DOI: 10.7860/JCDR/2016/16938.7736

Original Article

Pharmacology Section

Retrospective Analysis of Pattern of Cutaneous Adverse Drug Reactions in Tertiary Hospital of Pauri Garhwal

DEEPAK DIMRI[1], RANGEEL SINGH RAINA[2], SWATI THAPLIYAL[3], VIJAY THAWANI[4]

ABSTRACT

Introduction: Cutaneous Adverse Drug Reactions (CADR) are the common drug induced adverse reactions which usually have wide range of manifestations and severity.

Aim: To describe the prevalence and clinical spectrum of CADR's in a tertiary hospital of the Garhwal region in Uttarakhand, India.

Materials and Methods: All patients suspected of having CADRs reported in the various out-patient departments, and in-patients of HNB Base & Teaching Hospital, from 1st January 2012 to 31st December 2014 were retrospectively analysed. Drug history was recorded in a format specified in Indian National Pharmacovigilance Programme.

Results: Total 111 cases of CADRs were reported from Jan 2012 to Dec 2014. Mean age of patients was 33.34±18.7 years and maximum ADRs were reported in the age group of 20-39 years (36.9%). Female were affected more than male (W:M :: 66:45). Most of the ADRs were exanthematous eruptions (EE) type (33.3%). Medicine department reported maximum cases of CADRs (47.7%), followed by Dermatology. Most of the CADRs were reported with antimicrobial agents (69.4%). Significant associations of different types of various cutaneous reactions were observed in relation to the duration (in days) of ADRs (p = 0.038), types of outcome (p= 0.006), different departments (p= 0.014) and between different groups of medicines (p = 0.008).

Conclusion: CADRs have proved a significant problem in healthcare for decades. Major bulk of CADR result from physician prescribed drugs. Hence, awareness on part of the physician can help in timely detection of cutaneous reactions, thereby restricting damage from them.

Keywords: Prevalence, Pharmacovigilance, Skin manifestations

INTRODUCTION

Adverse Drug Reactions (ADR's) represent the most frequent cause of injuries due to medical care in hospitals in developed countries [1,2]. Heightened interest in ADRs was stimulated by the thalidomide tragedy in the 1960's [3].

The study has shown that medications are commonly responsible for most of the adverse events [1]. ADRs have developed less among adult inpatients (6.5%) [4] than outpatients (27.4%) [5] whereas only 2.3% of paediatrics in-patients had ADRs [6]. In a Southern Indian Hospital, 0.7% of total admission and 1.8% of total deaths were mainly due to ADRs [7]. Whereas a meta-analysis of 39 prospective studies done in the United States over a period of 32 years found a rate of 6.7% for serious and fatal ADRs [8].

Although ADRs are a common problem in hospital and community setting, data has revealed that maximum number of patients due to adverse drug reactions usually suffer from cutaneous reactions. Cutaneous adverse drug reactions (CADRs) account for the most common and challenging type of different adverse reactions. A CADR is any unwanted harmful changes in the skin, its appendages or mucous membranes, and it includes all adverse events related to drug eruption [9].

The incidence of CADRs in developed countries range from 1-3% among in-patients [10], whereas in developing countries such as ours, some studies peg it at 2-5% of the in-patients [11-14].

Although we do not have sufficient data of out- patients, but one study depicts the relative incidence of CADRs in out-patient in the skin department was 2.6% [15] whereas CADRs comprise approximately 2-3% of all ADRs [16].

Gross variations in the effects of medicines exist among populations of different countries and also various regions of the same country which may be attributed to the differences in prescribing practices, diseases, genetics, food habits, environmental variables and pharmaceutical manufacturing protocols [17].

With the paucity of such comprehensive data from different corners of world, it is not possible to implement generalized approach for this problem in local settings [18].

Thus the epidemiology and nature of ADRs in our region is essential from both local and global perspectives, and would be very helpful for understanding differences by nation, region and race. This study aims to describe the occurrence of CADR's in a tertiary (referral) hospital in the Garhwal region of Uttarakhand, India. We have presented the data on clinical spectrum of various cutaneous ADR patterns and causative drugs.

