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RESEARCH ARTICLE

DETECTION OF CUTANEOUS ADVERSE DRUG REACTIONS IN TERTIARY CARE HOSPITALS

***Sindhu, V., Misbah Uddin, M. K., Syed Akheel, Dr. A. V. Kishore Babu, Dr. A. Raj Kirit and Dr. A. Srinivasa Rao**

Department of Pharmacy Practice, Bhaskar Pharmacy College, Yenkapally Village, Moinabad, Hyderabad, Telangana

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ABSTRACT

The World Health Organization defines an adverse drug reaction (ADR) as "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 modification of physiological function." The fact that drugs might have effects on humans other than the ones intended has been known for many years. The first remarkable adverse drug reaction (ADR) reported in Japan was anaphylactic shock caused by penicillin. The malformation of limbs, etc. caused by thalidomide was a global problem, and thalidomide was withdrawn from the market. Teratogenicity testing during new drug development has been implemented since 1963. During the six month study period, a total 192 patients visited Dermatology department. Highest number of patients from the age group of 21-30 i.e. 35.1%. Majority of the CADRs from the drug class antibiotics 12 (22.2%). According to *Naranjo's causality assessment scale*, out of 54 CADRs the dechallenge was done in all cases, out of which 28 cases (51.8%) were probable and 14 cases (25.9%) were possible where as remaining 12 cases (22.2%) were fall into unlikely category. We also assessed the severity by using *Hartwigand Siegelseverity assessment scale;* it shows that highest number of 32 (59.2%) cases fall into moderate type and 10 (18.5%) cases were mild type whereas 12 (22.2%) cases fall into severe CADRs.

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INTRODUCTION

Early history

The fact that drugs might have effects on humans other than the ones intended has been known for many years. On 29 January 1848 a young girl called Hannah Greener was given an anaesthetic before treatment for an in-growing toe nail. The anaesthetic was chloroform which had only been introduced a year earlier. Sadly Hannah died during the anaesthetic from what was thought to be an episode of ventricular fibrillation. (The Royal Pharmaceutical Society) In 1922: Jaundice associated with the use of Salvarsan, an organic arsenical used in the treatment of Syphillis. (Robert V. Sager, 1936) 1937: In USA, 107 people died from taking an elixir of sulfanilamide that contained the solvent diethylene glycol. (Sulfanilamide Disaster FDA Consumer magazine, June 1981) The first remarkable adverse drug reaction (ADR) reported in Japan was anaphylactic shock caused by penicillin. The malformation of limbs, etc. caused by thalidomide was a global problem, and thalidomide was withdrawn from the market. Teratogenicity testing during new drug development has been implemented since 1963. (Takahashi and Yakushigaku Zasshi, 2009) In 1959 - 1961, it was reported in that there was an outbreak of phocomelia (hypoplastic and aplastic limb deformities) in the new born babies. Subacute Myelo-Optico-Neuropathy (SMON) developed due to quinoform (antiflatulent) administration. Difficulty in walking, ananastasia, and vision impairment caused by degenerated bone marrow, optic nerve, and peripheral nerves. (PMDA, 2015)

Drugs withdrawn from Market

Fenfluramine – Anti obesity, 1973-1997, Heart valve disease, pulmonary hypertension, cardiac fibrosis.

Cerivastatin – Hypolipidemic Agents, 1990-2001, 52 deaths from rhabdomyolysis, results in Renal failure.

Rofecoxib – NSAID, osteoarthritis acute pain conditions, 1999 – 2004, increased risk of heart attack and stroke associated with long-term, high-dosage use.

Definition: (WHO, 1972)

The **World Health Organisation** defines an adverse drug reaction (ADR) as "a response to a drug which is noxious and

Corresponding author:* **Sindhu, V.
Department of Pharmacy Practice, Bhaskar Pharmacy College, Yenkapally Village, Moinabad, Hyderabad, Telangana.

unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."

Cutaneous adverse drug reactions

Cutaneous adverse drug reactions represent one of the most common adverse events (AEs) reported in drug therapy. The overall incidence rate of such events is between 2–3% in hospitalised patients. (Adverse Drug Reactions, 2006; Profile and Pattern of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in a General Hospital in Singapore, 2012) In many cases, these reactions are reported simply as a "rash" to the H The clinical presentation of cutaneous drug reactions is highly variable, ranging from benign reactions such as exanthematous or maculopapular eruption, photosensitivity, and urticaria, to severe and potentially life-threatening reactions such as drug induced hypersensitivity syndrome (DHS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). (Arndt *et al*., 1976)

Epidemiology

Among all hospitalized patients, the incidence of CDRs has been found to range from 1 to 3%. (Van der Linden *et al*., 1998) The highest reported frequency of CDRs has consistently been found to be with antimicrobial agents, for which there is also limited data regarding the incidence of CDRs in ambulatory patients. In a population of 13,679 Dutch patients who received a prescription for an antimicrobial agent, the frequency of CDRs was approximately 1%. (Baldo and Pharm, 1994) The most frequent reactions were observed in patients receiving a trimethoprim-sulfonamide combination (2.1%), fluoroquinolones (1.6%), and penicillins (1.1%). A higher frequency of CDRs (7.3%) was recently noted in an ambulatory pediatric population receiving penicillins, sulfonamides, or cephalosporins.

