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Drug safety and Pharmacovigilance: An overview

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ABSTRACT

Adverse drug reactions (ADRs) have a major impact on public health, reducing patient's quality of life and imposing a considerable financial burden on the health care systems at a time when many health care systems are under considerable financial strain. All healthcare providers have roles to play in maintaining a balance between a medicine's benefits and risks. Once a drug is available to the public, making a determination about its safety is the shared responsibility of all who are part of the prescribing process, including patients. The role of healthcare professionals is vital in recording and reporting suspected ADRs in order that regulatory agencies are alerted of emerging safety concerns and thereby facilitating timely and appropriate action. Pharmacovigilance is an important exercise for monitoring of drug related issues after marketed in "real world setting". Pharmacovigilance and all drug related issues are important for everyone whose life is being impacted any way by medical interventions. The evolution of Pharmacovigilance in recent years has growing importance as a science critical to effective clinical practice and public health science. The national Pharmacovigilance centers have become a significant influence on the drug regulatory authorities, at a time when drug safety concerns have become increasingly important in public health and clinical practice. This paper unfolds the basics of drug safety and other important aspects of Pharmacovigilance.

Keywords: Adverse drug reactions, Pharmacovigilance, Drug regulation.

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INTRODUCTION

Drug Post-marketing surveillance programs are essential in every country for monitoring the occurrence of ADRs, as the data derived from within the country may encourage national regulatory decision making. These programs may contribute to decrease in morbidity, mortality, hospitalization and healthcare costs, and liability associated with ADRs. Majority ADRs often go unrecognized or unreported. An organized ADR monitoring program is one mechanism to more actively detect ADRs, and consequently positively affect the quality of patient care [1]. To prevent or lessen harm to patients and improving public health, the various mechanisms for evaluating and monitoring the safety of medicines in clinical use are important. In Clinical practice this implies having in place a well-organized Pharmacovigilance system. Pharmacovigilance in the early 1990s was entirely about monitoring adverse drug reactions and hence was defined as "The detection in the community of drug effects, usually adverse. Pharmacovigilance may be passive (the collection of spontaneous reports) or active (structured) where patients and prescribers are recruited and surveyed" [2, 3]. The WHO defines Pharmacovigilance as the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, herbalism and traditional medicines with a view to identifying new information about hazards associated with medicines and preventing harm to patients[4]. Pharmaco vigilance has been elucidated as: "The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem[5]. Pharmacovigilance is an important exercise for monitoring of drug related issues after marketed in "real world setting". Pharmacovigilance and all drug related issues are important for everyone whose life is being impacted any way by medical interventions. The evolution of Pharmaco vigilance in recent years has growing importance as a science critical to effective clinical practice and public health science. The national Pharmacovigilance centers have become a significant influence on the drug regulatory authorities, at a time when drug safety concerns have become increasingly important in public health and clinical practice. Pharmacovigilance is now firmly based on strong scientific principles and is basis to effective clinical practice. The discipline needs to develop further to meet public expectations and the demands of modern public health [6, 7].

Pharmacovigilance is aimed at;

- Improving patient care and safety in relation to the use of medicines and all medical and paramedical interventions,
- Improving public health and safety in relation to the use of medicines,
- Contributing to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost effective) use, and
- Promotion of understanding, education and clinical training in pharmacovigilance and its effective communication to the public [8].

Need for Pharmacovigilance:

Not everything is known about a medicine when it receives its license for marketing. The merits of a new drug, balancing its beneficial and its untoward effects become established only after sufficient experience has been gained from its use in real practice. The reasons for the necessity of Pharmacovigilance are:

- Information on drug safety collected during drug development is incomplete as preclinical drug development processes involve the evaluation of drug safety and efficacy in animal experiments and often it may not be appropriate to extrapolate the results of animal experiments to human.
- Clinical trials are evaluated for limited duration and limited numbers of carefully selected patients in carefully selected settings and so it is extremely difficult to accurately determine actual efficacy, adverse effects and total risk-benefit ratio under actual clinical setting.
- information is often incomplete or not available on
- Rare but serious reactions.
- Use of drugs in vulnerable groups (pregnant women, children, geriatric).
- Risks of long term, repeated use and drug-drug, drug-food, drug-nutritional supplement interactions.
- At the time of licensing, the drug is exposed to less than 5,000 human subjects. This allows only the most common ADRs to be detected.
- At least 30,000 people are required to be treated with a drug to be sure not to miss at least one patient with an ADR which has an incidence of 1 in 10,000 exposed individuals[9].

