%), and antiemetics (4.4%). Among the antibacterial drugs, beta-lactam antibiotics caused 30% of CADRs followed by quinolones (9.8%) and anti-tubercular therapy-fixed dose combination (ATT-FDC) (6%). Ceftriaxone caused 7.4% (n = 15) of CADRs among beta-lactams. Ciprofloxacin was the main drug among quinolones to cause 6.4% (n = 13) of CADRs. Cefoperazone + Sulbactam and Piperacillin + Tazobactam caused 5.4% (n = 11), 4.9% (n = 10) of CADRs, respectively. Vancomycin caused 3.9% (n = 8) of CADRs. Paracetamol caused 3.4% (n = 7) of CADRs among NSAIDs. Among the antiepileptics, phenytoin caused 6.9% (n = 14) of CADRs. Among the antiemetics, 4% (n = 9) of CADRs were due to Ondansetron. The various drugs causing pruritus are depicted in Figure 1. The drugs causing rashes are described in Figure 2. The proportion of serious reactions was 7%. SJS, angioedema and mucocutaneous syndrome were the reported serious types of CADRs. The drugs implicated in SJS were due to Enalapril, Levodopa + Carbidopa and Ciprofloxacin.

There was one case of mucocutaneous syndrome due to Ciprofloxacin. The suspected drug was withdrawn (dechallenged) in 89% of cases and the dose of the drug was reduced in 5% of cases. About 85% of the reactions were recovered and the rest (15%) were in the recovery phase at the time of reporting. Causality assessment of 94% cases was probable, 4% was possible, and 1% was certain.

**DISCUSSION**

CADRs were seen more frequently among females in this study. Fifty–60 years age group was the maximally affected followed by 60–70 years. Various patterns of CADRs were observed in this study. But certain types such as FDEs, erythema multiform, and DRESS were not reported during the study period. The most common group of drugs implicated in this study was antibacterial drugs. Among the antibacterial drugs beta-lactam antibiotics were the most common group. Ceftriaxone was the most common beta-lactam antibiotic to cause CADRs. Rashes, erythema, and pruritus were the common CADRs associated with Ceftriaxone and none of these reactions were serious. The combination of beta-lactam with beta-lactamase inhibitors (Cefoperazone + sulbactum, Piperacillin + Sulbactum) caused various patterns of CADRs and even one case of SJS was reported with Amoxicillin + Clavulanic acid. Ciprofloxacin which belongs to the fluoroquinolone group was the second most common drug and caused almost all patterns of CADRs including the serious types. No serious CADRs were reported with ATT-FDC which was the third most common type and predominantly caused pruritus and rashes. No information was obtained on rechallenge with individual anti-TB drugs and hence the exact culprit drug was not identified. The most frequent drug causing CADRs among antiepileptic, antiemetic, and NSAIDs were Phenytoin, Ondansetron, and Paracetamol, respectively. Pruritus was the most common CADR encountered in this study and none of the reactions were chronic in nature. Ciprofloxacin was the most commonly implicated drug for pruritus. Rash was the second common type of CADR and Phenytoin was the commonly implicated drug. Serious type of reactions reported were SJS, angioedema, and mucocutaneous syndrome. Ciprofloxacin was found to cause all these three serious reactions. Paracetamol was the most frequent drug to cause SJS. Other drugs causing SJS were Phenytoin,
Amoxicillin+Clavulanic acid, Ciprofloxacin, Sulfasalazine, Allopurinol, Piroxicam, Erythromycin, and Fluconazole. Ciprofloxacin, Levodopa + Carbidopa and Enalapril caused angioedema. Suspected drug was withdrawn for majority of the reactions and almost all reactions were recovered following that. On causality assessment by the WHO-UMC scale, most of the reactions were grouped in the “Probable” category. As per this, almost all suspected drugs in this study were assumed to be the probable causes and CADRs were not due to progression of the associated disease.

