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Research Article

ASSESSMENT OF CUTANEOUS ADVERSE DRUG REACTIONS REPORTED BY SPONTANEOUS REPORTING SYSTEM

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ABSTRACT

The safety profile of a drug requires a continuous monitoring of its adverse drug reactions (ADRs) by means of an effective Pharmacovigilance system. Spontaneous reporting system plays a vital role in the assessment of risk-benefit profile of a drug. Our present study aims to assess the cutaneous adverse drug reactions associated with commonly used drugs in the clinical practice. A prospective non-interventional observational study was conducted from January 2017 to July 2017 with prior orientation on the importance of pharmacovigilance and spontaneous reporting system. A total of 71 ADR reports were collected and were assessed for incidence, age group involved, common drug class and individual drugs associated with cutaneous ADRs, causality assessment and the outcome of the patient. Majority of cutaneous reactions were occurred in female patients (43, 60.56) in the age group of 18-44 yrs. The most common cutaneous ADRs were found to be rash (28, 39.44%) followed by Urticaria (09, 12.68%) and the common offending suspected class were found to be antimicrobials (42, 59.15%). About (61, 85.92%) reactions were recovered and causality assessment was probable in 60 (84.51%) cases. Current study contributes to the patient safety and rational use of drug by assessing, reporting and treating ADRs.

INTRODUCTION

Drugs being the most common medical interventions for various ailments may also cause either expected or unexpected adverse drug reactions (ADRs). The Product's effectiveness with limited safety profile can be provided with preclinical and clinical studies during the drug development process. Indeed many clinical trials fail to detect side effects which may manifest as adverse drug reactions where the limited population is being exposed to the drug. Thus a continuous monitoring system for the drug that has been introduced into the market is essential with adequate awareness (Vimmi *et al.* , 2015, Ramesh at al., 2016).

It has been proved long ago by publishing a letter received by Dr. Mcbride from Australia on increased frequency of limb malformations (phacomelia) (unexpected ADR) among babies due to intake of new hypnotic drug-thalidomide by their mothers for morning sickness (Ramesh at., 2016). Adverse drug reaction (ADR) is defined by the World Health Organisation (WHO) as "any noxious, unintended or undesired effect of a drug that occurs at doses used in humans for prophylaxis diagnosis, therapy or modification of physiological functions" (Roy *et al*., 2015).

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ADRs may range from mild reaction to severe ones & may be even fatal and account for significant morbidity and mortality in health sector. Serious and fatal adverse cutaneous drug reaction is common causes of hospitalization and prolongation of indoor patient stay in hospital (Mahapatra *et al*., 2012,. Reena *et al*., 2014).

Approximately 5-8% of all hospitalizations worldwide are due to ADR and Cutaneous adverse drug reactions (CADR) are the commonest ADRs and are responsible for about 2% of hospital admissions. Cutaneous drug eruptions are one of the most common types of adverse reaction to drug therapy, with an overall incidence rate of 2–3% in hospitalized patients (Reena *et al*., 2014).

Spontaneous adverse Drug Reaction Reporting: India

The Pharmacovigilance Programme of India (PvPI) was initiated by the Government of India in July 2010 with AIIMS, New Delhi as NCC for monitoring ADRs in the country for safe-guarding public health by assuring the safety of medicinal products. The NCC was shifted from AIIMS, New Delhi to IPC, Ghaziabad on 15th April 2011. NCC has identified various teaching and corporate hospitals all over India as adverse drug reaction monitoring centers (AMCs) with the objective to improve the reporting rate of ADRs by collecting ICSRs (Individual case safety reports) (Guidance

document for adverse drug reaction reporting, IPC, NCC-PvPI, 2014).

Madras Medical College (MMC), Chennai is one of the AMCs under PvPI and is involved in spontaneous (passive) reporting of ADRs since 2010 through VIGIFLOW, an ICSR management system provided by WHO-UMC.

Aim & Objectives

To assess the cutaneous adverse drug reactions associated with commonly used drugs in the clinical practice at Rajiv Gandhi Government General Hospital (RGGGH)

METHODS

A prospective non-interventional observational study was conducted over a period of 7 months from January 2017 to July 2017. The clinicians and support staff was oriented towards the importance of pharmacovigilance and spontaneous reporting system by conducting lectures and meetings. They were also briefed on the method of filling the suspected adverse drug reaction reporting forms (sADR reporting form – PvPI).

The ADR reporting form contains patient details, reaction details, suspected and concomitant drug(s) details, medical history, relevant investigation details, seriousness of the reaction, outcome, causality assessment and reporter's details and the same were evaluated/reviewed by the PV personnel (PvPI- Coordinator & Pharmacovigilance Associate) for quality of the ICSR.

All the spontaneously reported cutaneous adverse drug reactions were assessed for incidence, age group involved, common drug class and individual drugs associated with cutaneous ADRs, causality assessment (WHO-UMC scale) (WHO-UMC system for standardized case causality assessment), seriousness of the reaction according to ICH (ICH Harmonised Tripartite Guideline) and the outcome of the patient.

