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INVESTIGATION OF ADVERSE DRUG REACTIONS RELATED TO METFORMIN USE IN PATIENTS OF TYPE 2 DIABETES MELLITUS IN A TERTIARY CARE HOSPITAL IN KOLKATA, WEST BENGAL, INDIA

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ABSTRACT: Metformin is one of the most widely used oral anti-diabetic drugs currently considered to be one of the first-choice drugs for Type 2 Diabetes mellitus (T2DM). However, some adverse drug reactions (ADRs) were frequently observed with the treatment with Metformin and its combinations. This study was planned to investigate the ADR profile of Metformin in Type 2 Diabetes mellitus patients attending diabetic Out Patient Department (OPD) of a Tertiary care hospital, Kolkata. An observational cross sectional study with diagnosed cases of Type 2 Diabetes mellitus both male and female, with age group 30-60 years were randomly selected. Present study data revealed that, 61.60% (154) out of 250 patients within age of 46-50 yrs had experienced maximum adverse drug reactions where majorities belonged to female 70.12%. Occurrence of hyper acidity and flatulence (61.03%) was high in patients treated with Metformin and its combinations, followed by weakness (29.87%), dizziness (28.57%) and bodyache (20.77%) are other adverse reactions present in majority of patients. Special attention must be provided by the medical professionals to prevent the possible occurrence of ADRs in the patients treated with Metformin and its combinations. This may improve the adherence of Metformin by reducing the prevalence of Metformin-induced ADRs.

Key words: Metformin, Diabetes, Adverse drug reactions, Tertiary care hospital.

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INTRODUCTION

The World Health Organization (WHO) estimated that in the year 1995 there were 135 million diabetic individuals and this number will increase to 300 million by the year 2025. Considering the large population and increasing prevalence of Diabetes mellitus of nearly 33 million diabetic subjects, the burden of diabetes in India could be enormous (Ramachandran *et al.* 2001).

Numerous studies have shown metformin to be highly effective and safe in the treatment of Type 2 Diabetes (De Fronzo and Goodman 1995, Johnson *et al.* 2002, UK Prospective Diabetes Study group 1998). It is the only currently available biguanide. Indeed, it is one of the most widely used oral anti-diabetic drugs. Metformin improves insulin resistance by inhibiting gluconeogenesis and enhancing peripheral glucose uptake through stimulation of adenosine monophosphate (AMP)-activated kinase (Scarpello and Howlett 2008). Metformin is the only anti-diabetic agent that has been shown to reduce mortality in patients with newly diagnosed Type 2 Diabetes and the only anti-diabetic agent not shown to be associated with increased morbidity and mortality in patients with cardiac disease, including heart failure (Johnson *et al.* 2002, UK Prospective Diabetes Study group 1998, Eurich *et al.* 2005, Smooke *et al.* 2005). It is the most frequently prescribed drug given alone or in combination with other drugs.

Metformin is generally well tolerated. However, it is well known that Metformin frequently causes adverse drug reactions (ADRs) including gastrointestinal adverse events, especially diarrhea (Nathan *et al.* 2009). These ADRs occasionally leads to withdrawal of Metformin treatment (Garber *et al.* 1997, Belcher *et al.* 2005). Present study evaluated the Metformin use pattern in patients of Type 2 Diabetes mellitus in a Tertiary care hospital in Kolkata, West Bengal, India followed by identification of the risk-factors related to ADRs in the patients, treated with Metformin, to ensure the appropriate use of Metformin.

MATERIALS AND METHODS

The study was carried out in the OPD of R. G. Kar Medical College & Hospital, Kolkata, West Bengal, India. This was an observational, cross sectional study on diagnosed cases of Type 2 Diabetes mellitus by random selection. The prescriptions and medical reports were collected from the patients & later evaluated. Only those patients, following inclusion and exclusion criteria attending Diabetes OPD and Medicine OPD of R. G. Kar Medical College & Hospital were requested to join this study, and a written consent was taken from the patients. A questionnaire was developed, standardised and validated for this work. Ethical clearance was taken from Institutional Ethics Committee. A total of 250 patients were included in the study.

