Study of Causality, Preventability and Severity of Cutaneous Adverse Drug Reactions in a Tertiary Care Institute

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Abstract :

Aims and objectives : To find out the most common drug causing cutaneous ADRs (adverse drug reactions), most common pattern of cutaneous ADR and new emerging drugs causing cutaneous ADRs. To assess causality, severity and preventability of cutaneous ADRs. **Material and methods :** Analysis of 100 patients who presented with cutaneous ADRs as a part of pharmacovigilance program was done. Causality assessment was done according to naranjo's algorithm and by guidelines of WHO (world health organization). Severity was assessed by modified hartwig and siegel scale. Preventability was assessed by modified schumock and thornton criteria. **Results :** 65% of patients were between 20 to 50 years. Male to female ratio was 0.75:1. Most common cutaneous ADRs was urticaria and angioedema (35%) followed by fixed drug reaction (FDR-19%), maculopapular rash(12%) and others. Antimicrobials (35%) were the most common culprit followed by NSAIDs (27%) and others. Fluoroquinolones (54.28%) were the most common antimicrobial responsible for cutaneous ADRs. Most common drugs responsible for urticaria were NSAIDs and for FDR were fluoroquinolones. Majority (82%) ADRs were moderately severe. 34% of cutaneous ADRs were preventable. **Conclusion :** Among antimicrobials, fluoroquinolones is emerging as common drug group causing cutaneous ADRs. Many of the cutaneous ADRs are preventable.

Key Words : Cutaneous adverse drug reactions, severity, preventability

Introduction :

An adverse drug reaction (ADR) may be defined as an undesirable clinical manifestation resulting from administration of a particular drug; this includes reactions due to overdose, predictable side effects and unanticipated adverse manifestations. Another definition is that of 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product[1]. ADRs are underreported and are an underestimated cause of morbidity and mortality [2].Under-reporting of ADRs is a major problem; reasons include lack of time and report forms, and misconception of its importance [3].

The wide and indiscriminate use of drugs has increased the incidence and the modes of presentation of cutaneous ADRs. A more detailed description of cutaneous eruption is necessary to know mechanism as well as prognostic factors. Common cutaneous ADRs are urticaria/ angioedema, FDR, and exanthematous eruptions. Antimicrobial, antipyretic and anti-inflammatory agents remain the common culprits. [4]

Aims and objectives: To find out the most common drug causing cutaneous ADRs (adverse drug reactions) and to find out the most common form of cutaneous ADR. To assess the causality, severity and preventability of cutaneous ADRs.

Material and methods :

Analysis of total 100 patients with cutaneous ADRs reported to department of Dermatology of a tertiary care institute as a part of established pharmacovigilance programm was done. All patient's data were collected in 'suspected adverse drug reaction reporting form' by CDSCO (central drugs standard control organization), India. Causality assessment was done according to modified naranjo's algorithm-1891 [5] and by guidelines of WHO (world health organization) Upapsala Monitoring centre-2002 [6]. Severity was assessed by modified hartwig and siegel scale 1992 [7]. Preventability was assessed by modified schumock and thornton criteria 1991 [8].

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Results :

Out of total 100 patients 65% of patients were between 20 to 50 years with majority 35% were of 20 to 30 years (Figure-1). Out of total 100, 43 were male and 57 were female patients. Male to female ratio was 0.75:1.

Antimicrobials (35%) were the most common culprit followed by NSAIDs (27%) and others (figure-2). Out of total 35 cases due to antimicrobials; 54.28% (n=19) were due to fluoroquinolones; 20% (n=7) were due to penicillin group of drugs; 14.28% (n=5) were due to cycline group of drugs and 11.42% (n=4) were due to antitubercular drugs. Tropicamide eye drops were culprit in 3 patients. Other drugs which were implicated were doxofylline, hydroxychloroquine, progesterone, isoxsuprine, acetazolamide, amifostine, naproxen, statin, fluconazole, PPD (purified protein derivative), sitagliptin, dextromethorphan and topical minoxidil (n=1 each).

