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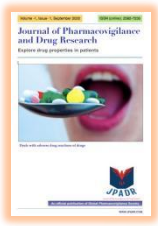

RESEARCH ARTICLE

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Cutaneous adverse drug reactions in a tertiary care hospital: An observational study

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ABSTRACT

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Introduction: Cutaneous adverse drug reactions (CADRs) are one of the most common ADRs caused by drugs causing a lot of morbidity and mortality. The overall incidence of CADRs in developed countries is 1-3 %, while that in the developing countries is reported to be higher between 2 % and 5 %. Changes in drug metabolism drug interactions, oxidative stress, and various cytokines are the various factors that cause cutaneous adverse drug reactions.

Aim and objective: This study aims to evaluate the patterns of CADRs, the causative drugs along with causality and severity assessment.

Methods: A total of 50 Patients with cutaneous adverse drug reactions who were included in our last study attended skin OPD, VIMSAR Burla, from June 2018 to September 2018 and were analyzed for causality assessment using the WHO-UMC scale and severity assessment using Hartwig and Siegel's scale.

Results: Out of 50 patients, 48 % belong to the age group 21-40 years. Around 44 % of CADRs were fixed drug eruptions. NSAID was found to be the most offending drug and it contributed to a maximum of 32 % of ADRs. 16 % of ADRs were found to be caused by antitubercular drugs. Paracetamol was the key NSAID, contributing 87.5 % of ADRs. Causality was certain, probable, and possible for 8 %, 24 %, and 60 % of ADRs respectively. Severity was mild for 64 % and moderate for 34 % of ADRs.

Conclusions: NSAID and antitubercular drugs are the commonest drugs causing CADRs. Fixed drug eruption is the most common CADRs and the commonest drug was paracetamol. Causality grade was possible and the severity grade was mild.

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Introduction

An adverse drug reaction (ADR) is defined as any response to a drug that is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or modification of physiological function (Pirmohamed *et al.*, 2004). The burden of ADRs is high and accounts for considerable morbidity, mortality, and extra cost. Cutaneous adverse drug reactions (CADRs) are one of the most common ADRs caused by drugs causing a lot of morbidity and mortality (Patel *et al.*, 2008). The incidence of ADRs globally varies with studies that show incidences ranging from as low as 0.15 % to as high as 30 % (Nandha *et al.*, 2011). The overall incidence of CADRs in

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developed countries is 1-3 %, while that in the developing countries is reported to be higher between 2 % and 5 % (Lazarou *et al.*, 1998). Changes in drug metabolism drug interactions, oxidative stress, and various cytokines are the various factors that cause cutaneous adverse drug reactions. Indian reports on ADR monitoring have been very few. This may be because ADR monitoring is still developing in India. Pharmacovigilance (PvPI) is the pharmacological science that deals with the detection, assessment, understanding, and prevention of adverse effects and promotes the safe use of drugs (Gruchalla *et al.*, 2000). In 2005, the national pharmacovigilance program (NPP) was introduced by the Ministry of Health and Family Welfare further, which was revised in July 2010. This program is monitored by the central drugs standard control organization (CDSCO), New Delhi (Roujeau *et al.*, 1994; Ajayi *et al.*, 2000). The pharmacovigilance program of India plays a vital role in improving the safety of medicines in the Indian population. Under PvPI, various regional ADR monitoring centers (AMCs) have been established at various medical institutions throughout the country. This study aims to evaluate the patterns of CADRs, the causative drugs along with causality and severity assessment.

Methods

A total number of 50 Patients with cutaneous adverse drug reactions who were included in our last study attended skin OPD, VIMSAR Burla, from June 2018 to September 2018. This study analyzed all antimicrobial drug-related individual case safety reports (ICSRs) reported at AMC, VIMSAR Burla. Causality assessment of ADRs was done by using the world health organization- Uppsala monitoring center (WHO-UMC) causality assessment scale as certain, probable, possible, unlikely, unclassified, and unassessable /unclassifiable (Hartwig *et al.*, 1992). The severity of ADRs was assessed by the modified Hartwig and Siegel scale (Chatterjee *et al.*, 2006). The study was approved by the institutional ethics committee. Descriptive statistics were used to analyze the data and values are expressed in numbers and percentages.