MATERIALS AND METHODS

This was a retrospective study carried out in our tertiary care teaching hospital, involving CADRs reporting from various clinical departments from 1st January 2012 to 31st December 2014, which was conducted after the approval from the Institutional Ethics Committee of Veer Chander Singh Garhwali Government Medical Science & Research Institute, Srinagar, Uttarakhand, India. The study was conducted by the Department of Dermatology in association with the Department of Pharmacology. Average number of OPD patients in the hospital was approximately 31436 per year whereas average number of patients in skin OPD was found 3465 patients (11%) per year (or 289 patients per month) in last three years (January 2012 to December 2014). We have found from the available data that incidence rate of CADRs was 3-4 CADRs per month (1%). So we had selected three year period for the more than 100 sample size for this study.

All patients reported to derma OPD with cutaneous manifestation after consumption of the drug and those referred from other department were included in the study. Following groups of cases were included in the study:

- Retrospective cases of all age groups and clinical settings (outpatient and/or inpatient) of both genders having CADRs.
- Only drug induced skin lesions which were not related to

any disease (e.g., viral exanthems or rashes of rickettial infections)

- Patients who have not consumed any indigenous (ayurvedic, herbal and homeopathic) medicines.
- If suspected drugs or groups could be identified.

The diagnosis was confirmed by senior dermatologist consultant. Patients suspected of having CADRs reported in the various out-patient departments, and in-patients of HNB Base & Teaching Hospital were retrospectively analysed for clinical and epidemiological variables. No rechallenge, i.e. the point at which same drug is again given to a patient after its previous withdrawl due to ADR, was performed on any patient.

The demography, nature of reaction, suspect medication use, and concomitant medication details were recorded in a format recommended by Indian Pharmacopoeia Commission, Ghaziabad under the Pharmacovigilance Program of India (Suspected adverse drug reaction) reporting form [19].

All reactions were classified into dermatological distinct morphological patterns by the consultant dermatologist and recorded by the resident on duty in the prescribed ADRs reporting form. All the patients were given adequate treatment like Tab Cetrizine 10 mg upto twice daily, Tab Hydroxyzine 25 mg upto four times a day, Tab chlorpheniramine maleate 2 mg upto four times a day, tab Prednisolone upto 1 mg/kg body weight once daily and calamine lotion for local application depending upon the severity of CADRs.

Causality assessment is the method by which the extent of relationship between a drug and a suspected reaction is established. This assessment was done with the help of a questionnaire, Naranjo causality assessment algorithm in which probability is established as Definite, probable, possible or doubtful on the basis of scoring [20].

Descriptive statistics was used for data analysis and significance of the associations of different parameters was evaluated by using Chi-Square test.

RESULTS

Total 111 cases of cutaneous adverse drug reactions (CADRs) were reported from Jan 2012 to Dec 2014 from our tertiary care teaching hospital, Srikot. Most of the CADRs were reported by Medicine followed by Dermatology, Surgery, Obstetrics and Gynaecology, Chest and Tuberculosis, Psychiatry, Paediatrics and Radiology departments of Veer Chandra Singh Garhwali Government Medical Sciences and research Institute, Srikot, India.

On collating the data it was found that the mean age of patients suffering from CADRs was 33.34±18.7 (mean±std. deviation) years and maximum number of CADRs were reported in the age group of 20-39 years (41,36.9%) followed by 40-59 years (32,28.8%) and 0-19 years (26,23.4%). Females were affected more than males as gender variation as seen in incidence of CADRs (W:M :: 66:45, 59.5% :: 40.5%). Maximum number of affected patients (86, 77.5%) recovered within seven days whereas 17 (15.3%) patients recovered in between 8 to 15 days. When we analysed different type of cutaneous manifestations, most of the CADRs were exanthematous eruptions (EE) (37, 33.3%). Fifteen cases (13.5%) had urticarial eruptions and 16 cases (14.4%) had pruritus. Ninety one (82%) cases recovered without any intervention whereas 17 (15.3%) cases required some intervention for recovery. Department of Medicine reported maximum cases of skin related ADRs (53, 47.7%), followed by Dermatology (29, 26.1%) and Surgery (17, 15.3%) [Table/Fig-1].

