ORIGINAL ARTICLE

A COMPARATIVE STUDY OF THE EFFECTS OF HYPOGLYCEMIC AGENTS ON SERUM ELECTROLYTES IN THE DIABETIC PATIENTS

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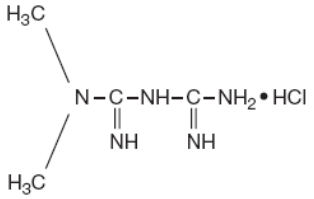
ABSTRACT
30 patients comprised of 3 equal groups which were given 3 types of treatment. **Group I** given metformin HCl (1+1), maintained a sugar level of 129-340mg/100ml**. Group II** given glibenclamide(1+1), maintained a sugar level of 120-325mg/100ml. **Group III** given a combination of both drugs, maintained a sugar level 112mg - 46mg/100ml. The most suitable of the 3 was the last treatment. Serum electrolytes were measured in all the three groups. Patients taking metformin HCl and glibenclamide showed non significant low sodium with high potassium values respectively. When used in combination, they maintained normal values. On the other hand, serum calcium levels were significantly high in patients taking metformin HCl only; when compared with glibenclamide. However, when both drugs were given to patients, serum calcium remained at normal levels.

Keywords: Oral hypoglycemic agents, sulfonylureas, type II diabetes, metformin.

INTRODUCTION

Metformin HCl

Glucophage (Metformin hydrochloride tablets) are oral antihyperglycemic drugs used in the management of type II diabetes. Metformin HCl is a white to off-white crystalline compound with a molecular formula of C4 H11 N5.HCl and a molecular weight of 165.63. The structural formula is as shown:



Metformin HCl is freely soluble in water and is practically insoluble in acetone, ether and chloroform. It is the only oral antidiabetic approved by FDA and EMEA for children above 10 years of age.

Metformin HCl is used alone as initial therapy or in combination therapy with a sulfonylurea.A reduction of diabetic complications has been shown in overweight type II diabetic patients treated with metformin HCl as first line therapy who have not responded to diet, weight reduction and exercise (Kirpichnikov *et al*., 2002).

Metformin HCl decreases intestinal absorption of glucose, suppresses glucose production, especially hepatic gluconeogenesis and improves peripheral tissue insulin sensitivity by increasing peripheral glucose uptake and utilization (Kirpichnikov *et al*., 2002). With metformin HCl therapy insulin secretion remain unchanged while, fasting insulin levels and day long plasma insulin response may actually decrease (Katzung, 1998).

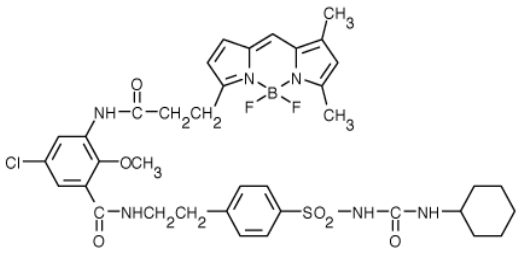
Care is advised to use metformin HCl in case of renal insufficiency.The patients on long term metformin HCl therapy should have a prophylactic annual serum vitamin B12 evaluation. Recent work has indicated the possibility of an existing interaction between metformin HCl and certain anticoagulants. Some adjustment of anticoagulant dosage may therefore be necessary (Kumar and Clark, 2002).

Gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain and loss of appetite are very common. A rare but important complication associated with this drug is the development of lactic acidosis (DePalo *et al*., 2005).

Glibenclamide

Daonil (Glibenclamide) is a member of the sulfonylurea family which is used for the treatment of non – insulin – dependent type II diabetes mellitus. Its molecular formula is C44 H42 BCIF2 N6 O7 S2 with molecular weight 915.23.

The structural formula of glibenclamide is:



Glibenclamide is the drug of choice to initiate treatment in non–insulin–dependent diabetes mellitus when diet and weight control fails (Arayne *et al*., 2004). It is usually administered as a single daily dose of 2.5 mg preferably

given 30 minutes before breakfast or the first main meal. For requirements of greater than 10mg daily, divided doses may be prescribed usually as a twice-daily regime (Rendell, 2004). Glibenclamide is not indicated in children, as Type II diabetes mellitus is not usual in this age group.

Glibenclamide is a potent oral hypoglycemic agent. It lowers blood glucose concentration in diabetic and non-diabetic patients by stimulating the release of insulin from the pancreatic beta cells (Rendell, 2004). Other mechanisms of the hypoglycemic action associated with short-term therapy appear to include reduction of basal hepatic glucose production and enhancement of peripheral insulin action at post receptor sites. The principle mechanism appears to be due to inhibition of hepatic glucose production and enhanced peripheral sensitivity to insulin.