Partners in Pharmacovigilance

Management of the issues related to the use of medicines demands close and effective association between the key stakeholders in the Pharmacovigilance. The people responsible should jointly anticipate, elucidate and respond to the continually enhanced demands and expectations of the public, health administrator policy officials, politicians and health professionals. However, there is little prospect of this happening in the absence of strong and comprehensive systems which make such associations possible. The obstacles typically encompass lack of training, resources, political support, and especially scientific infrastructure. Understanding and tackling these are a necessary prerequisite for future development of the science and practice of Pharmacovigilance [10]. Pharmacovigilance is the responsibility of everyone so that all drugs can be used safely. Furthermore, the Ministry of Health (MOH) or its equivalent in any country of the world is not only responsible for monitoring drug safety but also needs commitment and collaboration between the different Pharmacovigilance partners [11].

A comprehensive list of these 'partners' includes:-

1. Healthcare professionals:-

A. Prescribers

B. Nurses

C. Pharmacist

2. Patients.

3. Hospitals and academia.

4. Pharmaceutical Industry.

5. The WHO Quality Assurance and Safety (Medicines Team).

6. National Pharmacovigilance Centers (NPC).

7. Uppsala Monitoring Center (UMC).

8. Others.

1. Healthcare professionals:

Safe medication use is critical for physicians, dentists, pharmacists and nurses. They have the responsibility to be vigilant of their patients of any issues related with drug therapy including,

a) Nature of the disease,

b) Purpose of medication, and

c) Any potential risks involved in its use.

They also have an additional responsibility to ensure that their patients have an adequate understanding of the nature of the treatment(s) they are taking.

A. Prescribers:

It is a prerequisite that all involved in the process of prescribing of medicines have some knowledge of the potential ADRs, so that an assessment of the balance between the beneficial and harm is considered before a drug is prescribed, dispensed and administered to a patient. Any medication or any kind of treatment should take in consideration all these factors including, the individual patient and their predisposition to drug toxicity. The intention of the prescriber is to use a medicine to help the patient, not harm them, as they hope all drugs used are without any risk. This should facilitate the key recognition that if the patient develops any undesired signs and symptoms it may be drug related and eventually turn out to be due to an ADR [12]. Therefore, all the members of the healthcare team are required to be aware of the importance of ADR reporting and that they are competent to provide practical information for reporting of ADRs. They should have a familiarity with the policy and procedures of ADRs reporting and guidance as to how and when to report and where to actually send it.

Healthcare professionals usually consider that they have a major responsibility to be a Pharmacovigilance partner by reporting suspected ADRs. The best management of ADRs needs to involve all healthcare professionals in any type of hospital whether government or private so as to both observe and report unwanted or unexpected ADRs. Sometimes, due to inadequate information from the pharmaceutical company or industry or even a Food and Drug Administration (FDA), a healthcare professional cannot always be blamed if a patient has an ADR especially so, if it is of an idiosyncratic type where its prediction is clearly impossible. But, even when healthcare professionals have

enough safety information they may misuse it due to not having the patient's full medical history and that can lead to ADRs. A good example is Spironolactone which is contraindicated in patients with renal dysfunction or hyperkalemia. However, some doctors are not aware of this well reported effect and yet still prescribe it [13].

