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Research Article

Monitoring and Scrutinizes of Adverse Drug Reactions Related with Newly Approved Medicines For The Treatment Of Cardiovascular Disease: A Prospective Study

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ABSTRACT

Background: The aim of this Project Report is to contribute to the knowledge regarding safety profile of new marketed cardiovascular drugs using reports collected in the Pharmacovigilance Programme of India (PvPI). A group of cardiovascular drugs launched in India between 2012 and 2018 was selected. All the spontaneous reports involving the study drugs until the end of 2015 were retrieved and carefully analyzed. Statistical methods were applied to strengthen the potential ADR-drug associations. Gliptins are a new antidiabetic class that inhibits the action of dypeptidil peptidase-4 enzyme for controlling the glucose blood level in type 2 diabetic patients.

Methods: 112 patients were screened with the help of a predefined inclusion and exclusion criteria for the study and followed up for three months. The drugs which are relatively new and have been in the market for around 5 years were taken as new drug. These include specifically the following drugs: DPP-IV Inhibitors, PPAR α/γ agonist, SGLT-2 inhibitors. They were screened and investigated suitably for any ADRs. The severity of the adverse drug reactions was graded according to the Hartwig's Severity Assessment Scale and Naranjo Scale was used for causality assessment between the drug and suspected reaction.

Results: Maximum ADRs reported belonged to gastro intestinal system (53%). DPP-IV inhibitors showed maximum number of ADRs i.e. 70.6%. Majority of ADRs reported were mild i.e. 52.9%. Overall 15.2% patients reported ADRs. Majority of ADRs reported (70.6%) belonged to category 'possible'.

Conclusions: All three class of newer oral hypoglycemics seems reasonably safe to be used in general practice. As the number of patients were small, we need larger study to substantiate the findings.

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INTRODUCTION

WHO (2002) defines that 'Any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function'.About one-third of the elderly patients are hospitalized due to adverse drug reactions (ADRs), which have also reported to be amongst the most important reasons of morbidity and mortality[1]. The majority of type adverse drug reactions (80%) contribute to morbidity and mortality.The majority of studies haverevealed that incidence of ADRs is higher in the olderthan adults.

The incidence of cardiovascular diseases (CVDs) has been increased in recent decades, it has been estimated that CVDs are the most common cause of death in India[2]. As a result cardiovascular drugs has moved to the third place among all drug classes prescribed in the country. With introducing new cardiovascular drugs to the market, Pharmacotherapy of CVDs has improved rapidly during last few years. The problem of adverse drug events accompanied with different drug therapies has been reported since 1961. It has been reported that adverse drug events are considered as 4th to 6th cause of death in the US.[3] Studies show that cardiovascular drugs are among the most commonly cause of adverse events in hospitalized patients.4 Some studies report that cardiovascular drugs may cause half of all hospital admissions due to adverse drug reactions.[5] Another study describes that 4% of adverse events induced by cardiovascular drugs are serious ADEs.[6] Almost 10% of all medication-related office visits result from cardiovascular drug reactions, and most of those visits are related to dermatological reactions.[7] In a literature review of ten studies published between 2014 and 2018, cardiovascular drugs were implicated for 17.9% of preventable adverse drug events.[8] There are several studies on hospitalized patients to detect the rate of adverse events induced by cardiovascular drugs but there are no studies on outpatients to the best of our knowledge. This is the first study evaluating adverse events following cardiovascular drugs use in outpatients.

Hypertension represents the most common disease in the world; up to 50 years of age it is more common in men, whereas, after this age, the incidence of BH is the same for both sexes.[9] Usually, five major classes of antihypertensive agents such as thiazide diuretics, calcium antagonists, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor antagonists and beta-blockers are used.[10] Monitoring of ADRs through pharmacovigilance (PV) is useful to improve the safety of each patient. PV supports public health programs providing reliable and balanced information for the effective assessment of the risk-benefit profile of each drug.[11] In light of this, the aim of this article is to critically evaluate the ADRs in patients treated with antihypertensive drugs.

