

Pattern of cutaneous adverse drug reactions at a tertiary care hospital in southern India

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ABSTRACT

Background: The objective of the study was to assess the pattern of cutaneous adverse drug reactions reported by active surveillance to the Pharmacovigilance center of a tertiary care hospital in southern india, and also to establish the drugs causing the same and observe the age wise and gender based incidence of such reactions.

Methods: The cutaneous ADRs (CADRs) reported to the Pharmacovigilance center of the institution were analysed retrospectively during the period of March 2013 to December 2015. The various pattern of skin reactions and the most frequent drugs causing the same were established. An age wise and gender based incidence of CADRs and drugs causing them were also reported.

Results: A total of 293 cases were taken for analysis. The male female ratio was 0.89-1.in our study. Among the age wise distribution of CADRs, 57(19.4%) were seen in paediatric, 194(66.2%) in adults and 33(11.2%) in geriatric age groups. The most frequent drugs to cause the CADRs were antimicrobials 183(62.4%) followed by NSAIDs 38(12.9%) and antacids 17(5.8%).Among the skin reactions urticaria/ angioedema was the most common 109(37.2%) followed by generalised pruritis 57(19.5%) and fixed drug eruption 37(12.6%). In all the age groups and both the sexes urticaria/angioedema and generalised pruritis were the leading skin reactions observed.

Conclusions: As CADRs are the most common ADRs among others, it is prudent to monitor them closely, as any change in pattern with older or newer agents can alert the health care personnel in instituting the appropriate prescription patterns, which can overall impact the quality of health care positively.

Keywords: Antimicrobials, Cutaneous adverse drug reaction, Pharmacovigilance

INTRODUCTION

Adverse drug reaction (ADR) is defined as “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 seen in increasing numbers in patients both hospitalized, and in those on outpatient care.²⁻⁶ It is also well known that ADRs contribute significantly to hospital admissions.⁷ ADRs as such is a cause of significant economic burden because it has been proven that hospitalization cost of patients who experience ADRs is comparatively more, than their counterparts who don't.⁸ It is also a significant burden

economically to health care providers as well.^{9,10} Many studies have shown that cutaneous drug reactions are one of the most frequently encountered ADRs during patient care.^{11,12} Since there is an advent of newer drug molecules periodically and change in treatment protocols, it is prudent to evaluate the cutaneous ADRs (CADRs) continually.¹³ Information obtained through such studies can give inputs on those ADRs that can be avoided with an increase in the quality of health care, apart from bringing down the costs involved in their management.¹⁴ The purpose of the current study is to elicit the pattern of CADRs, the drugs responsible and the age and gender based incidence of such reactions, in patients treated at a public tertiary care hospital in the southern part of India.

METHODS

A retrospective analysis of the CADR_s retrieved from the Pharmacovigilance center database reported by active surveillance was carried out. The data pertains to the period from March 2013 to December 2015. The CADR_s obtained so were confirmed by a team consisting of a senior dermatologist and pharmacologists.

The CADR_s were grouped as certain, probable, possible, unlikely, unclassified, and unclassifiable based on the WHO causality assessment criteria. Only those CADR_s classified as certain, probable and possible were included in this study. The pattern of CADR_s and the drugs causing them, as well as the age and gender wise incidence of CADR_s were analysed from the above mentioned data.

The data was entered in MS excel and analyzed using SPSS v20.0. The data was summarized using means and proportions.

RESULTS

During the above said period a total of 510 ADR_s were reported, of which 388 (76.08%) were CADR_s. Among these CADR_s, only 293 (75.5%) were taken for analysis, as they satisfied the above mentioned WHO criteria (Figure 1).

