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PHARMACOVIGILANCE AS AN ESSENTIAL COMPONENT OF PHARMACOTHERAPY AT TERTIARY HOSPITALS IN RURAL AREAS OF PAKISTAN

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ABSTRACT

Pharmacovigilance (PV) is reporting of ADRs, which may cause increase in hospital stay. All drugs can produce ADRs, but not all patients develop the same level and type of ADRs. The majority of ADRs occur as a result of the extension of the desired pharmacologic effects of a drug, often due to the substantial variability in the pharmacokinetics and pharmacodynamics seen among patients. This study was designed to collect data of ADRs from Tertiary Hospital in Rural Area. This would help the regulatory bodies to implement Pharmacovigilance as an essential component of patient-care. This observational prospective study was conducted at tertiary hospitals to evaluate reporting practices of ARDs using Adverse Drug Reaction Reporting Form of PNPC. From January 2020 to March 2020, thirteen hundred and eighty in-patients from various wards were interviewed after taking their written informed consent. Of the 1380 patients, only 346 informed the Principle Investigator about their experience regarding ADRs. It was concluded that ADRs monitoring and reporting needs to be improved. In rural areas, reporting of ARDs is ignored. DRAP should take drastic steps to ensure reporting of ADRs so that the concept of Pharmacovigilance can be implemented at least at Tertiary Hospitals.

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Introduction

Pharmacovigilance (PV), as defined by the World Health Organization (WHO), is the activities and science related to the understanding, assessment, detection, and prevention of side effects and drug-related problems [1]. The European

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Commission (EU) defines PV as "The science and process of monitoring the safety of medicine and taking necessary actions to minimize the risks and enhance the benefits of medicines" [2]. PV aims to detect unknown adverse drug reactions once clinical development has been completed to improve the benefits of medicine and to reduce the risk associated with or exposed to every patient [3]. The WHO defines an adverse drug reaction (ADR) as "a response to a drug which is unintended and noxious and occurs at a dose normally used by people for the modification of physiological functions or diagnosis, therapy, or prophylaxis of a disease" [4]. They cause an increase in hospital stay as their occurrence in hospitalized patients is about 10-20% and is considered as the 4^{th}-6^{th} leading cause of death [5-7]. ADRs are the significant health-affecting problem, which can be preventable through analyzing the pattern and severity in different clinical conditions, which in turn help in decreasing the cost of health, minimize hospital stay, and can increase the quality of life [8, 9]. All drugs can produce ADRs, but not all patients develop the same type and level of ADR [10]. Most ADRs occur due to the extension of the desired pharmacologic effects of a drug, often as a result of considerable variability in the pharmacodynamics and pharmacokinetics seen among patients. Factors that cause ADRs include pharmacogenetics, immune system, gender, polypharmacy, and age [11]. In order to ensure safer use of drugs, a vibrant pharmacovigilance system is needed at all levels of health care. Therefore, establishing a better system for reporting ADR is recommended as a top priority to prevent ADR in hospitals. Hospital-based monitoring is a system used to collect data on drug prescription and this data has become an important component of monitoring and evaluation activities performed in hospitals [12]. Reporting the activity of adverse events (AE) is most commonly associated with PV, and consumes a significant amount of resources for drug safety departments in pharmaceutical companies (or similar government agencies) and drug regulatory authorities. AE reporting involves the receipt, triage, entering data, evaluation, distribution, reporting (if suitable), and archiving and documentation of AE data. The source of an AE report includes: reports from the media (including websites and social media); reports from literature sources; reports from post-marketing or clinical studies; solicited reports from patient support programs; spontaneous reports from patients or healthcare professionals (or other intermediaries); and reports reported to drug regulatory authorities themselves. In most countries, AE reporting is a legal requirement for pharmaceutical companies. It also provides data for these companies and drug regulatory authorities that play a significant role in the assessment of the risk-benefit profile of a particular drug [13]. This study was performed to collect data of ADRs from Tertiary Hospitals in Rural Areas. This would help the regulatory bodies to implement Pharmacovigilance as a vital component of patient care.

Materials and Method:

The study was conducted in Rural Tertiary Hospital and the study design was prospective and observational. Suspected Adverse Drug Reaction Reporting Form (PV form) of Pakistan National Pharmacovigilance Centre (PNPC) was adopted to collect data of Adverse Drug reactions (ADRs). From January 2020 to March 2020, thirteen hundred and eighty in-patients from various wards were interviewed after taking their written informed consent. Of the 1380 patients, only 346 informed the Principle Investigator about their experience regarding ADRs. The patients interviewed were above 18 years of age regardless of their gender. However, Patient from ICUs, Emergency Department, drug abuse or medico legal cases and patients with unclear drug history were not included. Patients were counseled regarding monitoring of Adverse Drug Reactions. They were also explained about Suspected Adverse Drug Reaction Reporting Form of PNPC, published by Drug Regulatory Authority of Pakistan (DRAP). After counselling, the PV form was filled out by Principle Investigator, through a semi-structured interview of the patient, review of the medical history / record, and direct communication with medical personnel rotating in the ward.

Results:

Of the 346 valid PV forms, 217 (62.71%) were males and 129 (37.28%) were females. The highest participation was from 18-27 years of age group (29.77%) followed by the age group equal to and above 68 years (Table 1).

