The Role of Pharmacovigilance in combatting Drug-Related Adverse Events

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Abstract

Pharmacovigilance is used to detect, assess, understand and prevent the adverse effects of the medications. The need for safety monitoring has arose from unpleasant instances in history, such as deaths caused by Anesthesia and Congenital malformations as a result of thalidomide use. Reports of adverse drug Reaction (ADR) are maintained in global database and can be used to evaluate various Drugs and associated ADRs. Clinicians play an important role in the recognition and reporting of ADRs to NPCs. The purpose of NPCs is to make the clinicians understand their functions, including the monitoring investigation and assessment of ADR reports along with periodical benefit-risk assessment of medications. The types of safety issues evaluated by them are provided to illustrate their role in medicine safety surveillance further more ADR monitoring was combined with vaccine safety surveillance approaches. Overall the study provides importance of Pharmacovigilance in combatting various drug related adverse events in maintaining Patient safety with proper use Medications.

Keywords: Drug related side effects, Adverse Reaction, Patient safety, Pharmacovigilance

Introduction

Pharmacovigilance is used to detect, assess, understand and prevent the adverse effects of drugs or other related problems [1]. For Example, The need for safety monitoring has evolved around unfortunate occurrences in history, like deaths caused by anesthesia and congenital defects owning to thalidomide use [2]. However, thalidomide use during pregnancy resulted in aberrant fetal development and limb deformities, this has underlined the significance of safety monitoring of medications after commercialization, Independent of any industrial influence [3].The thalidomide disaster prompted the establishment of the WHO International Drug Monitoring Program and the development of regulatory frameworks on Drug safety. As a result, the spontaneous reporting of ADRs become Systematic organized and regulated. A Database such as The WHO-Uppsala Monitoring center (WHO-UMC), based in Sweden, it manages vigibase, a WHO global Database of individual case safety reports [4, 5].This Database can be used to evaluate the association between various medications and their associated ADRs. Medication safety monitoring was especially important During COVID-19 Pandemic to assess the safety of medication, including novel drugs, such as remdesivir or repurposed treatments such as lopinavir/Ritonavir, against COVID-19[6].

Role of clinician in Pharmacovigilance and Drug safety

Clinicians play a crucial role in Preventing ADRs by recognizing, managing and reporting ADRs to the National Pharmacovigilance services (NPCs) [7]. Safe and rational prescription of drugs require therapeutic reasoning and appropriate selection of drugs for each patient. Factors that may increase the risk of ADR include age, medication error, Polypharmacy and Patient-specific risk factors such as comorbidities.[8,9]Recognizing ADRs and differentiating them from other diseases or comorbidities is challenging and requires the clinicians to have knowledge of the clinical pharmacological principals of ADRs, including their types, Dose relatedness, Hypersensitivity reactions, time relationships and risk factors. For Examples, long term complication such as atypical femoral fractures secondary to bisphosphonates, may only occur after prolonged exposure [10]. Discontinuing medications may also cause rebound of medical conditions, such as the increased risk of osteoporosis with denosumab cessation[11]. To managing complication, clinicians also need to communicate and counsel patients to ensure ongoing compliance, treatment of underlying conditions and to maintain appropriate documentation of the patient's clinical records to avoid further

exposure to the medication. Finally clinicians should be encouraged to report ADRs to ensure that the safety profile of medications is logged in and recorded nationally, which assists in formulating regulatory actions to minimize the risks to consumers.

Role of National Pharmacovigilance Centers

The main role of NPCs is to coordinate National ADR Monitoring programs. This usually involves Monitoring, investigating and assessing ADR reports received from health care professionals and product license holders [12]. This includes a prompt response to request for information required to conduct a benefit-risk evaluation so that appropriate regulatory actions cab be taken. The International conference on Harmonization (ICH) and council for international Organizations of Medical sciences (CIOMS) provide a scientific guidance for Pharmacovigilance and risk Management of medications throughout their life cycle, from pre-clinical and clinical development to post Marketing stages [13].

As NPCs have to investigate ADRs, spontaneous ADR reporting should be done immediately after identification by Clinicians, preferably within 3 days. Investigation of ADR enables causality assessment. This should follow a standardized approach. The two commonly used methods for causality assessment include applying the WHO-UMC criteria and the Naranjo algorithm [14]. The findings of these ADR reports, investigation and causality assessment are submitted to the global adverse event data base at WHO-UMC [4].

