

Pharmacovigilance of cutaneous drug reactions: A prospective observational study

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Abstract

Objective: To determine the frequency, severity and morphological pattern of ACDRs and their correlation with various risk factors.

Methodology: A prospective, observational study was conducted in Muzaffarnagar Medical College & hospital, Muzaffarnagar Uttar Pradesh from Feb 2013 to Jan 2014 for one year. All patients of either sex and all age groups with suspected ACDRs attending/referred to Dermatology department were included.

Results: Total of 90 cases were reported over a period of one year. ACDRs were observed with 0.5% incidence of patients attending OPD. ACDRs were commonly seen in adult age group (mean age 36.93 yrs) and have 3 or more drugs prescribed with equal gender distribution. As per Naranjo Algorithm, maximum number of ACDRs were of Possible type (74%), while 23 cases were of 'Probable' category with female and male preponderance respectively. 71 of ACDRs were Moderate in severity (79%) followed by 11% of mild and 10% of severe category. Most common clinical pattern was Urticaria with 32 cases followed by 24 cases of Maculopapular Eruptions, 9 cases of Acneiform eruptions and 8 of fixed drug reactions and SJ Syndrome. Commonest Drug groups causing ACDRs were Antibiotics (38%) and Antiepileptics (30%). This was followed by NSAIDs induced ACDRs (9%). Phenytoin was the most common drug causing 12 ACDRs followed by 6 with Cabamazine and Ceftriaxone each and 5 cases with ATT.

Conclusion: Incidence was low as compared to global incidence; better steps must be needed to strengthen the activity of pharmacovigilance in this state of the country.

Keywords: Antibiotics, Antiepileptics, Pharmacovigilance.

1. Introduction

Modern medicine is blessed with much better medical care, but at the expense of greater harm too. Awareness on unexpected hazards of modern medicine was triggered by a letter to the editor of the Lancet published on the 16th December 1961, by Dr. McBride from Australia on increased frequency of limb malformations (phocomelia) among babies due to intake of new hypnotic drug-thalidomide by their mothers [1].

According to WHO, adverse drug reactions (ADRs) are defined as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. This basic definition includes all doses prescribed clinically, but is intended to exclude accidental or deliberate overdose [2]. The incidence of ADRs as reported from all over the world varies from 0.15% to 30% [3]. Whereas skin reactions (adverse cutaneous drug reactions [ACDRs]) can be a subset of ADRs

that are noxious, unintended morphological skin changes with or without systemic involvement, developed after local or systemic administration of drugs [4].

A definite proportion of these ADRs belong to skin reactions that are far over early presentation and concern of patients [5]. The drug availability/use pattern, the disease prevalence and the various environmental and geographical factors etc determine the pattern and severity of ACDRs in a particular area that needs to be monitored and documented as in the case of ADRs.

To our knowledge there has been no pharmacovigilance study on ACDRs in Uttar Pradesh state till date hence this prospective, observational analysis of ACDRs at MMC&H was done to provide useful information on ACDRs associated with commonly prescribed drugs in Muzaffarnagar Medical College & Hospital, Muzaffarnagar Uttar Pradesh.

2. Material and Methods

A prospective, observational study was conducted in Muzaffarnagar Medical College & hospital, Muzaffarnagar Uttarpradesh. The study was conducted from Feb 2013 to Jan 2014 for one year. All patients of either sex and all age groups with suspected ACDRs attending/referred to Dermatology department were included. Patients with history of drug abuse/addiction, documented psychiatric illness and overprescribed, over dosage and excessive consumption of medication were excluded.

ADRs reporting form, as per Central drugs Standard Control Organization (CDSCO) guidelines, was used to generate data from patients. All the documented ACDRs were analysed for incidence, type of ACDRs, drug classes and individual drug causing cutaneous reaction, association of cutaneous reaction with drugs, predisposing factors, management and outcome of ACDRs. ACDRs were also assessed for causality assessment using Naranjo's algorithm [6] and WHO-UMC scale [7], and severity by using modified Hartwig et al scale [8]. Hallas scale for avoidability [9].

