Adverse Cutaneous Drug Reaction

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Abstract
Drug-induced skin disease or cutaneous adverse drug reaction (CADR) is a term encompassing clinical manifestations of the skin, induced by drugs or their metabolites. The skin is the organ most commonly affected by drug reactions, affecting up to 10% of hospitalized patients and can occur in 1–3% of her polypharmacy patients. Most CADRs are mild or self-resolving conditions. The most frequently reported are macular papular rash, urticaria/angioedema, fixed drug eruption and erythema multiforme. Less common but more severe patterns include, drug reactions with eosinophilia and systemic symptoms, and the Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum. Almost any drug can induce CADR, but antibiotics (especially sulfa drugs), nonsteroidal anti-inflammatory drugs, and antiepileptic drugs are most commonly implicated. Various mechanisms are involved in the pathogenesis of CADR, some of which are still unknown. Which may be immune mediated or non-immune mediated. Recognition of a specific CADR depends primarily on the physician's ability to perform a detailed clinical examination, an accurate description of the skin lesion morphology, and corroboration of laboratory and/or skin biopsy findings.

Introduction
Cutaneous adverse drug reactions (CADR), also known as toxidermia, are cutaneous manifestations resulting from systemic drug administration. These reactions range from mild erythematous skin lesions to more severe reactions such as Lyell’s syndrome. The skin is the most commonly affected organ for drug reactions, affecting up to 10% of hospitalized patients and can occur in 1-3% of polypharmaceutical patients. Most CADRs are mild or self-resolving conditions. However, 2-6.7% of cases may develop into a potentially life-threatening condition. CADR can be difficult to diagnose as it represents a heterogeneous area and can mimic any skin disease. Currently, 29 to 35 different cutaneous drug reaction patterns have been reported in patients with mild dermatitis to extensive burns [1]. SCAR can manifest in a variety of ways, the most common being Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), followed by Drug reaction with eosinophilia and systemic symptoms (DRESS) and Acute Generalized Exanthematous Pustulosis (AGEP). Antibiotics are the drugs most commonly associated with SCAR, followed by antiepileptic drugs (AEDs), allopurinol, and nonsteroidal anti-inflammatory drugs (NSAIDs) [2]. In addition to clinical and non-clinical factors, genetic mutations greatly influence the development of SCAR [3].

Drug reactions can be classified into immunologic and nonimmunologic etiologies (see Table 1). Predictable, non-immunologic effects cause the majority (75-80%) of adverse drug reactions, the remaining 20-25% of adverse drug events are caused by unpredictable effects that may or may not be immune-mediated. [4] Immune-mediated reactions account for 5-10% of all drug reactions and constitute drug allergies falling into this category [5].
Another classification is the Gel and Coombs classification system, which describes the predominant immune mechanisms leading to clinical manifestations of drug hypersensitivity. However, some drug hypersensitivity reactions are difficult to classify due to lack of evidence for a prevailing immunological mechanism. These include certain cutaneous drug reactions (i.e. maculopapular rashes, erythema, exfoliative dermatitis and fixed drug reactions) and specific drug hypersensitivity syndromes [6,7].

Genetic Factors and Cutaneous Drug Reactions
Genetic determinants may predispose individuals to severe drug reactions by affecting either drug metabolism or immune responses to drugs. Polymorphisms in cytochrome P450 enzymes, drug acetylation, methylation (such as thiopurine methyltransferase activity and azathioprine) and other metabolic forms (such as glucose-6-phosphate dehydrogenase) can increase susceptibility to drug toxicity or overdose. Have different pharmacokinetic or pharmacodynamic roles. Pharmacodynamics effect [8].

Associations between drug hypersensitivities and HLA haplotypes also suggest a key role for immune mechanisms. Hypersensitivity to the anti-HIV medication abacavir is strongly associated with HLA-B*57:01. In Taiwan, within a homogeneous Han Chinese population, a 100% association was observed between SJS/TEN (but not DIHS) related to carbamazepine and HLA-B*15:02. In the same population, another 100% association was found between SJS, TEN, or DIHS related to allopurinol and HLA-B*58:01. These associations are drug and phenotype specific; that is, HLA-specific T cell stimulation by medications leads to distinct reactions and may explain why the reaction patterns are so clinically diverse. However, the strong associations found in Taiwan have not been observed in other countries with more heterogeneous populations [9].

