

Cutaneous Adverse Drug Reactions in a Tertiary Care Teaching Hospital in India: An Intensive Monitoring Study

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Abstract

Background:

The epidemiological data based on intensive monitoring studies are limited for the cutaneous adverse drug reactions (CADRs) in terms of incidence. Most of earlier Indian studies focused only on types and causative drugs of CADRs.

Aim:

The aim of this study is to analyze the CADRs with reference to the incidence, its subgroup analysis, causative drugs, and other clinical characteristics in Indian population.

Methodology:

Intensive monitoring study was carried out over a period of 3 years in the dermatology outpatient and inpatient department. CADRs due to only systematically administered drugs were considered. The WHO definition for CADR, the WHO causality definitions, modified Schumock and Thornton's criteria for preventability, and International Conference on Harmonisation E2A guidelines for seriousness were considered. Incidence was expressed in percentage and its 95% confidence interval. The incidence was analyzed on basis of characteristics of study population and CADRs.

Results:

A total of 171 CADRs were observed from 37,623 patients. The CADR incidence was 0.45% (95% CI: 0.39–0.53). The incidence did not significantly differ in different age groups and gender. Commonly observed CADRs were maculopapular rash (23.98%), urticaria (21.64%), and fixed drug eruptions (FDEs) (18.13%). Antimicrobials (35.18%) and nonsteroidal anti-inflammatory drugs (NSAIDs) were suspected in all common CADRs. Anti-infective and NSAIDs were most commonly suspected drugs in overall CADRs, maculopapular rash, urticaria, FDEs, and erythema multiforme. The exact nature of drugs remained inaccessible in one-fourth cases due to use of the over-the-counter self-medications. The incidence of preventable and serious and fatal CADRs was 0.08% (95% CI: 0.05–0.11), 0.04% (95% CI: 0.02–0.06), and 0.003% (95% CI: 0.000–0.001), respectively.

Conclusion:

Ethnic characteristics should be considered while interpreting incidence from the international studies. The demographic characteristics of study population do not affect the incidence of CADR. Indian patients should be sensitized about hazards of self-medications.

Keywords: *Causative drugs, cutaneous adverse drug reactions, incidence*

What was known?

Cutaneous adverse drug reactions (CADRs) are one of the most common types of adverse drug reactions. The common CADRs are maculopapular rash, fixed drug eruptions, and urticaria. The drugs causing CADRs could vary according to prescribing patterns.

Introduction

Cutaneous reactions are one of the most common types of adverse drug reactions (ADRs).[1] Cutaneous ADRs (CADRs) may vary from mildly discomforting to those that are life-threatening.[2] They affect the patient in the form of prolonging or requiring hospitalization, systemic complications, mortality, and economic burden.[3,4] The disability such as blindness as a consequence of severe CADR could affect employment and quality of life.[5] The commonly reported CADRs are maculopapular rash, fixed drug eruptions (FDEs), and urticaria.[4] The wide range of pharmacology group of drugs can cause CADRs and its patterns could change due to different prescribing patterns, use of newer drugs, self-medications, and referral bias.[6,7]

The Pharmacovigilance Programme of India was launched in 2010, and it operates through spontaneous reporting system to monitor ADRs. There are several advantages of this system in terms of being less cumbersome, generation of early safety signals about newer drugs, and identification of serious as well as rare ADRs.[8] However, it is less reliable to estimate incidence and other clinical characteristics due to under-reporting. Prospective intensive monitoring can overcome these drawbacks and is also an important tool to identify the pattern and causative drugs of CADRs. The studies conducted in this field from India are scarce. Hence, this study was undertaken at a tertiary care teaching hospital of Western India to assess the incidence, pattern, and clinical characteristics of CADRs.

Methodology

This prospective, observational, intensive monitoring study based on outdoor and indoor patients was started after the approval from the Institutional Human Ethics Committee. All information collected during study was kept confidential and oral informed consent was obtained from the patients before collecting the data. The study was conducted from October 2012 to September 2015 (3 years) at the department of dermatology, a 600-bedded tertiary care teaching hospital in Western India.