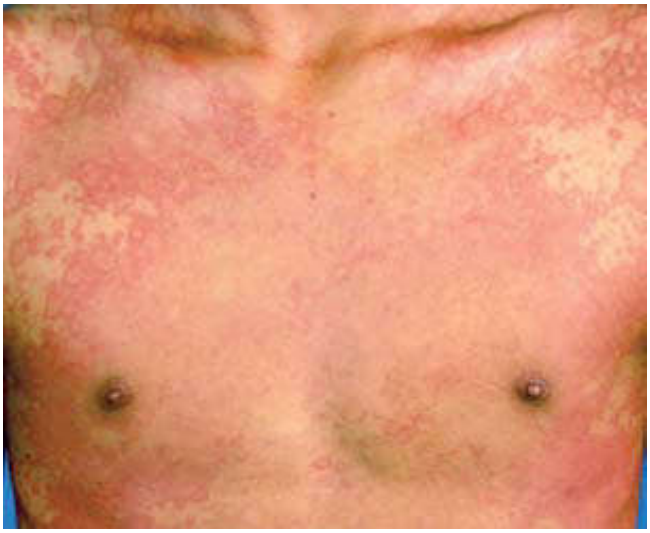
Common cutaneous adverse drug reactions

1. Maculopapular/Exanthematous Drug Eruption

This is the most common cutaneous adverse drug reaction and is also known as a morbilliform or maculopapular eruption. Erythematous macules may become popular and confluent. Lesions on the legs and feet may appear purpuric. The clinician should be alerted to the possibility of toxic epidermal necrolysis if the skin is tender or duskylooking, and if there are mucous membrane erosions. Drug hypersensitivity syndrome should be considered if there is associated oedema, pustules, lymphadenopathy, hepatitis and peripheral eosinophilia. Many drugs have been implicated to cause drug exanthems and these include betalactams, quinolones, sulfamethoxazole and diuretics. The rash typically begins 5-14 days after the start of a new medication and occasionally occurs a few days after the drug has been discontinued.

2. Photosensitive drug eruption (Phototoxic or Photo allergic)

Erythema with or without blistering occurs in sun-exposed sites when light interacts with the drug. Drugs commonly associated with cutaneous phototoxic reactions include griseofulvin, tetracyclines, NSAIDS and fluoroquinolones; those associated with photoallergic reactions include thiazide diuretics, sulfonamides, sulfonylureas and phenothiazines. Onset maybe delayed by as long as 24-72 hours.



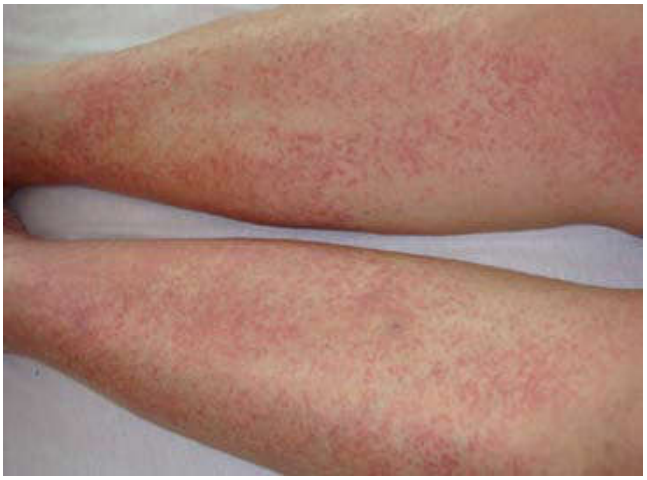


Figure 1B. Purpuric macules on the shins

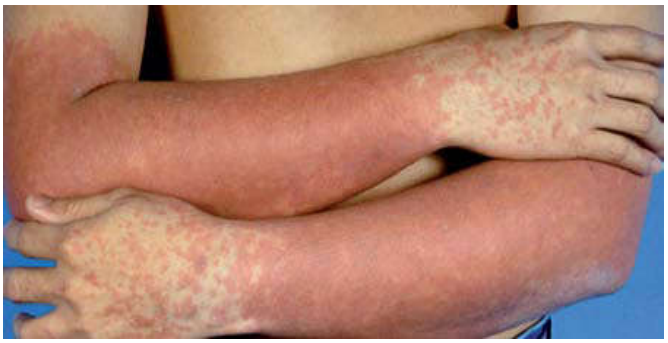


Figure 2. Intense erythema and erythematous papules over sun-exposed sites on the distal arms, forearms and dorsal surfaces of the hands

3. Urticaria

Urticaria, commonly referred to as hives, appears as raised, well-circumscribed areas of erythema and oedema involving the dermis and epidermis that are very pruritic. Lesions may appear within minutes to days following drug administration, and individual lesions usually last less than 24 hours. Examples of commonly implicated drugs include beta-lactams, non-steroidal anti-inflammatory drugs (NSAIDs), anaesthetics and contrast media.

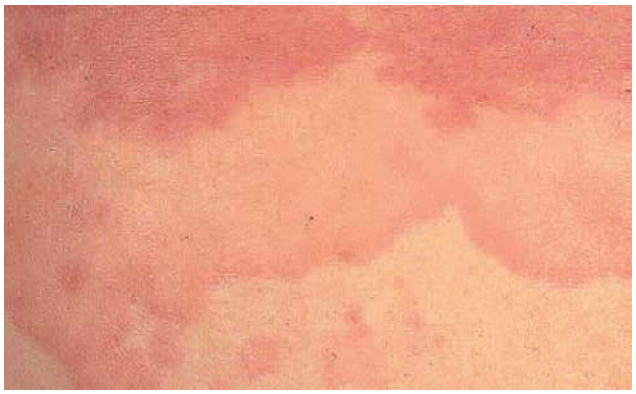


Figure 3. Erythematous oedematous plaques

3. Fixed drug eruption (FDE)

Fixed drug eruptions (FDEs) characteristically recur in the same site or sites each time a particular drug is taken; with each exposure however, the number of involved sites may increase. Common sites of occurrence include the lips, genitalia, hands and feet. Lesions resolve with post-inflammatory hyperpigmentation and recur at the same site with re-administration of the causative drug. Lesions may be single, or less commonly, few or multiple (generalized FDE). They appear 1 to 2 weeks after initial exposure to the drug, and within 24 to 48 hours with subsequent exposures. Drugs frequently associated with FDE include NSAIDS, sulfonamides and tetracyclines.