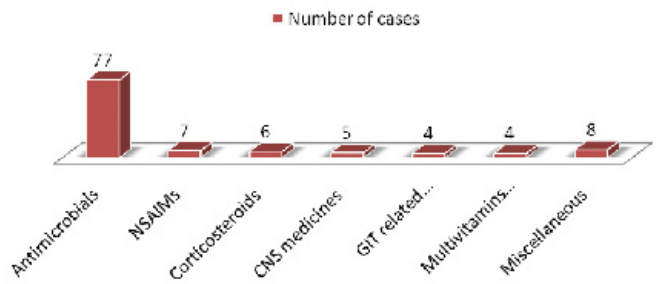
Most of the skin related ADRs were reported with antimicrobial agents (AMAs) (n=77, 69.4%) followed by Non-steroidal anti inflammatory medicines (NSAIMs) (n=7, 6.31%) [Table/Fig-2]. Amongst AMAs, cephalosporins (30, 39.5%) and quinolones (15, 19.7%) were the most frequent culprits. Causality assessment by Naranjo's scale showed that maximum CADRs had probable (57, 51.3%) relationship and forty seven (42.3%) had possible relationship with the drugs, whereas IV (42.3%) and Oral (40.5%) routes were the commonest routes of administration causing dermal ADRs.

On applying the chi-squares test to analyse the relationships, significant association was observed in relation to the duration (in days) of ADRs to the different types of cutaneous reaction (p = 0.038) [Table/Fig-3].

Similarly there were significant associations of various cutaneous reactions with outcome (p= 0.006) [Table/Fig-4], different departments (p= 0.014) [Table/Fig-5] and with different groups of medicines (p=0.008) [Table/Fig-6]. Out of total 77 ADRs due to antimicrobials, 40 (51.9%) cases were mainly of either exanthematous eruption or urticarial eruption types of cutaneous reactions.

1. Age distribution		
Number (n)	Mean age	Std deviation
111	33.34	18.689
2. Age range of patients		
Age range (years)	Frequency	Percentage
0-19	26	23.4%
20-39	41	36.9%
40-59	32	28.8%
60-79	12	10.8%
Total	111	100.0%
3. Male female ratios		
Gender	Frequency	Percentage
Female	66	59.5 %
Male	45	40.5 %
Total	111	100.0%
4. Number of affected days		
Duration	Frequency	Percentage
1-7 days	86	77.5%
8-15 days	17	15.3%
more than 15 days	8	7.2%
Total	111	100.0%
5. Different types of dermal reactions		
Dermal reactions	Frequency	Percentage
Exanthematous eruption	37	33.3%
Urticarial eruption	15	13.5%
Pruritus	16	14.4%
Pustular eruption	3	2.7%
Bullous eruption	3	2.7%
Drug induced vasculitis	4	3.6%
Photosensitivity eruptions	3	2.7%
Irritant dermatitis	5	4.5%
Mucosal ulcers	3	2.7%
FDE	3	2.7%
Others	19	17.1%
Total	111	100.0%
6. Different outcomes after ADRs		
Types of Outcome	Frequency	Percentage
Recovering	2	1.8%
Recovered	91	82.0%
Required intervention	17	15.3%
Unknown	1	0.9%
Total	111	100.0%

[Table/Fig-1]: Descriptive Table (n=111).



[Table/Fig-2]: Pharmacological group of medicines involved in ADRs.