Results

During the study, a total of 50 patients with cutaneous adverse drug reactions were studied. The most common age group is 21- 40 years with a male to female ratio of 44 % and 56 % as presented in **Table 1**. In the age group 21- 40 years, CADRs are found most common. Fixed drug eruption was the most common type of drug reaction (44 %). This was followed by a maculopapular rash (24 %) and steven johnson syndrome (16 %), as presented in **Table 2**. Other types of drug reactions like DRESS syndrome (10 %), bullous eruption (4 %), drug-induced lupus erythematosus (2 %) were seen in this study. From **Table 3**, it was inferred that NSAIDs were the most offending drugs (32 %). Followed by antitubercular drug 16 % and ofloxacin14 %, ornidazole 12 %, antiretroviral drug 8 % with least by fosphenytoin, ciprofloxacin eye drop, bicalutamide, ceftazidime, and vecuronium with 2 % each.

Among individual drugs with NSAID, Paracetamol 87.5 %, ibuprofen 6.25 %, and Aspirin 6.25 % responsible for fixed drug eruptions, as presented in **Table 4**. Causality assessment by using the WHO-UMC Scale (n=50). It was seen that 4 % ICSRs could be assessed as certain and 12 % could be assessed as probable. Most (30 %) ICSRs were assessed as possible. The majority (8 %) of the ICSRs to antitubercular drugs could be assessed as possible and 2 % of the ICSRs to NSAIDs could be certain, as presented in **Table 5**. Severity assessment of ADRs by modified Hartwig and Siegel's severity Scale(n=50) indicates (9 %) of NSAIDs related ADRs were of level-2 (moderate) severity in nature with 1 % of ofloxacin was of level-5 (severe) on the severity scale, as presented in **Table 6**.

Table 1: Age and gender distribution of individual case safety reports. (ICSRs) to drugs (n=50).

Characteristics	Value	Percentage (%)
Age		
< 20 years	15	30
21 - 40 years	24	48
41 - 60 years	7	14
Above 60 years	4	8
Gender		
Males	28	56
Females	22	44

Table 2: Reaction pattern distribution:

No.	Reaction pattern	No.of patient	% of patient
1	Fixed drug reaction	22	44
2	Maculopapular rash	12	24
3	Steven Johnson syndrome	8	16
4	DRES's syndrome	5	10
5	Bullous eruption	2	4
6	Drug-induced lupus erythematous	1	2

Table 3: Commonest Drug causing cutaneous ADR

NSAID	No. of patient	% of patient
Paracetamol	14	87.5
Ibuprofen	1	6.25
Aspirin	1	6.25

Table 4: NSAID Causing fixed drug eruption

Offending drug	No of patient	%of patient
NSAID	16	32
Antitubercular	8	16

Ofloxacin	7	14
Ornidazole	6	12
Antiretroviral therapy	4	8
Artesunate	2	4
Amoxiclav	2	8
Bicalutamide	1	2
Ceftazidime	1	2
Ciprofloxacin eye drop	1	2
Fosphenytoin	1	2
Vecuronium	1	2

Table 5: Causality assessment of outpatients to drugs by using WHO-UMC scale (n=50)

	Certain *n(%)	**Probable n(%)**	**Possible n(%)**	**Unlikely n(%)**	**Conditional n(%)**	**Unassessable n(%)**	**Total n(%)**
NSAID	2(12.5)	3(18.75)	8(16)	1(6.25)	1(6.25)	1(6.25)	16(32)
Antitubercular	0(0)	4(50)	4(50)	0(0)	0(0)	0(0)	8(16)
Ofloxacin	1(14.28)	2(28.57)	3(42.85)	1(14.28)	0(0)	0(0)	7(14)
Ornidazole	1(16.66)	0(0)	5(83.33)	0(0)	0(0)	0(0)	6(12)
Antiretroviral therapy	0(0)	1(25)	3(75)	0(0)	0(0)	0(0)	4(8)
Artesunate	0(0)	0(0)	2(100)	0(0)	0(0)	0(0)	2(4)
Amoxyclav	0(0)	0(0)	2(100)	0(0)	0(0)	0(0)	2(4)
Biclutamide	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	1(2)
Ceftazidim	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	1(2)
Ciprofloxacin eye drop	0(0)	1(100)	0(0)	0(0)	0(0)	0(0)	1(2)
Fosphenytoin	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	1(2)
Vacuronium	0(0)	1(100)	0(0)	0(0)	0(0)	0(0)	1(2)
Total	4(8)	12(24)	30(60)	2(4)	1(2)	1(2)	50(100)

