REVIEW ARTICLE

Patterns of Cutaneous Drug Reactions: A Review

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Abstract

Introduction: A cutaneous adverse drug reaction (CADR) is defined as any undesirable cutaneous clinical manifestation resulting from administration of a particular drug. The CADRs are a common problem in our country and can range from simple rash to severe reactions. Early recognition of CADRs enables early identification and withdrawal of offending drugs, thereby reducing morbidity and mortality. This article is a review of the patterns of presentation of CADR and common causative drugs in our country.

Materials and methods: Literature search was performed across PubMed Central and Google Scholar search engine using key words like adverse cutaneous drug reaction, adverse cutaneous drug reaction, India, and articles selected.

Results: The most common drug groups causing CADR in our country are antimicrobials, anticonvulsants and nonsteroidal anti-inflammatory drugs (NSAIDs), and antigout agents. Common presentations of CADR are in the form of exanthematous skin eruptions, urticaria, fixed drug eruption (FDE), contact dermatitis, angioedema, Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), and various morphologic permutations and combinations.

Conclusion: A CADR is a common problem and an economic burden to our healthcare. The presentation of CADR and the drugs causing CADR have a geographic variation in our country. Understanding common causative drugs, the presentation of CADR can help in early diagnosis, identification, and withdrawal of the culprit drug resulting in early recovery and preventing complications of CADR.

Keywords: Adverse cutaneous drug reaction, Cutaneous reactions, Severe cutaneous drug reactions.

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Introduction

The most common presentation of an adverse drug reaction (ADR) is a cutaneous adverse drug reaction (CADR). A CADR is defined as any undesirable change in the structure or function of the skin, its appendages, or mucous membranes caused by a drug, and it encompasses all adverse events related to drug eruption, regardless of the etiology.[1,2] The CADR can be as mild and transient or severe, requiring hospitalization leading to morbidity and occasional mortality. The CADRs are seen in 10 to 45% of ADRs, and approximately 2–3% of hospital admissions are due to CADR.[3,4] A systematic review on CADR in Indian population revealed a pooled incidence of 9.22/1,000 total among inpatients and outpatients.[5] Most of the CADRs are mild, self-limiting, and resolve on discontinuation of the culprit drug, approximately 2% of these CADRs are severe in nature, potentially life-threatening, and sometimes ending in fatalities.[4]

Till date, the diagnosis of CADR is purely clinical. Most drug eruptions are reversible and self-limiting on withdrawal of the causative drug. Prompt diagnosis, early recognition, and discontinuation of the causative drug with symptomatic treatment and corticosteroid therapy/antihistamines can lead to early recovery and complication-free outcome. It will also help in significantly reducing the economic burden caused by ADR on the healthcare of our country.

Materials and Methods

Literature search was conducted after using the key search words of adverse cutaneous drug reaction, adverse cutaneous drug reaction, India, in combinations from PubMed Central and Google Scholar search engines. Time period was not considered, and of the 176 articles found, around 100 articles were not accessible. The results of rest of the articles have been complied and analyzed, and inferences were made.

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Causative Drugs

The most common drug groups causing CADR are antimicrobials, anticonvulsants and NSAIDs, and anti-gout agents.[5] Other less common drugs leading to CADR are antidepressants, antipsychotics, oral contraceptives, radio contrasts, antihypertensives, antidiabetics, insulin, vaccines, pancreatic enzyme supplements, and homeopathic and ayurvedic preparations.[6] Antimicrobials are the commonest group causing CADRs. Among antimicrobials, sulfa drugs (cotrimoxazole), β-lactams (penicillin and cephalosporins), fluoroquinolones, nitro-imidazole, and antitubercular drugs were common offending. Severe CADR is commonly noted with carbamazepine and phenytoin, while non-severe CADR is commonly seen with sulfa or β-lactam antimicrobials. All antiepileptics are associated with a high frequency of CADRs.[5] Antihistamines, local anesthetics, digoxin, steroid hormones, acetylsalicylic acid, acetaminophen, and coumarins are very rarely associated with CADR.[7]

The most common drugs causing CADR in our country are antimicrobials followed by analgesic/anti-inflammatory drugs and antiepileptics as reported by Dhar,[8] Patel et al.,[5] Jha et al.,[3] and Pudukadan and Thappa.[9] In a systematic review in Indian patients done by Patel et al.,[5] sulfa drugs and β-lactams are commonest drugs followed by carbamazepine, fluoroquinolones, and ibuprofen. In a study by Pudukadan and Thappa[9] from a tertiary care center in South India, the commonest drugs causing CADR are cotrimoxazole followed by dapsone, phenytoin, and carbamazepine. The regional variation in prescription of drugs can be a reason for the mild variation in the drugs causing CADR.