Long term use of glibenclamide produces hypoglycemia as a result of reduction in insulin producing capacity by the pancreatic beta cells (Rendell, 2004). Gastrointestinal effects e.g. nausea, vomiting, epigastric fullness, heartburn, anorexia, dyspepsia and diarrhea are the most common adverse reactions (Katzung, 2002). Anemia, leucopenia, thrombocytopenia, agranulocytosis, hemolytic anemia, bone marrow aplasia and coagulation disorders have been reported with sulfonylureas (Kumar and Clark, 2002).

In the present study an attempt has been made to find out the efficacy of metformin HCl- glibenclamide based combined therapy over the treatment with single oral hypoglycemic agent in patients of type II diabetes mellitus.

MATERIALS AND METHODS

Blood samples of 30 diabetic patients receiving oral antihyperglycemic treatment for more than one year; were collected from Liaquat National Hospital, Karachi. Patients were divided into 3 groups, according to three specific treatments.

Group I: This was comprised of 10 diabetic patients each taking a dose of metformin HCl (Glucophage) twice a day (1+1).

Group II: This was also comprised of 10 diabetic patients taking 5mg glibenclamide (Daonil) morning and evening (1+1) daily.

Group III: This group was again comprised of 10 diabetic patients taking 5 mg glibenclamide and 500mg metformin HCl morning and evening.

Blood samples along with history of each patient, including complete information of the drugs taken, were recorded.

Blood sampling

Blood was drawn from the cubital vein of the arm of each patient by a 3CC disposable syringe and transferred into C.P. bottle and finally into centrifuge tube. After centrifugation (Model YJ03- 043-4000) for 5 minutes at 25000 rpm, serum was transferred in eppendorf tubes and stored at 4°C in refrigerator. Simultaneously blood glucose was measured by the help of a glucometer (i.e., Roche, Glucotrend 2).

Bio-chemical estimations

Serum was used for the determination of electrolytes i.e. sodium (Na^+), potassium (K^+) and calcium (Ca^{++}) by using commercially available biochemical kits (Randox, Cat. No. NA 7167; PT 1600; CA 590). The absorbance of samples was read on the photoelectric colorimeter (Model AE-11M ERMA INC.). The collected data was analyzed statistically by performing two-way ANOVA.

RESULTS

Glucose

In group I, the estimated range of blood glucose in patients given metformin HCl (1+1) was 129 - 340 mg/ 100 ml. The effect of metformin HCl was not similar in all the individuals. 4 patients out of 10 showed 120-180 mg/100 ml of blood glucose; the other 4 showed 210 - 268 mg/100 ml blood glucose, and the remaining 2 showed over 300 mg/100 ml of glucose (fig. 1).

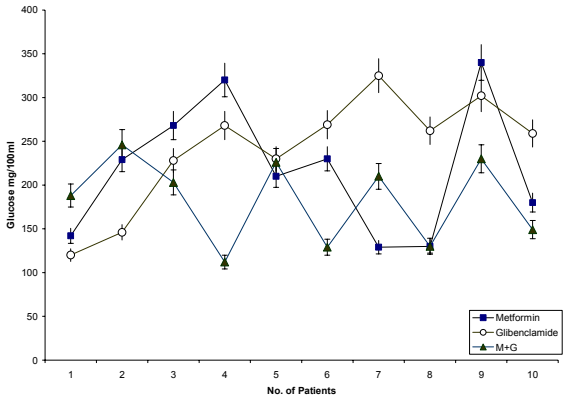


Fig. 1: The separate and combined effect of metformin and glibenclamide on blood glucose.

In group II, patients treated with glibenclamide (1+1) also showed a variable effect. Only 2 patients showed blood glucose of 120-146 mg/100 ml. 6 patients of this group showed glucose level of 228-269 mg/100 ml and only 2 patients showed a blood glucose level over 300 mg/100 ml (fig.1).

In group III, 10 patients treated with glibenclamide and metformin HCl (1+ 1) showed a different variation. 5 patients showed glucose level 112-188 mg/100 ml of blood. Whereas 5 patients showed 203-249 mg/100 ml blood glucose (fig. 1); however when all the groups were compared; they showed statistically a non-significant difference in the blood glucose level.

Sodium (Na^+)

In group I, the blood Na+ ranged from 120–148 mmol/l. Altogether 10 patients were taking metformin HCl (1+1) daily; 6 out of them showed blood Na^+ values lower than that of the normal level i.e. 140 mmol/l (fig. 2).