Identification of cutaneous adverse drug reactions and suspected drugs The WHO definition of ADR – “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function” – was considered.[9] Active surveillance method was followed to identify CADRs, and all patients attending dermatology outpatient unit as well as admitted in the inpatient unit, referred to dermatology unit, with findings suggestive of CADRs were assessed. CADRs were identified with patient interview, history of drug intake before the development of ADRs, clinical examination, review of case records, and dechallenge (effect of drug withdrawal on reaction). Rechallenge (re-introduction of suspected drug on improvement) was avoided for the ethical reasons. However, information about accidental rechallenge whenever available was used to identify suspected drugs. CADRs due to the systematically administered drugs were only included in the study; CADRs from locally applied drugs were excluded from the study. All patients were followed up till the recovery of CADR. The follow-up was also done in patients who have not brought the prescription or record of drug(s) taken before the development of the reactions.

Data collection A pro forma was used to collect data of demography, diagnosis, investigations, adverse

reactions, their clinical morphology, causative drugs with dosage, route, frequency, and duration of administration, lag period to develop reaction (period between administration of drugs and appearance of lesions), its treatment and cost, outcome, severity, and concomitant medications. Anatomical therapeutic chemical classification system was used to code the causative drugs.[10]

Assessment of cutaneous adverse drug reactions The WHO causality definitions were used to assess drug – CADR pair. It classifies ADRs into “certain,” “probable,” “possible,” “unlikely,” “unclassified,” or “unclassifiable” causality based on the time sequence of events, dechallenge, rechallenge, and alternative explanation to reactions provided by other concomitant drugs or underlying disease.[11] The preventability of CADR was assessed according to Schumock and Thornton’s criteria modified by Lau *et al.*[12] It categorizes ADRs into “definitely preventable,” “probably preventable,” and “not preventable” based on the presence or absence of one or more of the predisposing factors. The definitely preventable reactions include those with known drug allergy or previous reactions, suspected drug inappropriate for the patient’s clinical condition or disease state, toxic serum drug concentration or laboratory monitoring test, and a known treatment for the adverse drug reaction. The “probably preventable” reactions include those associated with lack of required laboratory tests, due to drug interaction, poor compliance, and lack of preventive measures. Otherwise, reaction is classified as a “not preventable.” Two pharmacologists performed the causality and preventability assessment. Any disagreements were resolved through consensus and consultation with dermatologists. The dermatologists assessed the seriousness of reactions as per the International Conference on Harmonisation (ICH) E2A guidelines which classify serious reactions as those that result in death are life-threatening and require hospitalization or prolongation of hospitalization, results in disability/incapacity, or a congenital anomaly.[13]

Outcome measures and statistical considerations Data were entered into Microsoft excel sheet. Two investigators cross-checked the data entry to ensure accuracy. The primary outcome variable was incidence of CADR. An Excel sheet was used to estimate incidence in percentage and its 95% confidence interval (CI). Incidence was estimated with number of patients with CADR as numerator and total number of outpatients and inpatients in dermatology department as denominator. Subgroup analysis of incidence based on characteristics of study population (age groups, genders) and CADR (individual types, preventable, serious, and fatal) was also performed. The patients of <12 years old were considered as pediatric based on ICH E11 guideline of clinical investigation of medicinal products in pediatric population[14] and >65 years old as elderly population based on ICH E7 (R1) guideline of studies in support of geriatric population.[15] Chi-square test was used to compare incidence in different subgroups.

The secondary outcome variables were pattern of CADR (their types, presenting features, lag period, and site of involvement), causative drugs and their pharmacological groups, outcome, causality, preventability, and seriousness. A subgroup analysis of causative drugs for common CADR was performed.

$P < 0.05$ was considered as statistically significant difference. GraphPad Prism 6.0 demo version (GraphPad Software, Inc., La Jolla, CA 92037 USA) was used to apply statistical test.

Results

Characteristics of the patients During the study period, a total of 37,623 patients (male- 20,899; female- 16,724) attended the dermatology outpatient department. A total of 171 CADR were observed in 170 patients (male - 89; female - 81). Male-to-female ratio was 1.10. The youngest CADR patient was 1 year old and the eldest was 75 years old. The average number of drugs used (suspected drug [SD]) was 2.46 (1.69). It ranged from 1 to 9.