The incidence of ADR varies with studies. A published meta-analysis of the incidence of adverse drug reactions (ADRs) in hospitalized patients concluded that ADRs rank as the fourth to sixth leading cause of death in the United States and the overall incidence of serious ADR accounted for 6.7% of hospitalized patients [12]. According to a study carried out at a private tertiary care hospital in South India, the incidence of ADRs was found to be 1.8%, out of which 12% of suspected ADRs were severe and 49% ADRs were moderate in severity[13]. A study by Arulmani et al. in India carried out in a secondary care hospital reported an overall 9.8% incidence of ADRs, of which 3.4% of ADRs were associated with hospital admissions . Another study carried out in a tertiary care referral center in South India showed that admissions due to ADRs accounted for 0.7% of total admissions and deaths due to ADRs accounted for 1.8% of total ADRs[14]. Monitoring of ADRs is an ongoing, ceaseless, and continuing process. Though ADR monitoring is still in its infancy in India, this is likely to expand in the times to come. As the newer drugs are striking the Indian market, the need for ADR monitoring is growing more than ever before. Therefore, monitoring of the adverse effects particularly those of serious nature is obligatory.

MATERIALS AND METHODS

Study design

The study was conducted in a cross-sectional manner and involved spontaneous and solicited pharmacovigilance monitoring of currently prescribed newer oral anti-diabetic drugs. The study was conducted at Fortis Hospital Gurugram for a duration of 03 months and patients were followed for three months. The study was conducted in accordance with the principles of

Declaration of Helsinki and Good Clinical Practice (GCP).

Study sample and eligibility

The patients diagnosed with Type 2 diabetes attending Medicine outpatient clinic and on treatment with at least one newer oral anti-diabetic drug were screened for possible inclusion in the study. They were screened with the help of a predefined inclusion and exclusion criteria for the study. The drugs which are relatively new and have been in the market for around 5-7 years were taken as new drug. These include specifically the following drugs: DPP-IV inhibitors: gliptins–sitagliptin, saxagliptin, and their combinations with metformin, PPAR α/γ agonist: saroglitazar. SGLT-2 inhibitors: dapagliflozin were introduced in the market later on and hence included subsequently during the course of the study. All patients were asked to follow up at monthly interval and whenever they develop any side effect. They were screened clinically and investigated suitably for any ADRs. All ADRs reported were submitted to ADR monitoring centre under Pharmacovigilance Programme of India (PvPI).

Selection criteria

Inclusion criteria

• Patients of >18 yrs age of either sex diagnosed to have Type 2 diabetes.

• Patients with T2DM currently were taking at least one newer oral anti-diabetic drug.

Exclusion criteria

• Diabetic patients not taking the newer oral antidiabetic drugs.

•Newly diagnosed naïve diabetic patients.

• Patients with chronic co-morbidities.

• Patients not willing to give consent.

Study conduct

Adverse event (AE) monitoring

Adverse event monitoring was carried out by Spontaneous reporting. The patient's data including the demographic, clinical and biochemical details was entered into patient's case record form (CRF). The Central Drugs Standard Control Organization (CDSCO) proforma was used and filled as and when AE was reported. The details regarding the ADR was filled in the CDSCO ADR proforma and subsequently uploaded in the WHO-UMC using the Vigiflow software. The CDSCO ADR proforma is divided into 4 parts i.e. A- Patient information, B- Suspected Adverse reaction, C-Suspected medication and D- Information about the Reporter.

ADR severity

The severity of the adverse drug reactions was graded according to the University of Virginia Health System Adverse Drug Reaction Reporting program criteria as "mild": a reaction that does not require treatment or prolongation of the hospital stay; "moderate": a reaction that requires treatment and/or a prolonged hospitalization by at least one day and "severe": a reaction that is potentially life-threatening or that which contributes to the death of the patient, that which is permanently disabling, that which requires intensive medical care (including extended hospitalization), or that which result in a congenital anomaly, cancer.[6]

Causality Assessment of ADRs

In the present study, Naranjo Scale[7] were used to analyze the causality assessment between the drug and suspected reaction. The severity of the adverse drug reactions was graded according to the Hartwig's Severity Assessment Scale which is as under.

Hartwig's severity assessment scale

• Level 1 An ADR occurred but required no change in treatment with the suspected drug.