Durations of reaction Classification	1-7 days	8-15 days	>15 days	Total
Exanthematous eruption	29	6	2	37
Urticarial eruption	14	1	0	15
Pruritus	12	3	1	16
Pustular eruption	0	1	2	3
Bullous eruption	3	0	0	3
Drug induced vasculitis	2	1	1	4
Photosensitivity eruptions	3	0	0	3
Irritant dermatitis	4	1	0	5
Mucosal ulcers	1	2	0	3
FDE	3	0	0	3
Others	15	2	2	19
Total	86	17	8	111

[Table/Fig-3]: Association of different dermal reactions and duration of reaction (n=111). (p = 0.038)

Classification	Recovering	Recovered	Required intervention	Unknown	Total
Exanthematous eruption	0	32	5	0	37
Urticarial eruption	0	12	3	0	15
Pruritus	0	14	2	0	16
Pustular eruption	0	3	0	0	3
Bullous eruption	0	1	2	0	3
Drug induced vasculitis	1	2	1	0	4
Photosensitivity eruptions	0	3	0	0	3
Irritant dermatitis	0	3	1	1	5
Mucosal ulcers	0	1	2	0	3
FDE	0	3	0	0	3
Others	1	17	1	0	19
Total	2	91	17	1	111

[Table/Fig-4]: Association of different dermal reactions with outcomes (n=111). (p= 0.006)

DISCUSSION

Cutaneous reactions are the most common manifestations of ADRs [21]. A wide spectrum of cutaneous manifestations ranging from exanthematous rashes to TEN can be produced by different classes of drugs. Reactions include exanthematous eruption, pruritis, erythema multiforme, fixed drug eruption, exfoliative dermatitis and others. Some severe Cutaneous adverse drug reactions (CADRs) may result in serious morbidity and even death [22].

In the present study, a total of 111 CADRs were reported. This number may not represent the true prevalence of CADR's during

Classification	Dermatology	Medicine	Obs.& Gyn.	pediatrics	Radiology	Surgery	Total
Exanthematous eruption	7	23	0	2	0	5	37
Urticarial eruption	1	6	2	3	0	3	15
Pruritis	1	7	0	0	1	7	16
Pustular eruption	0	1	1	0	1	0	3
Bullous eruption	1	2	0	0	0	0	3
Drug induced vasculitis	2	2	0	0	0	0	4
Photosensitivity eruptions	2	0	0	1	0	0	3
Irritant dermatitis	5	0	0	0	0	0	5
mucosal ulcers	0	3	0	0	0	0	3
FDE	2	1	0	0	0	0	3
Others	7	8	1	0	1	2	19
Total	29	53	4	6	2	17	111

[Table/Fig-5]: Association between reporting departments and types of dermal reactions. (n=111). (p= 0.014)

Classification	Anti-microbials	NSAIDS	Cortico-steroids	CNS drugs	GIT drugs	Multi-Vitamins	Misc.	Total
Exanthematous eruption	27	3	0	2	2	3	0	37
Urticarial eruption	13	1	0	0	0	0	1	15
Pruritus	12	0	1	0	0	0	3	16
Pustular eruption	2	0	1	0	0	0	0	3
Bullous eruption	1	0	0	1	1	0	0	3
Drug induced vasculitis	1	2	0	0	0	0	1	4
Photosensitivity eruptions	3	0	0	0	0	0	0	3
Irritant dermatitis	1	0	3	0	0	0	1	5
Mucosal ulcers	3	0	0	0	0	0	0	3
FDE	2	1	0	0	0	0	0	3
Others	12	1	2	2	0	1	1	19
Total	77	8	7	5	3	4	7	111

[Table/Fig-6]: Association between different groups of medicines and types of cutaneous reactions (n=111). (p= 0.008)

this period as patients in whom the drug could not be identified as well as those with reactions due to herbal or homeopathic drugs were not included. The mean age of the present study population was 33.34±18.68 years, and the majority (36.9%) of the patients belonged to the age group of 20-39, which is similar to the previous studies [14].

It was observed that lesser number of ADRs in Children than adult like other study [23]. Here it might be due to the reason that children are usually treated with lesser number of drugs and have normal kidney and liver function. Unlike our observations, some studies have shown more percentage of ADRs in elderly patients only when they were interviewed (20%), otherwise percentage was too less on spontaneous reporting (7%) [24]. Other factors like variation in awareness of health care among the regional population and approachability to health care centre may be responsible for difference in reporting of ADRs among elderly patients. We observed from Medical Records Department (MRD) of our hospital that elderly patients reporting in OPD is comparatively less than the other age group of patients. Reason for this might be correlated to surrounding demographic condition around the hospital, where it may not be easy for elderly patients to visit our tertiary centre from far-flung rural hilly areas. It has been observed in the study that the prevalence for CADRs in paediatric and geriatric patients was only 26 (23.4%) and 12 (10.8%) respectively. Unlike the experience of other investigators, our data showed that at least cutaneous ADR's are not more prevalent in these age groups.