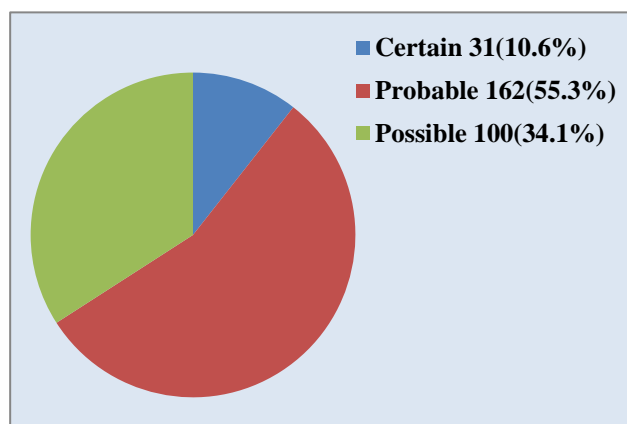


Figure 1: Distribution of CADR_s as per WHO causality criteria.

Table 1: Demographic variables.

Sample size (N=293)	
Male: Female*	135 (47.2%): 151 (52.7%)
Age [€]	Paediatric 57 (20.07%)
	Adult 194 (68.3%)
	Geriatric 33 (11.61%)

* Missing data= 7; € Missing data= 9

Among these 135 were seen in males, 151 were seen in females. They were grouped into paediatric (0-18), adult

(19-59) and geriatric (60 and >) age groups. Most of the CADR_s were reported in the adult age group (Table 1).

Among the drug groups, antimicrobials were the most frequent to cause CADR_s- 183 (62.4%) (Table 2), followed by NSAIDs- 38 (12.9%) and antacids- 17 (5.8%). Among the antimicrobials, ciprofloxacin was the most frequent- 46 cases, followed by cefotaxime -23 cases and ceftriaxone- 21 cases. Among NSAIDs, CADR_s were most frequently caused by diclofenac-21 cases, followed by paracetamol- 7 cases.

Table 2: Frequent drug groups and drugs causing CADR_s.

No.	Drug group	No. of cases (%)	Most frequent drugs-Nos.
1	Antimicrobials	183 (62.4%)	Ciprofloxacin 46 Cefotaxime 23 Ceftriaxone 21 Cotrimoxazole 20 Doxycycline 12
2	NSAIDs	38 (12.9%)	Diclofenac 21 Paracetamol 7 Aspirin 3
3	Antacids	17 (5.8%)	Ranitidine 13 Pantoprazole 3
4	Anesthetics	9 (3%)	Lignocaine 9
5	Antiepileptics	8 (2.7%)	Carbamazepine 4 Phenytoin 4

A total of 20 different CADR_s were observed in our study (Table 3). Of these the most common were urticaria/angioedema-109 (37.2%), followed by generalised pruritis-57 (19.5%), fixed drug eruption-37 (12.6%), local reaction-35 (11.9%), morbiliform rash-22 (7.5%) and Stevens-Johnson Syndrome-6 (2%). In all the above CADR_s, antimicrobials were the most common causative agents followed by NSAIDs. However among local reactions and morbiliform rash antimicrobials were followed by antacids and antivirals as the most common causative agents respectively. With regard to Stevens - Johnson syndrome-6 (2%) the leading causative agents were antiepileptics followed by antimicrobials. Erythema multiforme-6 (2%) cases were caused by antimicrobials.

In the age and sex wise distribution of ADR_s (Table 4), again it was found that urticaria/angioedema were the most common CADR_s followed by generalised pruritis. The most common drugs to cause such reactions were again found to be antimicrobials.

DISCUSSION

CADR_s are the most common ADR_s when compared with the prevalence of other ADR_s.¹² The cost involved in their management is significantly more for both the patients and health care providers.

Table 3: CADR and causative agents.