• Level 2 The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS)

• Level 3 The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. An Antidote or other treatment was required. No increase in length of stay (LOS)

• Level 4 Any level 3 ADR which increases length of stay by at least 1-day or The ADR was the reason for the admission

• Level 5 Any level 4 ADR which requires intensive medical care

• Level 6 The adverse reaction caused permanent harm to the patient

• Level 7 The adverse reaction either directly or indirectly led to the death of the patient. Mild= level 1 and 2,

moderate= level 3 and 4, severe= 5, 6 and 7

Causality assessment of ADRs

In the present study, Naranjo Scale will be used to analyze the causality assessment between the drug and suspected reaction.

Naranjo scale

According to Naranjo Criteria, the ADRs are analyzed on the basis of a questionnaire comprising 10 questions in which each question is given a score of +2, +1, 0 or -1 depending on the analysis. When totalled if the score is >9 - labelled as definite ADR, if 5-8 - probable ADR, if 1-4 - possible ADR, if 0 - doubtful ADR.

The classification of all the ADRs into different system organ class (SOC) involved was done according to the WHO-ART classification. The ADRs were categorized into gastrointestinal system disorders, musculoskeletal disorders, metabolic disorders, CNS disorders, genito-urinary disorders and few ADRs were categorized as "others" which could not be classified under any SOC.

RESULTS

This observational study was conducted between May 2018 and July 2018. A total of 152 cases were recruited and eventually 112 remain in follow up. All Patients were also taking conventional oral hypoglycemic agents and no patient was prescribed insulin.

Table 1 shows the demographic profile of patients. The mean age of patients was 41.5 years with 53.5% patients were male. Maximum number of patients (38.4%) belonged to age group of 41-50 years. The mean weight of the patients was 63.1 kg with average height 161cm. 40.1% patients were having family history of T2DM rest were diagnosed for the first time in their family. Substance abuse was common and commonest being tobacco chewing 38.2%.

Table 1: Demographic profile of the patients on newer Oral Hypoglycemic Agents (OHAs).

Parameter	Group	No. of patients	% of patients
Age years (MEAN±SD) Mean 41.5±12.1	21-30 years	28	25
	31-40 years	21	18.8
	41-50 years	43	38.4
	51-60 years	13	11.6
	61-70 years	06	5.3
	>70 years	01	0.9
Gender	Male	60	53.5
	Female	52	46.5
Drug Abuse	Smoking	21	27.7
	Tobacco	29	38.2
	Alcoholism	26	34.2
	Others	00	00
Family history of T2DM	Yes	45	40.1
	No	67	59.9
Weight (Kg) (MEAN±SD) 63.1±10.3			
Height (cm) (MEAN±SD) 161cm±9.4			

Table 2 represents clinical and drug profile of the patients. Majority of patients (41.1%) were having duration of illness between 5-10 years. Among newer oral hypoglycemic agents DPP-IV inhibitors were most frequently prescribed (71.4%). 15.2% were taking two newer oral hypoglycemic agents. 50% of patients having fasting plasma glucose between 151-180 mg/dl. 50% of patients were having 2-h plasma glucose between 226-250 mg/dl. HbA1C also followed similar trend as 52.7% of patients were having HbA1C between 7-8%.

Table2:Clinical and drug profile of the patients on newer Oral Hypoglycemic Agents (OHAs).

Parameter	Group	No. of patients	% of patients
Duration of T2DM	<5 years	32	28.6
	5-10 years	46	41.1
	11-15 years	20	17.9
	16-20 years	12	10.8
	>20 years	02	1.6
Drug category	Sitagliptin	51	45.5
	Saxagliptin	29	25.9
	Saroglitazar	10	9
	Dapaglifozin	22	19.6
No. of newer OHAs taken	1	95	84.8
	2	17	15.2
	3	00	00
Concomitant other anti-diabetic drugs	Older OHAs	112	
	Insulin	00	
Fasting plasma glucose (mg/dl)	126-150	32	28.6
	151-180	56	50
	>180	24	21.4
2-h Plasma Glucose (mg/dl)	201-225	37	33
	226-250	56	50
	>250	21	17
HbA1C %	6.5-7	30	26.8
	7-8	59	52.7
	>8	23	20.5

Table 3 represents, ADRs with different classes of newer oral anti-diabetic drugs as per the involvement of different system organ class (SOC). Maximum ADRs reported belonged to gastro intestinal system that is 53%. DPP-IV inhibitors showed maximum number of ADRs i.e. 70.6%. Diarrhoea was found to be the most common encountered adverse drug reaction
.

