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Full Length Research Paper

Evidence based study of side effects of drugs used in the treatment of diabetes mellitus

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Diabetes mellitus occurs throughout the world but is more common in developed countries. More than 150 million people were found with diabetes in 2004. In 2005, there were about 20.8 million people with diabetes in United State alone. While an estimated 14.6 million have been diagnosed with diabetes, unfortunately 6.2 million were unaware that they have diabetes. To focus on the adverse effects of drugs prescribed for the treatment of diabetes mellitus, a search about data regarding side effects of drugs used in the treatment of diabetes was made using "pubmed", "medline" and "google" published during 1970 to 2011. These drugs included: insulin, metformin, glibenclamide and glimpiride. Search was made by using the terms given in "keywords" and some other terms given in article. Eighty research articles of these drugs were found. The side effects of these drugs were compared with each other to avoid duplication of data. Out of 20 articles of each drug, percentage of hypoglycemic effect produced by insulin, glibenclamide, glimpiride and metformin was 90, 80, 40 and 0%, respectively, while hypersensitivity reactions showed a percentage of 50, 15, 10 and 5%, respectively. Percentage of hepato-toxicity produced by these drugs was 0, 35, 10 and 10%, respectively. Only metformin produced lactic acidosis and vitamin B12 deficiency and percentage of these effects are 60 and 30%, respectively. It is necessary to focus on the side effects of the drugs prescribed for the treatment of diabetes mellitus.

Key words: Diabetes mellitus, insulin, glibenclamide, glimpiride, metformin, side effects.

INTRODUCTION

Diabetes is a disorder of metabolism and represents the way by which body uses or converts food for energy and growth. There are two types of diabetes type 1, type 2 and gestational diabetes. It affects 23.6 million people (7.8%) of the United States population. It is a leading cause of death and disability which costs 174 billion dollars per year (Ahmet, 2007). Diabetes mellitus occurs throughout the world but is more common in more developed countries. More than 150 million people were found with diabetes in 2004. In 2005, there were about 20.8 million people with diabetes in United State alone. While an estimated 14.6 million have been diagnosed with diabetes, unfortunately 6.2 million were unaware that they have diabetes (Salas and Caro, 2002). The people of any age, people with a family history of diabetes and others at high risk for type 2 diabetes: older people, overweight and sedentary people can be at risk of diabetes (Harrower, 2000; Krentz et al., 1994).

Insulin is a hormone produced by beta cells of Islets of Langerhans of pancreas. It is used for the treatment of diabetes mellitus. The adverse effects produced by insulin are the following: Hypoglycemia, hypersensitivity reactions, lipoatrophy, oedema and weight gain. Metformin

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Table 1. Side effects found for insulin, metformin, glibenclamide and glimpiride.

S/N	Side effect	Insulin	Metformin	Glibenclamide	Glimpiride
1	Hypoglycemia	18	0	16	8
2	Hypersensitivity reactions	10	1	2	3
3	Weight gain	7	0	2	2
4	Hepatotoxicity	0	7	2	2
5	GI disturbances	0	2	2	6
6	Lactic acidosis	0	12	0	0
7	Vitamin B12 deficiency	0	6	0	0
8	Ocular disturbances	0	0	2	1
9	Lipoatrophy	6	0	0	0

is an oral anti diabetic biguanide that in the presence of insulin suppresses hepatic insulin action. Adverse effects produced by metformin include: Lactic acidosis, cholestatic hepatitis and vitamin B12 deficiency (Asplund et al., 2008). Glibenclamide is oral hypoglycemic agent of class sulfonylureas.

The side effects of this drug include: Hypoglycemia, hypersensitivity reactions, blurred vision, GI disturbances and intrahepatic cholestasis. Glimpiride is medium to long acting sulfonylureas anti-diabetic drug. It lowers blood sugar level by stimulating insulin release. Adverse effects produced by this drug include: Hypoglycemia, chronic cholecystitis, allergic reactions, weight gain and GI disturbances include nausea, vomiting, heart burn, anorexia and diarrhea (Bhatia et al., 1970).