Figure: 1: Age distribution of study participants

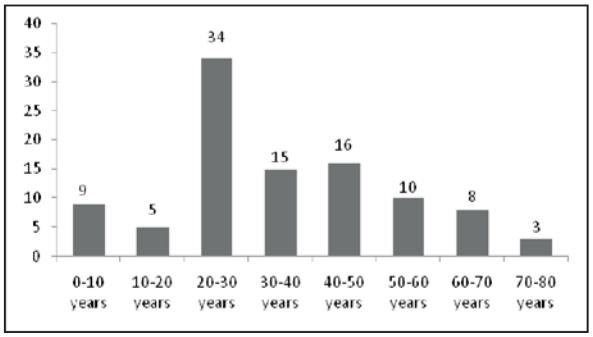
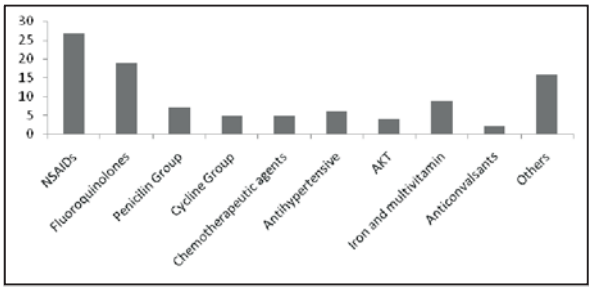
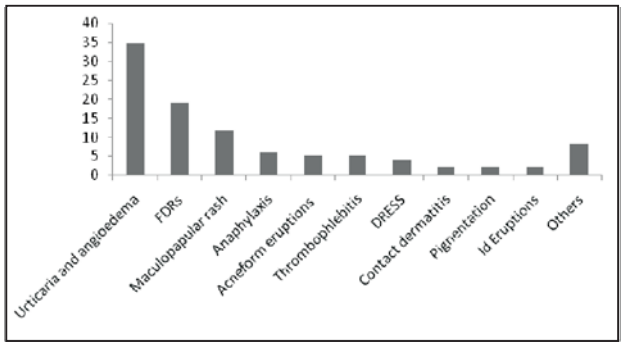


Figure: 2: Number of patients with drugs causing cutaneous ADRs.



Most common cutaneous ADR was urticaria and angioedema (35%) followed by fixed drug reaction (FDR-19%), maculopapular rash (12%) and others (figure-3). NSAID (51.42%) was the most common class of drug responsible for urticaria and angioedema.

Figure: 3: Distribution of Different types of cutaneous ADRs



Out of total 19 patients of FDR, in 15(78.94%) patients fluoroquinolones were responsible and amongst which ofloxacin (66.66%) was most common. Most common drugs causing maculopapular rash (n=12) were antimicrobials (50%, n=6).Drugs causing urticaria and angioedema, FDR and maculopapular rash in order of frequency mentioned in Table-1. Figure 4 shows photographs of angioedema, DRESS syndrome and FDR in patients.

Anaphylaxis was seen in 6% (n=6) of patients, with NSAID (50%, n=3) being most common offending drug. Acneform eruption was seen in total 5% (n=5) of

Table: 1: Various drugs causing urticaria, FDR and maculopapular rash

Urticaria and angioedema (n=35)	NSAIDs (n=19) Antimicrobials (n=6) ACEI (angiotensin converting enzyme inhibitors; n=4) Naproxen (n=1) Isoxsuprine (n=1) Dextromethorphan (n=1) Topical minoxidil (n=1) Purified protein derivative (n=1) Folic acid (n=1)
FDR (n=19)	Fluoroquinolones (n=15) NSAIDs (n=4)
Maculopapular rash (n=12)	Antimicrobials (n=6) NSAIDs (n=4) Acetazolamide (n=1) Chemotherapy (n=1)

patients, with antitubercular drug (AKT) being major culprit (80%, n=4). Thrombophlebitis was observed in 5% (n=5), all cases were due to injectable iron sucrose. Drug rash eosinophilia and systemic sign symptoms (DRESS) was seen in total 4 (4%) patients; 2(50%) cases were due to anticonvulsants and other two were due to meloxicam and AKT. Other reactions like hyperpigmentation, contact dermatitis and id eruptions were observed (n=2 each).

Other reactions included pruriginous papules, lichenoid dermatitis, acute generalized exanthematous pustulosis (AGEP), psoriasiform dermatitis, photo dermatitis, nicolau syndrome, xerosis and toxic epidermal necrolysis (n=1 each).The drug implicated in single patient of TEN was amifostine which is used as radioprotective agent.