Table 3: ADRs with different classes of newer oral anti-diabetic drugs as per the involvement of different system organ class (SOC)

System organ class	Adverse drug reaction	DPP-IV inhibitors (80)	SGLT-2 inhibitors (22)	PPAR-γ agonist (10)	Total
Gastro-intestinal tract disorders	Diarrhoea	04	01	-	09
	Constipation	-	-	-	
	Dyspepsia	-	-	-	
	Abdominal Pain	01	-	-	
	Gastritis	-	-	01	
	Nausea / Vomiting	02	-	-	
Metabolic disorders	Hypoglycemia	01	-	-	01
Musculoskeletal disorders	Joint pain	02	-	-	04
	Myalgia	-	-	-	
	Fatigue	01	01		
CNS disorders	Headache	01	-	-	01
	Dizziness	-	-	-	
Genito-urinary tract disorders	Burning micturition	-	02	-	02
	Increased frequency of urination	-	-	-	
	Pus cells in urine	-	-	-	
Total		12	04	01	17

Table 4 shows severity assessment of ADRs with different classes of newer oral anti-diabetic drugs. Majority of ADRs reported were mild i.e. 52.9% and no severe ADR was reported.

Table 4: Severity assessment of ADRs with different classes of newer oral anti-diabetic drugs. (Hartwig's Severity Assessment Scale).

	DPP-IV inhibitors (80)	SGLT-2 inhibitors (22)	PPAR-γ agonist (10)
Mild	07	02	0
Moderate	05	02	01
Severe	0	0	0
Total	12	04	01

Table 5 represents causality assessment of ADRs with different classes of newer oral anti-diabetic drugs according to Naranjo scale. Majority (70.6%) ADRs were having possible correlation with the drug. No certain causal relation was established.

Table: 5 Causality assessment of ADRs with different classes of newer oral anti-diabetic drugs according to Naranjo scale.

Newer OHAs	Certain	Probable	Possible	Unlikely
DPP-IV inhibitors (12)	0	02	10	0
SGLT-2 inhibitors (04)	0	02	02	0
PPAR-γ agonist (01)	0	01	0	0

DISCUSSION

Current study was planned to actively generate data on the safety profile of currently prescribed newer oral antidiabetic drugs among type 2 diabetic patients by spontaneous ADR monitoring. In the current study, out of 80 patients on DPP-IV inhibitors, ADRs were reported in 15%. Kajiwara et al, evaluated safety profile of DPP-IV inhibitors in 1550 patients and reported an incidence of 5.9% ADRs.

The studies carried out in the context of the present Project Report have contributed to the knowledge of the safety profile of new medicines for the treatment of CVD. So, the results provided useful information regarding: (i) the suspicion of musculoskeletal complaints associated with the use of gliptins (sitagliptin, vildagliptin, saxagliptin), an ADR that has been recently alerted by the FDA. As regards with 10 patients on PPAR- α/γ agonist: saroglitazar, ADRs were reported in 10%. The incidence of ADRs with saroglitazar in the present study was in accordance with a similar study by Chatterjee et al which demonstrated 11.8% of ADRs with saroglitazar.

DPP-IV inhibitors

Out of 12 ADRs reported due to DPP-IV inhibitors, it was seen that gastro-intestinal (GI) system disorders constituted the maximum number (58.3%) followed by musculoskeletal (25%). The incidence of diarrhoea constituted the maximum number of ADRs due to GI involvement by DPP-IV inhibitors. Most of the ADRs were usually mild and either subsided with time or on dose reduction. The results were consistent with that of the present study where the maximum incidence of GI related ADRs were seen with combination of sitagliptin. With saxagliptin, out of 5 reported ADRs, were attributed due to involvement of GI system: In a

study by De Fronzo et al which assessed the safety of saxagliptin as add-on therapy in type 2 diabetic patients, it was seen that incidence of adverse events related to gastrointestinal disorders was similar in patients treated with saxagliptin (23.0%) versus placebo plus metformin (24.0%) and saxagliptin was not associated with an increased incidence of gastrointestinal disorders as compared to placebo. In the present study, 01 ADR of hypoglycemia was reported amongst 80 patients on DPP-IV inhibitors. These patients were on concomitant treatment with conventional OHAs.

