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A Study of Pharmacovigilance System in Diabetes and HIV

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Abstract - The method of combating HIV with drugs is antiretroviral therapy (ART). It does not kill the virus but only slows down virus growth and reproduction. In industrialized countries, it has proven extremely effective in treating HIV/AIDS infection. HIV-infected patients first received HIV antiretroviral therapy in 1986 and zidovudine was first used for treatment as a nucleoside-reverse transcriptase inhibitor. It has been observed that single drug therapy is short-term, so 2-3 drugs have been used later because it provides a long-term advantage. Current ART regimes are available for NRTI, including stavudin, zidovudine, lamivudine and so on; NNRTI (inhibitors of the reverse nucleoside transcriptase) including nevirapine, efavirenz; protease inhibitors, fusion inhibitors and many others. NRTI's NRTI is available in current ART regimen. Two NRTIs are combined with one NNRTI for antiretroviral therapy. Because this is a combination therapy, several uncommon and severe adverse effects are related, including anaemia due to zidovudine, stavudine induced peripheral neuropathy, lactic acidosis, hyperlactatemia (hyperlactatemia), lipodystrophy, nevirapine induced rash, etc.Patients with HIV infection are immunocompromised, which makes them more likely to develop adverse drug reactions. Antiretroviral treatment can damage trust and adherence of the patient. These medicines can be stopped by patients, and they cause themselves and society as a whole to have problems. Therefore, a timely management of antiretroviral drug adverse reactions is essential to improve patient adherence to the therapy. Insulin and oral antidiabetic agents are included in antidiabetic treatment. Diabetic patients usually take drugs for dyslipidemia, hypertension and antiplatelet therapy in combination with those drugs. As a result, diabetic patients, especially the elderly, are likely to develop an adverse reaction due to multiple medications for different conditions. Hypoglycemia, hypoglycemic coma and hepatotoxics, multiform medication-induced erythema and photo dermatitis, are unusual events associated with antidiabetic treatment.

Keywords - Pharmacovigilance System, Diabetes and HIV, antiretroviral therapy, HIV/AIDS infection

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INTRODUCTION

India has special factors and conditions that differ from those of the developed world such as TB, malaria, other infections, malnutrition, heavy reliance on traditional medicine systems, absence of sufficiently trained physicians, the irrational use of medicine, and medical interactions, which are likely to make a significant difference in drug safety. Furthermore, the local health system is unaware of the importance of drug surveillance and very few studies are therefore carried out. This has led to incomplete and inadequate data on potential adverse drug reactions in the Indian population with antiretroviral and anti-diabetic drugs. Unfavorable drug reactions affect patients' quality of life and compliance. This shows that adverse drug reactions must be studied and risk reduced or risk management plans developed for preventable adverse drug reactions. There is currently no such strong system of pharmacovigilance, particularly in the field of antiretroviral and antidiabetic medications in our set-up. The present study included the development of a pharmacovigilance system to collect data on suspected adverse drug reaction; analyzing the data; tracking known adverse drug reaction incidence and intensity; investigating data for potential new harm signals; minimising risk of avoidable adverse drug reactions and testing the established system by implementing pharmacovigilance.

PHARMACOVIGILANCE IMPACT IN PATIENT MANAGEMENT IN INDIA

Pharmacovigilance is the scientific field of pharmacology for determining, evaluating, understanding and preventing adverse effects, in particular the long- and medical or treatment long-term adverse effects. In response to the Thalidomide disaster detected in 1961, a Pharmacovigilance program was established by the World Health Organization (WHO). In 1998, India

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joined a surveillance program for adverse drug reactions (ADR) based in Uppsala, Sweden. The CDSCO, Directorate General for Health Services, is a National Co-ordinating Centre, under the aegis of the Indian Ministry for Health and Family Welfare, in collaboration with India's Indian Pharmacopoeia Committee, Ghaziabad (NCC). In the collection and follow-up of patient ADR reports, indigenous Drug Monitoring Centers (AMCs) under the India Pharmacovigilance Program (PvPI) play a critical role in drug testing (Phase I–III), because the drug study does not accurately predict adverse drug events. The risk of improved medicinal events exists in patients with chronic kidney disease (CKD) / liver disease. These patients should be carefully monitored and reported for any adverse events. Therefore, it helps to generate data for Indians and contributes to patient security by inculcating the habits of ADR report. This also contributes to the change in the treatment given to patients, since early identification of ADRs helps to reduce patient disease and deaths.