Incidence of cutaneous adverse drug reactions As shown in [Table 1](#), the overall incidence of CADR was 0.45% (95% CI: 0.39–0.53). There was no significant difference in the incidence of CADR between male and female patients ($P = 0.44$; Chi-square test) as well as among different age groups ($P = 0.41$; Chi-square test).

Pattern of cutaneous adverse drug reactions A total of 21 different CADR were observed. As shown in [Table 2](#), the most commonly observed CADR were maculopapular rash, urticaria, and FDEs in both outdoor and indoor patients. Their incidence ranged from 1.09 to 0.82/1000 patients. There was no

significant difference in incidence among maculopapular rash, urticaria, and FDEs ($P = 0.50$; Chi-square test). The lag period of CADR varied from ½ h to 7 months. The median lag period in maculopapular rash, urticaria, and FDEs was 3, 2, and 1 day, respectively. The angioedema and acneiform eruption showed shortest and longest lag period, respectively.

As shown in [Figure 1](#), the most common presenting symptoms of CADR were itching, burning sensation, and pigmentation. The most commonly involved sites in CADR were trunk and extremities (35.09%), upper limb (26.90%), and face (20.47%).

Causative drugs A total of 240 drugs were suspected in 170 cases (1.41 drugs per patient). The average (SD) number of drugs was 1.52(0.80). It ranged from 1 to 4. The oral and parenteral drugs were involved in 92.08% and 7.90% of cases, respectively. Causative drugs of CADR are presented in [Table 3](#). The common causative agents were of anti-infective, musculoskeletal, and nervous system class in both outdoor and indoor patients. Commonly suspected antimicrobial pharmacology groups were fluoroquinolones and penicillins in outdoor and indoor patients. Commonly suspected nonsteroidal anti-inflammatory drug (NSAIDs) were diclofenac and ibuprofen in outdoor patients while diclofenac and indomethacin in indoor patients.

Single drug was culprit in 110 cases. Anti-infective and musculoskeletal drugs were observed as a single causative agent in 27 (24.54%) and 20 (15.45%) cases, respectively, among which fluoroquinolones (8 cases) and diclofenac (6 cases) were most common. Subgroup analysis of causative drugs was performed in case of maculopapular rashes, urticaria, FDEs, and erythema multiforme (EM) [[Table 4](#)]. Anti-infective and musculoskeletal drugs were the most common causative pharmacological groups in all CADR. NSAIDs were suspected in one-fifth of maculopapular rashes, urticaria, and FDEs. Anti-infective drugs were suspected in almost one-third of maculopapular rashes and FDEs cases and in half of the EM cases [[Figure 2](#)]. Fluoroquinolones were the most common anti-infective agents to cause urticaria and FDEs while penicillins lead to maculopapular rashes. Nitroimidazoles caused maculopapular rash, urticaria, and FDEs in similar frequency. Chloroquine mainly caused maculopapular rash. NSAIDs were found to cause maculopapular rashes, FDEs, and urticaria in almost one-fourth of cases. Antiepileptic drugs were mainly to cause maculopapular rashes.

Dechallenge and rechallenge Dechallenge (suspected drug withdrawal) was performed in 159 (93.58%) patients. It was positive (improvement in CADR) in 122 patients (71.35%). The lesions of FDEs were static/recovering in 29 cases at the time of last assessment. A total of 9 patients were lost to follow-up after dechallenge. No deliberate rechallenge was attempted to diagnose CADR. However, the department of pulmonary medicine performed rechallenge in two cases of category 1 antitubercular drugs induced EM to identify safer drugs. Rechallenge was positive for rifampicin and ethambutol one in each case. Accidental rechallenge occurred in a patient with a history of previous anaphylactic reaction with ibuprofen and paracetamol where the patient took paracetamol for fever as over-the-counter (OTC) medication and developed the same reaction again. In another case, a patient with a history of pruritus with amoxicillin + clavulanic acid took the same drug and developed the same reaction.