3. Results

A total of 18,726 patients attended the dermatology OPD during the study period of one year. Among them, 90 patients were diagnosed as ACDRs with the incidence of 0.5%.

The ratio of male and female patients with ACDRs was 1.14:1. the mean age of occurrence of ACDRs was 36.93 ± 2.88 years while maximum number of patients (71%) affected were in adult age group, followed by pediatric age group (22%) and least were in geriatric group. ACDRs were most common (67%) in patients taking more than 3 drugs.

As per Naranjo algorithm, maximum numbers of ACDRs were of possible type (74%), while 23 cases were of 'Probable' category. According to WHO-UMC scale, most common category was 'possible' with 61(68%) cases while probable severity (79%) followed by 11% mild and 10% severe category.

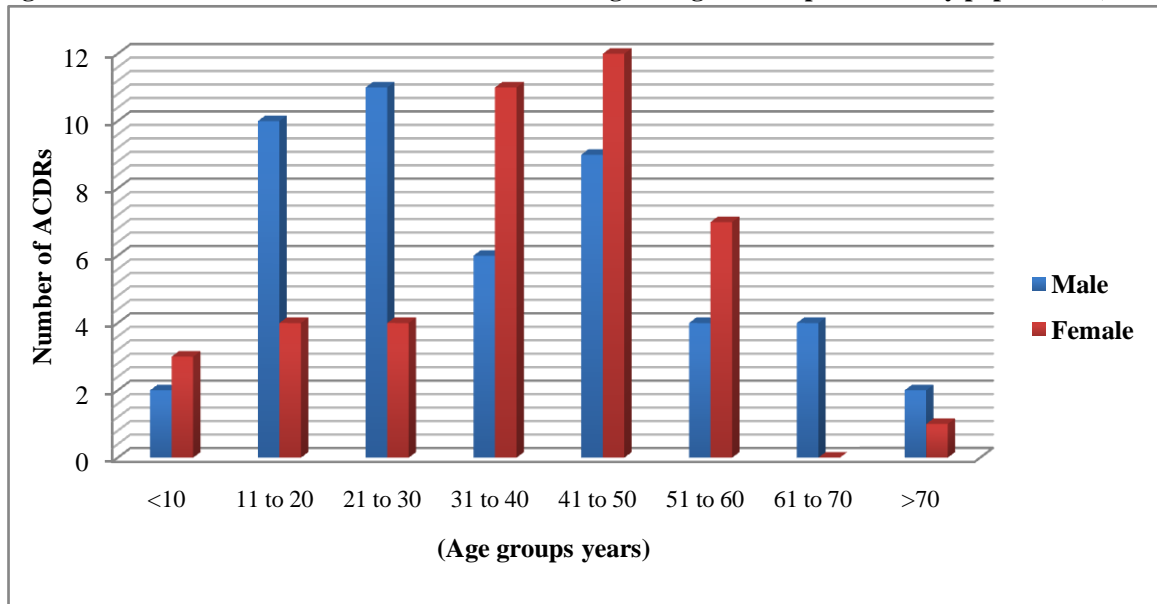
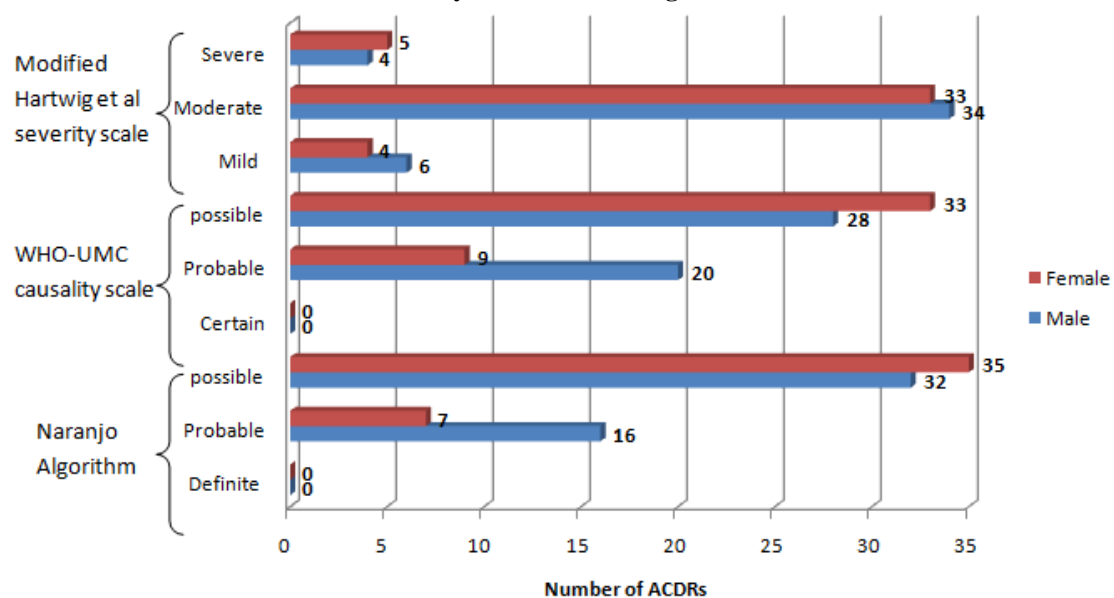
Most common clinical pattern seen in study were 29 (32%). 71 of ACDRs were Moderate in population was Urticaria with 32 cases followed by 24 cases of Maculopapular Eruptions, 9 cases of Acneiform eruptions and 8 of fixed drug reactions and SJ Syndrome. Commonest Drug groups causing ACDRs were Antibiotics (38%) and Antiepileptics (30%) followed by NSAIDs (9%). Phenytoin was the most common drug causing 12 ACDRs followed by 6 with Carbamazepine and Ceftriaxone each and 5 cases with 1st line antitubercular drugs. Out of 90 cases only 2 cases were 'definitely avoidable'. In Outcome, 71 cases required medical intervention and 11 were requiring hospitalization or prolongation of hospital stay.

