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Chapter 5

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5.1 ADR Monitoring

Almost all drug possess more than one pharmacological actions. Except the action that is exploited clinically, all others are unwanted effects which are refereed to as undesirable since they may adversely affect the recipient. Some of these adverse effects may be severe enough to discontinue the therapy and even may warrant the use of other drugs. Considering the magnitude of ADR related health problems, there is utter need for identifying them and disseminate the related information among the clinicians, so as to minimize their incidence to ensure safety of modern drug therapy. These pharmacovigilance activities are therefore needed in all the health care delivery centers, since these ADRs vary from person to person and population to population.

The well organized pharmacovigilance activities under well trained personnel can complement the health care system in assessing the safety of drug therapy, with relevance to ADRs. Continuing education program for healthcare profes-
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sionals regarding ADRs, adverse drug drug interaction are essential to ensure drug safety. The monitoring and reporting ADRs is a continuous process since new drugs continue to enter clinicians armamentarium and new drug combinations are likely to evolve in therapeutics. Despite significant prevalence, ADRs are under reported and there are several reasons for the same. The present study attempted to explore the reasons for not reporting ADRs by participating clinicians and other personnels involved in health care delivery. The outcome was - mainly believed that there was no need to report the ADRs they encountered, as they were well known/common. Other reasons for under reporting include lack of incentive, fear of personal liability, labour intensive etc, these findings are similar to that of Vitillo [28].

The findings of the present study indicate that the overall incidence of ADRs in hospitalized patients to be 4.50%. In female patients the incidence was higher (5.57%) when compared to that in male patients (3.71%). The ADR incidence in our patients was very low when compared to that of the meta analysis conducted by Lazarou et al. where 15.1% of hospitalized patients developed ADRs [2]. The discrepancy could be explained on the basis of relatively smaller sample size of the present study and also due to heterogenous sample.

The higher incidence of ADRs in female population (5.57%) in contrast to male population (3.71%) observed in this study is in agreement with the results reported by Aline Lins Camargo et al. Various reasons have been proposed to explain the higher incidence in females. The possible ones include, the difference in pharmacodynamic response to various drugs, particularly for those having low therapeutic range, differences in drug metabolism through CYP 3A4 whose ac-
tivity is higher in females than in males though other enzyme activities are higher in males. In contrast to the findings of the present study, Jimmy Jose et al. have shown that male population experienced more ADRs than female population. It is not known whether or not cyclic changes in circulating sex hormones in females also contribute for such variations. 129, 130.

The results of the present study indicated that geriatric patients experienced higher number (8.2%) of ADRs than adults (3.72%) despite the number of admitted old patients (≥60 years) which was lesser (25.51% of the total patients population) than that of adult patients (74.4%) admitted. The present study observations are similar to the spontaneous study conducted in India, wherein incidence of ADRs among geriatrics (0.21%) were significantly higher than adults (0.15%) 130, though the magnitude of ADRs in contrast to the recent study observations was very low. Discrepancy could be because of relatively smaller population size and inclusion of only the medical wards patients in the present study.

Correlating polypharmacy with the incidence of ADRs, the findings of the present study showed that 48.97% of the reported suspected ADRs came from patients who were receiving between 2 and 4 medications. These findings agree with the earlier report where in majority (51.35%) of the patients who developed an ADR were receiving two or more drugs at the time of experiencing an ADR 18.

Type A reactions were seen to be most common (53.06%) followed by the Type H reactions (40.81%), in the present study and these finding concur with those reported by Wills and Brown, (the proposers of the new classification of medication related adverse reactions) where in Type H reactions were the most common
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adverse reactions after Type A reactions. Type A reactions are due to dose-dependent actions of a medicine, and can be minimized by reducing the dose of the suspected drug(s).

Predisposing factors for ADR development considered in the present study were found to be- use of multiple drugs in a single patient (48.97%) geriatric age group (26.53%) and the patients with co-morbidities necessitating multiple drug therapy. The prominent components of co-morbidities were hypertension, diabetes, gastritis, congestive heart failure (CHF), myocardial infarction (MI) etc. Considering the drug category associated with ADRs, the findings of the present study revealed that antibiotics (21.42%) were responsible for the maximum ADRs and this findings agrees with earlier reports. The incidence of ADR are reported in descending order with anti mycobacterial drugs (15.30%) cardiovascular (18.36%) and digoxin (7.14%) being the most commonly implicated drug in this group.

Of the various categories of drugs used ampicillin, atenolol, cefotaxim, insulin were the frequently encountered drugs that caused ADRs (3.06%).

Gastrointestinal system with the incidence of (31.63%) was the main organ system affected by the ADRs in the present study, diarrhoea being the most common (12.24%) ADR. Similar findings are reported by earlier studies.

Dermatological system was the next organ system to be affected with the incidence of (20.40%) in the present study and majority of ADRs were in the form of rashes (19.38%).
The findings of the present study, that antibiotic drugs had the highest percentage (21.42%) followed by the Cardiovascular drugs (18.36%), is consistent with the study conducted by Gurwitz et al. However, the other study reported antibiotics as the most commonly associated drug-class. These findings probably indicate the pattern of drug usage in clinical practice.