In this study, mild predominance of CADRs was seen in females as compared to males (66:45) in concordance with some studies [14,25] but not with others [26]. This disparity might be there because of more consciousness of female towards cutaneous reactions and its reporting than the male counterpart. It can be justified by the finding that out of total of 29 cases reported from dermatology, 24 (82%) were females. The rate of adverse drug reaction in females is usually more than male [27]. Another point to consider is the trend of self-medication prevalent in our society, especially of analgesics and antipyretics. A very large number of females regularly self-medicate for ailments like headache, acidity, joint pain, seasonal fevers, premenstrual symptoms, acne and melasma (author's experience). Some of these drugs are easily available in general stores in our region and therefore females may be exposed to additional risk due to excess and unsupervised consumption of over the counter medicines.

The duration of individual reactions ranged between 1 to 21 days. Maximum number of affected patients (77.5%) had reaction for seven days whereas 15.3% patients had reactions for 8 to 15 days. So, most of the patients were relieved from the symptoms within one week. Significant associations have been observed in between various types of cutaneous reaction and duration of reaction (in days) ($p = 0.038$). Out of 37 cases of EE, 29 (78.4%) cases had reaction period for less than one week, whereas six EE cases (16%) had reaction period between 1 to 2 weeks.

On analysis of dermal manifestations, most of the CADRs were of EE type (33.3%). Fifteen cases (13.5%) were urticarial eruptions and 16 cases (14.4%) had pruritis. Similar type of finding was observed when out of 144 cutaneous reactions 72 (50%) patients had maculopapular rashes, whereas urticaria in 31 (21.5%) patients [13].

There was a significant association in between dermal manifestations and reporting departments ($p=0.014$). Maximum number of EE (62%) and urticarial eruption (40%) were reported by medicine department. Maximum incidence of exanthematous rash was seen with antimicrobials, followed by NSAIM. Significant association has been found in between different groups of medicines and various types of dermal reactions. Maximum incidence of EE, urticarial rashes and pruritus were seen in cases of antimicrobial use, followed by NSAIM use. This is in concordance with the results of other studies [28]. The current study also found the most common CADR with antiepileptic was exanthematous eruption (EE).

On applying the chi-squares test, it was revealed that outcomes from the reactions had significant association with the types of cutaneous reactions ($p= 0.006$). Ninety one (82%) cases recovered without any intervention which depicted that most of the CADRs were self limiting. Only stoppage of the suspected medicine was sufficient to relieve the reaction. So the early diagnosis of adverse drug reaction is of utmost importance. Out of the recovered cases, 32 cases were of EE type whereas 14 cases had pruritus. However, Seventeen cases (15%) required some kind of medical intervention to recover. The fact that 77.5% patients recovered within a week and 82% recovered without any active medical intervention indicates that, though CADR's are a common manifestation of ADR's but they are usually mild. Although they are alarming enough for the patient to seek medical help.

In this study, maximum CADRs were reported with use of AMAs (69.4%) followed by NSAIMs (6.31%) and corticosteroid (5.41%). Among the AMAs, cephalosporins were maximally associated with CADRs (39.5%) whereas in 15 cases (19.7%) fluroquinolones were responsible. Such a high rate of cephalosporins induced CADR's (30% as compared to penicillins-6%) might actually be depicting the irrational and more widespread use of this group as first-line or empirical therapy by the prescribers of this region, which is quiet alarming, from a completely different perspective, considering the possibility of emergence of resistant Microbasin. In such a remote region of the Himalayas. We need to be more rational and vigilant on the use of AMAs and should encourage their judicious prescription. The use of these medicines should be accompanied by an assessment of relative benefit risk ratio, and measures put into place to maximise benefits, although it is not so easy to achieve. For example, some medicines might be associated with bizarre type of adverse reactions. It is therefore necessary that we learn from our clinical experiences and attempt to employ prevention strategies for ADRs.