Causality assessment of cutaneous adverse drug reactions As per the WHO causality assessment definitions, the distributions of “certain,” “probable,” and “possible” categories were 2.92, 35.08, and 38.01, percentage respectively. The exact nature of drugs remained inaccessible in 39 (24.56%) cases – “unclassifiable” causality. The patients took OTC medications in such cases and produced only loose medications on next visit [[Figure 3](#)]. The reasons to use OTC medications were fever, common cold, diarrhea, upper respiratory tract infections, and joint pain. They were categorized as “unclassified” causality. These patients were educated about avoiding medications without the prescription and physicians’ monitoring in future.

Preventable cutaneous adverse drug reactions A total of 29 (16.95%) CADR were considered preventable. All preventable CADR belonged to definitely preventable category. Incidence of preventable CADR was 0.08% (95% CI: 0.05–0.11). The reasons of preventable CADR were inappropriate use of drugs for the patient’s clinical condition (12.86%) and ignorance of the history of previous allergic reactions (4.09%).

Morbidity and mortality of cutaneous adverse drug reactions A total of 14 (8.19%) out of 171 reactions were considered serious. Incidence of serious and fatal CADR was 0.04% (95% CI: 0.02–0.06) and 0.003% (95% CI: 0.000–0.001), respectively. The reasons of serious CADR were requirement of hospitalization/prolongation of hospitalization (6.43%), life-threatening (1.17%), and death (0.58%). Serious CADR were EM (4), Stevens–Johnson syndrome (SJS) (3), maculopapular rash (3), bullous FDEs (1), anaphylactic reaction (1), drug reaction with eosinophilia and systemic symptoms (DRESS) (1), and dapsone syndrome (1). Dapsone syndrome patient died of septicemia with uncontrolled diabetes mellitus [Figure 4].

Management of cutaneous adverse drug reactions CADR required the withdrawal of suspected drugs in 160 (93.61%) cases. Almost 4 out of the 5 patients were treated with antihistaminic [Figure 5]. The frequently used antihistaminic was chlorpheniramine maleate followed by levocetirizine. Almost one-third of the patients were treated with oral steroid and calamine lotion. The most commonly used oral steroid was prednisolone. Patients were followed up till the recovery of CADR. The follow-up was also done in patients who have not brought the prescription or record of drug(s) taken before the development of the reactions. Once identified the drug responsible for CADR, patients were given a drug card mentioning the name of drug which had caused this reaction, and also, a list of drug, which can cause such reactions in future, should be taken under doctors' guidance only.

Discussion

This study analyzed the incidence, pattern, causative drugs, and other characteristics of CADR. Many studies were conducted on CADR in India with primary objectives to describe pattern and causative drugs of CADR.[3,7,16,17,18] Subgroup analysis of maculopapular rashes, FDEs, and urticaria was performed to identify the pattern of causative drugs. Earlier Indian studies interpreted the influence of demography of CADR in a descriptive way. The impact of CADR on Indian population was assessed in terms of incidence through intensive monitoring over a period of 3 years.

The observed incidence (0.45%) was lower than previous Denmark study (1.38%).[19] This is in accordance with the finding of larger studies showing lower incidence of ADRs.[20,21] Choon and Lai observed the incidence of 0.86% over a period of 10 years in a tertiary care center of Malaysia. In subgroup analysis, they found that Indian origin patients (0.35%) had significantly lower rate of CADR than Malay (0.89%) and Chinese (1.07%) patients.[22] This suggests need to consider ethnic characteristics of study population while interpreting the incidence of CADR. Based on literature review, Svensson *et al.* suggested that the incidence of CADR to range from 1% to 3% among hospitalized patients.[2] The incidence in the present study represents both ambulatory and hospitalized patients.