The aim of this study was to focus on the adverse effects of the drugs prescribed for the treatment of diabetes mellitus.

METHODS

A search (in English only) about data regarding side effects of drugs used in the treatment of diabetes was made using electronic databases: “Pubmed”, “medline” and “google”. The articles published during 1970-2011 were included in this study. The anti-diabetic drugs included: insulin, metformin, glibenclamide and glimpiride. Search was made by using the terms given “keywords” or “title” and some other terms given in article. Eighty research articles of these drugs were found. The side effects of these drugs were compared with each another to avoid duplication of data.

To make certain a comprehensive review, investigation of literature was supplemented by probing the reference lists of the papers created from the original investigations. The authors selected the potentially appropriate papers identified by the electronic searches. The published literature eligible for inclusion were the *in vitro* studies and the randomized trials were presented in English language. All the literature selected was confirmed for duplications, which if observed, were excluded.

This study was approved by the Board of Advanced Studies and Research, Faculty of Pharmacy and Alternative Medicine, The Islamia University of Bahawalpur, Bahawalpur, Pakistan.

RESULTS

Hypoglycemia is the most common and frequent side effect of insulin, glibenclamide and glimpiride (Table 1). But hypoglycemic effect of insulin is more than that of other two drugs (Figure 1). Metformin does not produce hypoglycemia. The aforementioned three drugs (insulin, glibenclamide and glimpiride) result in weight gain while metformin reduces body weight. The risk of hepato-toxicity by metformin is greater than that of the other three drugs, that is, insulin, glibenclamide and glimpiride. The main risk of metformin therapy is lactic acidosis that may result in death. Suspicion of lactic acidosis is high in diabetic patients who are taking biguanide present with acidosis. Absorption of vitamin B12 is reduced by metformin therapy resulting in vitamin B12 deficiency. Allergic reactions produced by insulin are greater as compared to other three drugs.

The percentage of hypoglycemic effect produced by insulin, glibenclamide, glimpiride and metformin was 90, 80, 40 and 0%, respectively, while hypersensitivity reactions showed percentage of 50, 15, 10 and 5%, respectively. Percentage of hepato-toxicity produced by these drugs was 0, 35, 10 and 10%, respectively. Only metformin produced lactic acidosis and vitamin B12 deficiency and percentage of these effects were 60 and 30%, respectively. The results of these comparisons are given Figures 2 to 6.

DISCUSSION

People with pre-diabetes have blood glucose levels that are higher than normal but not high enough for a diagnosis of diabetes. This condition raises the risk of developing type-2 diabetes, heart disease, and stroke. Diabetes is a disorder of metabolism and the way body uses digested food for growth and energy. Most of the food people eat is broken down into glucose, the form of sugar in the blood (Noakes and Lichenoid, 2003; Scheider, 1996). Glucose is the main source of fuel for the body. After digestion, glucose passes into the bloodstream, where it is used by cells for growth and energy. For glucose to get into cells, insulin must be present. Insulin is a hormone produced by the pancreas, a large gland behind the stomach. When people eat, the

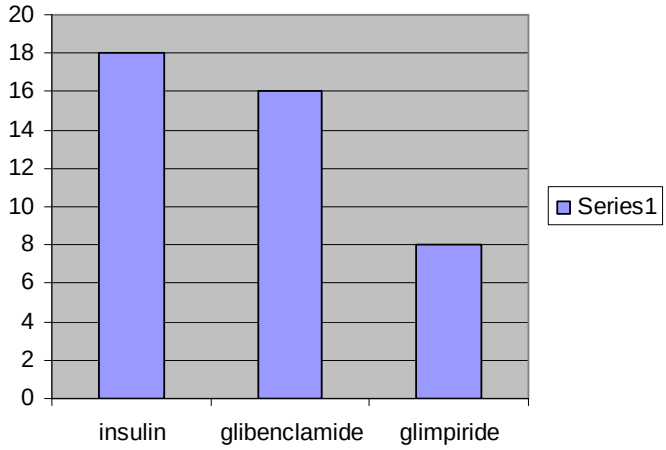

Figure 1. Comparison of hypoglycemic effect of insulin, glibenclamide and glimpiride.