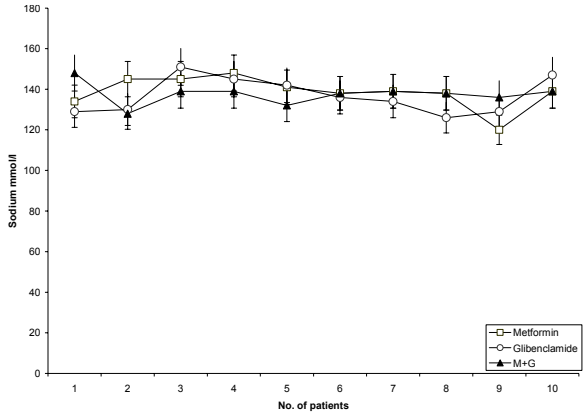


Fig. 2: The separate and combined effect of metformin and glibenclamide on blood sodium.

In group II, 10 patients were treated with glibenclamide. 4 of them showed blood Na^+ ranging from 126-151 mmol/l. However, 6 of them showed Na+ value less than 140mmol/l (fig. 2).

In group III, 10 patients kept on a combination of glibenclamide and metformin HCl, showed Na^+ value ranging from 128-148 mmol/l (fig. 2). When Statistically analysed the data showed a non significant difference in the mean Na^+ concentration of all the groups.

Potassium (K^+)

In group I, blood K^+ levels were estimated in 10 diabetic patients which were using metformin HCl. Blood K^+ levels ranged from 3–5.3 mmol/l (fig. 3).

In group II, blood K+ levels were estimated in the other 10 diabetic patients; taking glibenclamide, showed the blood K+ levels from 3.1–5.4 mmol/l (fig. 3).

In group III, 10 patients administered glibenclamide and metformin HCl showed blood K^+ levels of 3.1–4.6 mmol/l (Fig. 3). All the three groups compared statistically, showed a non-significant difference in the mean K+ concentration.

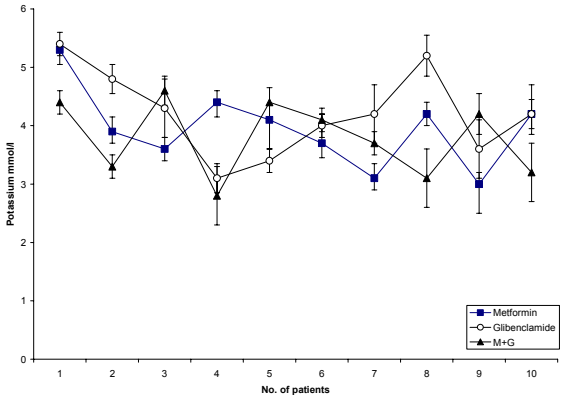


Fig. 3: The separate and combined effect of metformin and glibenclamide on blood potassium.

Calcium (Ca^{++})

Fig. 4 shows that Ca^{++} values of 10 diabetic patients receiving metformin HCl ranged from 0.8–7.94 mmo/l. However, 7 patients showed very high Ca^{++} values; whereas, the remaining 3 patients showed normal Ca^{++} values.

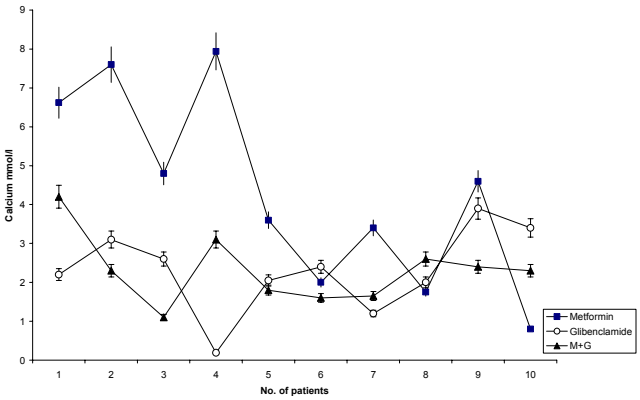


Fig. 4: The separate and combined effect of metformin and glibenclamide on blood calcium.

The Ca^{++} values of 10 diabetic patients receiving glibenclamide only were 1.9–3.9 mmol/l. However, 3 patients showed high Ca^{++} values (fig. 4).

But Ca^{++} values of 10 diabetic patients receiving both these drugs remained in the normal range of 1.1–4.2 mmol/l. The statistical analysis of the 3 types of treatment showed a significant difference ($p< 0.05$) in their mean calcium values.