Pharmacovigilance is based on the etiological basis Pharmakon = drug and Latin = Vigilare which means "to be vigilant or watchful," "to keep watch over drugs, especially their safety," and "to keep watch over medicinal products." As the pharmacologic science and activities related to the detection, appraisal, understanding, prevention and other drug related problem, pharmacovigilance is defined by the World Health Organization (WHO). The pharmacovigilance process is dominated by consumers, health care professionals, pharmaceutical companies and global regulatory bodies. The main purpose of pharmacovigilance is to ensure the processing and reporting of individual cases until now, with the aim of proactively identifying safety issues and taking appropriate measures to minimise and mitigated risk for patients. Pharmacovigilance has been largely a recordkeeping function. This review highlights the pharmacovigilance process and its effects on patient control and safety in adverse event reporting.

➢ Adverse Drug Reaction Monitoring Centers under PvPI

PvPI monitoring centers for drug reaction (AMCs) play a crucial role in collecting and monitoring patient ADR reports. They are established throughout India to collect information from patients concerning adverse events. These AMCs include medical schools, medical/center/autonomous instructors, public-service health programs and corporate hospitals approved by the Medical Council of India (MCI). They are charged with collecting the patient's adverse event information, monitoring ADR reports according to Standard Operating Procedures, entering information within the prescribed software (Vigiflow), and sending them to NCC through the same software. Some AMCs are also in charge of providing regional training and technical support. The PvPI began with >22 AMCs throughout the country in 2010 to be registered, which grew to 90. 60 of them are phase I AMCs and 30 are phase II AMCs by the end of 2012. All 90 AMCs are categorized under the zonal CDSCO offices in India in four areas, i.e. north, south, east and west, and function under the NCC. There are over 2,000 pharmaceutical schools, 90 PharmD Institutes, over 200 dical centers and more than 320 infirmiers throughout India. Patient care is associated with the provision of safe and effective medication for all pharmacological, dental and paramedic colleges. These colleges will be included in this program as AMCs for robust pharmacovigilance over the coming years. In India, there are over 360 medical colleges approved by MCI, 194 of which are private schools. All MCI and Pharmacy Councils approved for Indian pharmacy schools with pharmacy practice and PharmD will be properly channeled into PvPI. The program will cover the north, the south, the east and the west of India for all approved MCI medical schools and hospitals, and ultimately all government and company hospitals for the entire India programme.

➢ Aims of Pharmacovigilance

It is due to pharmacovigilance in India that the regulatory agencies, media, and consumers have become more aware about the benefits and risks associated with the use of medicines. The various aims of PvPI are:

- To monitor ADRs in the Indian population
- To create awareness among HCPs about the importance of ADR reporting in India
- To generate evidence-based data/recommendations on the safe use of drugs
- To support the CDSCO in formulating safety-related regulatory decisions of medicines
- To monitor benefit–risk profile of drugs and communicate information to all key stakeholders
- To create a national center of excellence at par with global drug safety monitoring standards
- To identify and analyze new signal from the reported cases
- To communicate the safety information on use of drugs to various stakeholders to minimize the risk
- To collaborate with other national centers for the exchange of information on adverse drug reports
- To promote rational use of medicine.

➢ Impact on Chronic Kidney Disease/ End-Stage Renal Disease Treatment

Chronic kidney disease (CKD) and renal end-stage disease patients have important challenges and complex therapeutic regimes. In addition to those necessary to manage renal failure, several

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pharmaceutical interventions are necessary for the presence of multiple comorbidities, such as cardiovascular disorders, hypertension and diabetes. The effect of chronic renal replacement therapy, which has its own set of adverse effects, but which can either play a causative role or interact with an evolving complication, is also part of this complex situation. The impact of a drug safety issue in a patient with end-stage renal failure may operate through different mechanisms and could include:

- Direct patient harm from the clinical sequelae of the adverse event.
- Interaction with the treatment of dialysis (e.g., the interaction of angiotensin-converting enzyme inhibitors with specific polyacrylonitrile hemodialysis membranes, causing an acute hypersensitivity reaction).
- The risk of intravenous immunoglobulin as demonstrated by case studies, inducing renal insufficiency.

As information on the use of pharmaceutical products in the CKD/dialysis population is at best limited, the concept and implementation of pharmacovigilance should be understood by nephrologists and other healthcare workers managing patients with end-stage renal disorder. This helps to increase the safety of the patient for this risky population and reflects the drive by nephrology organizations to develop CKD-specific treatment safety indicators.