B. Nurses

Traditionally nurses did not report ADRs. But some new developments for ADRs reporting have taken place for nurses and as they are now also able to prescribe drugs in some countries such as USA and the UK as such prescribers they have the responsibility to report ADRs. For example, in the UK, some nurses after October 2002 played a valuable part in the improvement of Pharmacovigilance by ADRs reporting [14, 15]. A little later, in the Sweden, nurses could report ADRs and so contributed to the improvement of public health by the detection of suspected ADRs; [16]. Currently, the contribution of nurses to the rate of reporting in some countries is quite significant, for example, Sweden 12%, Canada 16% and in the UK 21%. In contrast, the spontaneous nurse reporting in the Italian database is still lower than that in other countries. It is quite clear that nurses do represent an important and valuable source of reporting for ADRs[17].

C. Pharmacist

A pharmacist, in a dispenser of medicines, is in a "*cornerstone position*", he/she should be fully aware of any suspected ADRs. The pharmacist specifically focuses in making a contribution to ADR reporting.

2. Patients

In 2005, the reporting system for suspected ADRs by patients to the regulatory authorities started in the UK via using YCS (yellow card system). In 2009, ADRs reporting by patients in the UK, Sweden, Australia and the USA were in the range of 18% to 20%, submitted using three major methods: postal, internet and telephone to provide assessment awareness. These methods were found fitting for the UK's general population and indicated that the awareness was low and could be improved [18, 19, 20].

In the study by Van Grootheest and Berg, 2004, which examined the role of patients in reporting ADRs, they concluded that, because patients have a positive value and involvement in drug therapy, their concern regarding possible adverse effects is a major factor in possible ADR reporting. As a consequence, patients' reports on ADRs should be accepted albeit with care as is now done in the UK. The literature, as yet, does not provide any major results in relation to the detection of ADRs by patients, more recent studies are required to show their contribution worldwide. In any system where patients have taken medicines, their views and options about their therapy can be of great knowledge for ADRs reporting. It is, however, a difficult problem to address. Often, because of the brevity of the physician's consultation process, patients have little time to understand any warnings that may be given about the potential problems of their treatment(s). It could be argued that the inclusion of the patient's information leaflet should avoid such difficulties. However, this applies to people whose first language is English and, when they are used in Saudi Arabia, where many people who use the medicine do not read a high level of English, their value is very difficult if not impossible to assess. On the other hand, in a study by Hughes et al. (2002) ADRs reporting by patients was not considered by Pharmacovigilance centers to be equivalent to those of the health care professionals as many of ADRs patient reports were incorrectly filled in, so increasing the overall workload for little gain [21]. Another study by Arson et.al (2011) concluded that direct patient reporting through the YCS is viewed as important by those who have used the scheme, in order to provide the patient experience for the benefit of Pharmacovigilance, as an independent perspective from those of health professionals.

3. Hospital and Academia

Collaborations between the pharmaceutical industry, academia and drug regulatory authorities has led to the development of Pharmacovigilance as a clinical discipline. Only a small number of medical institutions provide medical student education related to ADR during their curricula in pharmacology. So, the majority of healthcare professionals may graduate without an adequate background regarding drug ADRs. Therefore, academic centers of pharmacology and pharmacy should provide a knowledge of ADRs to healthcare professionals and the public by; training, teaching and research. In many schools of health and medical institutions the topic is still neglected. Consequently, there is a still greater need for integration of Pharmacovigilance by clinical practice so as to affect a system for ADR monitoring to protect public health as suggested by WHO 10 years ago.

4. Pharmaceutical Industry

Every company in the pharmaceutical industry has a vital role to play in the provision and supervision of drug safety and they must inspect all drug related information, from drug development to patient use, and should also consider the assessment of the safety of the drug and monitoring system. An important role exists in communication between the pharmaceutical company and drug regulatory authority that leads to an improvement by exchanged information [22].

