ORIGINAL RESEARCH

ISSN: 2456-8090(Online)
International Healthcare Research Journal 2017;1(6):25-33.
DOI: 10.26440/IHRJ/01_06/112

QR CODE

Information about Serious ADRs Explored by Pharmacovigilance Approaches

JATINDER SINGH[1], MANHARDEEP KAUR[2], AMANJOT SINGH[3], ANMOL KAUR[4]

ABSTRACT

BACKGROUND: Serious adverse events in relation to drugs may be life-threatening or fatal, may require hospitalization, can also result in significant, persistent, or permanent disability and impairment. These drug related events may also cause damage or disruption in the patient's body function/structure, affect physical activities or may result in congenital anomalies, leaving a transient or permanent affect on quality of life. In India, Pharmacovigilance Programme of India (PvPI) has a classification system for the analysis of ADRs which has been suggested based on dose relation, timing, and patient susceptibility. Despite all efforts, ADR monitoring and reporting activity is still poor in India. Data about serious ADRs is deficient so this study was planned as a preliminary initiative to contribute to PvPI.
AIM: To study incidence of serious ADRs at a Tertiary care hospital.
MATERIAL AND METHODS: This prospective observational study was carried out for duration of six months i.e. from July, 2014 to January, 2015 on patients admitted in a Medical College of North India. Data regarding the patient demographics and ADRs were collected by serial patient interviews in the Tertiary care Hospital collaborated by information in respective patient file. No changes in treatment decision, schedule or duration were made as part of study. The incidence rate of each ADR was calculated.
RESULTS: A total of 66 serious ADRs were reported during this duration in 60 patients (27 males, 33 females). Mean age of patients was 46.90 years. ADR incidence was found to be 1.11 per patient. The average number of drugs prescribed was 1.64 per patient. The most common drug leading to Serious Adverse Drug Reaction was Phenytoin (13%) followed by Paclitaxel (10%). The most common ADR noted was Rash leading to hospitalization (31.18%) and Steven Johnson Syndrome (31.18%), followed by Fever (16.60%), Anaphylactic Reactions (5%), DRESS (5%) and Toxic epidermal necrolysis (5%). Patients suffering from serious ADRs had presented with diagnosis of seizures (20.75%) followed by ALL (7.73%).
CONCLUSION: Most common serious ADRs reported were Rash and Steven Johnson Syndrome (31.18%).
KEYWORDS: Adverse Event, Serious Adverse Drug Reactions (ADRs), Pharmacovigilance

INTRODUCTION

Adverse event is defined as any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with treatment.[1] When a causal relationship is established between suspected drug and adverse event, it becomes adverse drug reaction (ADR) or adverse drug effect.[2] ADRs are a major problem worldwide. Serious adverse events include events which are life-threatening or lead to death, hospitalization (initial or prolonged), disability - significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life, congenital anomaly, require intervention to prevent permanent impairment or damage.[3]

Even in developed countries like US, where drugs are used cautiously, the mean number of SAEs per patient was 0.021.0, SAEs per patient per month was 0.0031.0, SAEs per site was 0.30.7, and SAEs per site per month was 0.040.07.[4] In India, due to malpractice by unqualified practitioners and unsupervised usage of drugs, serious ADR incidence is likely to be high and lead to mortality and high managing burden for society.[5] As ADRs result in significant morbidity, extended hospital stay, increased health expenditure and mortality, so drugs must be prescribed rationally and constant monitoring of ADRs especially causing serious ADRs is mandatory.