No episode of hypoglycemia exhibited marked severity. These findings are in accordance with those of the study conducted by Goossen and Graber who observed that hypoglycemic risk was similar to placebo when a DPP-IV inhibitor was used as monotherapy or as combination therapy with metformin. Overall, studies show a low risk of hypoglycaemia during treatment with DPP-IV inhibitors which does not mandate a discontinuation of treatment. In current study, 25% of ADRs with DPP-IV inhibitors were due to involvement of musculoskeletal system. Both fatigue and joint pain were mild and subsided in due course of time and did not lead to treatment discontinuation. Tarapues et al, reported that musculoskeletal disorders are adverse reactions often associated with gliptins that despite not being serious, may impair the treatment adherence in patients with type 2 diabetes. 8.3% of ADRs with DPP-IV inhibitors were due to involvement of CNS. Goossen and Graeber have also reported that treatment with DPP-IV inhibitors was associated with a slightly elevated risk for nervous system disorders, mainly dizziness and headache in comparison to placebo and showed that the risk was not increased compared to other antidiabetic drugs. As a whole, DPP-IV inhibitors appear to have a good safety profile for patients with type 2 diabetes. However, close pharmacovigilance is necessary to further confirm the association of drugs and ADRs.

PAR α/γ agonist

In the present study, out of 10 patients on saroglitazar, adverse drug reactions were noted in 01 patient (10%). There was one ADR of gastritis. PRESS V (Prospective Randomized Efficacy and Safety of Saroglitazar V) also showed incidences of similar ADRs. It was the first prospective confirmatory clinical study of saroglitazar in diabetic dyslipidemia.

In another multicenter study to evaluate the efficacy and safety of different doses of saroglitazar versus placebo (PRESS VI), gastritis was reported to be most common adverse effect. These studies did not provide any possible explanation of association of gastritis or fatigue with saroglitazar use but reported that the ADRs due to saroglitazar were mild to moderate in intensity. Our findings are similar to these studies. Saroglitazar seems to be safe and well tolerated in management of diabetic dyslipidaemia but the fact must not be generalized as the number of patients were very less to have a valid conclusion.

SGLT-2 inhibitors

Amongst 22 patients on SGLT-2 inhibitors: adverse drug reaction monitoring documented 04 ADRs (23.5%). Genito-urinary system disorders (50%), was major contributor in ADRs. A 2013 meta-analysis furthers confirms this which state that when compared to other antidiabetes agents, urinary tract infections were more common with SGLT2 inhibitors as were genital tract infections. These occurrences are usually mild to moderate and responsive to treatment and they rarely result in discontinuation of therapy. It appears logical that glucosuria, deliberately induced by SGLT2 inhibition, favors urinary tract infections, as glucose serves as nutrient for bacteria. Taken together, these results suggest that SGLT-2 inhibitors represent a valuable therapeutic option for the management of patients with type 2 diabetes.

New safety information of medicines for treatmen t of chronic diseases

Different areas have been covered in the present work such as new approaches for the treatment of type 2 diabetes mellitus, atrial fibrillation, angina and hypercholesterolemia.

Type 2 Diabetes Mellitus

The main objective of the management of Type 2 Diabetes Mellitus (T2DM) consists in controlling the glucose blood levels and the acute complications; notwithstanding this, the most important long-term therapeutic goals are related to control of microvascular complications including retinopathy, nephropathy and neuropathy, and macrovascular complications such as cerebral, coronary and peripheral artery disease. Metformin has been the unique

antidiabetic drug evaluated for decreasing long-term cardiovascular complications. New therapeutic options in T2DM have showed efficacy to reduce the glycated haemoglobin A1C (HbA1c). Specifically, DPP-4 inhibitors have demonstrated efficacy in reducing and controlling the levels of HbA1c, although their contribution for controlling the cardiovascular morbidity/morbidity is unclear. FDA, the regulatory agency has approved sitagliptin, vildagliptin and saxagliptin in monotherapy, dual therapy and in combination for triple therapy. Also, the current guidelines for managing T2DM have accepted the use of these new antidiabetic medicines as an effective pharmacological strategy[15].