Similar results have been obtained in other studies where antimicrobials were responsible for 48.30% of CADRs [28], while other has reported incidence of antimicrobials as a causative factor for CADRs in 56.94% of cases [13]. There was one fatal CADR in the form of SJS due to carbamazepine in the present study. NSAIMs were the second leading cause (6.31%) of CADRs in this study but Sharma et al., has reported NSAIMs as a third leading cause (18%) following antimicrobials (42.6%) and anticonvulsants(22.2%) [26].

Causality assessment by Naranjo's scale showed that maximum CADRs had probable (51.3%) relationship and 42.3% had possible relationship with the suspected drugs. Causality assessment had its share of uncertainty in polypharmacy cases, especially as rechallenge was not attempted deliberately owing to ethical reasons.

Although rechallenge is the most confirmatory clinical method for the confirmation of causative drug for the ADR, but it is still a debatable issue. According to Stubb et al., rechallange in a controlled condition is always better than the repeated reactions in future [29]. All the cases have been represented below (annexure 1).

LIMITATION

The limitations of the present study were its short duration with less number of CADRs and we did not assess preventability of ADRs. The actual number of patients registered in the Dermatology out-patient department, clinically diagnosed as a suspected case of CADR, was much higher than the reported cases, because in majority of the cases, the suspected drugs could not be identified. The problem of underreporting of ADRs is much bigger issue and

should be addressed immediately and lastly, due to ethical reasons, rechallenge was not performed and so, there were probable and possible CADR's but no definite CADR. Mild predominance of CADR's in females needs to be further corroborated from other future studies mapping different regions of the world in general, and the Indian-subcontinent in particular.

CONCLUSION

CADRs have found to be a significant problem in healthcare and most of these reactions may be iatrogenic. Hence it is of utmost importance that clinicians must have comprehensive knowledge of suspected adverse drug reactions with all older and newer medicines. Along with this, early reporting and prevention of adverse drug reactions by physician will definitely reduce the frequency and severity of ADRs and eventually the patient safety will be enhanced.

Similarly, dermatologist must be well aware of the protean cutaneous manifestations of CADR's and as well as have knowledge of the drugs which are most frequently associated with such reactions. Maximum CADR's is being reported with antimicrobial agents is something alarming and need to be carefully investigated further. As it might be an indicator of widespread irrational and erratic use of AMA's by both registered and unregistered prescribers (quack) around this region.

Hence, the clinicians should be encouraged for the reporting of ADRs, because in this practice they will certainly early recognize and respond to the reaction and improve the patient safety by prevention of these reactions in future.

REFERENCES

[1] Leap LL, Brennan TA, Laird NA, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Eng J Med.* 1991;324(6):377-84.

[2] Jha AK, Prasopa-Plaizier N, Larizgoitia I, Bates DW. Patient safety research: an overview of the global evidence. *Qual Saf Health Care*. 2010;19(1):42-47.

[3] D'Arcy PF, Griffin JP. Thalidomide revisited. Adverse Drug React Toxicol Rev. 1994;13(2):65-76.

[4] Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA*. 1995;274(1):29-34.

[5] Gandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E, et al. Adverse drug events in ambulatory care. *N Engl J Med*. 2003;348(16):1556-64.

[6] Kaushal R, Bates DW, Landrigen C, Mekenna KJ, Clapp MD, Federico F, et al. Medication errors and adverse drug events in paediatric inpatients. *JAMA.* 2001;285(16): 2114-20.

[7] Ramesh M, Pandit J, Parthasarthi G. Adverse drug reactions in a south Indian hospital- their severity and cost involved. *Pharmacoepidemiol Drug Saf*. 2003;12(8):687-92.

[8] Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA.* 1998;279(15):1200-05.