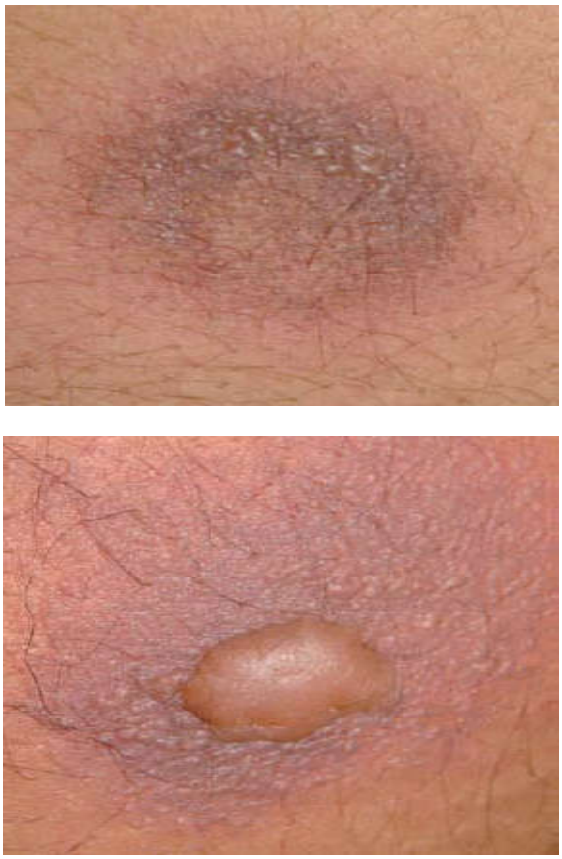


Figure 4. Brown plaques with vesicles and erythematous rim

4. Drug-induced vasculitis

Drug-induced ***vasculitis*** is a term for a group of rare diseases that have in common inflammation of blood vessels. Small vessel vasculitis is usually confined to the skin, but systemic involvement should also be excluded. Causative drugs include penicillins, sulfonamides, NSAIDS and thiazides. Onset is usually within 1 to 3 weeks of taking the drug.

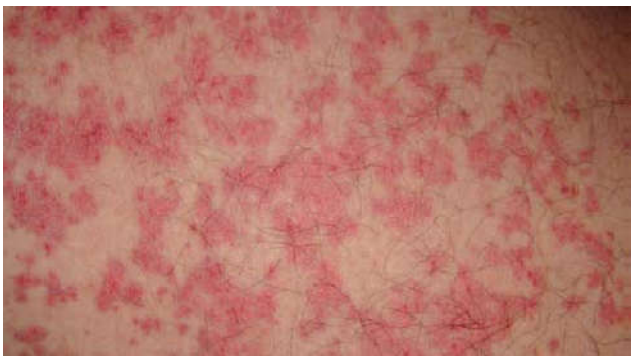


Figure 5. Purpuric macules and papules

5. Drug hypersensitivity syndrome (DHS)

Drug hypersensitivity syndrome is a severe, unexpected reaction to a medicine, which affects several organ systems at the same time. DHS, also known as drug rash with eosinophilia and systemic symptoms (DRESS), develops 2 to 6 weeks following commencement of the causative drug. Common culprit drugs include anti-convulsants (phenytoin, carbamazepine and phenobarbital), sulfonamides, dapsone and allopurinol. Clinical features include fever, rash, lymphadenopathy and arthritis. The cutaneous eruption is often a morbilliform exanthematous and oedematous rash, with occasional pustules, vesicles and purpura. Hepatitis may be severe and peripheral eosinophilia is usually prominent. The rash and hepatitis may persist for weeks to months after drug withdrawal. Mortality from DHS is usually due to fulminant hepatitis, hence the importance of recognising this syndrome. Systemic corticosteroids are usually recommended in the treatment of DHS. It is important to note that the duration of oral steroid treatment for DHS should be continued for a longer period as compared to the typical 2-week duration of treatment for other types of drug reactions. Oral steroids may be continued for up to 3 months or more and withdrawal must be very gradual to prevent relapse and rebound of the reaction.

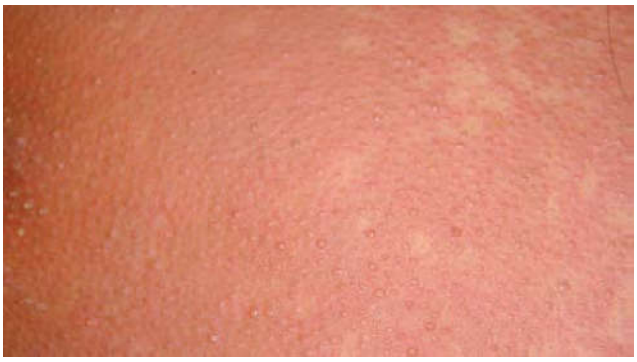


Figure 6. Erythematous oedematous plaques

6. Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN)

SJS (is an immune-complex–mediated hypersensitivity complex that typically involves the skin and the mucous membranes.) and TEN (is a potentially life-threatening

dermatologic disorder characterized by widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes, resulting in exfoliation and possible sepsis and/or death) are life-threatening severe cutaneous adverse drug reactions. Patients with epidermal detachment involving less than 10% of body surface area (BSA) are classified as SJS, those with >30% BSA involvement as TEN and those with 10 to 30% BSA involvement as SJS-TEN overlap. Examples of implicated drugs include allopurinol, anti-convulsants, sulfonamides and NSAIDs. SJS and TEN usually begin within 4 weeks of commencement of the implicated drug, but may occasionally be delayed up to 8 weeks. Mucous membranes are involved, and ocular sequelae may be serious, leading to corneal scarring and visual impairment. The clinician should be alerted to possible early TEN in any patient presenting a painful drug exanthem.