According to a systematic review on SJS and TEN in Indian population by Patel et al.,[10] antimicrobials and antiepileptics are the commonest drugs causing severe cutaneous adverse reaction (SCAR). Carbamazepine, phenytoin, fluoroquinolones, and paracetamol were the most commonly implicated drugs. Patients treated with polypharmacy are the most common association.

Presentation

The CADR can be classified according to its clinical presentation as a mild or benign form and severe CADR. The benign forms are usually self-limiting and are the commonest presentation of CADR. The most common presentation of CADR is a maculopapular rash (MPR). However, FDEs, urticaria, angioedema, and contact dermatitis are other common presentations. The morphological presentation of CADR has a geographic variation across India due to different ethnic group characteristics and region-specific endemic diseases requiring different patterns of drug usage.[1] The severe and life-threatening presentation of CADRs are TEN, SJS, drug hypersensitivity reaction (DHR) or drug reaction with eosinophilia and systemic symptom (DRESS) or drug-induced hypersensitivity syndrome (DIHS), and acute generalized exanthematous pustulosis (AGEP).

The likelihood of CADR is higher in women than in men.[1] A female preponderance of patients presenting with CADR in our country is noted in most studies as reported by Nandha et al.,[11] Farshchian et al.,[12] Dimri et al.,[13] Singh et al.,[14] and Pudukadan and Thappa.[9] However, a male preponderance is also seen in a few studies on CADR as reported by Sharma et al.,[15] Thakkar et al.,[16] and Patel et al.[5]

The incidence of CADR is higher in elderly patients, boys younger than 3 years, and girls older than 9 years of age. Most studies on CADR reveal 21–30 years as the commonest age group as reported by Sowmyanarayan et al.[17] and Nandha et al.,[11] with average age ranging between 20 years and 40 years in most studies.

The incidence of CADR increased with multiple drug intake, and these drug interactions can also result in CADR.[18] There is an increased risk of drug rash in the presence of viral infections. Topical and intramuscular routes of drug administration have an increased risk, but lesser with intravenous route, and oral route is considered the safest.[19]

According to a systematic review by Patel et al.,[5] benign CADRs are seen in 91.87% cases, while SCARs were seen in 8.17% cases. In a study by Pudukadan and Thappa,[9] the incidence of benign CADR and SCAR is noted to be 79% and 21% cases, respectively.

Benign CADR

The most common benign CADR is MPR followed by FDE and urticarial. Other common CADRs in this category include angioedema and contact dermatitis.

MPR

Maculopapular exanthems or morbilliform eruptions account for 95% of all CADR cases.[18] Approximately 2% of hospitalized patients are reported to have them.[7,18,20] These exanthematous drug eruptions can also present as eczematoid-, psoriasiform-, or lichenoid-like patterns. In some cases, the central parts of the trunk are spared, and the rash appears mainly in large body folds (perigenital, perianal, and intertriginous) and is called symmetrical drug-related intertriginous and flexural exanthema (or also known as Baboon syndrome). Aminopenicillins are the most common causative drugs; however, other drugs have also been associated with it.[21]

A study by Patel et al.[5] reveals exanthematous eruption, mainly MPR as the most common presentation followed by FDE and urticaria.

FDE

The pathognomonic feature of FDE is the recurrence of lesions at the same site on reexposure of the causative drug. New erupting lesions rarely present elsewhere. The common sites for FDE are lips, trunk, palms, groin, glans penis, and soles. The lesions typically appear 30 minutes to 8 hours post drug exposure, and it is often preceded or accompanied by itching and/or burning sensation. Fixed drug eruption usually resolves with persistent hyperpigmentation on withdrawal of the culprit drug. Extensive lesions in FDE may be associated with systemic symptoms of malaise, nausea, fever, and arthralgia.[22–25] Oral route of administration is more likely to cause FDE than parenteral administration. The most common drugs causing FDE are antibiotics (mainly sulfonamides and tetracyclines), analgesics (ibuprofen, acetylsalicylic acid, etc.), antifungals, and antipsychotics.

In the study by Pudukadan and Thappa,[9] FDE is the commonest presentation of benign CADR followed by exanthematous eruptions (MPR) and urticaria.

