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# Adverse events associated with antidiabetics: An analysis of Vigiflow data

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**Abstract**

The use of Antidiabetics has been increasing. However, sporadic reports of serious adverse effects associated with the use of these products have become a source of concern. Spontaneous adverse event reporting may be used to monitor the safety of these drugs. **Objective-** The objectives of this study is to analyze and describe the patterns of adverse events associated with the use of Antidiabetics in the Indian Pharmacovigilance database (VigiFlow) from 2010 to 06/07/2012 and to highlight areas of safety concerns. Methods- Adverse events associated with Anti diabetics reported in Indian Pharmacovigilance database (VigiFlow) for the period 2010-06/07/2012 were analyzed. The informations which extracted and collated were: patient demographics, type of antidiabetics, system-organ class affected, seriousness of the adverse event, hospitalization status, outcome of adverse event, and profession of the reporter. **Results-** In the period 2010-2012, 466 cases of adverse events due to antidiabetics were reported. Average onset age (mean±SEM) of male patients was 51.0±0.72 & female patients 50.433± 0.72. It was found that 40% of ADR related to antidiabetics were occurred in female where as 60 percent in counterpart. Twenty six percent cases were found to be of the serious, Metabolic and nutritional disorders constituted 13%, Gastro-intestinal system disorders constituted 5% and central nervous system disorders constituted 4%. Two cases of hypoglycaemia were responsible for the life threading condition during this period. One case of metformin induced encephalopathy without metabolic syndrome was found which is the unexpected. In most of cases reporter was doctor. **Discussion-**In conclusion, 465 adverse event reports associated antidiabetics had been successfully analyzed and described. They constituted ~0.60% of the total number of adverse events reported from 2010-06/07/2012. One case of metformin induced encephalopathy without metabolic syndrome was found which is the unexpected. Further work to confirm the metformin induced encephalopathy without metabolic syndrome is warranted. Reporting of suspected adverse events is strongly encouraged even if the causality is not confirmed because any signs of clustering will allow rapid regulatory actions to be taken. The analysis of spontaneously reported adverse events is important in monitoring the safety of antidiabetics and helps in the understanding of the benefits and risks associated with the use of such products.

**Keywords**: Adverse events, Adulteration, Hypoglycemia, Hepatotoxicity, Pharmacovigilance.

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## 1. Introduction

Although prescription drugs are subject to extensive premarket safety testing prior to approval, adverse drug reactions (ADRs) not identified in preclinical and clinical testing may become apparent following their introduction into the marketplace and their subsequent use within the highly heterogeneous general population [1]. Appropriate and effective monitoring of ADRs, i.e. Pharmacovigilance, is the only best way to safeguard the public health. In a vast country like India with a population of over 1.2 Billion with vast ethnic variability, different disease prevalence patterns, practice of different systems of medicines, different socioeconomic status, it is important to have a standardized and robust Pharmacovigilance and drug safety monitoring programme for the nation [2]. The use of Antidiabetics has been increasing. However, sporadic reports of serious adverse effects associated with the use of these products have become a source of concern. Spontaneous adverse event reporting may be used to monitor the safety of these drugs. In year 2009 Central Drug Standards Control Organization (CDSCO) with Ministry of Health & Family Welfare Govt of India is initiated a nation-wide Pharmacovigilance Programme for protecting the health of the patients by assuring drug safety. In April 2011 Indian Pharmacopoeia Commission (IPC), Ghaziabad was recognized as National Coordination Centre (NCC) for Pharmacovigilance Programme of India (PvPI). Currently there are 60 ADR monitoring centers spread all over country reporting to NCC [2]. The objective of PvPI is, to monitor ADRs in Indian population, to create awareness amongst health care professionals about the importance of ADR reporting in India, to monitor benefit-risk profile of medicines, generate independent, evidence based recommendations on the safety of medicines, support the CDSCO for formulating safety related regulatory decisions for medicines, communicate findings with all key stake holders and create a national centre of excellence as par with global drug safety monitoring standards [3,4]. In order to evaluate the safety profile of anti-diabetics, using data reported through the Indian Pharmacovigilance system (VigiFlow) [5] data from 2010 to 06/07/2012 were analyzed.