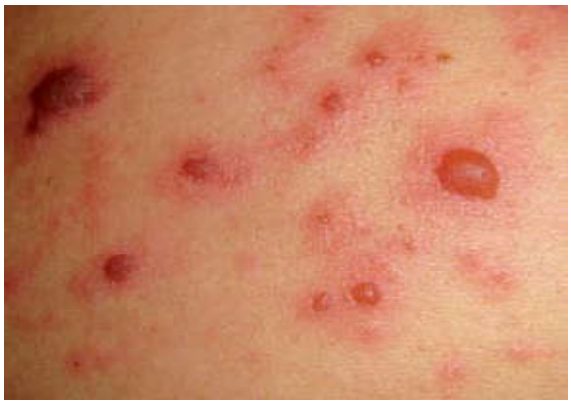


Figure 7A. Dusky and purpuric macules with vesiculation

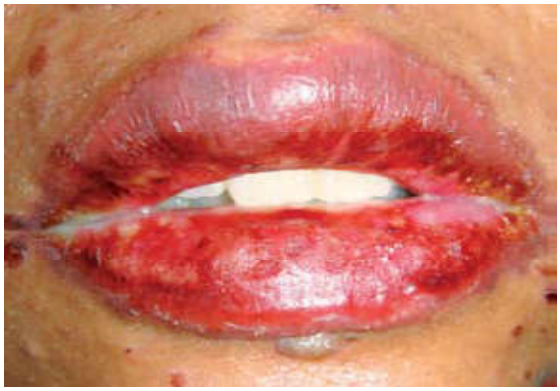


Figure 7B. Erosions on the lips and perioral skin

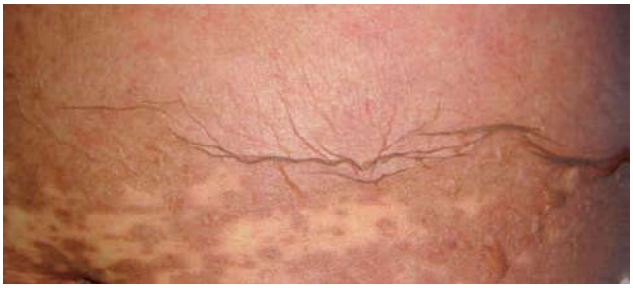


Figure 7C. TEN: Confluent epidermal detachment

7.Acute generalised exanthematous pustulosis (AGEP)

AGEP is a benign condition with spontaneous resolution with desquamation within 2-3 weeks. It is characterised by numerous small sterile pustules erupting over erythematous plaques. The eruption may begin within 3-5 days in intertriginous areas and mucous membranes may be involved. Additional features include fever, leukocytosis and eosinophilia. Common causative drugs include beta-lactam antibiotics, macrolides and calcium channel blockers. The main clinical differential diagnosis is acute pustular psoriasis.

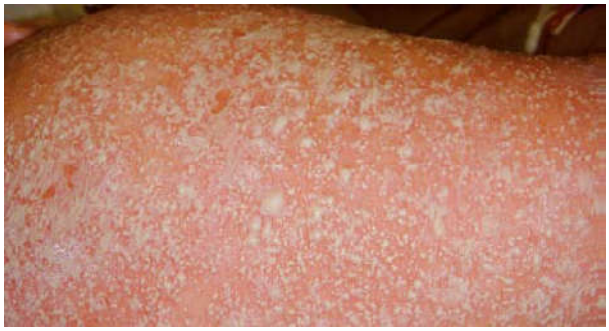


Figure 8. Superficial pustules coalescing to form small lakes of pus on an exanthematous background

Mechanism of cutaneous adverse drug reactions

A.Immediate-Type Immune-Mediated Drug Reactions

Immediate-type immune-mediated (also referred to as Type I hypersensitivity) reactions have been widely studied and are mediated by IgE. As such, a sensitizing exposure to the offending drug must occur prior to elicitation of an IgE response. The sensitizing period may occur during a previous administration of the drug or during the initial course of treatment, followed by elicitation as the drug regimen is continued. It is also important to recognize that sensitization may occur via environmental exposure to agents with antigenic determinants similar to those expressed by a drug or drug-protein complex, which may subsequently elicit an immediate-type immune-mediated reaction upon initial exposure to the drug. For example, (Weltzien *et al*., 1996) have demonstrated that sera in one patient with an anaphylactic reaction to a commercial hair treatment contained IgE, which reacted with neuromuscular blocking agents; a reaction that was inhibited by a quaternary ammonium derivative in the hair treatment preparation. Moreover, this component in the commercial preparation was able to inhibit the binding of d-tubocurarine to IgE in the sera of three patients who previously experienced life-threatening reactions to a neuromuscular blocker. Thus, failure to identify prior exposure to a drug does not rule out the possibility of an immediate-type immune-mediated drug reaction upon initiation of therapy.