Every medicine is tested on a relatively small number of the participants, in highly selected patients in pre-marketing trials excluding pregnant females, lactating women, children and elderly, those with complicated medical condition and on multiple drug combinations for only short-term period.[6-8] Therefore, adverse reactions having frequency less than 0.5 to 1% are missed and adverse reactions that appear within the predetermined duration of trial are reported.[9] Delayed reactions and ADRs occurring with

chronic use are missed in pre-marketing trials.[10] As the drug is marketed, it is administered to several thousand patients with multiple medical problems and on multiple drug therapies in different age groups.[11] Therefore, ADR monitoring should be started along with administration of drug and continued throughout life of the drug, so that we can understand safety profile of drug and compare it with benefits provided by the drug.[12]

After the Thalidomide disaster of 1962, Pharmacovigilance programs were set up in many countries like UK, Australia, New Zealand, Canada and Sweden in 1964-65 to monitor adverse events with special focus on finding serious adverse events.[13] Central Drugs Standard Control Organization (CDSCO) has initiated a well structured and highly participative Pharmacovigilance Programme of India (PvPI). In spite of all factors, pharmacovigilance has not picked up well in India and the reporting is still poor. India rates below 1% in pharmacovigilance as against the world rate of 5%.[14]

In India, DCGI has taken an initiative by establishing Adverse event reporting center in Medical college and creating awareness among patients and physicians to report adverse events to these centers or by mobile application (ADR monitoring), with focus on finding of Serious adverse events.[15] Serious adverse event are to be reported within seven days in post-marketing period and within 14 days by sponsor in clinical trial.[16] Data about serious ADRs is deficient so this study was planned as a preliminary initiative to contribute to PvPI.

MATERIAL AND METHODS

Source of Data

This prospective observational study was carried out on patients admitted in Medical College of North India for a duration of six months i.e. from July, 2014 to January, 2015 after taking clearance from the institutional ethical committee. A written informed consent was taken from the patients for participation in the study after screening for serious adverse event. All patients were interviewed and their data was recorded in a performa. Patient of any age and gender having serious adverse event were included in the study. All reactions were reviewed and causality assessment was done according to the WHO UMC causality assessment scale to label adverse event as adverse drug reaction. History of the disease along with the drug history, duration of drug intake and ADR associated with drug therapy was recorded. The performa filled for the adverse events experienced by the patients for ADR monitoring was designed on the basis of WHO guidelines and the form also included details like age, gender, other demographic details, past medical history, present drug treatment, description of adverse event, its assessment and treatment for the drug reaction. Regular follow up of the patient was done for a minimum of seven days to a maximum of 14 days to assess the response of treatment. The scoring of adverse events was done according to WHO UMC Casualty assessment scale.[17] No re-challenge with the drug was performed to confirm the relationship.

Statistical analysis

The data collected was recorded in a performa and was analysed using descriptive statistics.

OBSERVATIONS

The 2933 patients with adverse events were screened over a period of six months in Medical College of North India, out of which 66 serious ADRs were reported in 60 patients.

The most common drug leading to Serious Adverse Drug Reaction was Phenytoin (13%) followed by Paclitaxel (10%) as shown in Table 1. The most common ADR noted was Rash leading to hospitalization (31.18%) and Steven Johnson Syndrome (31.18%), followed by Fever (16.60%), Anaphylactic Reactions (5%), DRESS (5%) and Toxic epidermal necrolysis (5%) as shown in Table 2. Patients suffering from serious ADRs due to phenytoin and paclitaxel are shown in figure 1 and 2 respectively.

ADR incidence was found to be 1.11 per patient. The average number of drugs prescribed was 1.64 per patient. Incidence of Serious ADRs was 0.04%.Mortality was reported in 3 patients. Two patients died due to hypersensitivity reaction to contrast media while 1 patient having chronic liver disease died due to hypersensitivity reaction to flex albumin while 33 patients were hospitalized and in 24 patients stay was prolonged due to ADR.

A difference in adverse drug reactions according to age was also seen. Mean age of patients was 46.90 years. The adverse drug reactions were reported more in females i.e. 33(55.69) as compared to the males-i.e. 27(45.30) as shown in Table 3.

Demographic profile

There was difference in adverse drug reactions according to demographic profile. Urban patients constituted 40 (66.31%) of adverse drug reactions and rural patients constituted 20(32.69%).