5. The WHO Quality Assurance and Safety: Medicines Team

The provision of guidance and support to countries regarding drug safety matters is a function of the Quality Assurance and Safety: Medicines Team within WHO. The purpose of the department is stated to be: "to help save lives and improve health by closing the huge gap between the benefit that essential drugs have to offer and the reality that for millions of people–particularly the poor and disadvantaged– medicines are unavailable, unaffordable, unsafe or improperly used". Clearly, the purpose of Quality Assurance and Safety for Medicines team is "To ensure the quality, safety and efficacy of all medicines by strengthening and putting into practice regulatory and quality assurance standards". Hence, Pharmacovigilance needs to be applied to all related health technologies, including medicines, vaccines, blood products, biotechnology, herbal medicines and traditional medicines.

6. Uppsala Monitoring Center (UMC)

During early 1960s, after the infamous event of '*Thalidomide disaster*', various national schemes for collecting information concerning emerging drug hazards were implemented, and, in 1968, the WHO set up an international drug monitoring programme. 10 years later, in 1978, the UMC was started and was made responsible for leading and managing this programme. Working with the WHO Collaborating centre for international drug monitoring UMC, WHO promotes Pharmacovigilance at the country level[23], and encourages the participation in the WHO programme for international drug monitoring. In addition, WHO still highlights the importance of collaboration and communication at local, regional and international levels, so as to ensure Pharmacovigilance delivers the necessary protection to the public.

In 2004, the numbers of countries that were participating in this scheme was 86, and all these provided the necessary data for the WHO programme with the collaborating centre in Uppsala, Sweden. This contrasts with the initial established national reporting system for ADRs which was for only 10 countries. In March 2010, the number of countries had grown to 97 and in addition there were a further 33 countries as "*associate members*" [24]. At the end of 2010, the number had increased to 134 countries and they were all part of the WHO Pharmacovigilance Program. More recently, In May 2012, the number now stands at 142 countries. It can be seen that the Kingdom of Saudi Arabia (KSA) has been a member of the WHO IDMP since 2009. On 30 March 2010, new information from the Uppsala monitoring centre website showed that the global ADR database they maintain for the WHO programme contains 5 million ADR reports from all the countries who are members of the WHO programme. In 2011, the UMC-WHO, which managed the global database of Individual Case Safety Reports (ICSRs) and consists of reports of ADRs which were received from national centers in the WHO network database, is called "*VigiBase*". It currently contains over 6 million descriptions of individual cases which make a significant contribution to promoting a global ADRs awareness. This information about ADRs is extremely useful and helpful as, unfortunately, many hospital admissions are caused by drug use. The Uppsala centre can therefore clarify any problems should they occur. The Uppsala center, to function effectively, requires constant new information about ADRs, where and when they occur [25].

7. The National Pharmacovigilance Centers (NPC)

In addition, most MOHs in their own countries can support Pharmacovigilance National Centers fully or at least in part by comparing expenditure of medication with the NPC policies and regulatory guidelines. In addition, The International Conference for Drug Regulatory (ICDRA) at their Annual Meetings of National Pharmacovigilance provides an unparalleled opportunity for the WHO programme for International Drug Monitoring to be comprehensively and adequately discussed.

8. Others partners of Pharmacovigilance

The media, advocacy groups, and lawyers can help in the contribution directly or indirectly to the creation of policies and legislation on Pharmacovigilance by cooperation and communication with the proper authorities.

Pharmacovigilance in a country's national drug policy

The provision of good quality, safe and effective medicines and their proper use is the responsibility of national governments. The set up of a National medicine regulatory agency and an assigned center for the study of adverse reactions are critical to the achievement of these functions. Interdisciplinary association is of prime importance, in particular, links need to be forged between various departments of the ministry of health and also with other stakeholders, such as the pharmaceutical industry, universities, nongovernmental organizations (NGOs) and professional associations having responsibility for education on rational use of medicines and pharmacotherapy monitoring [26].

Methods of Pharmacovigilance

Pharmacovigilance methods that can be employed in specific circumstances is based upon de the local situation, experience, expertise, and resources available to achieve these objectives

Active surveillance

This method depends on active follow-up of patients after treatment, and all adverse reactions are detected either by asking patients directly or by screening the patient records.