[9] Nayak S, Acharjya B. Adverse cutaneous drug reaction. *Indian J Dermatol*. 2008;53(1):2-8.

[10] Craig KS, Edward WC, Anthony AG. Cutaneous drug reactions. *Pharmacol Rev.* 2001;53:357-79.

[11] Noel MV, Sushma M, Guido S. Cutaneous adverse drug reactions in hospitalized patients in a tertiary care centre. *Indian J Pharmacol*. 2004;36(5):292-95.

[12] Uppal R, Jhaj R, Malhotra S. Adverse drug reactions among inpatients in a north Indian referral hospital. *Natl Med J India*. 2000;13(1):16-18.

[13] Jhaj R, Uppal R, Malhotra S, Bhargava VK. Cutaneous adverse reactions in in-patients in a tertiary care hospital. *Indian J Dermatol Venereol Leprol.* 1999;65:14-17.

[14] Pudukadan D, Thappa DM. Adverse cutaneous drug reactions: clinical pattern and causative agents in a tertiary care centre in south India. *Indian J Dermatol Venereol Leprol*. 2004;70(1):20-24.

[15] Chatterjee S, Ghosh AP, Barbhuiya J, Dey SK. Adverse cutaneous drug reactions: a one year survey at a dermatology outpatients clinic of a tertiary care hospital. *Indian J Pharmacol*. 2006;38(6):429-31.

[16] Gruchalla R. Understanding drug allergies. *J Allergy Clin Immunol.* 2000;105:637-44.

[17] Chakrabarty M, Thawani V. Starting a pharmacovigilance centre: actions for implementation. *J Pharmacol Pharmacother*. 2011;2(4):295-99.

[18] Morimoto T, Fukui T, Lee TH, Matsui K. Application of U.S. guidelines in other countries: aspirin for the primary prevention of cardiovascular disease in Japan. *Am J Med.* 2004;117(7):459-68.

[19] Available from: http:// www.ipc.gov.in/PvPI/pv_adr.html [last accessed on 2015 Nov 26]

[20] Srinivasan R, Ramya G. Adverse drug reaction-causality assessment. *IJRPC.* 2011;1(3):606-12.

[21] Chawla S, Kalra BS, Dharmshaktu P, Sahni P. Adverse drug reaction monitoring in a tertiary care teaching hospital. *Pharmacol Pharmacother*. 2011;2(3):196–98.

[22] Sushma M, Noel MV, Ritika MC, James J, Guido S. Cutaneous adverse reactions: a 9-year study from a South Indian hospital. *Pharmacoepidemiol Drug Saf.* 2005;14(8):567–70.

[23] Gonzalez Martin G, Caroca CM, Paris E. Adverse drug reactions (ADRs) in hospitalized pediatric patients . A prospective study. *Int J Clin Pharmacol Ther.* 1998;36(10):530–33.

[24] Somers A, Petrovic M, Robays H, Bogaert M. Reporting adverse drug reactions on a geriatric ward: a pilot project. *Eur J Clin Pharmacol.* 2003;58(10):707–14.

[25] Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, Ghiotto E, et al. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *Br J Clin Pharmacol.* 1999;48(6):839–46.

[26] Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: clinical pattern and causative agents--a 6 year series from Chandigarh, India. *J Postgrad Med*. 2001;47(2):95–99.

[27] Bennett PN, Brown MJ. Unwanted effects and adverse drug reactions. Clinical Pharmacology. 10th ed. Edinburgh, London and New York: Churchill Livingstone; 2003. Pp. 115-29.

[28] Nandha R Gupta A and Hashmi A. Cutaneous adverse drug reactions in a tertiary care teaching hospital: A North Indian perspective. *Int J Appl Basic Med Res.* 2011;1(1):50–53.

[29] Stubb S, Heikkila H, Kauppinen K. Cutaneous reactions to drugs: a series of in patients during a five-year period. *Acta Derm Venereol* (*stockb*). 1994;74(4):289-91.