Nowadays, patients are exposed to polypharmacy as a consequence of multimorbidity, and the control of many diseases in one patient is a real challenge for the physicians in clinical practice. Within this framework, the post-marketing surveillance is crucial, and pharmacovigilance research has a role in the knowledge building-up process for new medicines.

Widening of therapeutic indications and its impact in pharmacovigilance

One of the main goals of pharmacovigilance is to describe unknown ADRs or new information on an already known association. However, the pharmaceutical market has changed over time and pharmacovigilance (spontaneous reporting system) had to adapt to the new challenges. Adding a new therapeutic indication to a product or widening the current indication is a new manner of being innovative in the pharmaceutical market and it means a variation in the drug lifecycle compared to few years ago. This phenomenon has been observed especially with oncological drugs or biologics, although it is a common practice in all pharmacological groups, included cardiovascular medicines. In the case of gliptins, either for sitagliptin, vildagliptin or saxagliptin the first therapeutic indication was dual therapy for management of T2DM, and later on monotherapy and triple therapy.

An investigation of the current trends of several new chemical entities and in the FAERS could not find any recognizable reporting pattern. Traditionally, a peak of spontaneous reports during the first 5 years post-commercialization was observed, this was called the Weber effect. However, several investigations have suggested that this effect is not observed nowadays and postulated that some peaks of reporting could be observed after the first 5 years post-commercialization. Considering the continuous changes in the drug-marketing process and widening of indications of use, it seems that the Weber effect might not be observed for some new medicines. These changes should encourage the pharmacovigilance activities for a continuous surveillance in order to identify new ADRs or other new safety information. The source of drug information for the physician is the SPC. This is a document addressed to health-care professionals in order to provide useful information about the drug and sometimes it is considered as a real prescription guideline. As the safety profile of a new drug is provisional when the drug reaches the market, the SPC should be continuously changing especially in the first post-marketing years. Notwithstanding this, some clinicians are unaware of this, and do not check for updates, and the information contained in the SPC is confusing, and its real usefulness in clinical practice is unknown due to the clinical practice guidelines, that are more frequently used regardless their well-known conflict of interest[16].

Risk minimization strategies and patient safety

The risk minimization strategies have been developed as activities to encourage a proactive pharmacovigilance in post-marketing settings by the pharmaceutical industry, though this compulsory procedure has raised serious concerns regarding its usefulness and its impact in terms of public health. An evaluation made by Giezen Et al., showed that the information in the post-authorization study protocols in pre-approval stages was partial or limited and could hamper the evaluation at the moment of drug approval. Moreover, a recent systematic review found several methodological gaps in the assessment of risk minimization interventions both in the EU and in the US. As an example, in the findings presented herein, renal impairment or renal failure is not described as itself in the risk management plan (RMP) of dronedarone. This risk or potential harm is described as the inappropriate management of the signal of serum creatinine increase, and the main actions to be taken are prescription surveys and cross sectional studies, even though since the launch date of this drug in

2009 until mid-2015 the results of such studies have not been published.

Regarding gliptins, each gliptin has different market authorization holders, and consequently each has a different RMP. For sitagliptin the risk of myopathy was found as a potential risk, and routine pharmacovigilance was described as activity, together with safety and warning changes in the SPC[17]. In vildagliptin, muscular events with or without statins were described and routine pharmacovigilance is the main risk minimization activity. In saxagliptin, there is no mention of musculoskeletal events in the RMP . None of the available RMP described arthralgia as a potential concern. Likewise, in the case of dronedarone, until mid-2017, there were no data which helped to elucidate the potential risk of muscular harm with their use. It should to be noted that an independent observational study to find an association between acute renal failure and the use of dronedarone was carried out in Italy recently. No differences were observed between the characteristics of renal failure in patients in treatment with amiodarone compared with patients on dronedarone. Despite this, the researchers suggested caution with the interpretation of the findings because of the few patients in the dronedarone group, which could be a limitation in the comparative analysis. Also, they recommended to be aware of renal reactions with dronedarone in clinical practice.