Table 1: Association of Implicated Drugs causing ACDRs and their correlation with the Clinical Morphological Pattern

DRUGS	U	MPE	AE	FDR	SJS	EM	ED	PPS	SS	P	H	DHS	AR	OU	Total (%)
Antiepileptic															27 (30)
Phenytoin		6 (6.7)	2 (2.2)		3 (3.3)				1 (1.1)						12 (13.3)
Phenobarbitone	1 (1.1)					1 (1.1)									2 (2.2)
Fosphenytoin	1 (1.1)	1 (1.1)													2 (2.2)
lamotrigine		3 (3.3)	1 (1.1)												4 (4.4)
Carbamazepine		3 (3.3)	1 (1.1)		1 (1.1)								1 (1.1)		6 (6.7)
Pregabalin			1 (1.1)												1 (1.1)
Antibiotics															34 (37.78)
Amoxicillin + clavulanate	1 (1.1)	2 (2.2)													3 (3.3)
Amoxicillin + cloxacillin	2 (2.2)														2 (2.2)
Ceftriaxone	2 (2.2)	2 (2.2)		1 (1.1)	1 (1.1)										6 (6.7)
Cefotaxim + Sulbactam	1 (1.1)														1 (1.1)
Ceftazidime + Tazobactam	1 (1.1)														1 (1.1)
Cefixime					1 (1.1)										1 (1.1)
Cefopodoxime				1 (1.1)											1 (1.1)
Vancomycin	3 (3.3)														3 (3.3)
Azithromycin	1 (1.1)	1 (1.1)		1 (1.1)											3 (3.3)
Ciprofloxacin	1 (1.1)											1 (1.1)			2 (2.2)
Ofloxacin	1 (1.1)														1 (1.1)
Levofloxacin	1 (1.1)														1 (1.1)
Norfloxacin				1 (1.1)											1 (1.1)