Annexure 1

Reference number mentioned in the discussion	Name of author	Year of publication	Findings of the study
[21]	Chawla S, Kalra BS, Dharmshaktu P, and Sahni P	2011	Cutaneous manifestations which included rash, urticaria, dermatitis, Steven Johnson syndrome, Toxic epidermal necrolysis, etc were most common ADRs with an incidence of 42%.
[22]	Sushma M, Noel MV, Ritika MC, James J, Guido S	2005	The most common type of ADR was maculopapular rash (42.7%), followed by Stevens-Johnson syndrome (SJS) (19.5%) and fixed drug eruption (11.4%).
[14]	Pudukadan D, Thappa DM	2004	The mean age of patients with cutaneous drug eruptions was 37.06 years (± 30.12; range, 9-75 years). Most of them (47/90) were in the age group of 20-39 years, followed by 22 patients in the 40-59 years age group, 11 in the 60-79 years age group, and 6 in the 0-19.
[23]	Gonzalez Martin G, Caroca CM, Paris E.	1998	Out of 227 children on average three drugs, Six of them developed ADRs (4 vomiting with antineoplastic or opioid, 1 diarrhoea and 1 rash with an antibiotic), i.e. 2.64% of children hospitalized taking a drug (6/227).
[24]	Somers A, Petrovic M, Robays H, Bogaert	2003	During the 8 months, for 168 patients, 12 spontaneous reports were received from physicians and nurses. Fifty-six of these patients were interviewed and 32 ADRs were reported. Only 2 ADRs detected by patient interview were also reported spontaneously. The interviews of the 56 geriatric patients indicated that 20% of them were admitted to the hospital because of an ADR. ADRs occurred during hospital stay in another 20% of those patients.
[25]	Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, Ghiotto E, et al	1999	The greater consumption of medications by women and the unbalanced sex ratio in the elderly population may at least partly account for the excess of reports in women.

[26]	Sharma VK, Sethuraman G, Kumar B	2001	A total of 500 patients with cutaneous ADR were enrolled during the study period. There were 298 (59.6%) males and 202 (40.4%) females, The drugs most often incriminated for the various cutaneous ADR were antimicrobials (42.6%), anticonvulsants (22.2%) and NSAIDs (18%).
[27]	Bennett PN, Brown MJ	2003	Females are more likely to experience adverse reactions.
[28]	Nandha R Gupta A and Hashmi A	2011	The drugs most commonly responsible for CADRs were antimicrobials (48.30%), followed by nonsteroidal anti-inflammatory drugs (NSAIDs) (21.90%) and anti-epileptics (13.20%).
[13]	Jhaj R, Uppal R, Malhotra S, Bhargava VK	1999	Maculopapular rashes were the most common reactions, reported in 72 (50% of all cutaneous reactions) patients [Table - 1]. Urticaria was reported in 31 (21.5%) patients. Antimicrobials were most frequently associated with cutaneous adverse events, being responsible for 82 (56.94%) reactions.
[29]	Stubb S, Heikkila H, Kauppinen K.	1994	Rechallenge involves only a minimal risk when performed rationally and with caution. Stubb et. al also concluded that verifying the drug responsible for the eruption is of paramount importance for detecting the causative agent. According to them it is better to induce a mild reaction under controlled conditions than to allow the patient to suffer repeated severe reactions at home.

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Dermatology, VCSGGMSRI and its Associated HNB Base & Teaching Hospital, Srikot, Pauri-Garhwal, Uttarakhand, India.
2. Associate Professor, Department of Pharmacology, VCSGGMSRI, Srikot, Pauri-Garhwal, Uttarakhand, India.
3. Technical Associate, Department of AMC, VCSGGMSRI, Srikot, Pauri-Garhwal, Uttarakhand, India.
4. Professor, Department of Pharmacology, People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr Rangeel Singh Raina,
Associate Professor, Department of Pharmacology, VCSGGMSRI, Srikot, Pauri-Garhwal, Uttarakhand- 246174, India.
E-mail: rainarangeel@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Sep 22, 2015**
Date of Peer Review: **Nov 16, 2015**
Date of Acceptance: **Dec 11, 2015**
Date of Publishing: **May 01, 2016**