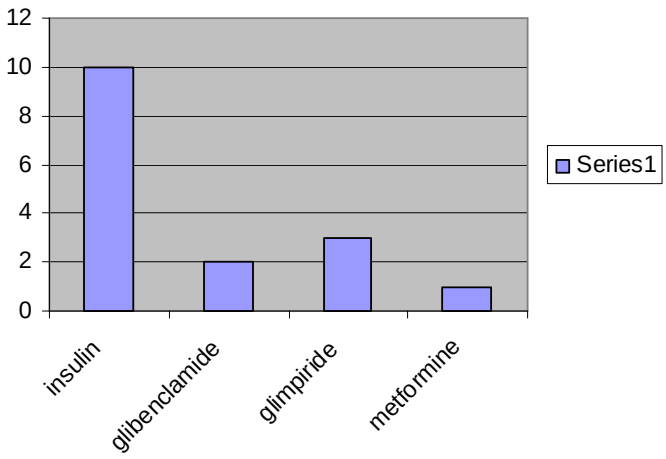

Figure 2. Comparison of hypersensitivity reaction of insulin, glibenclamid and glimpiride.

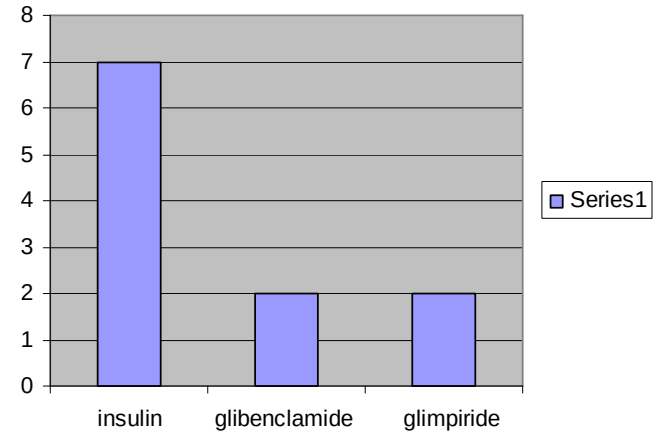

Figure 3. Comparison of weight gain by insulin, glibenclamide and glimpiride.

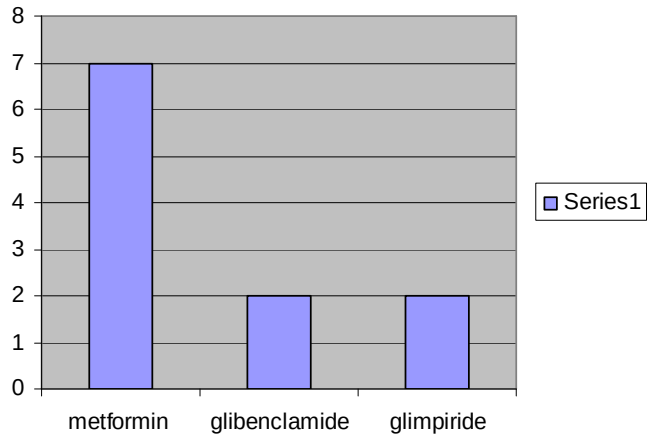

Figure 4. Comparison hepatotoxicity by metformin, glibenclamide and glimpiride.