A. Delayed-Type Immune-Mediated Drug Reactions

The clinical course of many CDRs suggests they are delayed-type immune-mediated drug reactions. Growing evidence indicates that T-cell recognition of drugs is a critical step in the generation of these responses. (Coleman and Blanca, 1998; Pichler *et al*., 1998; Mauri-Hellweg, 1995) T-cells possess clonally distributed receptors (TCR) that recognize antigen on the cell surface when presented by products of the major histocompatibility complex (MHC) genes. This cell surface-dependent recognition is referred to as MHC-restricted antigen recognition. CD4+ T-helper cells recognize antigen presented by MHC Class II, while those antigens presented by MHC Class I are recognized by CD8+ cytotoxic T-cells. Evidence for the role of T-cell activation in CDR derives from numerous

studies wherein drug-specific T-cell clones have been derived from the peripheral blood of patients with a history of such reactions to amoxicillin, carbamazepine, lidocaine, phenytoin, or SMX. (Zanni, 1997) Most of these drug-specific clones express the αβ TCR type, although some clones have been identified that express the γδ TCR type (Leyva, 2000) have demonstrated that dermal T-cells isolated from skin lesions in a patient with severe blistering exanthem caused by trimethoprim-SMX (TMP-SMX) proliferated in response to SMX (but not TMP) in the presence of autologous mononuclear cells (used as antigen-presenting cells, APC). Immunohistochemical studies have demonstrated the infiltration of CD4+ and CD8+ T-cells in drug-induced TEN (http://umm.edu/health/medical/altmed/condition/cutaneous-drug-reactions)

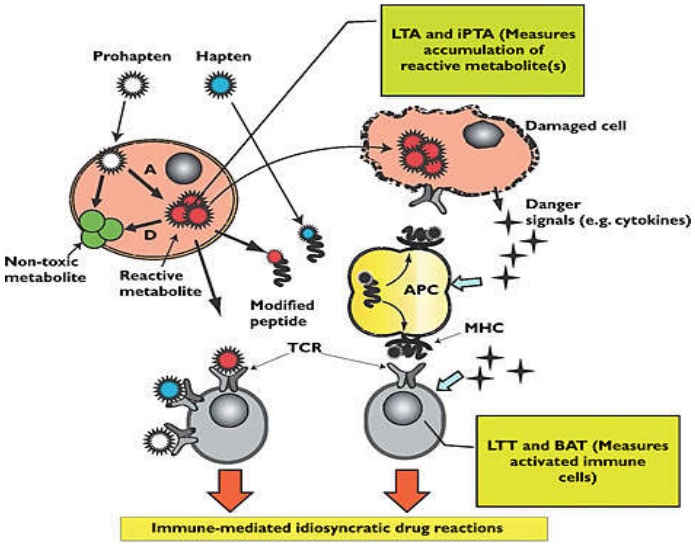


Figure 9. Molecular mechanisms of immune mediated idiosyncratic drug reactions

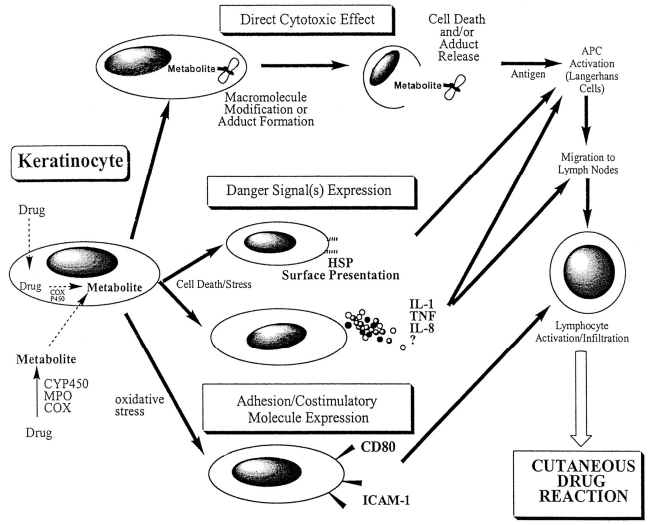


Figure 10. Delayed-Type Immune-Mediated Drug Reaction MANAGEMENT: (Martin and Li, 2008)

We all know that once an offending drug is identified, it is easier to plan the management of CADRs as a common procedure. The treatment depends on the type of reaction you are having and how serious it is. However, you may need treatment to recover. Your doctor may prescribe drugs to help stop the reaction, such as epinephrine, corticosteroids, antihistamines, or topical ointments. If you also have life-threatening symptoms, such as trouble breathing, you will be hospitalized until you are stable. A cutaneous drug reaction that occurs when first time you take a drug may cause a more severe reaction the next time you take that drug. It is important to keep a record of any drugs that cause reactions when you take them. (Martin and Li, 2008)

Drug Therapies

- Corticosteroids (applied topically, taken orally, or given intravenously), such as prednisone
- Antihistamines
- Antipruritic treatments (to stop itching)
- Epinephrine, for severe respiratory/cardiovascular implications
- Topical lotions or ointments. For itching, lesions, and other inflammatory skin reactions.
- Surgical removal of dead tissue may be necessary in very severe reactions.

Nutrition

- Vitamin C helps skin heal. Some studies suggest that vitamin C can lower histamine levels (which cause hives). Lower dose if diarrhea develops.
- B-complex with extra B12 aids in skin health. Vitamin B12 injections help reduce the severity of hives. But it is not clear whether taking B12 orally has the same effect. Vitamin B5 or pantothenic acid helps heal wounds.
- Vitamin E and zinc help skin heal. Both are also sometimes applied topically.
- Bromelain, an enzyme derived from pineapple, reduces inflammation. Avoid if you take blood-thinning medicines. Bromelain can interfere with certain antibiotics and can slow blood clotting.
- Omega-3 fatty acids, such as those found in fish oil, help maintain skin health and may have anti-inflammatory properties. If you take blood-thinning medication, talk to your doctor before taking omega-3 fatty acids.
- Rutin or quercetin may improve skin health.

Methodology

Study location

The study has been carried out in both outpatient and inpatient department of Dermatology including Bhaskar General Hospital and Celestee Skin, Laser and Hair Clinic, Hyderabad.