RESULTS

A total of 71 spontaneous ADR reports were collected during the period of January 2017 to July 2017 from Rajiv Gandhi Government General Hospital and were assessed.

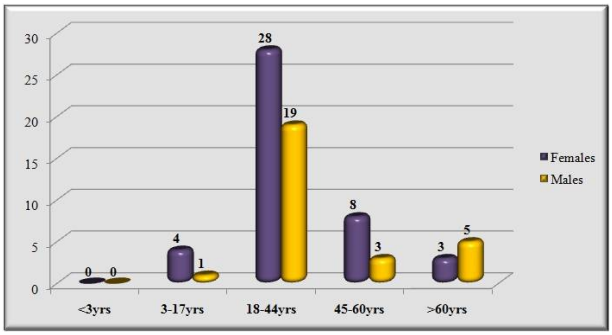

Figure 1 ADRs occurred in the age group

Out of 71 ADR reports, majority were occurred in female patients (43, 60.56%) followed by male patients (28, 39.44%) and found to be in the age group of 18-44 yrs (F-28 & M-19 respectively) and least were in 3-17 yrs age group.

Table 1 Suspected drugs with cutaneous reaction details

S.No.	Suspected Drugs	Reaction details	Frequency (n)
1	Ciprofloxacin	Rash (2) Erythematous macule (2) Urticaria (1) TEN (1)	06
2	Levofloxacin	Erythematous macules (1)	01
3	Norfloxacin	Hyperpigmentation (1) Urticaria (1)	02
4	Ceftriaxone	Rash (11) Erythematous rash (1) FDE (1)	12
5	Cefotaxime	Rash (2) Urticaria (1)	04
6	Cefixime	FDE (4)	04
7	Cefuroxime	Skin lesions (1)	01
8	Sulphasalazine	Rash (2) SJS-TEN overlap (1)	03
9	Amoxiclav	Urticaria (1)	01
10	Amoxicillin	FDE (1)	01
11	Ampicillin	Rash (1)	01
12	Vancomycin	Exfoliative rash (1) Rash (1)	02
13	Doxycycline	Maculopapular rash (1)	01
14	Azithromycin	FDE (1)	01
15	Fluconazole	Erythematous Rash (1)	01
16	Phenytoin	Maculopapular rash (1) Urticaria (1) SJS (1)	02
17	Carbamazepine	Maculopapular rash (1) rash (1)	03
18	Metformin	Lichen Planus (1)	01
19	Prednisolone	Acne (1)	01
20	Dapsone, Rifampicin, Clofazimine	Erythematous lesions (1)	01
21	Diclofenac	Maculopapular rash (1) Urticaria (1)	02
22	Aceclofenac	FDE (1)	01
23	5 Fluorouracil	Hyperpigmentation (1)	01
24	Tretinoin	Erythematous rash (2)	02
25	Iron sucrose	Rash (1)	01
26	Emeset	Rash (1)	01
27	Astymin	Rash (1)	01
28	Glimepiride+Metformin+Voglibose	Hyperpigmentation (2)	02
29	Iohexol	Urticaria (1)	01
30	Insulin	Maculopapular rash (1) Nodules at the injection site (1)	02
31	Magaldrate	Rash (1)	01
32	Chlorpheniramine maleate	Urticaria (1)	01
33	Human Albumin	Rash (1)	01
34	Ranitidine	Rash (1)	01
35	Bortezomib	Rash (1)	01
36	Danazol	Urticaria (1)	01
37	Meropenem	Rash (1)	01
38	Dicyclomine	Allergy (1)	01

The most common offending suspected class of drugs causing cutaneous ADRs were found to be antimicrobials (42, 59.15%) followed by antiepileptics (05, 7.04%) and NSAIDs (03, 4.23%). Among the 38 suspected drugs, the most frequent drugs causing cutaneous ADRs are Ceftriaxone (12, 16.90%), Ciprofloxacin (06, 8.45%), Cefixime (04, 5.63%) followed by Sulfasalazine (03, 4.23%) and Carbamazepine (03,4.23%).

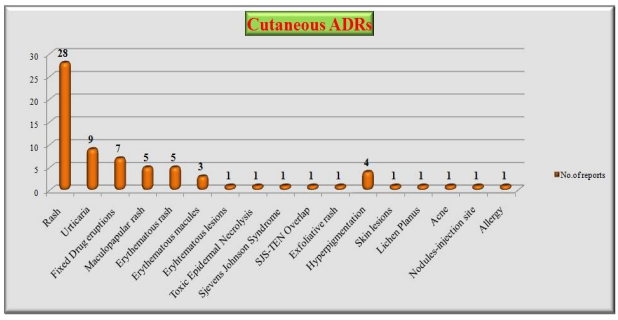

Figure 2 Cutaneous Adverse Drug Reactions

The most commonly reported cutaneous ADR is rash (28, 39.44%) followed by Urticaria (09, 12.68%), Fixed drug eruptions (07, 9.86%), Maculopapular rash (05, 7.04%), Hyperpigmentation (04, 5.63%), Toxic Epidermal Necrolysis (01, 1.41%) and Stevens Johnson Syndrome (01, 1.41%).