➢ **Impact on Other Clinical Situations**

- NutrinealTM (Baxter Healthcare Corporation, Deerfield, IL, United States), which occupe in October 2010 Europe, withdrawal of the specific lot of peritoneal dialysis (PD) solution. 32 A number of aseptic peritonitis reports associated with one particular lot of nutrineal have begun receiving from Baxter. Although the reporters informed Baxter on peritonitis, many people provided extremely limited information, no laboratory research data, little information on whether the patient improved after the Nutrineal had been stopped, no information on other PD solutions that might have been involved in the adverse event and no confirmation for Nutrineal's specific lot in use However, as more details are gathered during follow-up calls to HCPs, Baxter was able to identify the association of lot and take the necessary action to retire the lot from the market. The lack of these details makes it extremely complex to analyze this signal.
- Icodextrin and device interaction. ExtranealTM (icodextrin) is a PD solution that includes a colloid, water-soluble glucose-polymer derived from the starch, the icodextrin osmotic agent. During the treatment of Extraneal, an unexpected rare adverse event was not produced until Extraneal has been used by an enlarged population, although closely monitored and evaluated during clinical trials. Icodextrin, the oligosaccharide in Extraneal, is metabolized to maltosis and other high weight molecules. Certain glucometers are deemed to be "nonspecific" to not only measure glucose but metabolites like maltose as well. Maltose presence can lead to incorrectly high glucose measurements, which in turn could lead in patients with these glucometers to administer more insulin than is needed. Administrators of hypoglycemia, leading to loss of consciousness, coma, neurological injury and death, can cause more Insulin than necessary. In addition, untrue hypoglycemia may be masked by falsely high blood glucose measurements due to maltoses interference, which can have similar consequences. False elevation in glucose can be measured for up to 2 weeks after icodextrin therapy has been stopped. This problem did not occur in the clinical trials of Extraneal, but was identified as cases of false glucose readings started from Baxter after the product was launched. A published case report from a 59-year old patient on extraneal who was admitted to an elective procedure is best illustrated in this life-threatening problem. During the preoperative period, she informed the HCPs that she needed the use of a specific glucometer because of her foreign use. Regrettably, this message was not transmitted with the patient after surgery to the intensive health care unit (ICU). The readings on the non-specific handheld glucose monitors in the ICU resulted in a glucose overestimation that leads to too much insulin. In an extended health care facility the person suffered from hypoglycemic encephalopathy and died.
- Quinolones and tendon rupture: Quinolone antibiotics have been used in animal studies in

conjunction with the development of tendon rupture. This risk was largely identified from post-marketing rather than clinical trial data and shows another important point. Many clinicians may not consider reporting a tendon rupture to the antibiotic producer believing it to be "biologically impossible," but the adverse event was first reported as a case report in post-marketing journals. This adverse event has resulted in boxed alerts on all labels of quinolones. That is particularly important for patients with dialysis as the use of quinolone in this population is not uncommon.

- Drug-induced hepatic failure: It is a frequent source of pharmaceutical withdrawals. An example of this is troglitazone Diabetes. It has been removed in the aftermarket surveillance following cases of liver toxicity. Hepatic reactions are rare and difficult to detect before a drug is placed on the market. A test of 30,000 patients would be necessary to detect a reaction in a patient in 10,000 with reasonable certainty. Consequently, monitoring of hepatic reactions in new medicines following marketing is crucial. A serious reaction is drug-induced hepatic disease and should immediately be reported to the pharmacovigilance centre. This also applies to new medicines with known hepatotoxicity histories.

NEED PHARMACOVIGILANCE/ ADR MONITORING

Animal and human drug studies (phase I–III) don't provide detailed information on adverse drug reactions faced by doctors. The drug therapy information is not available from literature on drug information, such as page inserts, drug manuals, phase III clinical trials etc. related adverse events (such as rare/serious ADRs, drug interaction/chronic toxicity, and use in specific populations (such as pregnant women, geriatries, pediatrics)). Thus, pharmacovigilance helps to assess the efficacy, tolerability and safety of medicines while treating patients. This helps detect and control serious adverse drug reactions and thus encourages an overview of the benefit/risk profile of drugs as used by patients.

Under the World Trade Organization, globalisation, and the impact on the pharmaceutical sector has changed the world. The safety of pharmaceuticals poses different challenges. For example, in every country on the Internet, prescriptions and nonprescription medicines are becoming increasingly public. It is a challenge to monitor drug safety and quality. Thus, international pharmacovigilance needs to be improved and improved.

Although there have been major advances in pharmacovigilance in the West, little has been accomplished in India. The importance of drug surveillance and its impact on patient safety and treatment is immense. There is an enormous need.

Theadverse cases of myelo-optic neuropathy induced by ADR and intraventricular phenylpropanolamine were shown to be important in patients to report ADR to PvPI. The Indian regulatory agencies cannot, in these cases, count on the experience of other economies in the assessment of the benefits and risk of a drug.