Causality assessment

A causal relationship between the drug and the reaction was assessed depending upon the lag period between the start of the drug and appearance of the reaction, response to de-challenge, laboratory tests and the data available regarding the drug using the WHO UMC causality assessment scale. Dechallenge (discontinuation of the suspected drug) was done in 22 %cases, whereas in 78 % of the cases initial drug therapy was continued. Causality assessment was done according to WHO UMC causality assessment in figure 3. All data of serious ADRs was reported to PvPI in Vigibase through vigiflow software in regional ADR monitoring center.

DISCUSSION

A wide range of serious adverse drug reactions are caused by various drugs. The present study was conducted in patients admitted in a Medical College and Hospital of North India. The serious ADRs were recorded over a period of six months. The frequency and distribution of serious adverse drug reactions and drugs implicated in these reactions were studied.

A total of 66 serious ADRs were reported during this duration in 60 patients (27 males, 33 females). Mean age of patients was 46.90 years. ADR incidence was found to be 1.11 per patient. The average number of drugs prescribed was 1.64 per patient. The most common drug leading to Serious Adverse Drug Reaction was Phenytoin (13%) followed by Paclitaxel (10%). The most common ADR noted was Rash leading to hospitalization (31.18%) and Steven Johnson Syndrome (31.18%), followed by Fever (16.60%), Anaphylactic Reactions (5%), DRESS (5%) and Toxic epidermal necrolysis (5%).

Similar pattern of adverse reactions were observed in different studies. These studies included on average: 502311 patients, 301.5 clinical sites per study as well as 2.20.6 treatment arms lasting 7.79.6 months. There were 8616 (42.9%) males and 9298 (46.3%) females; 2017 (10.0%) African Americans, 15,248 (75.9%) Caucasians, and 1436 (7.1%) other races, as well as 18,724 monotherapy (93.2%) and 1379 (6.8%) adjunctive therapy patients. The average age was 63.41.8 years. There were 7 studies missing at least some demographic data. Of the included studies, 35 evaluated prostaglandins, 34 beta-blockers, 14 carbonic anhydrase inhibitors (CAI), and 7 alpha-agonists as well as studies evaluating prostaglandin (n=1), alpha-agonist (n=2), and CAI (n=2) based fixed combinations. 449 (2.3%) total SAEs were reported in the reviewed articles. Of these, 20 (4.5%) were deaths, 41 (9.1%) hospitalizations/ surgeries, and 377 (84.0%) with type not reported. Also, 11 (2.5%) SAEs were related to the study medicine by the investigator. The average number of SAEs per study was 11.23.1. In addition, there were 1.51.0 SAEs per month per study. The mean number of SAEs per patient was 0.021.0, SAEs per patient per month was 0.0031.0, SAEs per site was 0.30.7, and SAEs per site per month was 0.040.07.

Separate multilinear regression analyses for patient and study characteristics associated with SAEs demonstrated that risk factors were advanced age (P0.0001) and increased study length (P0.0001).In contrast, the risk for higher incidence of SAE potentially may be related to larger sample size, longer study length, and older age. However, any favorable effect of altering study design to potentially reduce SAE incidence should be carefully assessed by the impact on the study conclusions, especially patient safety, and the regulatory labeling.[18]

As any other study, our study too has few limitations. We studied only the patients reported for adverse events and study was limited for six months. We, however, feel that the duration of the study and sample size was adequate for the given period of study.

CONCLUSIONS

Serious ADR monitoring of drugs is important as it clarifies the safety of available drugs. ADR

monitoring and reporting activity is still in establishment phase in India.

The present study was conducted with an aim to determine frequency and distribution of serious adverse events in a Tertiary care hospital in North India for a duration of six months. Data regarding the patient demographics and ADRs was collected by patient interviews and entered in individual proforma. Causality was assessed by both WHO causality assessment scale. Most common serious ADRs reported were Rash (27.27%) and Steven Johnson Syndrome (27.27%). Incidence of Serious ADRs was 0.04%. All the ADRs were managed as per standard protocol. Mortality was reported in 3 patients. It can be concluded that high risk drugs are not entirely safe and there is an urgent need for monitoring these drugs. This can be done by post marketing surveillance at large number of centers over a long period of time.