Using modified Naranjo's Algorithm causality assessment score, 20% ADRs were definitly, 55% were probably and 25% were possibly caused by drug in question. Same analysis using WHO's criteria for causality assessment revealed that 29% of ADRs were certainly, 43% were probably/likely , 25% were possibly and 3% were unlikely caused by the drug in question.Most of cutaneous ADRs (82%) were moderately severe in nature, and 18% were mild in nature. Out of total 82, 4 patients showed severity of level 4a which means cutaneous ADR was the reason of increase in length of stay by at least one day and 3 patients showed level 4b severity which means cutaneous ADR was the reason for admission.

Out of total 100, 34% cutaneous ADRs were definitely preventable, 12% were probably preventable and 54% were not preventable. Out of total 7 patients with level 4 severity, in 4 patients cutaneous ADR was not preventable, in 2 patients it was probably preventable and in 1 patient it was definitely preventable.30% of patients reported to us within 24 hours of starting ADR after drug administration, 8% reported within 24-48 hours, 9% reported within 48-72 hours; while majority (53%) reported after 72 hours.

Discussion :

In our study most(65%) of the patients belonged to the age group of 20-50 years with majority 35% were of 20-30 years age group which was comparable to study by Pudukadan D et al[9] and Shah SP et al[10]. In our study male to female ratio was 0.75:1. Pudukadan D et al [9] also reported female preponderance. This might be due to females being more conscious about appearance.

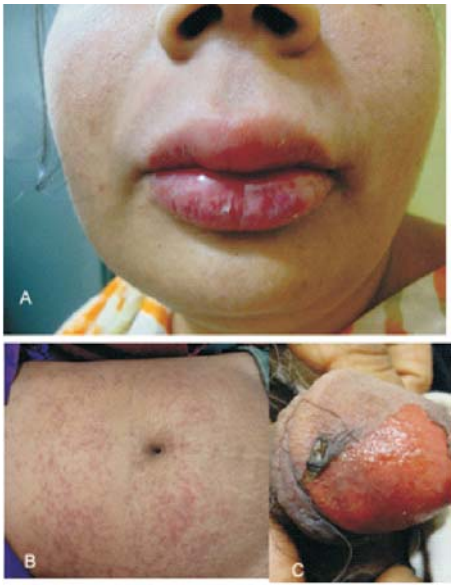
In our study we found most common drug group was antimicrobials (35%); which was comparable by frequency (34.1%) reported by Chatterjee S et al [11]. Other studies by Pudukadan D et al[9], Shah SP et al[10], Sharma VK et al[12] , Nandha R et al[13] and Ghosh S et al[14]; all reported antimicrobials as most common drug group responsible for cutaneous ADRs though in higher frequency. We found that most common antibiotic group responsible for cutaneous ADRs was fluoroquinolones (54.38%) in our study. Shah SP et al [10] reported most common antibiotic was co-trimoxazole(15%) and fluoroquinolones(15%). Pudukadan D et al [9], Chatterjee S et al [11] and Sharma VK et al [12] reported most common antibiotic was co-trimoxazole. This difference may be due to difference in prescribing pattern at various institutes and time of reporting as physician's choice of antibiotics has changed over the years.

Most common cutaneous ADR in our study was urticaria and angioedema (35%). Chatterjee S et al [11] also reported most common cutaneous ADR to be urticaria in 27.19% though less in frequency in comparison to our study.

Pudukadan D et al [9] and Shah SP et al [10] reported FDR being most common cutaneous ADR in their study. In our study FDR (19%) was second most common pattern of cutaneous ADR. Sharma VK et al [12],Nandha R et al [13] and Ghosh S et al [14] reported maculopapular rash being most common cutaneous ADR in their study. Maculopapular rash (12%) was third most common ADR in our study. This difference may be due to different genetic background of various ethnic groups as all studies mentioned above are from north and south India compared to ours which is from a region of western India.

We reported fluoroquinolnes being most common drug responsible for FDR in 78.94%; of which ofloxacin was culprit in 66.66% of patients. Sharma VK et al [12] reported sulfonamide was most common drug responsible for FDR in 43.3% of patients. Chatterjee S et al [11] reported cotrimoxazole being most common culprit for FDR in 51.6% of patients. They also reported only antimicrobials were responsible for FDR; in contrast to our study in which majority (89.47%) was due to antimicrobials but 10.53% were due to NSAIDs. Sharma VK et al [12] reported other drugs responsible for FDR which include NSAIDs. This difference again may be due to different prescribing pattern and genetic predisposition.