Causative drug
The most common group of drugs that cause CADR are antibiotics. Anticonvulsants, NSAIDs, antigout drugs [10]. Common drugs that lead to CADR are antidepressants, antipsychotics, oral contraceptives, radiographic agents, antihypertensive agents, antidiabetic drugs, insulin, vaccines. Is an antibiotic the most common group that causes CADR. Sulfa among antibacterial agents’ rags (cotrimoxazole), beta-lactams (penicillin and cephalosporins), fluoroquinolones, nitroimidazoles and antituberculosis drugs, local anesthetics, digoxin, steroid hormones [11]. Acetylsalicylic acid, paracetamol and coumarin are very rare it is related to CADR [12].

Methods
To construct the essay, both personal paper books and international online databases were employed. Keywords like "skin ADR," "severe drug responses," and "lyell or steven-johnson syndrome" connected with specific substance names were Entered. We concentrated on papers from recent times and only covered serious ADR.

Literature Review
This study is investigating the prevalence, clinical features, causes, and mortality rate of ACDR (an allergic reaction to a certain type of skin) among patients who attend the Department of Dermatology and Venereology at Dr. Sardjito Hospital in Yogyakarta in Indonesia. This study looked at medical records from the past five years. Of the 68,375 patients who were treated in the Department of Dermatology and Venereology, 397 of them were diagnosed with ACDR, which is a type IV hypersensitivity reaction. The doctor
gathered information about the patient’s age, sex, past medical history, and family history of drug reactions. The patch testing was done in as many places as possible. The study found that out of 68,375 patients, 397 patients had a type-IV hypersensitivity reaction, which resulted in a 5% mortality rate. The average age of the patients was 40.42 years (±16.30). Some patients were 18 to 89 years old. The female to male ratio was 1.1:1. The most common ACDR symptoms were a Maculopapular rash (50.88%) followed by Stevens-Johnson Syndrome (13.85%), Fixed Drug Eruption (12.85%), and Drug Reaction with Eosinophilia and Systemic Symptoms (10.08%). The most common reasons for sickness were antibiotics (16.55%), NSAIDs (12.18%), and acetaminophen (8.62%) [13].

Diabetes is a common and complex disease affecting multiple organ systems throughout the body, people with diabetes worldwide have been placed on medication regimens targeting glucose stability from a variety of pathophysiologic pathways. Each of these medications also possesses its own potential for adverse events. In recent years, there has been increased reports of skin reactions to diabetes medications, adding to the more widely known eruptions such as insulin-induced lipohypertrophy and contact dermatitis of subcutaneous injections. As a result, a total of 59 papers are included in this review. The great majority were case reports ranging from benign fixed drug eruptions to severe cutaneous reactions that threaten patients’ lives. Increasing physician awareness of both the potential for and presentation of, such reactions to diabetes medications can reduce hospitalizations and optimize care in an already vulnerable patient population [14].

**Results**

The most frequently reported are maculopapular rash, urticaria/angioedema, fixed drug eruption and erythema multiforme. Less common but more severe patterns include erythroderma, drug reaction with eosinophilia and systemic symptoms, and Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum. Almost any drug can induce a CADR, but antibiotics, nonsteroidal anti-inflammatory drugs and antiepileptics are the most frequently involved. Different mechanisms are involved in the pathogenesis of CADRs. CDRs could be classified in different ways: (i) type A (augmented) or type B (bizarre); (ii) immediate or delayed; (iii) immune-mediated or nonimmune-mediated; (iv) nonsevere or life threatening; and (v) by their phenotype, including exanthematous, urticarial, pustular and blistering morphology. Recognizing a specific CADR will mostly depend on the ability of the physician to perform a detailed clinical examination, the proper description of the morphology of the skin lesions and supporting laboratory and/or skin biopsy findings [15].

In another study Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalized exanthematous pustulosis are examples of severe Cutaneous adverse medication reactions, this outbreak which are from of delayed hypersensitivity reaction can be a fatal. Thorough clinical history and examination are needed for the assessment of severe cutaneous drug reaction in order to determine the offending drug and assess the allergy. Antibiotics, anticonvulsants, and allopurinol are frequently mentioned. The maculopapular exanthema or morbilliform drug eruption is the most Frequent benign cutaneous drug reaction [16].

A reaction known as the fixed- drug eruption is characterized by clearly defined, reddish-brown lesions that may burn or itch. On subsequent exposure to the drug, these lesions could return in the Same area on reexposure to drugs [17].

Evaluating drug causality in severe cutaneous adverse responses can be difficult since patients frequently take multiple medications [18].