NPCs receive notifications regarding possible safety and risk issues from regulatory agencies, product license holders for medications, and the WHO.A periodic Benefit-risk evaluation report (PBRE) contains comprehensive, concise and critical analysis of new or emerging information on the risk of a medicinal product and its benefit in approved indications [15]. This ensures a structured and systematic approach to define a medicines benefit risk profile, including its strength, limitations and uncertainties of available evidence [16]. Communicating safety information to relevant stakeholders, especially Prescribing Clinicians may occur in the form of a “Dear Healthcare professional” letter specifying any updates on the use of a particular medicine. Content and Communication plan, such as intended recipients and mechanism of dissemination, require mutual agreement between the license holders and NPCs [17]. These regulatory risk communications have resulted in significant changes in targeted prescribing with an impact on clinical outcome. Some NPCs also manage product defect reports, and may include cosmetics and personal care products in their Portfolios [18]. This may involve ongoing monitoring or active survivelance of specific medications or target groups for safety issues [19].They also evaluate the impact of regulatory interventions on patient safety [20].

Case study, illustrates the need for technical expertise in the evaluation of reports, a Pharmacovigilance advisory committee members have the following specialties, Geriatrics, Pediatrics, Public health, Internal medicine, Primary care and Pharmacy. This committee makes recommendations to the medicines control authority on matters related to the safety of medicines via information on ADR reports, causality assessments, emerging safety issues as identified [21,22].

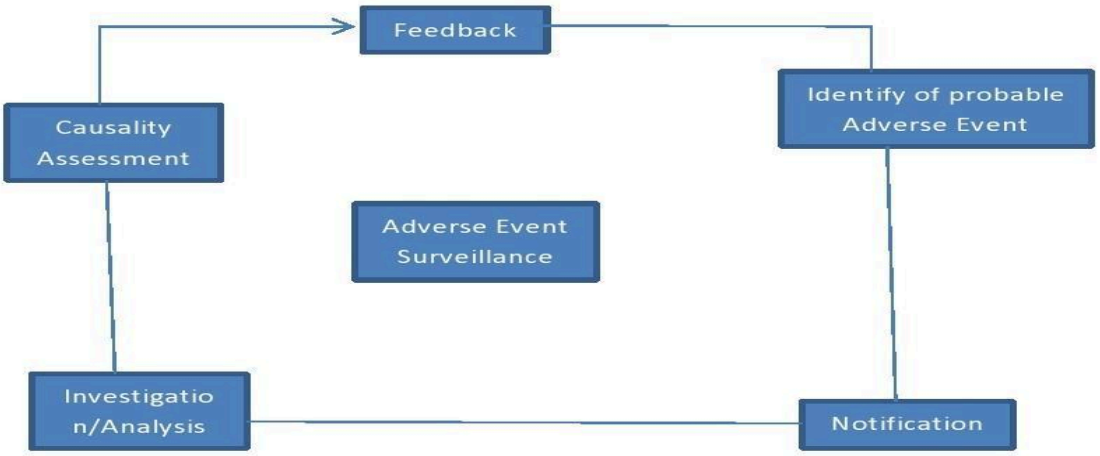
The below table illustrates examples of potential safety issues received from overseas reports and regulatory authorities
Examples of potential safety issues

Medication	Safety Alert
Fluoroquinolones	Concomitant use with ACEI or ARB contraindicated in patients with moderate to severe renal impairment (Cr Cl 30ml/min) and in older patients
Montelucast	Monitor for neuropsychiatric reactions,e.g., nightmares, depression, anxiety, change in behavior, speech impairment and obsessive compulsive symptoms for all age groups
Hydroxychloroquine	Risk of serious and life threatening OT prolongation, torsade de points, syncope, cardiac arrest and sudden death particularly in combination with other medications known to prolong OT interval
Denosumab	Risk of multiple vertebral fracture after stopping to consider benefits and risks before initiating treatment with Denosumab, to cover with an alternate bone sparing agent when stopping Denosumab
Methotrexate	Risk of fetal overdose due to inadvertent daily instead of weekly dosing
Fentanyl	Risk of overdose when used in opioid- naive patients
Empaglifozoin	Risk of Peri and post-operative Diabetic Ketoacidosis in surgical patients with SGLT-2 inhibitors, recommended temporary discontinuation before scheduled surgery
Domperidone	No longer licensed or indicated for use in children younger than 12 year old or those weighing less than 35kg due to lack of efficacy
Ticagrelor	Safety signal of severe cutaneous adverse reactions

NPC received an ADR report of a patient who sustained intracranial bleeding while on Dabigatran, which demonstrated the importance of causality assessment. Non vitamin K antagonist oral anticoagulants for patients with atrial fibrillation cause less intracranial bleeding compared to warfarin [23].