Dose alteration of suspected drug is usually the first step to be adopted for the management of an ADRs. In this study, the suspected drug was withdrawn in 26.53% after the occurrence of an ADR and this discontinuation is similar to studies of Gallelli et al. There are some discrepancies with regard to the causality assessment between the different assessment scales. The ADRs observed in the present study when analysed according to WHO scale majority of the reactions were probable (44) and unassessable (11). While analysis with Naranjo’s scale indicated majority of the reactions were possible (45) and probable (53). Most of the reactions were either possible or probable but not certain as in none of the reactions drugs were rechallenged. In majority of the reactions, there was definite improvement, after the dechallangeing of suspected drug which is an ideal way of managing the ADR. In the present study the ADRs which were trivial in nature were managed by counselling and close monitoring without changing dose (29.59%), where as the drug was withdrawn in some (26.53%) patients.

The primary objective of preventing ADR in hospitalized patients should focus on frequently implicated medications, as (32.64%) of ADRs were definitely preventable of all ADRs. The findings of the present study indicate that in ma-
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Majority of cases ADRs observed were not preventable (67.34%) and these findings are similar to that documented in the literature (30-70%).

The severity of ADRs was either level 3 (92.85%) or below ADR that required interventions include cessation of drug and/or specific/symptomatic treatment e.g. dextrose for insulin induced hypoglycemia. However no mortality was observed due to ADRs. These findings are in agreement with the literature where in severity level 3 was reported [134, 135].

5.2 Drug-Drug Interactions

Drug drug interactions often exploited in the clinical practice and a few fixed dose combinations eg. oestrogen with progesterone, levodopa with carbidopa, ampicillin with clavulanic acid etc. are universally accepted as rational therapy. However majority of them available in the market eg. diclofenac + paracetamol, metoclopramide + paracetamol may be irrational. Therefore there is a need to predict/suspect the adverse drug drug interaction from the patients safety point of view. Prediction is usually based on their pharmacokinetic and pharmacodynamic properties. In this hospital probably elsewhere also anti ulcer drug like omeprazole or ranitidine are routinely used to avoid concurrently administered other drug induced gastritis.

Glipizide a second generation sulphonylureas reduces blood glucose levels by acting on Sulphonylurease receptors of the β cells, leading to increase insulin secretion. Although the exact mechanism of action is not completely understood,
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the most widely accepted hypothesis is that their effect on insulin sensitivity is related to their well known ability to bind and activate the nuclear peroxisome proliferator activated receptor - gamma (PPAR-γ) and omeprazole, mainly a proton pump inhibitor has been reported to inhibit CYP2C9 and CYP3A4. Sulphonylureas are normally metabolised by microsomal enzymes, CYP 2B4 and CYP 3A6 and other enzyme to hydroxyl and then carboxy metabolites.

Based on the pharmacokinetic information about the two drugs there appears to be less likeliness of drug drug interaction. The results of present experimental study clearly support the view since, neither the onset and duration of hypoglycemic effect nor the time to peak effect of glipizide were significantly altered. Similarly suspected interaction between glipizide and ranitidine was also explored by experimental studies. Results clearly indicate onset, time to peak effect and duration of glipizide hypoglycemic effect was significantly enhanced in ranitidine pre treated animals. Magnitude of hypoglycemic activity was enhanced from 39.06±1.73% to 52.56±0.08% at 6th hour and similarly duration of hypoglycemic activity of glipizide was prolonged by 4 hours in ranitidine pretreated group. These observations clearly indicate pharmacokinetic drug interaction between ranitidine and glipizide.

Similar interaction between glipizide and ranitidine as observed in present study could not be traced in literature, however ranitidine has been reported to enhance hypoglycemic activity of sulphonylureas [Jefferys & Vale]. There are conflicting reports regarding such interaction, [Clark et al., ] have reported that no interaction was observed between sulphonylureas and ranitidine, while [Stubbs et al.] reported decrease in hypoglycemic activity of sulphonylurease. These dis-
crepancies could be explained by equivocal reports regarding inhibition of hepatic microsomal enzymes by ranitidine. Result of present study indicate that ranitidine do interact with glipizide. Mechanism of interaction could be speculated that ranitidine inhibits CYP2B4 and CYP3A6 which metabolize glipizide.

The estimation of plasma insulin/glipizide levels in both the animal group would have certainly helped to affirm the interaction. However as per our present findings patients on treatment with glipizide should be advised/educated about altered hypoglycaemic activity when administered along with ranitidine.

5.3 Assessing attitude and awareness of health care team regarding ADR

Pharmacovigilance activities depend upon active participation of healthcare team members and clinician in particular. Unfortunately such participation dose not occur, and hence it was decided to probe regarding inactiveness of heath care team in reporting ADRs. Investigation in this regard pointed few factors contributing for the under reporting of ADR. It was decided to expose the health care team to pharmacovigilance activities through formal discussions which ultimately culminated into short workshop for about 6 hours, Post workshop questioner revealed marked improvement.