The initial evaluation is creating a drug timeline from the patient’s history and conducting a thorough review of all medications used in the six to Eight weeks before to the reaction. The usual culprits are anticonvulsant for DRESS, antifungal and antibiotic for acute generalized exanthematous pustulosis, allopurinol for Stevens-Johnson syndrome. [19] In addition, study was carried out at Pakistan Aga Khan University Hospital and is descriptive cross-sectional study. Patients who met the study inclusion requirement were included in one hundred ninety—three cases. Following the receipt of informed consent, data were gathered from Patients using a preform. While qualitative factors were provided as frequency and percentages, Quantitative data were presented as simple descriptive statistics with mean and standard deviation [20]. To emphasize their impact on the outcome variable, effect modifiers were controlled by stratification.

The post-stratification chi-square test was used and statistically significant was set at 0.05. The most frequent reaction seen in 135 patients (69.9%) was a maculopapular eruption. Out of those, 50 (37%) patients experienced drug reactions after 24 hours, whereas 85 (63%) patients experienced reactions in less than 24 hours.
Twenty-one (20.4%) cases of erythema multiform (EM), fifty (24.9%) cases of acniform eruption, twenty (10.4%) cases of urticaria, eleven (5.7%) cases of fixed drug reaction, and six (3.1%) cases of toxic epidermal necrolysis (TEN); 75% of patients with urticaria, EM, and SJS had CADRs in 1 day as opposed to FDE, which showed the reaction in >1 day in 45.5% [21].

A total of 258 patients were enrolled in the study. The most common CADR observed in the study was exanthematous drug eruption in 42.63% patients followed by drug induced urticaria in 21.32% patients. Antimicrobials were the most common offending drugs in 64.73% of patients, followed by non-steroidal anti-inflammatory drugs (NSAIDs) in 15.50% patients. In the study, 12 patients (4.65%) were found to have severe cutaneous adverse drug reactions (SCADRs) [22]. Stevens–Johnson syndrome (SJS) - Toxic epidermal necrolysis (TEN) was the most common SCADR (50%) and antituberculous drugs were the most common causative group of drugs causing SCADRs [22].

Male: female ratio was 1.32:1. Maximum number of patients were in the age group of 20–40 years (32.94%).

Overall, 5.43% of patients developed fever, 2.33% had abdominal pain, and 7.36% had dyspnea after the intake of the causative drug. Fifty-eight patients (22.48%) with CADR recollected taking same drug or drug of the same group previously. Thirty-two patients (12.40%) had personal or family history of atopy. No significant association with underlying comorbidities was found [23].

The most common CADR observed was exanthematous drug eruption in 110 patients (42.63%), followed by drug induced urticaria in 55 patients (21.32%) and FDE in 24 (9.30%). Antimicrobials (64.73%) were the most common offending drugs followed by NSAIDs (15.50%) and antiepileptics (7.36%). Among the antimicrobials, cephalosporins were the most common (16.67%), followed by fluoroquinolones (8.91%) and carbapenems (7.75%).

Fluoroquinolones were responsible for causing CADRs in 23 patients (8.91%). Of the 23 cases, 18 (78.26%) were caused by first generation fluoroquinolones (ciprofloxacin, norfloxacin, and ofloxacin) and the remaining 5 (21.74%) were caused by newer generation fluoroquinolones (levofloxacin mainly). The most common drug group causing exanthemata's drug eruption was cephalosporin (22.73%), followed by carbapenems (17.27%), antiepileptics (11.82%), and beta lactamase inhibitors (11.82%).

Drug-induced urticaria was the second most common drug eruption noted in the study. Most common drug causing urticaria noticed was cephalosporin (27.27%), followed by NSAIDs (23.64%) and fluoroquinolones (14.54%). P value (for drugs causing urticaria) was found to be statistically significant (<0.05) for cephalosporins only. 8.14% of patients having urticarial or exanthematous rash had history of atopy.

The third most common drug eruption in the study was FDE. Most common drug causing FDE was NSAIDs (33.33%), followed by fluoroquinolones (29.17%) and nitroimidazoles (16.67%). P value (for drugs causing FDE) was found to be statistically significant (<0.05) for NSAIDs, fluoroquinolones, and nitroimidazoles. Mucosal involvement was seen in 27.52% patients Causality assessment was done by Naranjo adverse drug reaction probability scale. Definite drug rash was seen in (30.62%) and probable drug rash in 69.38% patients. Patients suspected to have possible drug rash were not included in the study [24].

The skin is the most frequent target organ of ADRs, which represent 18-20% of the reports reported in the WHO database. Rashes and urticaria are the most frequent clinical patterns, usually of moderate severity, while rare (on the order of a few cases per million population) are ADRs associated with significant mortality and morbidity rates such as stevens syndrome. –Johnson. TEN (toxic epidermal necrolysis) and DRESS (drug rash with eosinophilia and systemic symptoms) The clinical manifestations of cutaneous ADRs can derive both from the contact between the skin of a sensitized subject and the topical medicament (these are cases of allergic contact dermatitis or irritant contact dermatitis, with local reactions at the site of application and usually not serious) or by the development of more severe systemic hypersensitivity phenomena [25].