Figure: 4: (A) Angioedema (B) DRESS Syndrome (C) FDR



In our study we found that most common drug group responsible for urticaria and angioedema was NSAIDs (51.42%). Chatterjee S et al [11] and Sharma VK et al [12] also reported most common drug group responsible for urticaria being NSAIDs though in higher and less percentage respectively.

Ghosh S et al [14] reported majority (53%) of cutaneous ADR were moderately sever in nature, 21% being mild in severity and 25% being level 5(sever) in severity. In contrast in our study we found that majority (82%) of moderate severity and 18% being mild in severity and none in level 5 severity. Shah SP et al [10] reported 96.5% of reaction were moderately severe in nature near comparable to our study.Ghosh S et al [14] reported causality assessment according to naranjo's criteria; as definite in 5.66%, probable in 54% and possible in 39.62%. According to modified Naranjo's Algorithm causality in our study was definite in 20%, probable in 55% and possible in 25%. Causality assessment according to WHO's criteria showed certain in 29%, probable/likely in 43%, possible in 25%, and unlikely in 3%.

In our study; out of total 100, 34% cutaneous ADRs were definitely preventable, 12% were probably preventable and 54% were not preventable. Out of total 7 patients with level 4 severity, in 4 patients cutaneous ADR was not preventable, in 2 patients it was probably preventable and in 1 patient it was definitely preventable. So by proper history taking for past history of drug reactions, calculating proper dose, deciding proper route and frequency of administration and appropriate drugs for clinical condition many of cutaneous drug reactions can be prevented. One should also keep in mind about probable drug interaction related ADR, compliance of patient and therapeutic drug monitoring whenever necessary. One should advice patient for preventive measures if known to prevent ADR.

Conclusion :

Among the antimicrobials, fluoroquinolones is emerging as common drug group to cause cutaneous ADRs. With proper history taking, dose monitoring, having knowledge about drug interaction and choosing appropriate drug for patient's clinical condition we can prevent many of the cutaneous drug reactions.

Limitation: Rechallenge was not done in any of our patients.

References :

1. Edwards IR, Aronson JK. Adverse drug reactions: defi nitions, diagnosis, and management. Lancet 2000; 356:1255–9.
2. Brown SD Jr, Landry FJ. Recognizing, reporting, and reducing adverse drug reactions. South Med J 2001; 94:370–3.
3. Billimoria FE, Shah BJ. Drug reactions. In: Valia RG, Valia AR, editors. IADVL textbook of dermatology. 3rd ed. Mimbai: Bhalani Publication House; 2012.p.1633-68.
4. Bigby M, Jick S. Drug induced cutaneous reactios- A report from Boston collaborative drug surveillance programme. JAMA. 1986; 256:3358-63.
5. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981; 30:239–245.
6. World Health Organization (WHO). The Importance on Pharmacovigilance. Safety monitoring on medicinal products. Geneva (Switzerland): Office of Publications, World Health Organization; 2002.
7. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992; 49:2229-32.
8. Lau PM, Stewart K, Dooley MJ. Comment: hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother 2003; 37:303-05.
9. Pudukadan D, Thappa DM. Adverse cutaneous drug reactions: Clinical pattern and causative agents in a tertiary care center in South India. Indian J Dermatol Venereol Leprol 2004; 70:20-4.
10. Shah SP, Desai MK, Dikshit RK. Analysis of Cutaneous Adverse Drug Reactios at a Tertiary Care hospital- a prospective study. Trop J Pharm Res, August 2011; 10(4):517-22.
11. Chatterjee S, Ghosh A P, Barbhuiya J, Dey S K. Adverse cutaneous drug reactions: A one year survey at a dermatology outpatient clinic of a tertiary care hospital. Indian J Pharmacol 2006; 38:429-31.
12. Sharma V K, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: clinical pattern and causative agents--a 6 year series from Chandigarh, India. J Postgrad Med 2001;47:95
13. Nandha R, Gupta A, Hashmi A. Cutaneous adverse drug reactions in a tertiary care teaching hospital: A North Indian perspective. Int J Appl Basic Med Res 2011 Jan-Jun;1(1);50-53.
14. Ghosh S, Acharya LD, Rao PG. Study and evaluation of the various cutaneous adverse drug reactions in Kasturba hospital, Manipal. Indian J Pharm Sci 2006; 68:212-5.