There was no significant difference between males and females in developing CADR. The literature suggests both preponderance of male[7,18,23,24] and female[1,3,5] association with CADR. The present study supports Choon and Lai that descriptive analysis shows conflicting results (either male or female preponderance) in the absence of gender-based comparison of the CADR incidence.[22] The females, in comparison to males, have more body fat, lower organ size, and low glomerular filtration rate. These differences can affect the pharmacodynamics and pharmacokinetics of the drugs.[25] However, these changes are more important for the augmented type of the reactions that are dependent on the pharmacological actions of the drugs than allergic cutaneous reactions. High prevalence of ADRs has been found in elderly than nonelderly age groups in various systematic reviews.[20,21,26] The present study indicates that age groups do not modify the incidence of allergic cutaneous reactions. This could also be due to less importance of age-related pharmacokinetic- and pharmacodynamic-mediated changes in the intensity of pharmacological response in case of allergic CADR. Earlier Indian study showing drug utilization on elderly patients has reported that most commonly prescribed drugs are for alimentary tract and metabolism, blood and blood-forming organs, and cardiovascular system.[27] Other Indian studies reported antihypertensive, antidiabetic, and antiplatelet agents as most commonly used drugs in elderly patients.[28] These drugs mainly cause augmented type reactions (hypotension, hypoglycemia, and bleeding) in the elderly population. Literature suggests that they are not common agents to cause CADR.[3,7,16,17,18] There was low frequency of CADR due to these drugs in the present study

also.[3,7,16,17,18] Hence, unlike augmented type reactions, elderly populations are not at excess risk of CADR and showed a comparable incidence than nonelderly age groups.

The maculopapular rash, urticaria, and FDEs together represented 6 out of 10 CADR in our study which is in line with previous Indian systematic review.[4] The previous Indian studies reported maculopapular rash[7,16,29] and FDEs[3,17,18] as the most common CADR. There was no significant difference in the incidence rate of maculopapular rash, FDEs, and urticaria. The literature variation could be due to their descriptive nature of interpretation. However, Malaysian studies reported maculopapular rash and SJS as common CADR.[6,22] This could be due to HLA-B*1502-related carbamazepine-and phenytoin-induced CADR in Malaysian studies.[6,22] SJS was relatively rare in this study. This is in accordance with the Choon and Lai subgroup analysis of study population based on ethnic origin. The proportions of carbamazepine-induced CADR in Malay, Chinese, and Indian patients were 74.2%, 22.6%, and 3.2%, respectively.[22] The FDEs are also reported rarely with roughly 1 case/year/hospital in European literature.[30] The incidence difference among different populations could be due to variation in patterns of drug usage and ethnic characteristics.

Anti-infective and NSAIDs are commonly suspected groups which are in accordance with the earlier studies.[7,16,18] Other studies reported anti-infective and antiepileptic drugs as commonly suspected groups.[3,6,22] Among anti-infective drugs, CADR due to fluoroquinolones were more frequently than cotrimoxazole[1,3,6,7] and penicillins[5,22,24] in contrast to earlier studies. Among NSAIDs, diclofenac was the most frequent culprit as compared to aspirin[1,3] and mefenamic acid[22] in earlier studies. This could be due to the widespread use of fluoroquinolones and diclofenac in our setup.

In line with earlier studies, anti-infective drugs caused all patterns of CADR.[1,7,29] Anti-infective drugs caused 3 out of 10 cases of maculopapular rash and FDEs and 7 out of 10 cases of EM. Individual anti-infective groups showed specific pattern of CADR. The fluoroquinolones commonly caused urticaria and FDEs while penicillins mainly caused the maculopapular rash. Fluoroquinolones, penicillins, and sulfa drugs are equally involved to cause EM. The earlier study reported sulfonamides as the most common culprit antimicrobials to cause maculopapular rash and FDEs while penicillins to cause urticaria.[7] Antiepileptic drugs were mainly suspected to cause maculopapular rash.

Causative drugs remained inaccessible in almost one-fourth cases due to use of OTC self-medications. This is in line with 29% of inaccessible drugs to cause CADR in earlier Indian study.[29] The indications of drug use suggest possibility of NSAIDs, fixed dose combinations of cough preparations, and antibiotics in such cases. The regulatory authority needs to sensitize the patients about the possible hazards of self-medications. It should restrict the dispensing of OTC medications through community pharmacists and involve them to monitor ADR in India.