A total of 78 patients with CADRs was reported, while the total number of patients attending the dermatology clinic during the study period was 27,093 patients. The primary incidence of reported CADRs in our study was 0.28%. They included 78 patients, 29 men (37.1%) and 49 women (62.8%) with a male to female ratio of 1:1.69. Ages ranged from 18-80 years of age with a mean of 41.7±14.84 years (mean ± SD). A comparison of the demographic parameters in both severe CADRs and other non-severe types of CADRs regarding sex, age, education, occupation, and total number of patients showed no statistically significant difference (P-value >0.05) [26].
A retrospective hospital-based study was carried out at the Department of Dermatology, Sexually Transmitted Diseases and Clinical Immunology at the University of Warmia and Mazury in Olsztyn, Poland, over a period of 10 years (January 2012 to January 2022). [30]. CADRs were diagnosed in a total of 140 patients, 45 (32.14%) of whom were men and 95 (67.86%) were women. The mean age of the patients was 66.33 years (minimal 12 years, maximal 96 years). The majority of the patients were in the age group of 70 years.

The observed CADR included MPR 23.57%, DIHS 37.14%, drug-induced urticaria 12.86%, erythema dyschomicum perstans 9.29%, erythema multiforme 5.00%, AGEP 2.86%, post-drug phototoxic and photoallergic reactions 2.86%, SDRIFE 2.86%, SJS 2.14%, and drug-induced vasculitis 1.43%. The most commonly suspected drugs were Amoxicillin with clavulanic acid 10%, Amoxicillin 9.29%, Paracetamol 6.43%, Metronidazole 5%, and Carbamazepine 5%. Both Amoxicillin with clavulanic acid 10% and Amoxicillin 9.29% were suspected of causing CADRs.

A prospective hospital-based study over a period of one year (October 1, 2002 to September 30, 2003) was carried out by the Department of Pharmacology in the Department of Dermatology of St. John’s Medical College Hospital [31]. A total of 56 patients diagnosed with cutaneous ADR were included in the study. Only drugs with a clear probable causal relationship to response were considered for analysis. One reaction was clearly causally related, but 45 patients fell into the possible related category. The most common ADR type was macular papular rash (35%), followed by toxic epidermal necrolysis (TEN) (20%) and Stevens-Johnson syndrome (SJS) (15%). Drugs associated with his ADR in the skin were antiepileptic drugs (AEDs) commonly used in epilepsy outpatients in southern China from 2003 to 2015. purpose [29]. A total of 3069 epilepsy outpatients were included (1807 outpatients with 5049 eligible ADRs and 1262 outpatients without ADR). His ADR rate overall he was 58.88% (1807/3069). An average of 2.79 of his ADRs (5049/1807) occurred per ADR patient. Of the 5049 ADRs, 53.8% were reported in women and 50.4% were caused by monotherapy. Serious adverse reactions (SARs) accounted for 10.6% (537/5049) of ADRs, including 34 serious adverse reactions (SAEs). The SAR rates induced by 1, 2, and 3 or more AEDs were 9.9, 10.0, and 19.6%, respectively (p<0.001). Eighteen SOC categories were identified, the top three being psychiatric disorders (1633/5049, 32.3%), neurological disorders (1222/5049, 24.2%) and gastrointestinal disorders (564/5049, 11.2%). Of the 537 suspicious activity reports, 24.4% (131/537) were related to skin and hand/foot diseases. Of the 34 SAEs, severe allergies, fetal malformations, kidney stones, and pancreatitis accounted for the majority.
which takes several weeks the subside gradually but may be more severe form such as Toxic Epidermal Necrolysis and Steven Johnson syndrome which required specific protocol, for treatment.

Urticarial rash in another form of drug reaction due to excessive release of histamine and other mediators from skin mast cell. After rash appearance exclude alternative cause such as infection especially viral and onset of rash after taking new drugs and note any improvement after discontinuance of drugs

Antibiotic is the most common drug taken without prescription and is most common cause of adverse cutaneous drug reaction especially sulfa drugs such as sulfonamides sand sulfonylurea oral hypoglycemic drugs.

In addition to antiepileptic and NSAIDs.

**Conclusion**

The most frequently identified clinical form was exanthema, and antibiotics and anticonvulsants were the most frequently involved drug classes. Cutaneous drug reactions are frequent in clinical practice, and the dermatologist should be called in as soon as possible to assist in the diagnosis and management of these cases.

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