DISCUSSION

Present study is made to compare and evaluate the efficacy of metformin HCl and glibenclamide combination with the respective monotherapies in patients

with type II diabetes mellitus. Blood glucose, Na^+, K^+ and Ca^{++} were measured in diabetic patients, receiving three different types of treatment for more than one year.

Present observations showed high glucose levels in patients treated with metformin HCl, suggesting that metformin is a poor hypoglycemic agent (Barnett *et al*., 2006). Similarly, the treatment of diabetes with glibenclamide alone is again less effective in maintaining the blood glucose level (Reaven *et al*., 1992). However the patients receiving the combination of glibenclamide and metformin HCl (1 + 1), restricted the blood glucose levels to a lower range (Marre *et al*., 2002; Davidson *et al*., 2004; Blonde *et al*., 2004). This intensified hypoglycemic effect of combined therapy could be expressed by the patients with type II diabetes. The reduced insulin secretion is indeed more important than that of the tissue insulin resistance. In addition, the main problem here is the presence of excessive amount of glucose exterior to the cell membrane (Waller *et al*., 2001). Glibenclamide acts mainly by increasing the release of insulin from the pancreatic beta cells in response to stimulation by glucose (Waller *et al*., 2001) whereas, metformin HCl does not affect insulin secretion, instead it reduces hepatic gluconeogenesis and glucose uptake from the gut (Bruce *et al*., 2006). It seems that hypoglycemic effect adequately controlled following combined therapy is significantly due to the enhanced glucose uptake and decreased hepatic glucose production (Reaven *et al*., 1992).

This study also indicates that, the patients using metformine HCl and glibenclamide did exhibit slightly low Na+ alongwith slightly high K^+ values. This appears to be due to metabolic inhibition of ATP-sensitive K^+ channels by glibenclamide (Ashcroft and Ashcroft, 1992; Bijlstra *et al*., 1996; EriMukai *et al*., 1998; Waller *et al*., 2001). Since, if glucose level rises in diabetic patients, it will increase acidosis by dropping down the concentration of Na^+ to produce a large volume of acidic urine; causing dehydration and loss of Na^+ and Cl^- in urine. Whereas, K^+ moves out of the cells increasingly in exchange for hydrogen ions, leading to hyperkalemia (Hawks, 1988; Franzetti *et al*., 1997). Similarly the patients taking both the drugs in combination, maintained a balanced level of Na^+ and K^+. And Na^+ levels are extremely closely regulated by kidney function. So K^+ is easily filtered in the glomerular portion of the kidneys and most of it is restored through the active transport in the kidney tubules. The rate of excretion is directly affected by the rate of filtration of Na+ in the glomerulus (GFR).

On the other hand patients prescribed metformin HCl 10–30g have evidence of reduced vitamin B12 absorption. Vitamin B12 intrinsic factor complex uptake by ileal cell surface receptors is a common knowledge; and this process is dependent upon Ca^{++} availability. Metformin HCl affects the Ca^{++}-dependent membrane function; because of its, Ca^{++}-dependent ileal membrane antagonism (Bauman *et al*., 2000). Thus patients taking metformin are required to supplement vitamin B12 and folic acid.

However in this study, patients taking metformin HCl showed a very high Ca^{++} value or slightly high Ca^{++} value while taking glibenclamide. The later observation is supported by the investigation made on the isolated guinea pig ventricular myocytes; which showed that glibenclamide increases the intracellular Na^+ by Na^+-K^+ pump and at the same time decreases the Ca^{++} by blocking the L– type Ca^{++} channels (Lee and Lee, 2005). However, Ca^{++} values are maintained to normal when both drugs are taken in combination (fig. 4). Ca^{++} is found mainly in extracellular fluids. If the level of Ca^{++} falls, the parathyroid gland is stimulated to secrete parathyroid hormone (PTH) and if Ca^{++} level rises the thyroid gland releases a hormone called calcitonin. This indicates that when both the drugs are taken simultaneously they affect the parathyroid and thyroid glands to maintain a normal level.

Finally the inability of any single hypoglycemic agent to achieve the improved glycemic control in the majority of type II diabetic patients (Rendell, 2004; Feinglos *et al*., 2005), suggests that combinations of metformin HCl and glibenclamide (i.e., sulfonylurea) are an effective therapeutic option for intensifying oral anti–diabetic therapy to reduce the risk of long term complications (Marre *et al*., 2002; Blonde *et al*., 2004; Davidson *et al*., 2004).

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