Because of its large population, high enrollment rates and low cost, India becomes a hub for clinical research activities. Late information on ADRs/long-term safety data decreased markedly in the period from drug discovery to marketing in India as it did in America, Europe, Japan and other countries. This is clear from the fact that all high-profile drugs, such as nimesulids, flupentixol-melitracenes, metamizols, phenylpropanolamines, and phenolphthaleins recently withdrawn in other countries, remain on the Indian market.

PHARMACOVIGILANCE AND DRUG SAFETY MONITORING

Pharmacovigilance plays an important role in management and ensuring safety of treatment in patients. The various ways that help in this regard are as follows:

- **Post marketing drug safety monitoring:** This includes the identification of interactions with drugs, measurement of the environmental burden of medicines used in large populations, assessment of the contribution to the safety profile of "inactive" elements, systems for comparing safety profiles for similar medicines, monitoring of adverse human health effects of drug residues in animals, such as antibiotics and hormones. The Council for International Medical Organizations has contributed to a more systematic approach for determining the merits of medications available in the context of benefit-risk assessment after marketing.
- **Pharmacovigilance in national drug policy:** It is the responsibility of national governments to provide good quality, safe and effective medicines and to use them properly. 20 The need to build links between the Ministries of Health and with other stakeholders including pharmaceutical industries, universities, NGOs and those professional associations that are responsible for education on the rational use of medicines and pharmacotherapy is of

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major importance. In national drug policy, six key elements of pharmacovigilance are:

1. Establishment of national drugs surveillances systems, including national and, where necessary, regional pharmacovigilance centers, for the reporting of adverse events.
2. Development of medical surveillance legislation/regulation.
3. Development of national policy (to include costing, budgeting, and financing).
4. Continuing education on safe and efficient pharmacotherapy for healthcare providers.
5. Provide up-to-date information to professionals and consumers about adverse reactions.
6. Monitoring the impact of pharmacovigilance through process indicators and outcome.

- **Pharmacovigilance in disease control public health programs:** The monitoring of medical safety has been identified as a matter of concern in countries where there is no regulatory system or safety monitoring in place or in remote areas with little or no medical attention or infrastructure. The problems are particularly apparent in situations involving medicine use in particular communities, such as tropical diseases, such as paludism, leishmaniasis and schistosomiasis, as well as in the treatment of human immunodeficiency virus / acquired tuberculosis and immune deficiency syndrome. The WHO recommends that all countries with public health disease control programs must prioritize pharmacovigilance.
- **Drug utilization studies (DUSs):** Patterns of drug use are a key determinant of the safety of medicinal products. For example, in developing countries the use of injectable drugs is more common. Many countries have become commonplace in direct advertising for the consumers of prescription medicines. With this information, without the assistance of a doctor or a pharmacist patients feel more able to make their own therapeutic decisions. As a result, self-medication, licensing and illegal sales of medicines have increased on the Internet and doctors have been overprescribed on patients' demand. This has had a significant impact on increased drug prescription. But such public health programs do not only need to be patient-oriented, they could also be used for the benefit of the general public. Such awareness-raising and learning initiatives should also cover children and elderly populations, as well as partnerships with the media, educational institutions and governmental and non-governmental organisations. The success of World Health Organization's International Drug Monitoring programs depends entirely on national pharmacovigilance contributions. Thus, the importance of pharmacovigilance in DUS is to be more closely linked with other areas, such as public health, rational use of drogues, evidence-based use of drugs, pharmacoeconomics.

CONCLUSION

A Pharmacovigilance program for anti-diabetic and anti-retroviral drugs was developed with different components of the pharmacovigilance system. The second goal was to develop an antidiabetic drug pharmacovigilance system. In order to develop the adverse drug reactions, a future follow-up was conducted for the diabetic patients who visited the Endokrinologydepartment in the hospital. 38.63% of ADRs of hypoglycemia are preventable in kind, and the commonly observed preventable ADR is hypoglycemia. The root cause analysis of ADRs has shown that patients' failure to respect dietary instructions and the misuse of insulin management methods has led to the development of preventable ADRs. Although the department did its utmost to reduce the ADRs that could be prevented by patients, such as information was supplied about possible side effects of the treatment, an adequate insulin method and dietary instructions to be followed during treatment, the instructions were not understood by patients. Missing patients' understanding and ignorance could be incompetence. Therefore, short documentary on diabetes, diabetic treatment, possible side effects and measures in the case of hypoglycemia should be prepared and played at OPDs that can reduce the incidence of preventable ADRs. This information should be provided.

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