However these results need to be verified in multi-centric studies as sample size for some of them were small and hence cannot be extrapolated to large population. Since all the serious adverse effects of the drugs cannot be prevented, it is necessary to create awareness about patterns of adverse reactions and the common drugs implicated in these reactions. Patients should be aware of these ADRs so that these can be taken care of at an early stage. We should monitor safety of high risk drugs monthly by starting task specifically oriented towards monitoring serious adverse events in patients taking these drugs. This will enhance the safety of high risk drugs.

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Source of support: Nil, **Conflict of interest:** None declared

Cite this article as:
Singh J, Kaur M, Singh A, Kaur A. Information about Serious ADRs Explored by Pharmacovigilance Approaches. Int Healthcare Res J 2017;1(6):25-33.

AUTHOR AFFILIATIONS
1. Department of Pharmacology, Dayanand Medical College, Ludhiana
2. Post Graduate Resident, Social and Preventive Medicine, Rajindra Medical college ,Patiala
3. Senior Resident, Department of Surgery
4. Post Graduate Resident, Department of Chest and TB
Sri Guru Ram Institute of Medical Sciences & Research Amritsar

Corresponding Author:
Dr.Manhardeep Kaur
Post Draduate Resident
Social and Preventive Medicine
Rajindra Medical College
Patiala
+91- 8146559031
sandhumanu56@gmail.com

LEGENDS

DRUG	Frequency of ADRs
PHENYTOIN	10
PACLITAXEL	7
RIFAMPICIN	6
PYRAZINAMIDE	5
ETHAMBUTOL	5
LEVITERACETAM	4
ISONIAZID	4
CLONAZEPAM	3
QUETIAPINE	3
CYTOCARBOPLATIN	3
PHENOBARBITONE	2
AZITROMYCIN	2
CEFUROXIME	2
CLOXACILIN	2
PROGESTERONE	2
ISOXPURINE	2
CYCLOPHOSPHAMIDE	2
DEXAMETHASONE	2
VALPROATE	2
CONTRAST MEDIA	2
FLUROURACIL	1
GEMCITABINE	1
STREPTOMYCIN	1
METHOTREXATE	1
CYTARABINE	1
AMIKACINE	1
DICLOFENAC	1
PARACETAMOL	1
INDOMETHACIN	1
SULFASALAZINE	1
ALLOPURINOL	1
CARBAMEZAPINE	1
IVIG	1

PROBIOTICS	1
ALBUMIN	1
ASPIRIN	1
HYDROCLORTHIAZIDE	1

Table 1. Frequency of ADRs caused by drugs

ADR	DRUG CATEGORY	DRUG		FREQUENCY
SJS	ANTICONVULSANT	PHENYTION		3
		PHENOBARBITONE		1
		LEVETRICITAM		1
	ANTITUBERCULAR	RIFAMPICIN		2
		PYROZINAMIDE		2
		ETHAMBUTOL		2
		ISONIZID		1
	ANTI BIOTICS	AZITHROMYCIN		1
		CEFOPODOXIME		1
		CLOXACILLIN		1
	ANTI PSYCHOTICS	QUETIAPINE		1
	ANTI ANXIETY	CLONAZEPAM		1
	HORMONE	PROGESTRONE		1
	VASODILATOR	ISOXPURINE		1
			TOTAL	21
RASH	ANTICONVULSANT	PHENYTION		3
		LEVETRICITAM		1
		PHENOBARBITONE		1
	ANTITUBERCULAR	RIFAMPICIN		2
		PYROZINAMIDE		2
		ETHAMBUTOL		2
		ISONIZID		1
	ANTI BIOTICS	AZITHROMYCIN		1
		CEFOPODOXIME		1
		CLOXACILLIN		1
	ANTI PSYCHOTICS	QUETIAPINE		1
	ANTI ANXIETY	CLONAZEPAM		1
	HORMONE	PROGESTRONE		1
	VASODILATOR	ISOXSUPRINE		1
			TOTAL	21
FEVER	ANTICANCER	PACLITAXEL		2
		CYTOCARBOPLATIN		2
		CYCLOPHOSPHAMIDE		1
		FLUROURACIL		1
		GEMCITABINE		1
	CORTICOSTEROID	DEXAMETHASONE		2
			TOTAL	9