Study design:

Prospective Observational Study.

Study period:

November 2016 to April 2017

Study setting:

The study was conducted on patients those who are experiencing Cutaneous Adverse Drug Reactions to medicine used during their hospital stay or visiting the outpatients department of dermatology.

Study criteria:

***Inclusion criteria*:**

- Study includes adults, pediatric and geriatric patients.
- Subjects who are under multidrug therapy.
- Subjects under long term treatment.
- Subjects detected with Cutaneous ADR's.

Exclusion criteria:

- ADR's other than Cutaneous.
- Expectation of surgery
- Pregnant Women's and Lactating mothers.

Study population

The patients who were coming to the Sai Nath Clinic, dermatology department of Bhaskar General Hospital and Celestee Skin, Laser and Hair Clinic Hyderabad during November 2016 to April 2017 were enrolled in the study.

Data collection

The data was collected on regular basis with direct patient interaction at inpatient and outpatient wards of dermatology departments. It includes patient's demographic details, medical history, medication history, social history and present medications which are the main sources to find out the possibility of adverse drug reactions.

Analysis of ADRs

The reported CADRs can be analyzed by considering the following methods:

Causality assessment of the ADRs based on the scores of the Naranjo's probability scale: Probability is assigned via a score termed definite, probable, possible or doubtful. Values obtained from this algorithm are sometimes used in peer reviews to verify the validity of author's conclusions regarding adverse drug reactions. Severity assessment of ADRs analyzed by using the Modified Hartwig's and Siegel Severity assessment scale this can be classified into Mild, Moderate, severe.

RESULTS

During the six month study period, a total 192 patients visited Dermatology department. The demographic details as follows:

Gender wise distribution of CADRs

Among 192 patients, 54 patients were reported with CADRs. Out of 54 CADRs, males were 25 (46.2%) and females were 29 (53.7%). The male to female ratio was 0.86:1.16.

Table 1.

	No. of CARDs	Incidence %
Males	25	46.3 %
Females	29	53.7 %
Total	54	

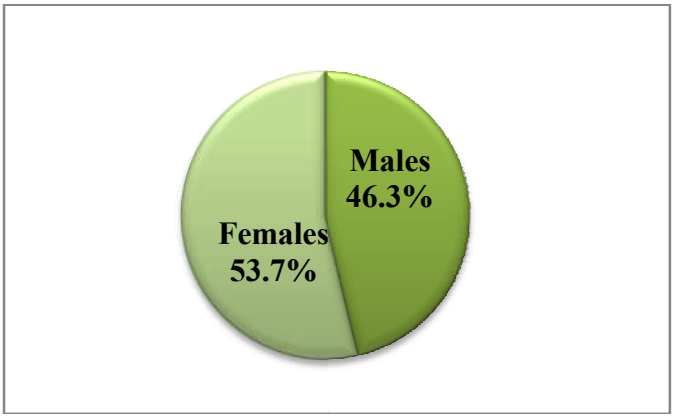


Figure 1

Age wise distribution of CADRs

Out of 54 CADRs, 0-10, 11-20 and 41-50 age groups patients have same number of CADRs i.e. 7 (12.9%), 21-30 age group patients have highest number of CADRs i.e. 19 (35.1%), 31-40 age group patients have 12 (22.2%) CADRs, 51-60 and 61-70 age group patients have lowest number of CADRs i.e.1 (1.85%).

Table 2

Age(Yrs)	No. of CADRs	Incidence
0-10	7	12.9%
11-20	7	12.9%
21-30	19	35.1%
31-40	12	22.2%
41-50	7	12.9%
51-60	1	1.85%
61-70	1	1.85%

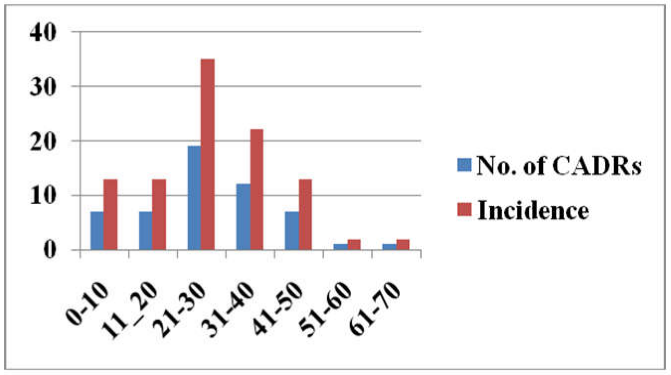


Figure 2

Age distribution of CADRs among gender

Out of 54 CADRS, males between 0-10 years have 3 (12%) CADRs, females have 4 (13.7%) CADRs, males between 11-20 years have 4 (16%) CADRs, females have 3 (10.3%) CADRs, males between 21-30 years have 8 (32%) CADRs, females have 11 (37.9%) CADRs, males between 31-40 years have 6 (24%) CADRs, females have 6 (20.6%) CADRs, males between 41-50 years have 3 (12%) CADRs, females have 4 (13.7%) CADRs, None of males have ADRs between 51-60 years, females have only 1 (3.4%) CADRs, males between 61-70 years have only 1 (4%) CADRs, none of females have ADRs from this age group.

Table 3.