The Spontaneous Reporting system, its contribution to the patients' safety - Old problems and new solutions

Nowadays, post-marketing surveillance is the result of several complementary methods of study. Spontaneous reporting system is one of the most traditional methods in pharmacovigilance, although it has serious well-known limitations that have prompted to use other data sources and analyses. Spontaneous reporting has many limitations that should be acknowledge: underreporting, lack of information, unknown drug use factors, and competition bias are the most important. Underreporting is one of the main concerns, it is estimated that <10 % of adverse reactions are reported[14]. Another factor that limits the findings in these databases is the lack of knowledge about the denominator exposure.

Frequently, the use of pharmacoepidemiological strategies helps to overcome the limitation of spontaneous reporting with the use of consumption databases in order to elucidate or verify any potential signal detection. Other strategies are the linkage of spontaneous reports and consumption or reimbursement databases. Thus, many authors suggest that the whole approach of pharmacovigilance should integrate traditional methods as the spontaneous reporting with other new ones in order to overcome limitations. Different pharmacoepidemiology studies have complemented and strengthened or discarded signals generated from spontaneous reports. In the future, probably more accurate clinical records and automated databases would be enough to calculate exposures and risks without biases, but at present, data mining of databases or electronic medical records are just a helpful method to explore the use of drugs in population. In terms of patient's safety, many cases that end in drug withdrawal have started with case reports or case series, especially in Europe. Some countries have strengthened pharmacovigilance and the spontaneous reporting by reinforcing the regional centres inside their national networks. This effort includes a careful causality assessment at individual level of each spontaneous report prior its inclusion in the national database. This assessment has improved the whole process of passive pharmacovigilance and helped greatly signal detection. This assessment is unfeasible in schemes such that of the US.

Another useful strategy in pharmacovigilance is the automated methods for detection of new safety signals. Despite of their continuous and more ubiquitous use, the automated signals generated from disproportional observation in big databases have to be managed with caution due to high rates of false signals. Some strategies have been developed in order to decrease this disadvantage, and more complex analyses for improving the automated signal detection are still under study. Another important strategy in safety signal generation is the use of meta-analytical techniques applied to RCT. This information allows getting a general overview and comparative analysis of the all RCT regarding a specific medicine. Patients' safety will improve with the interaction among prescribers, regulatory agencies and pharmaceutical industry; this is the ideal balance but hardly ever reached. Regulatory agencies have the responsibility to the generation of independent information; however, nowadays

academia also has a crucial role in independent evaluation of drug safety. Besides this, manufacturers are increasingly interested in speeding up premarketing stages and penetration of new medicines in the market, a process that is contrary to the slowness of knowledge building. Knowledge regarding the safety profile of new drugs on the market (in this case cardiovascular medicines) is always under construction while the medicine remains available in the market. So, the right prescription is sometimes a challenge in clinical practice, and a careful risk-benefit assessment is always necessary to ensure the maximum level of patients' safety.

CONCLUSIONS

Overall, newer oral antidiabetic drugs like gliptins and SGLT-2 inhibitors appear to have a good safety profile, but they also have potential to cause ADRs. Gastro-intestinal, musculoskeletal, metabolic disorders were most common ADRs. As the newer drugs are increasingly being prescribed in Indian scenario, hence the need for ADR monitoring is growing than ever before. Therefore, active pharmacovigilance should be carried out for risk identification and management. It is also important to motivate healthcare providers to understand their role and responsibility in the detection, management, documentation, and reporting of ADRs for optimizing patient safety.

1. A detailed analysis of the spontaneous reporting databases still contributes to the never- ending process of knowledge acquisition regarding toxicity profile of new medicines, the necessary counterbalance of the often excessively enthusiasm that involve new products.
2. Notwithstanding this, post-marketing surveillance should be understood as the result of several complementary methods. These methods should also include meta-analysis of published RCT's and complex pharmacoepidemiological studies

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