TEN	ANTICONVULSANTS	LEVITERACETAM	2
		VALPROATE	2
		PHENYTOIN	1
	ANTIBIOTICS	STREPTOMYCIN	1
	ANTI PSYCHOTIC	QUETIAPINE	1
	ANTI ANXIENTY	CLONAZEPAM	1
		TOTAL	8
DYSPNEA	ANTICANCER	PACLITAXEL	2
		CYCLOPHOSPHAMIDE	1
		CYTOCARBOPLATIN	1
		METHOTREXATE	1
		CYTARABINE	1
	ANTI BIOTICS	AMIKACIN	1
		TOTAL	7
HEPATITIS			
	ANTI CONVULSANTS	PHENYTION	1
	ANTI TUBERCULAR	RIFAMPICIN	2
		ISONIZID	2
		PYROZINAMIDE	1
		ETHAMBUTOL	1
		TOTAL	7
DRESS	ANALGESICS	DICLOFENAC	1
		PARACETAMOL	1
		INDOMETHACIN	1
	ANTI BIOTICS	SULFASALAZINE	1
	XANTHINE OXIDASE INHIBTOR	ALLOPURINOL	1
	ANTICONVULSANT	CARBAMEZAPINE	1
		TOTAL	6
ANAPHYLACTIC REACTION			
		CONTRAST	2
	IMMUNO GLOBULINS	IVIG	1
		PROBIOTICS	1
		ALBUMIN	1
		TOTAL	6
ANGIODEMA			
	ANTICONVULSANT	PHENYTOIN	1
	ANALGESIC	ECOSPIRIN	1
		TOTAL	2
HYPONATREMIA			
	DIURETIC	HYDROCHLORTHIAZIDE	1
		TOTAL	1
VERTIGO	ANTICONVULSANT	PHENYTOIN	1