Confirmed cases of Diabetes mellitus Type 2 both male and female, age group between 30-60 years; continuous and uninterrupted treatment with Metformin and its combination for at least one month, were included in the study.

RESULTS AND DISCUSSION

Present study evaluated that maximum number of patients were prescribed a dose between 500-1000 mg of Metformin. This dose was used extensively by both male and female patients. Only 1.2% of patients had received a dose more than 2500 mg of Metformin. The

daily frequency of the drug in majority of patients was 2 *i.e.* 43.2%, which is closely followed by 3, with 41.6%.

The Fig.1 showed that 61.60% (154) out of 250 patients had experienced adverse drug reaction and the rest 38.40% (96) experienced no adverse drug reaction. The following graphical presentation shows the pie-chart of distribution of the total study population (n=250 patients) according to patients with ADR and patients with No ADR.

Out of 154 patients with ADR, male patients were 29.87% (46) and female patients were 70.12% (108). Therefore it was found that majority of the patients who experienced ADRs of Metformin were females.

Histogram in Fig.2 showed that patients within age between 41-45 yrs and 46-50 yrs had experienced more ADR's. Patients within age of 30-35 yrs had experienced minimum ADR's and patients within age of 46-50 yrs had experienced maximum ADR's.

Table 1 showed the list of adverse drug reactions experienced by the 154 patients treated with Metformin and its combinations. This table clearly showed that the occurrence of Hyper acidity and flatulence (61.03%) was high in patients treated with Metformin and its combinations, followed by weakness (29.87%), dizziness (28.57%) and body ache (20.77%) are other adverse reactions which were present in certain majority of patients.

Table 1: Distribution of adverse drug reactions of Metformin & its combinations (n=154)

Body systems mostly affected by ADRs	Types of adverse drug reactions	No. of patients	Percentage (n=154) n=Total no. of Patients
Gastrointestinal system related	Hyper acidity, Flatulence	94	61.03%
	Diarrhea	24	15.58%
	Abdominal discomfort	10	6.49%
	Nausea & Vomiting	6	3.89%
	Weight loss or Anorexia	3	1.94%
Respiratory system related	Respiratory Distress	11	7.14%
Muscular-skeletal system related	Muscular pain	20	12.98%
	Numbness of hands	6	3.89%
	Numbness of legs	7	4.54%
	Body ache	32	20.77%
CNS related	Weakness	46	29.87%
	Dizziness	44	28.57%
	Headache	5	3.24%
Immune system related	Skin rash	1	0.64%

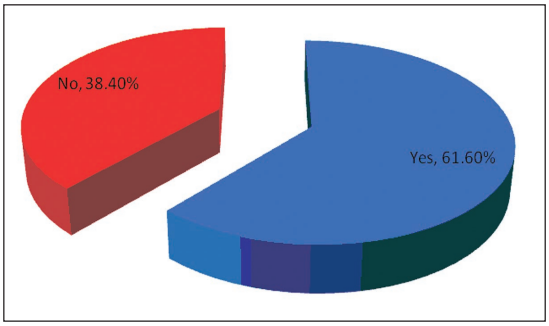

Fig.1: Distribution of the study population according to ADR of Metformin.

Present study report showed that maximum number of patients *i.e.* 42.8% of study population, extensively received Metformin dose between 500-1000 mg. The number of daily dose of Metformin in majority (43.2%) of total patients is 2. Similar report also available from a study in Japan, which reflected the dose of Metformin administered were 500 mg in 51.5% and 750 mg in 48.5% of the total study population (Okayasu *et al*. 2012).