In pre-intervention survey 84 healthcare professionals had reported ADR previously, though 124 had experienced ADR in their day to day practice. Sixty two healthcare professionals had never reported ADR. The reason for under report-
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ing mentioned were lack of awareness, lack of time, lack of interest and misinformation that reporting does not affect patient care. Similar reasons were identified as discouraging factors to reporting an ADR in various other studies. Hence various steps like educational interventions to create awareness for ADR reporting and utilising assistance of pharmacist to report ADR are needed to be taken in the direction to overcome these deterrents. Studies have shown that creating awareness can improve ADR reporting. The effect of educational interventions can be observed from the results of post-intervention survey which clearly showed that there is a significant improvement in attitude towards ADR reporting with 18% increase in number of healthcare professionals reporting the ADR. The results show that there is improvement in attitude towards ADR reporting. This may be attributed to short term interventions. Further studies should be done to assess the change in attitude after continuous and long term interventions. It is also important to note that there is significant improvement in the knowledge of ADR and its reporting system. There was 7.34% increase in knowledge regarding ADR definition, while 21.34% increase in knowledge regarding grading of ADR based on severity and 31.33% improvement in knowledge regarding grading of ADR based on causality. Increased number of healthcare professionals now knew the information to be included while reporting an ADR, which can facilitate ADR reporting. Hence results of this study are consistent with the results of previous studies in which educational interventions had played an important role in creating awareness for ADR and its reporting.

Busy schedule (75) and lack of assistance (54) were found to be deterrent in ADR reporting. The same reason was identified as barrier in many other studies. Hindering factors like busy schedule and lack of assistance can be overcome by
provision of assistance by clinical pharmacists. The same was done to overcome these deterrent factors. Pharmacists were appointed to assist the doctors and nurses in filling ADR forms and reporting ADR and the improvement was reflected in the post survey. Previous studies have shown that the ADR reports submitted by pharmacists provide valuable information, which is complimentary to physician’s reports. Studies have also shown that pharmacists have adequate knowledge for reporting an ADR and their assistance can definitely improve ADR reporting. Moreover in most countries as the pharmacist are considered eligible to report, they can also forward adverse drug reaction reports to national centres. It is found that reports from pharmacists are more complete and appropriate when compared to other healthcare professionals.

According to International Pharmaceutical Federation (FIP), “An important clinical responsibility of the pharmacist is in the early detection of ADRs and other drug-related problems as well as monitoring the effectiveness of medicines. The pharmacist, as a part of the healthcare team is a source of both information and critical evaluator of drug information. The pharmacist’s expertise is vital to the application of the safety profile of a medicine to the needs of a particular patient.”

Many studies have shown that pharmacists have highly positive attitude and believe that ADR reporting is their professional responsibility, indicating that appropriate education regarding reporting can make significant improvement in ADR reporting. Pharmacists must understand their role in promoting safe use of medicines and hence actively involve in detection as well as reporting of ADRs.

Inadequate availability of ADR reporting forms was identified as another discouraging factor for reporting ADR. To overcome this, ADR reporting forms
were made freely available at the nursing stations in all the wards. ADR drop boxes were provided in each ward so that it becomes easy for doctors and nurses to fill the ADR form and drop in the ADR drop box while working in the wards. The reports were later collected by the pharmacists. Patients were followed up for more detailed information. This reduced the burden on doctors and nurses to submit ADR reports to ADR reporting centers. Moreover this whole process becomes less time consuming. Studies have shown that providing ADR reporting forms in sufficient quantity to the healthcare professionals can raise the number of ADR reporting. Same was observed in our study, where in reporting of ADR in written form after providing ADR reporting forms and ADR drop boxes at nursing stations increased to 11.33%.

Thus this study shows that by overcoming the barriers mentioned by healthcare professionals, ADR reporting can be improved. There was significant improvement in awareness and how to report ADR. Though the improvement was not statistically significant in some of the components viz. lack of incentives which may be attributed to short term study interventions, there might be significant improvement in attitude towards ADR reporting if the long term interventions are done continuously.

Forteen healthcare professionals also felt that lack of incentives/remuneration could be a barrier to ADR reporting. A study showed that providing monitory reward for reporting an ADR can considerably increase the rates of reporting drug reactions, but more evaluation of the use of remuneration is required.
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More than 96% participants in the present study felt that inclusion of pharmacovigilance in UG/PG curriculum, teaching pharmacovigilance as professional ethics and establishment of pharmacovigilance centre in tertiary care hospitals are worth considering and implementing to improve ADR reporting. It is important to note here that teaching the students right from the Under Graduate level regarding pharmacovigilance can stimulate them and major obstacles like lack of awareness can be overcome. Majority (84%) of the participants suggested that compulsory reporting or legal compulsion to report can improve ADR reporting. This suggestion was also valuable as it is observed that maximum number of ADR reports come from nations in which ADR reporting is compulsory.