Table 2. Frequency of serious ADRs along with drugs

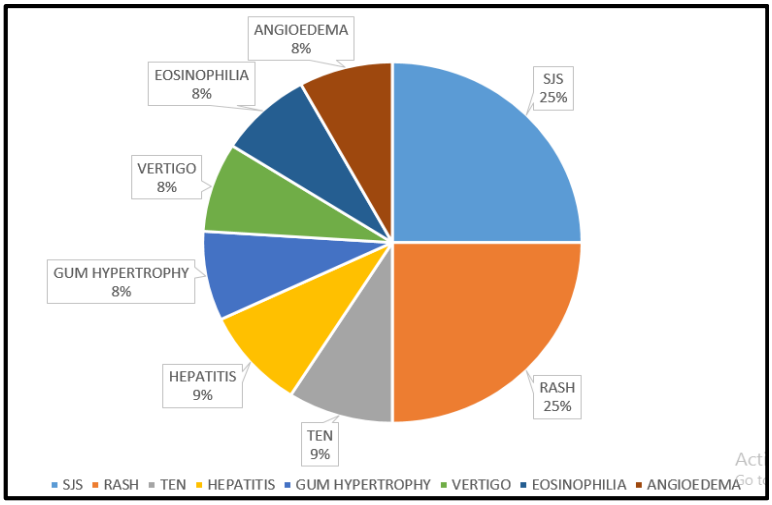

Figure 1. Serious ADRs due to Phenytoin

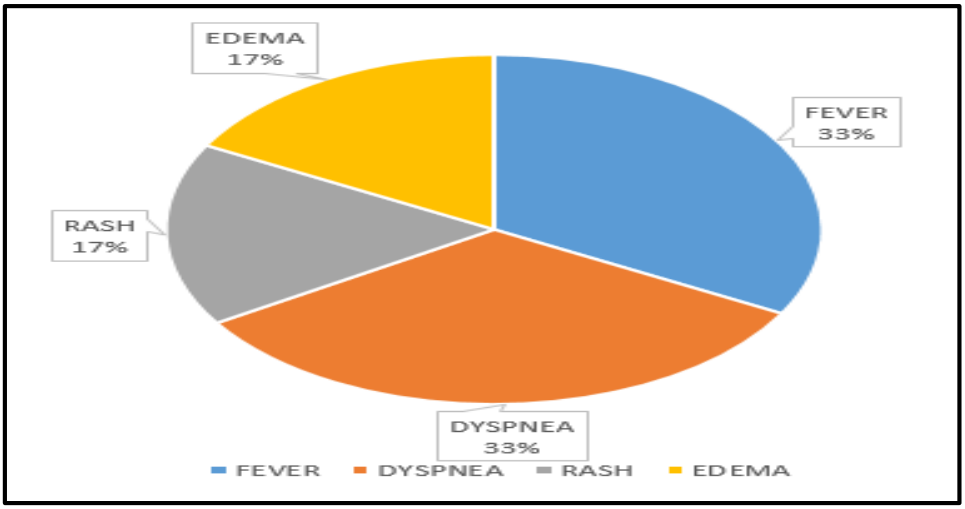

Figure 2. Serious ADRs due to Paclitaxel

	Males	Females
No of Patients enrolled (%)	27(45.30)	33(55.69)
Mean Age ± Standard deviation (Years)	48.41 ±4.89	46.05 ±5.47

Table 3. Gender Distribution of ADRs

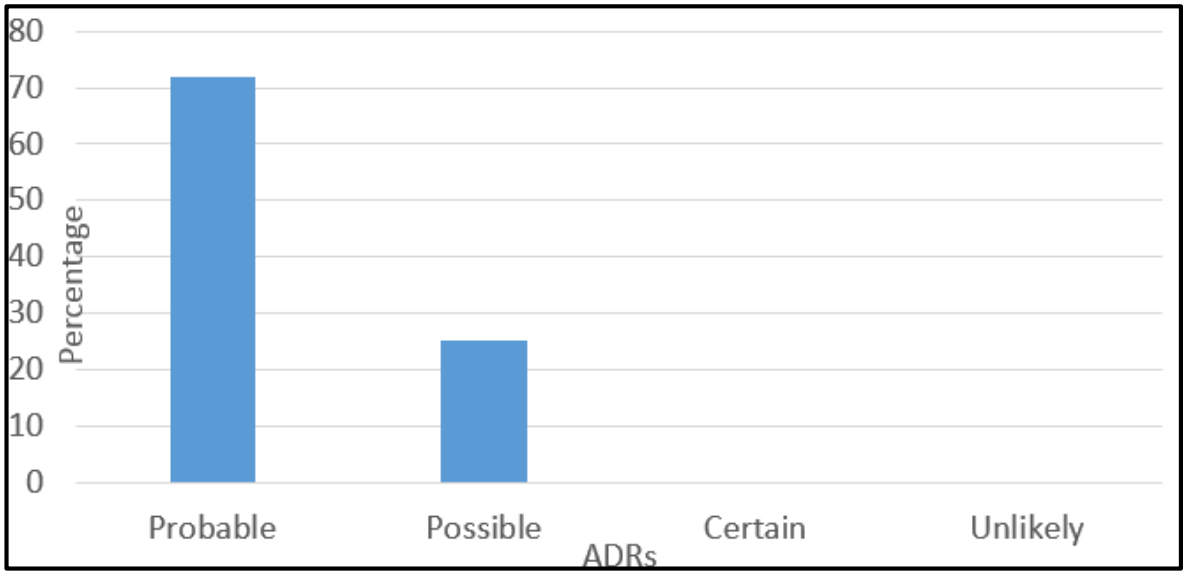

Figure 3. Causality assessment by WHO UMC scale