Age(Yrs)	Males	Incidence	Females	Incidence
0-10	3	12%	4	13.7%
11-20	4	16%	3	10.3%
21-30	8	32%	11	37.9%
31-40	6	24%	6	20.6%
41-50	3	12%	4	13.7%
51-60	0	0%	1	3.4%
61-70	1	4%	0	0%
Total	25		29	

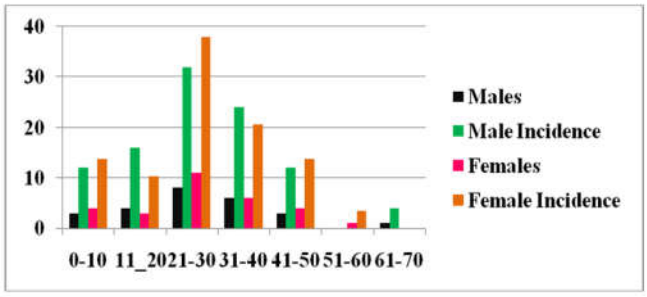


Figure 3

Distribution of CADRs by Pharmacological drug category

Out of 54 CADRs anti tubercular, anti-fungal drugs causes 1 (1.85%) CADRs, NSAIDs cause 9 (16.6%) CADRs, antibiotics cause 12 (22.2%) CADRs, anticonvulsant agents cause 4 (7.4%) CADRs, corticosteroids cause 6 (11.1%) CADRs, ayurvedic medicine causes 8 (14.8%) CADRs, anti diabetics cause 2 (3.7%) CADRs, other classes of drugs like anticancer, anti-inflammatory and immunosuppressant' cause 11 (20.3%) CADRs.

Table 4

Pharmacological class	No. of CADRs	Incidence
Anti-tubercular	1	1.85%
NSAID's	9	16.6%
Antibiotic	12	22.2%
Anticonvulsants	4	7.4%
Corticosteroids	6	11.1%
Ayurvedic medicine	8	14.8%
Anti-Fungal	1	1.85%
Anti-diabetic	2	3.7%
Others	11	20.3%
Total	54	

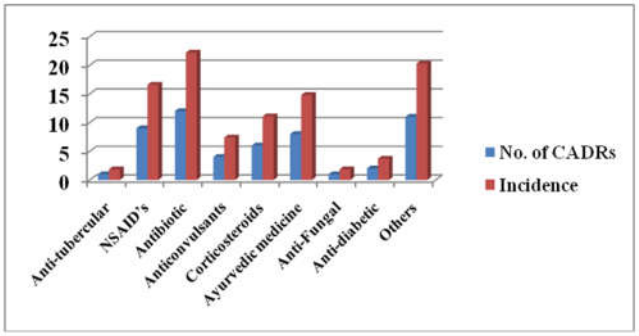


Figure 4

Distribution of Type of CADRs

Out of 54CADR's 2 (3.4%) CADRs from *Steven Johnson syndrome*, 10 (18.5) CADRs from *drug induced Urticaria,* 12 (22.2%) CADRs from *fixed drug eruption,* 8 (14.8%) CADRs from *Steroid induced acne,* 16 (29.6%) CADRs from *local dermatitis,* 6 (11.1%) CADRs from EMF.

Table 5.

Type of ADRs	No of CADRs	Incidence
Steven Johnson Syndrome	2	3.7
Drug induced Urticaria	10	18.5
fixed drug eruption	12	22.2
Steroid induced Acne	8	14.8
Local dermatitis	16	29.6
EMF	6	11.1
Total	54	

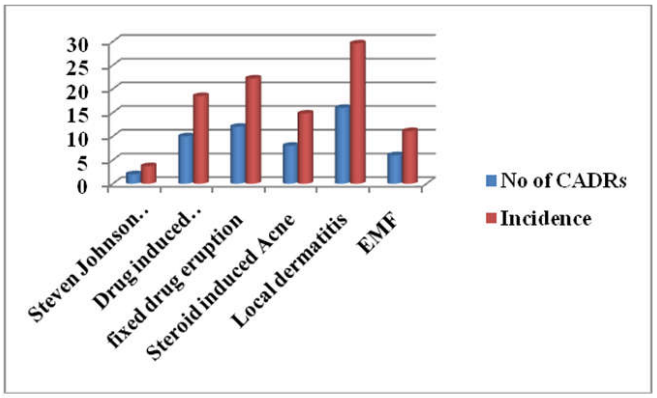


Figure 5

Distribution of Morphological types of CADRs and Suspected Drugs

Out of 54 CADRs, 2 (3.7%) *SJS* CADRs induced by *Ofloxacin and Phenytoin*, 10 (18.5%) *Drug induced Urticaria* CADRs induced by *Diclofenac sodium, Sodium Valproate* and *Ayurvedic Medicine induced*, 8 (14.8) *Steroid Induced Acne* CADRs induced by *Clobetasol propionate, Betamethasone dipropionate, Clotrimazole and Betamethasone valerate*, 12 (22.2%) *Fixed drug Eruption* CADRs induced by *Dilcofenac sodium and Metranidazole*, 16 (29.6%) *Local Dermatitis* CADRs induced by *Lingnocaine, diclofenac and ciprofloxacin*, 6 (11.1%) *EMF* CADRs induced by *Ciprofloxacin hydrochloride, Metronidazole, Ceftriaxone*.

Table 6

S. No	Type of ADR	Drug implicated	No. of CADRs	Incidence
1	Steven Johnson syndrome	Ofloxacin, Phenytoin	2	3.7%
2	Drug induced Urticaria	Diclofenac sodium, Sodium Valproate, Aceclofenac, Ayurvedic Medicine	10	18.5%
3	Steroid Induced Acne	Clobetasol propionate, Betamethasone dipropionate, Clotrimazole, Betamethasone valerate	8	14.8%
4	Fixed drug Eruption	Dilcofenac sodium, Metranidazole, glimipride	12	22.2%
5	Local Dermatitis	Lingnocaine, diclofenac, ciprofloxacin	16	29.6%
6	EMF	Ciprofloxacin hydrochloride, Metronidazole, Ceftriaxone	6	11.1%
	Total		54	

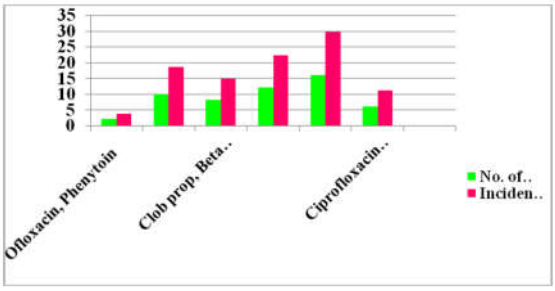


Figure 6

Distribution of Route of drug Administration with CADRs

Out of 54 CADRs, 26 (48.1%) CADRs caused by oral route drug administration, 22 (40.7%) CADRs caused by external route of drug administration and 6 (11.1%) CADRs caused by parenteral route of drug administration.