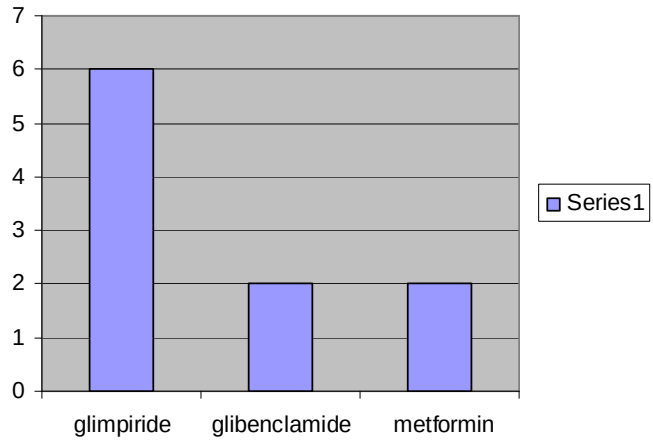

Figure 5. Comparison of GI disturbances by metformin, glibenclamide and glimpiride.

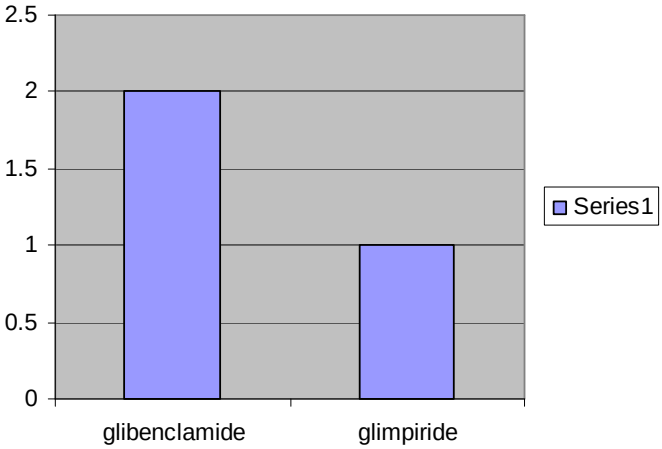

Figure 6. Comparison of ocular disturbances by glibenclamide and glimpiride.

pancreas automatically produces the right amount of insulin to move glucose from blood into the cells. In people with diabetes, however, the pancreas either produces little or no insulin, or the cells do not respond appropriately to the insulin that is produced (Afieroho et al., 2011). Glucose builds up in the blood, overflows into the urine, and passes out of the body in the urine. Thus, the body loses its main source of fuel even though the blood contains large amounts of glucose (Fujita et al., 2011).

The Look AHEAD (Action for Health in Diabetes) trial is the largest clinical trial to date to examine the long-term health effects of voluntary weight loss. This multicenter, randomized clinical trial is studying the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long-term through decreased caloric intake and increased exercise. Look AHEAD will focus on the disorder most associated with being overweight or obese, type-2 diabetes and on the outcome that causes the greatest morbidity and mortality in people with type 2 diabetes, CVD. Results after 1 year of the study show that people receiving the lifestyle intervention lost an average of 8.6 percent of their initial body weight (Rosenstock et al., 1996; Yoo et al., 2011). In addition, they showed improved control of diabetes as well as improvements in cardiovascular risk factors, such as high blood pressure and blood fat levels.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a multicenter, randomized trial, is studying three approaches to preventing major cardiovascular events in individuals with type II diabetes. ACCORD was designed to compare current practice guidelines with more intensive glycemic control in 10,000 individuals with type 2 diabetes, including those at especially high risk for cardiovascular events because of age, evidence of sub Clinical atherosclerosis, or existing clinical CVD. More intensive control of blood pressure than is called for in current guidelines and a medication to reduce triglyceride levels and raise HDL, or “good,” cholesterol levels will also be studied in subgroups of these 10,000 volunteers. Each treatment strategy will be accompanied by standard advice regarding lifestyle choices, including diet, physical activity, and smoking cessation, appropriate for individuals with diabetes (Schondof et al., 2011; Plantin et al., 1988; Gin et al., 2009).

The primary outcome to be measured is the first occurrence of a major cardiovascular event, specifically heart attack, stroke, or cardiovascular death. In addition, the study will investigate the impact of the treatment strategies on other cardiovascular outcomes; total mortality; limb amputation; eye, kidney, or nerve disease; health-related quality of life; and cost-effectiveness (David and Bell, 2010; Kyun et al., 2008).