Almost 2 out of 10 CADR were classified as preventable that is in accordance with the previous studies.[5,24] The main reason of preventable reaction was inappropriate drug use as per patient's clinical condition against the ignorance of the past reactions with the similar drugs in the Western studies.[5,24]

We observed 1 out of 10 reactions as serious. Earlier French study observed 1 out of 3 reactions as serious.[24] This difference could be due to the inpatient setting and high frequency of DRESS and erythroderma in the French study. However, we observed similar pattern of seriousness in the form of requirement of hospitalization/prolongation of hospitalization followed by life-threatening.[24] Literature suggests that fatal CADR occur in 0.1% of clinical and 0.01% of surgery patients.[31] The observed lower fatal CADR incidence (0.003%) could be due to ambulatory and inpatient setting of this study.

The management of CADR is mainly supportive and withdrawal of suspected agents. Antihistamines are commonly used to alleviate pruritus. Mild topical steroids and moisturizing lotions are helpful during the late desquamative phase.[32] The CADR require hospitalization in case of severe reactions such as SJS/toxic epidermal necrolysis and DRESS. The suspected drugs were withdrawn in 93.58% of cases.

Conclusion

Ethnic characteristics should be considered while interpreting the incidence and pattern of CADR. Our

study observed lower incidence than other Asian and European studies. Age and gender do not affect the incidence of CADR in our population. Data of this study confirm the earlier studies about the pattern of common CADR and their incriminated drugs. Almost one-fourth of CADR remained inaccessible about causative drugs. There is a need to sensitize the patients about hazards of self-medications. Large-scale multicentric Indian study is recommended to confirm the findings of this study.

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Conflicts of interest There are no conflicts of interest.

What is new?

Ethnic characteristics of study population affect the incidence and pattern of cutaneous adverse drug reactions (CADRs). Sizable proportion of CADRs occurs due to over-the-counter drugs. Indian patients should be sensitized about hazards of self-medications.

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Figures and Tables

Table 1

Variable	Populations	Number of CADR patients	Incidence (95% CI) %
Overall	37,623	170	0.45 (0.39-0.53)
Male	20,899	89	0.43 (0.35-0.52)
Female	16,724	81	0.48 (0.39-0.60)
Pediatric	4050	13	0.32 (0.19-0.55)
Adult	31,714	149	0.47 (0.40-0.55)
Elderly	1859	8	0.43 (0.22-0.85)