Table 7

Route	No. of CADRs	Incidence %
Oral	26	48.1
External	22	40.7
Parenteral	6	11.1
Total	54	

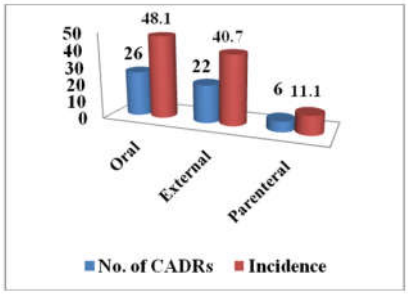


Figure 7

Distriibution of Naranjo's causality assessment scale

Out of 54 CADRs definite type CADRs were found 0, Probable type CADRs were found 28 (51.8%), Possible type CADRs were found 14 (25.9%) and Unlikely CADRs were found 12 (22.2%).

Table 8.

Casualty	No. of Patients	Incidence %
Definite	0	0
Probable	28	51.8
Possible	14	25.9
Unlikely	12	22.2
Total	54	

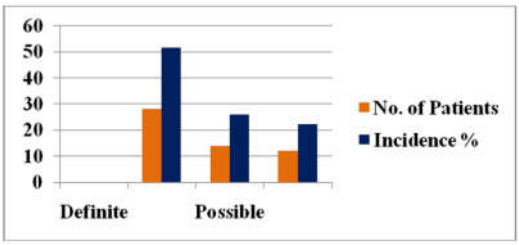


Figure 8

Distribution of Hartwig and Siegel Severity assessment scale

Out of 54 CADRs Mild type CADRs were found 10 (18.5%), Moderate type CADRs were found 32 (59.2%), Severe type CADRs were found 12 (22.2%).

Table 9

Severity	No. of patients	Incidence %
Mild	10	18.5
Moderate	32	59.2
Severe	12	22.2
Total	54	

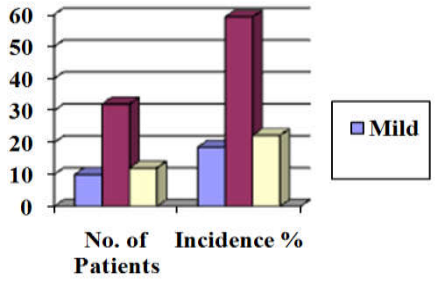


Figure 9

DISCUSSION

In our study, CADRs in Indian population are systematically reviewed from selected published studies. Cutaneous reactions are the most common manifestations of ADRs. (Martin and Li, 2008) A wide spectrum of cutaneous manifestations ranging from Steven Johnson Syndrome to fixed drug eruption can be produced by different classes of drugs. The study was aimed at assessing the incidence of CADRs in the population of age group from 1- 70 years. Out of 192 patients 54 cases were suspected with CADRs in the dermatology department. In that 25 CADRs are from males and 29 CADRs from females. Highest number of patients from the age group of 21-30 i.e. 35.1% followed by 31-40 i.e. 22.2%, which is in accordance with the Sharma *et al.* study that also reported similar observations. (Sharma *et al*., 2001) Various types of cutaneous ADRs seen in this study include local dermatitis i.e. skin rashes 29.6% are the commonest one, observation of Solensky *et al.* and Hafner *et al* study shows fixed drug eruptions and urticaria are also reported frequently is similar to our study. (Solensky and Mendelson, 2001; Hafner *et al*., 2002) Majority of the CADRs from the drug class antibiotics 12 (22.2%) shows that irrational prescribing and lack of rational use and oral route of drug administration has highest incidence rate of 26 (48.1%). According to *Naranjo's causality assessment scale*, out of 54 CADRs the dechallenge was done in all cases, out of which 28 cases (51.8%) were probable and 14 cases (25.9%) were possible where as remaining 12 cases (22.2%) were fall into unlikely category. We also assessed the severity by using *Hartwig and Siegel severity assessment scale;* it shows that highest number of 32 (59.2%) cases fall into moderate type and 10 (18.5%) cases were mild type.

Conclusion

Our study screened a number of subjects and corresponding wide spectrum of commonly used drugs. With the number of

drugs being marketed increasing every year, it is importance to have an in-depth understanding of their possible adverse reactions and this is possible only when the physician is trained adequately and is actively looking for any ADRs. However, there were also some limitations. Causality assessment might be uncertain especially as rechallenge was not attempted due to ethical reasons. Hence, the practitioners and patients should be motivated to report any untoward incidence occurring with the drug. Patients' awareness regarding OTC drugs and self-medication should also be strengthened. ADR monitoring can also reduce patient suffering and cost of treatment. Finally all the patients identified with Cutaneous ADRs were explained and given with "Drug Alert Card" to overcome the drug allergies to particular medicines. The present analyses indicate characteristics and mechanisms of cutaneous ADRs among patients, which provide clues for future intervention strategies and management issues in healthcare settings. Whereas 12 (22.2%) cases fall into severe CADRs. (Noel *et al*., 2004)

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