Cohort event monitoring: Cohort studies are studies that identify subsets of a defined population and follow them over time, looking for differences in their outcome. Cohort studies generally are used to compare exposed patients to unexposed patients or one exposure to another [27].

Cohort studies have many advantages. They are the best way to ascertain both the incidence and natural history of disorder, temporal sequence between cause and outcome is usually clear, useful in investigation of multiple outcomes that might arise after a single exposure, useful in the study of rare exposure. It also has some disadvantages such as selection bias is built into such studies, follow up can be difficult [28].

Cohort event monitoring can be done with different epidemiological designs as follows:

1. Observational

This means that the studies are "non-interventional and are undertaken in real life situations. Patients are not selected according to any criteria: all patients who receive treatment are included until the desired cohort size is achieved. Patients of all ages, those with other diseases and those on other medicines are included in this. Treatment is given according to the usual local guidelines [29].

Prospective

This means that CEM is planned before the patients are treated and treatment is monitored until the end of the program, or until they cease to receive treatment for whatever reason.

3. Inceptional

In this every patient is followed-up for adverse events from the time of commencement of their treatment.

4. Dynamic

In this new patients are added as the study continues until such time as there are sufficient numbers in the cohort.

5. Longitudinal

In this the occurrence of any events in patients are observed over a period of time until the end of the programme, or until they cease to receive treatment with the monitored medicines.

6. Descriptive

In this all events are identified and described, their frequency is measured and their distribution in different subgroups of interest in the cohort is recorded and analyzed [29].

b. Sentinel Sites

Active surveillance can be achieved by reviewing medical records or interviewing and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse reactions from these sites. The selected sites can provide information, such as data from specific patient subgroups that would not be available in a passive system and information on the use of a drug can be targeted at sentinel sites.

c. Registries

A registry is a patient list presenting with the same characteristics. This characteristic can be a disease (disease registry) or a specific drug exposure. Pregnancy is also recorded as an event as part of the cohort event monitoring study. This helps to estimate the exposure to medicines during pregnancy [30].

D. Deaths

As part of cohort event monitoring, all deaths can be recorded, and their causes assessed by verbal autopsy. Where possible the data will be cross-tabulated with data from governmental records of deaths. In a study done by U. Mehta [31], they have carried out confidential enquiry into malaria related deaths which proved to be useful tool for identifying the preventable factors ,health system failures, and adverse events affecting the malaria case management.

Passive surveillance

Passive surveillance or spontaneous reporting is reporting of adverse events that are entirely dependent on the initiative and motivation of the reporters. Spontaneous reporting is the most common method, easy to establish, cheapest to run, but reporting rates are low. In districts where active surveillance cannot be done due to constraints of manpower and funds, passive surveillance can be done by spontaneous reporting using National ADR reporting forms if available, suitably modified if necessary. Spontaneous reporting is dependent on clinicians and other health professionals who need to be trained and encouraged to report details of suspected adverse reactions in patients on ART treatment [32].

CONCLUSION

Pharmacovigilance is important for the protection of public health as it prevents, detects and assesses adverse reactions to medicinal products for human use. It encompasses whole life-cycle management of medicinal products for human use keeping safety aspect in mind. Consequently, we must stress on the necessity of the Pharmacovigilance as a continuation and completing of the analysis performed on medicines beginning from the clinical trials when the medication is administered for the first time in humans, and not only after they have been marketed. Pharmacovigilance continues to play an important role in meeting the threats posed by the ever increasing list of medicines, each of which carry an inevitable risk of unpredictable potential for harm. Whenever adverse effects and toxicity occur, especially when previously unknown, it is obligatory that these are reported, analyzed and their significance is communicated effectively to the people having knowledge to interpret the information. The harm can be reduced by ensuring that medicinal products of good quality, safety and efficacy are used rationally. In addition, the expectations and concerns about outcomes of the patient are taken into consideration when therapeutic decisions are taken. To obtain this goal and to boost a sense of trust among patients, ensure that risk in drug use are predicted, well manage and communicated to the regulatory authorities and other health care professionals.

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