Table 1: Demographic Distribution of Patients encountered ADRs

Age Range Years	Males n (%)	Females n (%)	Patients n (%)
18-27	69 (31.80 %)	34 (26.36 %)	103 (29.77 %)
28-37	13 (5.99 %)	9 (6.98 %)	22 (6.36 %)
38-47	17 (7.83 %)	20 (15.50 %)	37 (10.69 %)
48-57	26 (11.98 %)	11 (8.53 %)	37 (10.69 %)
58-67	35 (16.13 %)	23 (17.83 %)	58 (16.76 %)
≥68	57 (26.27 %)	32 (24.81 %)	89 (25.72 %)
Total	**217 (62.71 %)**	**129 (37.28 %)**	**346 (100 %)**

Table 2 exhibits the involvement of the organ/system among the documented ADRs. It was found that the highest number of ARDs involves the Gastrointestinal System (26.3%) followed by involvement of the Cardiovascular System (16.76%).

Table 2: Organ systems involved in causing adverse drug reactions

Organ-systems	**ADRs n (%)**
Cardiovascular System	58 (16.76 %)
Gastrointestinal System	91 (26.30 %)
Skin and mucous membrane	35 (10.12 %)
Respiratory System	43 (12.43 %)
Musculoskeletal System	23 (6.65 %)
Nervous System	24 (6.94 %)
Ophthalmological	19 (5.49 %)
Renal System	33 (9.54 %)
Hematological /	6 (1.73 %)
Others	14 (4.05 %)
Total	**346 (100 %)**

ADRs associated with routes of administration were also asked from the participants of the study. It was found that the major involved route of administration was the oral route (48.56%). However, 19.65% of the ARDs reported involved a topical route. The intravenous route was also associated with 16.76% of the reported ARDs (Table 3).

Table 3: ADRs Associated with the Route of Administration

Route	**ADRs n (%)**
Oral	168 (48.56 %)
Intravenous	58 (16.76 %)
Subcutaneous	28 (8.09 %)
Intra-vaginal	6 (1.73 %)
Topical	68 (19.65 %)
Intra-muscular	18 (5.20 %)
Total	**346(100 %)**

Table 4 depicts the risk factors associated with reported ADRs. According to the statistics of Table 4, 33.53% of the patients who had experienced ADRs were smokers, followed by 17.93% hepatic patients, and 12.72% renal patients.

Table 4: Risk Factors Associated with ADRs

Co-morbid conditions	**ADRs n (%)**
Alcoholic	36 (10.41 %)
Smoker	116 (33.53 %)
Known allergy to Dust	22 (6.36 %)
Known allergy to NSAIDs	4 (1.16 %)
Known allergy to Penicillins	10 (2.89 %)
Pre-existing Medical Problem	27 (7.80 %)
Hepatic Problems	62 (17.92 %)
Renal Problems	44 (12.72 %)
No Co-morbid Conditions	25 (7.23 %)
Total	**346 (100 %)**

NSAIDs: Nonsteroidal anti-inflammatory drugs

Co-morbid conditions also contributed to the ARDs. In this study, 18.5% of patients who had experienced ADRs were diabetic, followed by 15.61% hypertensive, 11.56% with urinary tract infections (UTI), 11.56% with constipation and 10.12% were having microbial infections.

Table 5: Co-morbid Conditions Associated with ADRs

Co-morbid conditions	ADRs n (%)
Diabetes	64 (18.50 %)
Hypertension	54 (15.61 %)
Anemia	4 (1.16 %)
Gastritis	20 (5.78 %)
Constipation	40 (11.56 %)
Microbial Infection	35 (10.12 %)
Hypothyroidism	30 (8.67 %)
Urinary tract infection	40 (11.56 %)
Pain abdomen	24 (6.94 %)
Cholelithiasis,	9 (2.60 %)
Fatty liver	10 (2.89 %)
Diabetic nephropathy	13 (3.76 %)
Others	3 (0.87 %)
Total	**346 (100 %)**

Discussions:

Generally, women have a higher incidence of ADRs compared to men [14]. However, in this study, males were almost double the females. This might be due to the demographic and cultural variations of the rural population. Female sex was considered to be a risk factor for the development of ADRs. Women in comparison to men have lower organ size and bodyweight, more body fat, different gastric motility, and lower glomerular filtration rate [15] for having higher ADRs. But in District Khairpur Miris of Sind Province in Pakistan, the female sex is found to be stronger and work side by side their men in various fields. The atmospheric condition is also better than in urban areas. Another factor may be that female sex usually does not visit Tertiary Care Hospitals and used to go to their nearby dispensaries and primary healthcare centers.
The adult group showed a higher percentage of ADRs. This was similar to Ingale *et al*. and Venkatesan *et al*. [16, 17] who also observed maximum ADRs among the adult age group. This study also highlighted a higher rate of incidence of ADRs among elderly patients, which is similar to other studies on spontaneous reporting, that have depicted a higher rate of incidence among elderly patients [18]. The major involvement of the GI System among patients who faced ADRs was found in this study. However, many other studies exhibited major involvement of Skin among most of the patients who faced ADRs [19-21]. The most common route of administration contributed to ADRs was the oral route unlike other studies, which exhibited the intravenous route as the most common factors among ADRs [19]. In this study, diabetes and hypertension were found to have a major contribution to the incidence of ADRs. Similar results were expressed in other studies [17, 22].

Conclusion:

It was concluded that ADRs monitoring and reporting need to be improved. In rural areas, reporting of ARDs is ignored. DRAP should take drastic steps to ensure the reporting of ADRs so that the concept of Pharmacovigilance can be implemented at least at Tertiary Hospitals.

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Author's contribution:
All authors contributed equally

Conflict of interest:
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