Table 1 Continue.....															
Sulfamethoxazole + Trimethoprim	1 (1.1)														1 (1.1)
Albendazole	1 (1.1)														1 (1.1)
Metronidazole	1 (1.1)														1 (1.1)
Antitubercular	1 (1.1)		1 (1.1)	1 (1.1)				2 (2.2)							5 (5.6)
NSAIDs															8 (8.9)
Diclofenac	3 (3.3)	1 (1.1)			1 (1.1)										4 (4.4)
Acefenac	1 (1.1)														1 (1.1)
Ibuprofen + PCM	1 (1.1)			1 (1.1)											2 (2.2)
PCM										1 (1.1)					1 (1.1)
DMARDs															4 (4.4)
Sulfasalazine	1 (1.1)														1 (1.1)
Methotrexate		1 (1.1)	1 (1.1)											1 (1.1)	3 (3.3)
Corticosteroids															2 (2.2)
Dexamethasone			2 (2.2)												2 (2.2)
Anti-parkinson drugs															2 (2.2)
Pramipexole	1 (1.1)														1 (1.1)
Ropinerole				1 (1.1)											1 (1.1)
Opioid analgesic															1 (1.1)
Proxyvon (paracetamol + dextropropoxyphene hydrochloride)				1 (1.1)											1 (1.1)
Anti-cancer drugs															3 (3.3)
Gemcitabin + Cysplatin	1 (1.1)	1 (1.1)													2 (2.2)
Cyclophosphamide/ Epirubicin/5-FU										1 (1.1)					1 (1.1)
Uricosuric drugs															1 (1.1)
Allopurinol					1 (1.1)										1 (1.1)
H₂-receptor antagonist															1 (1.1)
Ranitidine	1 (1.1)														1 (1.1)
Calcium channel blockers															1 (1.1)
Verapamil		1 (1.1)													1 (1.1)
Anti-leprotic drugs															1 (1.1)
Dapsone							1 (1.1)								1 (1.1)
Others															5 (5.6)
Multivitamins	1 (1.1)	1 (1.1)													2 (2.2)
Iron sucrose	1 (1.1)														1 (1.1)
Propranolol	1 (1.1)														1 (1.1)
Ursodeoxycholic acid	1 (1.1)														1 (1.1)
Total (%)	32 (35.6)	24 (26.7)	9 (10)	8 (8.9)	8 (8.9)	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	90

U: Urticaria, MPE: Maculopapular Eruptions; AE: Acneiform reactions; FDR: Fixed Drug Reactions; SJS: Steven Johnsons Syndrome; EM: Erythema Multiforme; ED: Exfoliative Dermatitis; PPS: Palmoplantar Psoriasis; SS: Serum Sickness; P: Purpura ; H:Hyperpigmentation ; DHS: Drug Hypersensitivity Syndrome; AR:Anaphylactoid Reaction ; OU:Oral Ulceration.

Figure 1: Distribution of ACDRs cases in relation to age and gender in present study population (n=90)**Figure 2 : Genderwise Casualty assessment of ACDRs according to Naranjo Algorithm, WHO-UMC scale & Severity assessment by Modified Hartwig et al scale**

4. Discussion

The diagnosis of drug induced cutaneous reactions (ACDRs) is one of the most challenging clinical problems in hospitalised patients. The challenge is two-fold: first, to accurately diagnose ACDRs and second, to attribute causality to a particular drug, if possible. This becomes even more difficult in an acute setting, where the patient is usually on multiple medications.

ACDRs are probably the most frequent of all the ADRs worldwide affecting 2-3% of all hospitalized patients [10]. From studies reported in India, the out-patient incidence of 2.66% and 1.6% was quoted in two previous studies [11, 12]. However, in our study the incidence was 0.5%, this may be due to poor reporting and unintentional ignorance of adverse effects by patients or less awareness of ADRs

reporting among medical personnel. Mild predominance of ACDRs was seen in males as compared to females in concordance with other studies [13, 14]. The reasons associated there were more males suffering from illnesses as being the bread earner of the family, their personal habits like alcohol and tobacco use and high consumption of medicines as a result of polypharmacy.