No.	Cutaneous ADR	No (%)	Frequent Drug group Nos:	Frequent Drugs
1	Urticaria/Angioedema	109 (37.2)	Antimicrobials 57: NSAIDs 19: Antacids 8:	Ceftriaxone, Ciprofloxacin, Cotrimoxazole Diclofenac, Ibuprofen, Paracetamol Ranitidine, Pantoprazole
2	Generalised Pruritis	57(19.5)	Antimicrobials 42: NSAIDs 6: Antacids 4:	Ciprofloxacin, Ceftriaxone, Cefotaxim Paracetamol, Diclofenac Ranitidine
3	Fixed Drug Eruption	37(12.6)	Antimicrobials 23: NSAIDs 8:	Cotrimoxazole, Doxycycline, Amoxicillin Diclofenac, Paracetamol
4	Local Reaction	35(11.9)	Antimicrobials 28: Antacids 4:	Ciprofloxacin, Cloxacillin, Cefazolin Ranitidine
5	Morbiliform Rash	22(7.5)	Antimicrobials 17: Antiviral 2:	Cefotaxim, Ampicillin, Ciprofloxacin Acyclovir, ART
6	Stevens- Johnson Syndrome	6(2)	Antiepileptic 4: Antimicrobials 2:	Carbamazepine, Phenytoin INH, Doxycycline
7	Erythema Multiforme	6(2)	Antimicrobials 6:	Doxycycline, Cefixime, Cotrimoxazole
8	Morbiliform Eruption	3(1)	Antimicrobials 6:	Doxycycline, Cotrimoxazole
9	Acneiform Eruption	3(1)	Antiepileptic: Antithyroid:	Phenytoin Carbimazole
10	Dapsone Syndrome	2(0.7)	Dapsone 2:	Dapsone
11	Irritant Dermatitis	2(0.7)	Anti inflammatory: Antiacneiform:	Retinoids Benzoyl Peroxide
12	Hyperpigmentation	2(0.7)	Antimicrobials 2:	Clindamycin, Tobramycin
13	Phototoxic reaction	2(0.7)	Antimicrobials: Diuretic:	Doxycycline Furosemide
14	Allergic contact Dermatitis	1(0.3)	Antimicrobials:	Ciprofloxacin
15	Alopecia	1(0.3)	Isotretinoin	
16	Aphthous ulcer	1(0.3)	NSAID:	Diclofenac
17	Eczematous drug rash	1(0.3)	Antidiabetic:	Repaglinide
18	Erythema Nodosum	1(0.3)	Antimicrobials:	Ciprofloxacin
19	Purpuric Rash	1(0.3)	Antimicrobials:	ATT
20	Scarletiform Rash	1(0.3)	Antiepileptic:	Phenytoin

Table 4: Most common CADR- Nos. (%) with most frequent Drug groups- Nos.: Age and sex wise distribution.

Most common cutaneous ADRs Nos.(%) with most frequent drug groups- Nos.: Age and sex wise distribution					
0-18 Age group	Urticaria/Angioedema 24(42.1%) Antimicrobials 18 Antacid 1	Generalised Pruritis 9(15.7%) Antimicrobials 8 Haematinics 1	Morbiliform Rash 7(12.2%) Antimicrobials 7	Local Reaction 7(12.2%) Antimicrobials 7 Antiemetic 1	Fixed Drug Eruption 5(8.7%) Antimicrobials 5
19-59 Age group	Urticaria/Angioedema 72(37.1%) Antimicrobials 32 NSAIDs 16	Generalised Pruritis 35(18%) Antimicrobials 25 NSAIDs 4	Local Reaction 27(13.9%) Antimicrobials 22 Antacids 4	Fixed Drug eruption 24(12.3%) Antimicrobials 11 Antacids 7	Morbiliform Rash 13(6.7%) Antimicrobials 8 Antivirals 2
60 and> Age group	Urticaria/Angioedema 11(33.3%) Antimicrobials 6 Diuretics 2	Generalised Pruritis 11(33.3%) Antimicrobials 7 Antacids 2	Fixed Drug Eruption 8(24.2%) Antimicrobials 7 NSAIDs 1	Eczematous Drug Rash 1(3%) Antidiabetics 1	Phototoxic Reaction 1(3%) Diuretics 1
Males	Urticaria/Angioedema 47(34.8%) Antimicrobials 27 NSAIDs 9	Generalised Pruritis 26(19.2%) Antimicrobials 21 NSAIDs 9	Fixed Drug Eruption 25(18.5%) Antimicrobials 15 NSAIDs 6	Local Reaction 17(12.5%) Antimicrobials 15	Morbiliform Rash 7(5.1%) Antimicrobials 5
Females	Urticaria/Angioedema 62(41%) Antimicrobials 30 NSAIDs 10	Generalised Pruritis 29(19.2%) Antimicrobials 19 NSAIDs 5	Local Reaction 17(11.2%) Antimicrobials 13 Antacids 3	Morbiliform Rash 13(8.6%) Antimicrobials 10	Fixed Drug Eruption 12(7.9%) Antimicrobials 8 NSAIDs 2