Participants in clinical trials can play a more active role in their own health care, gain access to new research treatments before they are widely available, and help others by contributing to medical research (Geories et al., 2011).

Conclusion

There is need to focus on the side effects of the drugs while prescribing these drugs for the treatment of diabetes mellitus. Glucose monitoring should be recommended to avoid severe hypoglycemia and liver function tests must be conducted during the therapy. Metformin therapy requires checking of vitamin B12 status as well as early recognition and treatment of lactic acidosis if it occurs.

REFERENCES

Ahmet K, Kagan G, Serdar K (2007). Severe anaphylactic reaction to human insulin in diabetic patient. J. Diab. Complicat., 21: 124-127.

Salas M, Caro J (2002). Adverse drug reactions and toxicological reviews,Are hypoglycemia and other adverse effects similar among sulphonylurease? Diabetes, 21: 215-217.

Harrower ADB (2000). Drug safety, comparative tolerability of sulphonylurease in diabetes mellitus. Diabet. Physiol., 22: 313-320.

Krentz AJ, Ferner RE, Bailey CJ (1994). Comparative tolerability of oral anti diabetic agents. J. Diabet. Pharmacol., 18: 223-241.

Asplund K, Wiholm BE, Lithener F (2008). Glibenclamid associated hypoglycemia: a report on 57 cases. Pak. J. Pharm. Sci., 24: 6-16.

Bhatia SK, Hadden DR, Montgomery DAD, Weaver JA (1970). Glibenclamide therapy in diabetes mellitus. J. Diabet. Pharmacol. Physiol., 13: 23-32.

Noakes R, Lichenoid H (2003). Drug eruption as a result of recently released sulfonylurea glimepride. Dermat., 44: 302-303.

Scheider J (1996). An overview of safety and tolerance of glempiride (Amaryl): A double blind comparison with glibenclamide. Horm. Metab. Res., 28: 419-425.

Afieroho OE, Okorie O, Okonkwo TJ (2011). An ultra violet-spectrophotometric method for the determination of Glemepride in solid dosage forms. Diabet. J., 42: 428-433.

Fujita Y, Honma H, Satoh J, Fujino Y, Onodera M, Inoue Y, Endo S (2011). Detection of glimepride and rosiglitazone from Chinese dietary supplement. Indian J. Pharm. Sci., 24: 51-56.

Rosenstock J, Samols E, Muchmore DB, Cchneider J (1996). Glimepride, a new once daily sufonylurea. A double blind placebo-controlled study of NIDDM patients. Glimepride study group. BMC Diabetes, 19: 1194-1199.

Yoo HD, Kim MS, Cho HY, Lee YB (2011). Population pharmacokinetic analysis of glimepride with CYP2C9 genetic polymorphism in healthy Korean subjects. Eur. J. Clin. Pharmacol., 34: 527-534.

Schondof T, Musholt PB, Hohberg C, Forst T, Lehmann U, Fuchs W, Lobig M, Muller J, Pfutzner A (2011). The fixed combination of pioglitazone and metformin improves biomakers of platelet function and chrinic inflammation in type 2 diabetes patients: results from piofix study. Diabetes, 5: 426-432.

Plantin P, Sassols B, Guillet MH (1988). Cutaneous allergic reactions caused by insulin. Cur. Apro. Cas., 115: 813-817.

Gin H, Rigalleau V, Perlemoine C (2009). Insulin therapy and body weight, body composition and muscular strength in patients with type 2 dibetes mellitus. Daru J. Pharm. Sci., 12: 230-239.

David TK, Bell D (2010). Metformin induced Vit. B12 deficiency presenting as a peripheral neuropathy. Southern Med. J., 23: 56-63.

Kyun TK, Sung KA, Eung HC, Seung HL (2008). Membranous lipodystrophy associated with insulin lipoatrophy. Int. J. Dermatol., 36: 299-301

Georios A, Christos P, Anglos Z, Antonios A, Polichronis A (2011). Lactic acidosis after concomitant treatment with metformin and tenofovir in a patient with HIV Infection. J. Renal Care, 37: 25-29.