Table 6: Severity assessment of ADRs by modified Hartwig and Siegels severity scale (n=50)

Severity levels	**Mild**			**Moderate**		**Severe**			**Total n(%)**
Level	**1**	**2**	**3**	**4a**	**4b**	**5**	**6**	**7**	
NSAID	-	9(56.25)	5(31.25)	1(6.25)	1(6.25)	-	-	-	16(32)
Antitubercular	-	-	6(70)	1(10)	1(10)	-	-	-	8(16)
Ofloxacin	-	-	2(28.57)	2(28.57)	2(28.57)	1(14.28)	-	-	7(14)
Ornidazole	-	2(33.33)	2(33.33)	1(16.66)	1(16.66)	-	-	-	6(12)
Antiretroviral therapy	1(25)	-	2(50)	1(25)	-	-	-	-	4(8)
Artesunate	-	-	-	1(50)	1(50)	-	-	-	2(4)
Amoxiclav	-	-	-	-	2(100)	-	-	-	2(4)
Bicalutamide	1(100)	-	-	-	-	-	-	-	1(2)
Ceftazidime	-	1(100)	-	-	-	-	-	-	1(2)
Ciprofloxacin eye drop	-	-	-	-	1(100)	-	-	-	-
Fosphenytoin	-	-	-	-	1(100)	-	-	-	-
Vecuronium	1(100)	-	-	-	-	-	-	-	-
Total	3(6)	12(24)	17(34)	7(14)	10(20)	1(2)	-	-	50(100)

Discussion

In previous studies, Maculopapular rash, exanthematous, urticaria, and erythematic multiform are the most common clinical type of drug reactions. Fixed drug eruptions were the most common drug reaction (44 %) in our study, which was very close to the result by Saha *et al.* (Saha *et al.*, 2012), [I]followed by a maculopapular rash (24 %). This is in contrast to studies were done by Tejaswini *et al.* (Tejashwani *et al.*, 2018), where the most common CADRs were maculopapular rash (16.66 %) and Fixed drug eruptions were only (13.33 %). The demographic data shows the age group of 21-40 years and male 56 % were most commonly affected. In the present study, NSAIDs were the most common drug-associated with ADRs among NSAIDs. Paracetamol 87.5 %was the commonest NSAID responsible for fixed drug eruptions. Antitubercular drugs were responsible for 16 % of the CADRs. There were 8 cases and Steven Johnson syndrome associated with antibacterial drugs and often requires immediate cessation of treatment. The Severity analysis by modified Hartwig-Siegel Scale showed that most of the reactions were moderate 46 %, only in one case reaction was severe i.e. with ofloxacin and patient required intensive medical care. Similar results have been obtained from previous studies (Padmavathi *et al.*, 2013).

Conclusions

The pattern of cutaneous adverse drug reactions is variable among previous studies. In this study, NSAIDs were commonly associated with dermatological reactions typically. Fixed drug eruptions followed by a maculopapular rash. The second most common drug of concern is antitubercular drugs. Most of the CADRs were attributed to antibacterial drugs like ofloxacin, ornidazole, other drugs like antiretroviral, and antimalarial like artesunate. Most of the reactions are moderately severe. Causality assessment was certain and probable for 18.9 % and 41.5 % of the reactions, respectively, and reactions were serious in 33.96 % (95 % confidence interval 21.21-46.71 %).

Conflict of interest

There is no conflict of interest between the authors.

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