CADR: Cutaneous adverse drug reaction, CI: Confidence intervals

Incidence of cutaneous adverse drug reaction

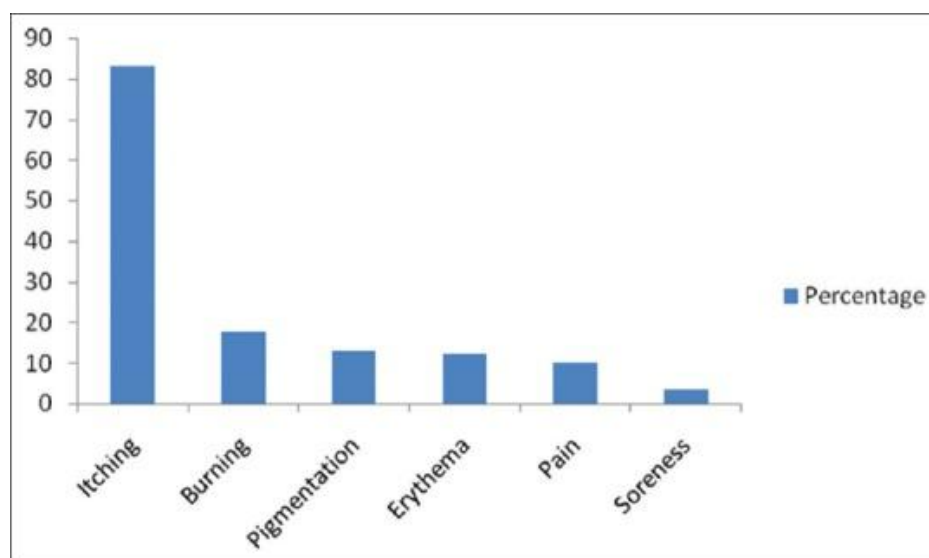
Table 2

Type of CADR	Total cases (%)	Inpatient cases (%)	Incubation period, median days (IQR)	Incidence (95% CI) %
Maculopapular rash	41 (23.98)	8 (30.79)	3 (1.25-5)	0.11 (0.08-0.15)
Urticaria	37 (21.64)	4 (15.38)	2 (1-4)	0.10 (0.07-0.14)
FDEs	31 (18.13)	3 (11.53)	1 (1-2)	0.08 (0.06-0.12)
EM	10 (5.85)	2 (7.69)	3 (1-5)	0.03 (0.01-0.05)
Urticaria with angioedema	8 (4.68)	1 (3.85)	1 (1-1.5)	0.02 (0.01-0.04)
Pruritus	7 (4.09)	0	2 (0.75-2)	0.02 (0.009-0.04)
Bullous FDEs	6 (3.51)	1 (3.85)	1 (1-5.5)	0.02 (0.007-0.04)
Stevens-Johnson syndrome	6 (3.51)	2 (7.69)	3.5 (1.5-12.25)	0.02 (0.007-0.04)
Angioedema	5 (2.92)	0	0.5 (0.44-0.75)	0.01 (0.006-0.03)
Acneiform eruption	4 (2.34)	0	25 (15.5-87.5)	0.01 (0.004-0.03)
Oral ulcer	3 (1.75)	0	1 (1-2)	0.008 (0.003-0.02)
Exfoliative dermatitis; bullous reactions; photosensitivity reaction	2 (1.17) each	2 (7.69); 1 (3.85); 0	4 (3-28); 4; 9 (6-12)	0.005 (0.01-0.02)
Palmoplantar exfoliation; local erythema; anaphylactic reaction; Cushing's syndrome; dapsone syndrome; DRESS; hyperpigmentation; lichenoid reaction	1 (0.58) each	1 (3.85) each for Cushing's syndrome; dapsone syndrome; DRESS	1; 0.5; 90; 10; 150; 210	0.003 (0.0005-0.01)

CADR: Cutaneous adverse drug reaction, FDEs: Fixed drug eruptions, DRESS: Drug reaction with eosinophilia and systemic symptoms, CI: Confidence intervals, IQR: Interquartile range, EM: Erythema multiforme

Frequency distribution, incubation period, and incidence per 1000 patients of observed cutaneous adverse drug reactions

Figure 1



Presenting symptoms of cutaneous adverse drug reactions

Table 3

Suspected drugs (ATC code)	n (%)
Anti-infective for systemic use (J)	68 (28.33)
Fluoroquinolones (J01MA)	20 (8.33)
Ciprofloxacin	11 (4.58)
Ofloxacin	6 (2.50)
Penicillin (J01CA)	18 (7.50)
Amoxicillin	11 (4.17)
Co-amoxiclav	6 (2.50)
Cephalosporins (J01D)	9 (3.75)
Cefpodoxime	3 (1.25)
Sulfa (J01E)	5 (2.08)
Cotrimoxazole	4 (1.67)
Musculoskeletal system (M)	48 (20.00)
NSAIDs (M01A)	43 (17.91)
Diclofenac	19 (7.92)
Ibuprofen	8 (3.33)
Aceclofenac	4 (1.67)
Nervous system drugs (N)	30 (12.50)
Analgesics (N02)	18 (7.50)
Paracetamol	13 (5.42)
Antiepileptic drugs (N03)	9 (3.75)
Phenytoin	4 (1.67)
Carbamazepine	3 (1.25)
Antiparasitic products (P)	23 (9.58)
Nitroimidazole (P01A)	13 (5.42)
Metronidazole	13 (5.42)
Antimalarial (P01B)	10 (4.17)
Chloroquine	9 (3.75)
Alimentary tract and metabolism (A)	18 (7.50)
Dicyclomine	5 (2.08)
Multivitamin	5 (2.08)
Other drugs	13 (5.42)
Unknown	39 (7.22)
Total	240 (100)