Urticaria

Urticaria usually appears within minutes of ingesting the culprit drug and presents as itchy, erythematous wheals. They resolve within 24 hours without leaving any trace. Nonsteroidal anti-inflammatory drugs and antibiotics are the most common drugs causing urticaria. Withdrawal of the offending drug and antihistaminic medication are the mainstay of treatment.[26]

SCARs

Over 200 drugs are known to cause SCARs in literature. SCARs account to only 2% of CADRs and are responsible for majority of the morbidity and mortality associated with SCARs.

Studies by Bushra et al.[27] and Patel et al.[10] reveal a mortality rate of 1.1% among patients with CADR and 12.94% among patients with SCAR.

SJS and TEN

Stevens–Johnson syndrome and TEN are severe medical emergencies with mortality rate of 1–5% for SJS and 25–35% for patients with TEN. It is drug induced in half to two-thirds of all cases and should be differentiated from erythema multiforme (EM) major. The drug association in SJS appears underestimated due to the difficulty in clinically differentiating between SJS and EM.

The incidence of SJS and TEN is 1.9 cases per million per year.[28,29] The incidence is affected by differences in drug prescription

as per region, genetic makeup of patients (human leukocyte antigen and metabolizing enzymes), concomitant radiotherapy, certain infectious diseases (human immunodeficiency virus), and coexistence of cancer.[30,31] According to the literature, approximately 100 drugs have been identified as triggers for SJS and TEN cases. The most common drugs being allopurinol, antibiotics, NSAIDs, and anticonvulsants.[32]

Current evidence suggests that SJS and TEN (SJS/TEN) should no longer be classified as separate clinical entities as they both belong to severe epidermolytic adverse reactions differing only by the extent of skin detachment, however SJS has to be differentiated from erythema multiforme (EM) major.[33] Cutaneous hyper- and hypopigmentation (62.5% cases), ocular complications (50% cases), and nail dystrophia (37.5% cases) are common sequelae in SJS and TEN.[34,35]

DHRs

They affect only a minority of patients, are unpredictable, do not show any relationship to dose, and cannot be reproduced in animal models.[36]

AGEP

It is among the less severe forms of SCAR. It has an incidence of 1–5 cases/million/year and presents as an acute febrile illness with rapidly progressing generalized pustular eruptions at a short interval between drug administration and the onset of disease.[37] The presence of eosinophils in the inflammatory infiltrate points toward a drug cause. The common drugs causing AGEP are antibiotics (ampicillin, amoxicillin, sulfonamides, macrolides, and fluoroquinolones); hydroxychloroquine; diltiazem; terbinafine; and, to a lesser extent, the oxicam family of NSAIDs, corticosteroids, and antiepileptics (except valproic acid). Viral infections like parvovirus are known to cause it.[38]

DRESS

Drug reaction with eosinophilia and systemic symptom, also known as DIHS or hypersensitivity syndrome, is a rare life-threatening SCAR with systemic involvement, affecting multiple organs. Only a limited number of drugs are known to cause it.[33] The systemic symptoms often lead to erroneous diagnosis of leukemia and includes lymphadenopathy (involves cervical, axillary, and inguinal regions in over 70% cases), hepatitis (in approximately 80% cases), lungs (in approximately 15% cases), kidney (interstitial nephritis), heart (myocarditis or pericarditis), pancreatic involvement, and hematologic abnormalities (i.e., thrombocytopenia, leukocytosis, eosinophilia, and atypical lymphocytosis).[39] The rash is preceded by fever by 1–2 days.

Conclusion

Cutaneous drug eruptions are the common and easily identifiable clinical presentation of ADR. The CADR can be as mild and transient or severe, requiring hospitalization leading to morbidity and occasional mortality. Early diagnosis and treatment requires a vigilant mind and knowledge of common drugs causing CADR and their presentations. This article highlights the common drugs causing CADR and the pattern of presentation of CADR in our country.

The presentation of CADR and the drugs causing CADR have a geographic variation. In our country, CADR is commonly caused by antimicrobials, mainly β-lactams, fluoroquinolones, and sulfa drugs. Antiepileptics and NSAIDs are other common drugs causing CADR. Most CADRs are benign and resolve just by withdrawal of the drug. Exanthematous eruptions (MPR) are the commonest presentation of CADR followed by FDE, urticaria, and angioedema. The SCARs are commonly seen with polypharmacy and are associated with antiepileptics. Stevens–Johnson syndrome/SJS-TEN and TEN are the most common presentations. Among SCARs, TEN can be associated with mortality.

Ethical Clearance

Institute ethical clearance has been taken.

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