Out of 250 patients, 61.60% had experienced adverse drug reaction and the rest 38.40% experienced no adverse drug reaction. Among the affected patients, male patients were 46 (29.87%) and female patients were 108(70.12%). Therefore it was found that majority of patients who were taking Metformin had experienced adverse drug reaction and females were more prone to the ADRs. This data is similar to other study in California where it was also found that female and BMI also became risk factors. It has been reported that genders and body weight failed to affect the pharmacokinetics of Metformin (Sambol *et al.* 1996). Thus, the further investigation would be needed to understand these data.

Patients within age of 30-35 yrs had experienced minimum ADR's than patients within age of 46-50 yrs had experienced maximum ADR's. This study data is an agreement with some similar study in Japan where the age less than 65 became a risk factor although it is well accepted that reduced functions of kidney, liver and other organs in elderly subjects might strengthen the effect of drugs (Okayasu *et al.* 2012). Our study report also reveals that reduction of the occurrence of these Metformin related ADRs with the increase in age after 50 years. This is a unique finding though it needs to be studied more extensively to conclude about the reason behind.

There was no study from Kolkata, West Bengal, India regarding the ADR related with Metformin use and a few numbers of studies were also conducted in India also. A study regarding the risk factors associated with Adverse Drug Reactions by Metformin in Type 2 Diabetes mellitus from Japan showed that most-frequently observed ADR was

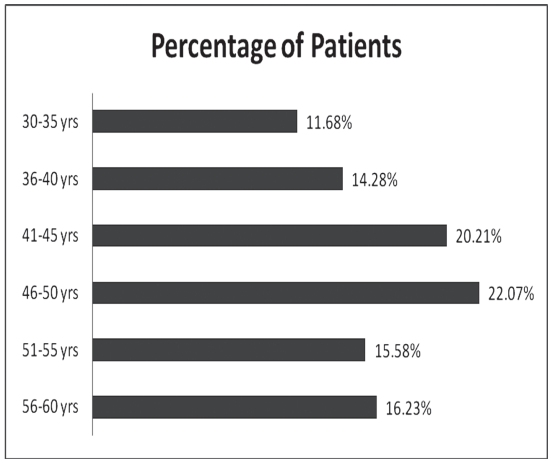

Fig.2: Distribution of the study population (n=154) with ADR of Metformin according to the age of the patient.

diarrhea that occurred in 27% of patients, which was consistent with the data 23.7% reported in a large clinical trial, A Diabetes Outcome Progression Trial (ADOPT) (Kahn *et al.* 2006).

ADR such as mild anorexia appeared in 3 patients (3%) without diarrhea. Nausea, vomiting, hepatic and renal dysfunctions were not observed. Although it is well known that one of serious ADRs caused by Metformin is lactic acidosis, (Salpeter *et al*. 2010) but no ADRs related to lactic acidosis (ex. blood pH *etc.*) were observed in the present study. But in the present study occurrence of hyper acidity and flatulence (61.03%) was high in patients treated with Metformin and its combinations, followed by weakness (29.87%), dizziness (28.57%) and body ache (20.77%) are other adverse reactions which were present in certain majority of patients. In comparison with the study in Japan less number of patients *i.e.* 15.58% of total study population suffered from Diarrhea and 1.94% from Anorexia.

There have been no detailed studies have conducted in West Bengal as well as in India about the ADRs related to Metformin and no such report of serious adverse events to the drug regulatory agencies or to the World Health Organization Adverse Drug Reaction Monitoring Centre. But the present study reveals 61.60% of study population had experienced adverse drug reaction related to the use of Metformin. Therefore physicians should take note of this adverse effect of Metformin, since this drug is used extensively.

CONCLUSION

In conclusion, we found 61.60% of total patients treated with Metformin experienced Metformin- induced ADRs, occurrence of hyper-acidity and flatulence as (61.03%) was high in patients treated with Metformin and its combinations. Some potential risk factors involved are females, age of 46-50 yrs etc. Therefore, checking the risk factors for Metformin-induced adverse drug reactions may aid medical professionals to prevent the possible occurrence of ADRs to the patients. Such type of study will improve the adherence of Metformin by reducing the prevalence of Metformin-induced ADRs.

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