### Method

Type 2 diabetic patients were identified and all suspected ADRs were evaluated using WHO – Uppsala Monitoring Centre causality scale [6,7]. The information from VigiFlow which extracted and collated were: patient demographics, type of antidiabetics, system-organ class affected, seriousness of the adverse event, hospitalization status, outcome of adverse event, and profession of the reporter. ADRs were coded according to WHO adverse event terminology (WHO-ART) [8] . Hospitalization due to adverse event was categorized into hospitalized, not hospitalized and already hospitalized. The term "already hospitalized" describes the group of patients who were admitted for other co-morbities when the adverse event was detected. The outcome of the adverse event associated with the use of antidiabetics were also analyzed by categorizing them into four category as patients who

**Table no-1:** Patients demography and profession of reporter

| | Characteristic | No. of cases (n=465) |
|---|---|---|
| **1** | Gender | |
| | Male | 273 |
| | Female | 182 |
| **2** | Avg. onset age | |
| | Male | 51.0±0.72 |
| | Female | 50.43± 0.72 |
| **3** | Profession of reporter | |
| | Doctor | 389 |
| | Pharmacist | 53 |
| | Other healthcare professional | 7 |

recovered, not recovered at the point of reporting, had uncertain outcome and died.

**3. Result**

In the period 2010-06/07/2012, 466 cases of adverse events due to antidiabetics were reported. Four hundred sixty five cases were included in analysis because complete data is not available for one case. Sigma State [9] ver-3.5 was used for analysis. Average onset age (mean±SEM) of male patients was 51.0±0.72 & female patients 50.433± 0.72. It was found that 40% of ADR related to antidiabetics were occurred in female where as 60 percent in counterpart. Twenty six percent cases were found to be of the serious, out of which metabolic and nutritional disorders constituted 13%, gastro-intestinal system disorders constituted 5% and central nervous system disorders constituted 4%.

Two cases of hypoglycaemia were responsible for the life threading condition during this period. One case of metformin induced encephalopathy without metabolic syndrome was found which is the unexpected. It was found that insulin caused highest number of ADRs (170 cases) in male patients followed by metformin (56 cases) and glibenclamide (23 cases) most of insulin induced ADRS were related to metabolic and nutritional disorders. Two cases of hypoglycemia induced by insulin were responsible for the life threading condition during this period. Fourty eight ADR cases caused by insulin and 25 ADR cases caused by pioglitazone in female were reported during this period. It was that in most of the ADR cases patients recovered & primary reporter was physician. Table-1 shows Patients demography, and profession of reporter & table 2 no. of cases of adverse events due to antidiabetics.

**4. Discussion**

The worldwide situations of drug safety have changed dramatically. Drugs are used based on the evaluation of safety data collected in clinical practice worldwide. NCC PvPI collects spontaneous reports and requires manufacturers to report adverse drug reactions (ADRs) of Indian marketed drugs occurring worldwide. These data are available through the VigiFlow. Adverse event reports associated antidiabetics had been successfully analyzed and described. Not much statistic was applied because the number of patients less. Total 465 ADRs were reported they constituted ~0.60% of the total number of adverse event reported from 2010-06/07/2012. One case of metformin induced encephalopathy without metabolic syndrome was found which is the unexpected [9,10].

Further work to confirm the metformin induced encephalopathy without metabolic syndrome is warranted. Reporting of suspected adverse events is strongly encouraged even if the causality is not confirmed because any signs of clustering will allow rapid regulatory actions to be taken. The analysis of spontaneously reported adverse events is important in monitoring the safety of antidiabetics and helps in the understanding of the benefits and risks associated with the use of such products.

**Table no-2** No. of cases of adverse events due to antidiabetics

| **Sr. No** | Sex | Acarbose | Insulin | Glipizide | Glimepiride | Human actrapid |
|---|---|---|---|---|---|---|
| **1** | M | 3 | 170 | 14 | 21 | 0 |
| **2** | F | 2 | 48 | 8 | 20 | 2 |
| **Sr. No.** | Sex | Glibenclamide | Metformin | Dpp4 anlogus | Glitazone | |
| **3** | M | 23 | 56 | 1 | 8 | |
| **4** | F | 13 | 18 | 1 | 25 | |

**Adverse events grouped according to system organ class classification**

Table-2 shows the classification of the adverse events into different system organ class (SOC) involved according to the WHO-ART classification. From the 465 reports, metabolic and nutritional disorders constituted 60%, gastro-intestinal system disorders constituted 17% and central nervous system disorders constituted 8%.

| NO of Adverse event cases | SOC Involved |
|---|---|
| 279 | Metabolic and nutritional disorders |
| 78 | Gastro-intestinal system disorders |
| 40 | Central and peripheral nervous system disorders |
| 30 | Skin and appendages disorders |
| 16 | Body as a whole - general disorders |
| 05 | Musculo-skeletal system disorders |
| 04 | Psychiatric disorders |
| 02 | Respiratory system disorders |
| 02 | Special senses other, disorders |
| 02 | Heart rate and rhythm disorders |
| 02 | Vascular (extracardiac) disorders |
| 02 | Cardiovascular disorders, general |
| 01 | Foetal disorders |
| 01 | Liver and biliary system disorders |
| 01 | Vision disorders |

**Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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