Females generally are more at risk of developing ADRs. Predominance of CADRs among female population is due to their pharmacokinetic, pharmacodynamic, hormonal peculiarities, and their frequent medication use compared to males. Immunological mechanisms play a key role in CADRs. Gender variation in T cell activity and higher prevalence of skin diseases such as systemic lupus erythematosus and photosensitivity contribute to higher incidence of CADRs among females. Various comorbidities, polypharmacy, impaired hepatic and renal function, variability in pharmacokinetics account for the higher frequency of ADRs among extreme age group. However, in another study, geriatric age group was not the most commonly affected and this might be due to the caution by prescribers in this age
group. Antibacterial drugs were the most common cause of CADRs reported in the studies done in other parts of the country too. High incidence of hypersensitivity reaction are associated with beta-lactam antibiotics due to the beta-lactam ring. This can also be attributed to over prescribing of beta-lactams due to their wide spectra and safety. Ceftriaxone was the most common beta-lactam antibiotic to cause CADR. Cephalosporins can precipitate IgE mediated fatal reactions in some individuals. However, there were no such reactions associated with ceftriaxone in this study. Quinolones were one of the common causes CADRs done in other studies. It can affect gastrointestinal system, musculoskeletal system, nervous system apart from skin, and mucus membrane. It is a cause of concern that quinolones also are involved in various ADRs as they are often chosen as an alternative to beta-lactam antibiotics. Phenytoin is a commonly used anti-epileptic and is associated with various kinds of ADRs including CADRs as seen in this study. Arene oxide metabolite of phenytoin is probably the cause of CADR including rash. Female gender, contraceptive use, and faster metabolism of Phenytoin may lead to the formation of excess arene oxide. CADRs are not very frequently associated with Ondansetron. Pruritus which was the most common pattern reported in this study can have multiple etiological mechanisms. Apart from drugs and dermatological conditions, systemic diseases also can cause pruritus. Elaborate laboratory check-ups and other diagnostic measures are required to rule out other causes. Drug induced pruritus can be acute or chronic lasting more than 6 weeks especially if associated with drug induced cholestasis. It is a generalized itch without skin manifestation. As per Tripathy et al. study, Quinolone were one of the most common causes of CADR and found to account for many cases of FDE. Quinolones are known to cause both IgE and T cell mediated hypersensitivity reactions. As per Kasyp et al. study, TEN, SJS, FDE, acute generalized pustulosis, and DRESS were the reactions seen with Ciprofloxacin. SJS is a fatal CADR affecting skin and mucus membrane. Multiple drugs cause SJS and the sulfonamides are the most frequent. As per electronic data bases, 6.17% of cases of SJS are due to Paracetamol. Paracetamol though considered to be safe and frequently prescribed is associated with various patterns of hypersensitivity reactions. Another serious type of CADR in this study was angioedema which is one of the criteria of diagnosing anaphylaxis. Blockers of Renin angiotensin aldosterone system such as Enalapril are mostly the culprit drugs to cause angioedema. Malignant melanoma and peripheral edema are seen to be associated with Levodopa+Carbidopa and angioedema is rare. Causality assessment of ADRs is based on temporal relationship, previous knowledge, results of dechallenge, and rechallenge. This is very relevant as many etiological factors can produce the same cutaneous reaction. This aids to identify the role of drugs to cause ADRs.

Limitation of this study was that many of the ADR forms were incomplete. The details of concomitant drugs were missing in many forms and thus the role of drug interaction could not be studied. This study did not represent the CADR data of the whole patients in the tertiary care center due to underreporting. However, this study is one of its kind analyzing CADRs in this tertiary care center.

CONCLUSION

CADRs constituted around 32% of the total ADRs reported to the tertiary care center. Beta-lactam antibiotics were the most common group of drugs causing CADRs. Pruritus was the frequently reported CADR followed by rash. Serious type of CADR reported was SJS and Paracetamol was the commonly implicated drug. Most of these reactions subsided when the suspect drugs were dechallenged. Beta-lactam antibiotics and Paracetamol are the frequently prescribed drugs and this explains partly their high frequency of association with CADRs. However, this also throws light on the need of concern on safety of such routinely prescribed drugs and requirement of more intense pharmacovigilance monitoring on them.


How to cite this article: George TC, Panattil P, Jom D, Sreedharan S, Palappallil DS. Retrospective study on cutaneous adverse drug reactions in a tertiary care center. Natl J Physiol Pharm Pharmacol 2023;13(05):1098-1102.

Source of Support: Nil, Conflicts of Interest: None declared.