Applying Pharmacovigilance in Clinical Practice

Effective pharmacovigilance relies on consistent, high quality data from clinicians regarding ADR, especially rare adverse effects that may require international Databases to detect safety signals [24]. There is a significant international variability in Pharmacovigilance approaches. For example, there is a greater reliance on industry funding to oversee post-marketing surveillance in Europe [25]. However there is low awareness of Pharmacovigilance programs and practical aspects, thus training programs to improve awareness and quality of ADR reporting are required [26].Generally, functional and behavioral competences should be based on different levels; Clinicians collecting information or evidence regarding any changes in outcome based on ADRs. A set of proposed core competences to support vigilance include analytical and assessment skills, communication and leaderships and system thinking skills for identifying and preventing ADRs [27].Participation of healthcare professional in Pharmacovigilance will lead to beneficial changes in practices related prescribing, shared therapeutic decision making and communication with patients. However further study is required to identify and measure the abstract benefits of additional patient engagement by primary care physicians from a prescriber or regulators' perspective[28].



Pharmacovigilance in Drug Regulation, The issues with which drug regulatory authorities have to contend besides the approval of new medicines, include:

- Clinical trials
- Safety of complementary and traditional medicines, vaccines and biological medicines
- Developing lines of communication between all parties with an interest in Drug safety and ensuring that they are open and are able to function efficiently particularly at times of crises [29]..

Regulators understand that pharmacovigilance plays a specialized and pivotal role in ensuring ongoing safety of medicinal products. Pharmacovigilance programs need to be adequately supported to achieve their objectives. Sufficient evidence is required to show the new drug to be

- Good quality,
- Effective and
- Safe for the purpose or purposes of which it is proposed

There is possibility that rare yet serious adverse events will not be detected in the pre-registration development of the drug. For example, fatal blood Dyscrasia occurring in 1 in 5,000 patients treated with a new drug is only likely to be recognized after 15,000 patients have been treated and observed, Provided that the background incidence of such a reaction is zero or a casual association with the drug is clear [30].

Clinical trial Regulation

There is also a growing alliance between Pharmaceutical and biotechnological industries. This has given rise to serious and widespread concern over ethical and scientific issues such as [31, 32].

- The potential for conflict of Interest
- Unethical patient recruitment practices

- Inadequacy of informed consent
- Lack of capacity to ensure on-going monitoring of clinical trials and adherence to principals of sound and ethical clinical practice
- Poor reporting and management of adverse events

Medicines that is required for diseases such as Tuberculosis, malaria, HIL/AIDS and meningococcus Meningitis, and those which have an uncertain effectiveness- safety profile, require careful surveillance when first introduced on large scale into communities [33]..

Safety Monitoring during Clinical trials is recognized as one of the major concerns for new drug development. This is currently being addressed by a CIOMS working group. Three main topic are being addressed

- The collection of adverse experience information
- Assessment/Monitoring of clinical Data
- Reporting/Communication of Clinical Data

Once Research into new drugs in the post marketing stage safety may be monitored to comply with the conditions of registration, particularly when they are unresolved concerns. This may lead to improved and more rapid changes in labelling or even withdrawal of a new drug from the market [34].Routine application of principals of Good Clinical Practice that ensure patient safety and strict compliance with prescribed regulatory requirements would substantially improve standards of clinical trials [35].

Conclusion

Pharmacovigilance is important for medication safety monitoring and Post-marketing safety surveillance, as ADR may occur after the completion of randomized controlled trials, Clinicians play an important role in recognizing and reporting ADRs so that Nutritional Rehabilitation Centre (NRC) can record and evaluate these concerns and take the required action to maintain patient safety associated with the use of medicines.

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