ATC: Anatomical therapeutic chemical classification,

NSAIDs: Nonsteroidal anti-inflammatory drugs

Causative drugs of cutaneous adverse drug reactions

Table 4

Causative drugs	MP rash (%)	Urticaria (%)	FDEs (%)	EM (%)
Anti-infective for systemic use	20 (32.23)	11 (24.44)	15 (34.09)	9 (64.28)
Fluoroquinolones	5 (8.06)	4 (8.89)	8 (18.18)	2 (14.29)
Penicillin	8 (12.90)	2 (4.44)	2 (4.55)	2 (14.29)
Cephalosporins	5 (8.06)	2 (4.44)	0	0
Sulfonamides	0	1 (2.22)	2 (4.55)	2 (14.29)
Musculoskeletal system	13 (20.97)	8 (17.78)	7 (15.91)	1 (7.14)
NSAIDs	13 (20.97)	8 (17.78)	7 (15.91)	1 (7.14)
Nervous system drugs	12 (19.35)	4 (8.89)	5 (11.36)	0
Antiepileptic drugs	6 (9.68)	1 (2.22)	0	0
Analgesics	5 (8.06)	3 (6.67)	5 (11.36)	0
Antiparasitic products	8 (12.90)	3 (6.67)	4 (9.09)	1 (7.14)
Nitroimidazole	3 (4.84)	3 (6.67)	4 (9.09)	1 (7.14)
Antimalarial	5 (8.06)	0	0	0
Alimentary tract and metabolism	3 (4.84)	5 (11.11)	3 (6.82)	0
Genitourinary system and sex hormones	0	3 (6.67)	0	0
Respiratory system	0	1 (2.22)	0	0
Unknown	5 (8.06)	9 (13.43)	10 (22.72)	2 (14.28)
Total	62 (100)	45 (100)	44 (100)	14 (100)

NSAIDs: Nonsteroidal anti-inflammatory drugs, MP: Maculopapular, FDEs: Fixed drug eruptions, EM: Erythema multiforme

Comparison of common causative drug groups for maculopapular rash, urticaria, fixed drug eruptions, and erythema multiforme

Figure 2



Bullous fixed drug eruption with unknown drug taken for diarrhea

Figure 3



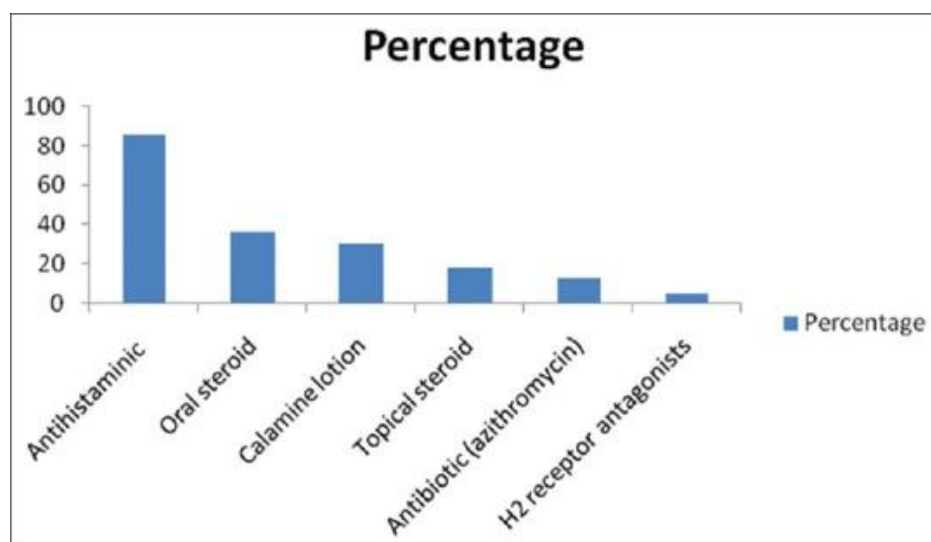
Urticaria with loose medication for fever

Figure 4



Dapsone Syndrome leading to mortality

Figure 5



Treatment of cutaneous adverse drug reactions

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