According to Naranjo algorithm and WHO-UMC causality scale majority of cases were 'possible' in nature which was not consistent with previous studies done in our country. In all those studies there was more number of "probable" grade than "possible" and they also reported few ACDRs of certain grade [12, 13]. While in our study none was certain due to ethical considerations for rechallenge procedure and in some history of dechallenge was lacking or

unclear. We also intended to compare the two causality scale which showed a disagreement of causality in 5 cases this may be due to differences in assessment of complex clinical phenomena depends upon the knowledge, experience and even with experts there may be frequent disagreement [15]. Avoidability assessment revealed only 2 were “definitely avoidable” which were due to already well known drug-drug interaction. One was due to Valproate and Lamotrigine, other was Methotrexate and Etorcoxib and there was a third, with Verapamil was prescribed for Vascular headache as it is not approved by FDA but in our country it is approved.

Most common drugs implicated in present study were Antibacterial agents followed by Antiepileptics and NSAIDs and this pattern was supported by many previous studies [11, 14]. In contrast, one study reported antimicrobials group followed by NSAIDs and antiepileptics [13] while other study observed NSAIDs as major group for causing ACDRs [16]. This indicates regional differences in occurrence of ACDRs due to difference in prescribing practices, incidence of diseases according to a particular area or state and may reflect a small sample size to comment on same prediction. Beta-lactams were the primary group causing 15(17%) ACDRs while predominance of Cotrimazole as causative agent for ACDRs has been reported from other studies conducted in India [11, 14]. This may be due to different time frame of previous study where Cotrimoxazole was prescribed more and that too in setting of a Government hospital unlike ours.

Out of various cutaneous manifestations of drug reactions, Urticaria was seen most commonly, following by Maculopapular Exanthem and Acneiform eruptions in patients in present study. Maximum incidence of urticaria was seen in cases of antimicrobial use, followed by NSAIDs use. In contrast NSAIDs were most common group followed by antimicrobial agents in another study [11]. Antiepileptics were the most common drug group followed by Antimicrobial agents causing Maculopapular reactions. This was in conformation with other studies for antiepileptic drugs like Phenytoin and Carbamazepine in our country [11, 17] but not for Lamotrigine. There have been reports of Lamotrigine induced rashes [18]. Antiepileptics were documented as major drug class (5/8) cases of Acneiform eruptions followed by Corticosteroids (2/8) and 1 from 1st line Antitubercular drugs. In the opposite, ACDRs study from Padukadan [19] reported only (3/91) cases of Acneiform eruption without the causative drugs information. Fixed drug eruptions (FDE) were most commonly due to antimicrobial agents without any prominent single agent out numbering the others. In contrast other studies showed Cotrimoxazole as major cause of FDE [11, 14]. This may be due to low prescribing pattern of Cotrimoxazole in our hospital, although we did not investigate the prescribing pattern.

In present study, 8 out of 90 (9%) ACDRs were of SJ Syndrome. Studies from Bangalore [17] and Chandigarh

[14] Showed both increased 7/56 (15%) and decreased 24/500 (4.8%) occurrence of SJ Syndrome, respectively. In our study Antiepileptics Phenytoin (n=3) and Carbamazepine (n=1) were leading drugs. In contrast to Carbamazepine was the most common drug that induced SJ Syndrome as previously reported [20].

Our study had some lacunas like smaller sample size owing to inappropriate reporting in OPD settings or sometimes cases might have been missed due to heavy burden of patients/misdiagnosed. In some instances prescribing pattern of harmful drugs was unavailable as lack of knowledge of patient and follow up of patient remains inadequate due to miscommunication. Advance methods for confirmation of drug allergy were not used to evaluate biochemical or immunological markers that confirm a particular immunologic pathway to explain the suspected ACDRs.

5. Conclusion

In our study the detected incidence of ACDRs was low as compared to overall worldwide figures as reported in literature. This may be due to patient's unawareness of ACDRs or diagnostic difficulties in detection of ACDRs. Larger studies are proposed to verify and refine the results of our study that is possible by strict and efficient pharmacovigilance system in our setup.

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