Moreover they pose a significant threat to the health of the patients as CADR may even be life threatening. A constant monitoring of CADR is a must, since identification of potential ones and newer ones would pave way to prevent or avoid them.

As per the WHO causality criteria, most of the CADR taken for analysis came under the probable causality, similar to the study done by Chatterjee et al.⁶ As far as the age wise distribution, most of them were observed in the adult age group population. Similar results were seen in other studies.^{4,13} This could be because of the fact that the health seeking behaviour of the adult age group is more when compared to their paediatric and geriatric counterparts.

In our study the females had a slightly higher incidence than the males with a ratio of 1:0.89, similar to the other studies conducted elsewhere.¹⁵⁻¹⁸

Among the drugs causing the CADR, the most common drug groups involved were antimicrobials. This is similar to many studies conducted elsewhere.^{3,5,18-22} The NSAIDs followed them as the next common drug groups to cause CADR, similar to other studies.^{12,18} Among the antimicrobials ciprofloxacin was the most common drug involved followed by cefotaxime. This again was similar to the study conducted by Vijeya kumar et al and similar results were obtained from the study by Qayoom et al, where quinolones were followed by cephalosporins as the most common antimicrobial groups involved.^{18,19} This was in contrast to other studies where sulphonamides were the leading cause.^{12,13} The difference in the pattern of antimicrobials between different studies could be due to the differences in the physician's preferences in using various antimicrobials and the varied disease prevalence from region to region.⁴

In the present study, urticaria/angioedema was the most common CADR detected followed by generalised pruritis and fixed drug eruption. Similar results were obtained in one study, where urticaria was the leading CADR.²³ This is different from the other studies where maculopapular rash was the leading cause and fixed drug eruption in some.^{4,5,13,18,22} The difference could be due to varied disease prevalence from place to place and the use of different kind of drugs for their appropriate management. In many of the studies describing CADR, the most common CADR were caused by antimicrobials.^{3,5,13,18,19,22} The reason for this could be due to the fact that antimicrobials are the most commonly used drugs among other drugs since infectious diseases are one of the most common ailment which patients present with, and apart from that they are also frequently used prophylactically both before and after surgical procedures. In many studies quinolones were the most common antimicrobials involved.^{18,19} The reason for this could be due to the fact that, quinolones being broad spectrum antimicrobials are the most frequently prescribed antimicrobials by clinicians.

Among the severe CADR we had six cases of Stevens - Johnson syndrome, of which 4 cases were due to antiepileptics and 2 were due to antimicrobials. There were six cases of Erythema multiforme, all were caused by antimicrobials. This widely correlates with many studies where anticonvulsants and antimicrobials were the frequently involved drugs in causing such severe CADR.^{5,13,18}

In the age wise distribution urticaria/angioedema was the most common CADR in all the age groups, followed by generalised pruritis. The drugs most commonly involved in the most frequent CADR in all the age groups were again found to be antimicrobials.

In the sex wise distribution the female sex had marginally more incidences of CADR compared to males. In both the sexes the most common CADR were urticaria/angioedema followed by generalised pruritis. In both the sexes, in all the frequent CADR, the most common drug groups involved were again antimicrobials.

CONCLUSION

As CADR are the most common ADR among others, it is prudent to monitor them closely, as any change in pattern with older or newer agents can alert the health care personnel in instituting the appropriate prescription patterns, which can overall impact the quality of health care positively.

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