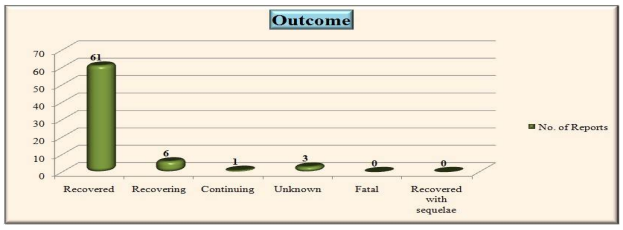

Figure 3 Outcome of the cutaneous adverse drug reactions

Among the 71 cutanepous ADRs reported no fatality was observed. And the outcome was found to be "recovered" in 61 (85.92%) patients, recovering in 6 (8.45%) patients, unknown in 3 (4.23%) patients and continuing in 1 (1.41%) patient.

Table 2 Dechallenge/Rechallenge details

S.No.	Action taken	No. of Reports
1	Drug dechallenge	65
2	No dechallenge/treatment given for ADR	06

It was found that in 65 (91.55%) cases the offending drug was dechallenged and in 6 (8.45%) cases no dechallenge was taken place and the ADR was managed with medications.

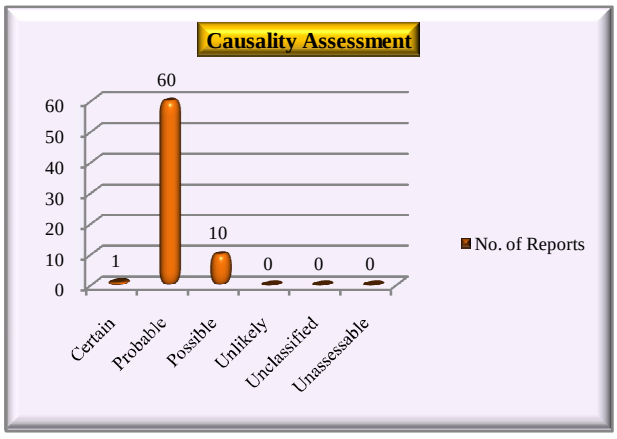

Figure 4 Causality Assessment

All the reported cutaneous ADRs were assessed for likelihood of the reaction with that of the suspected drug by using WHO-causality assessment scale and was found to be "probable" in 60 (84.51%) cases, "possible" in 10 (14.08%) cases and certain in 1 (1.41%) case.

DISCUSSION

A prospective non-interventional observational study was conducted over a period of 7 months from January 2017 to July 2017 and collected 71 cutaneous adverse drug reaction reports form Rajiv Gandhi Government General Hospital. More number of cutaneous reactions were found in females patients (43, 60.56%) than male patients (28, 39.44%) with an age group 18-44 yrs and was similar to the findings of *Reena et al., 2014* and *Lihite at al" 2013* but in contrast, *Sandipkumar et al., 2014* reported more in male patients than female patients.

Out of 71 reports, the most offending drug class causing cutaneous ADRs were antimicrobials (42, 59.15%) followed by antiepileptics(05, 7.04%) and NSAIDs (03, 4.23%) and was similar to the findings of *Ramesh et al., 2016* and with little variation in *Reena verma et al., 2014* as this study showed antimicrobials followed by NSAIDs and antiepileptics.

In our study the most commonly reported cutaneous ADRs were found to be rash (28, 39.44%) followed by Urticaria (09, 12.68%), Fixed drug eruptions (07, 9.86%), Maculopapular rash (05, 7.04%), Hyperpigmentation (04, 5.63%), Toxic Epidermal Necrolysis (01, 1.41%) and Stevens Johnson Syndrome (01, 1.41%) and was similar to the findings of *Sandipkumar et al* but contrast to the study of *Nivethitha et al., 2017* showed fixed drug eruptions followed by maculopapular rash, *Acharya et al., 2006* showed maculopapular rash followed by erythematus skin lesions and *Pudukadan D at al., 2004* showed fixed drug eruptions followed by maulopapular rash.

Most of the reports in our study were designated as "probable" with positive dechallenge followed by Possible and Certain with no fatality in contrast to the findings of *Sandipkumar et al., 2014, Lihite at al.2013, and Nivethitha et al., 2017* and showed "possible" in most of the reports.

Limitations

Short duration of the study with differences in the pattern of use of drugs, co-morbid conditions and other risk factors can also affect the outcomes and is limited only to the spontaneous reporting system.

CONCLUSION

Our study revealed that the most common drugs causing cutaneous ADRs were antibacterial drugs followed by antiepileptic drugs and NSAIDs. Current study contributes to the patient safety and rational use of drug by assessing, reporting and treating ADRs but need more data for assessing the risk benefit profile of the drugs. Thus healthcare system should promote the spontaneous reporting of adverse drug reaction to pharmacovigilance centers for ensuring patient safety.

Acknowledgement

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