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A Review on Drug Related Problems in Type 2 DM with Combination of Sulfonylureas and Biguanides

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ABSTRACT

Increased drug related problems in diabetic patients treated with combinations of high doses of sulfonylureas and metformin was recently reported. This review article is aimed towards the assessment of drug related problems in patients treated with low-doses of sulfonylureas and biguanides. Sulphonylureas the second most commonly used antidiabetic drugs after metformin; there have been concerns regarding the cardiovascular safety of sulfonylureas. These safety concerns initiated with the University Group Diabetes Program conducted in the 1960s, found a sulfonylurea, tolbutamide, where tolbutamide is a first-generation sulfonylurea and was associated with an increased risk of all-cause and cardiovascular problems compared with placebo. Indeed, sulfonylureas have been associated with known cardiovascular risk factors like weight gain, fluid retention, and hypoglycemia. Phenformin, a biguanide, was related to lactic acidosis and withdrawn from use after causing increased risk factors within the University Group Diabetes Program since then, a more modern biguanide, metformin, has risen to its current place because the leading oral therapy for diabetes supported its relative lack of hazard from lactic acidosis and evidence especially from a subgroup of participants in the UK Prospective Diabetes Study, that it can reduce cardiovascular risk and other drug related problems. But there are certain studies showing that combination treatment with metformin and sulfonylurea is more effective, than drugs alone in enabling glycemic control in type 2 diabetes. However, safety of such combinations deserves further investigation.

Keywords: Type2 diabetes mellitus, T2DM, drug related problems, sulfonylureas, biguanides

INTRODUCTION

Diabetes mellitus a large number of world's population is diagnosed with Type2 diabetes mellitus (T2DM). Treatment pattern of T2DM is often started by changing lifestyle and dietary measures are usually the first step. The second step is pharmacological treatment with an oral blood glucose-lowering drug Sulfonylureas were the most commonly prescribed class, but metformin (biguanide) was the commonest prescribed individual drug among oral hypoglycaemic agents (OHA). Determined dose combination of biguanide and sulfonylurea was prescribed frequently [4].

Patients with T2DM are in threat of drug-related problems (DRP), which might come off at any step during the treatment procedure especially those that are having comorbidities and it exert influence in therapeutic outcome. T2DM is related to an increased risk of cardiovascular morbidity and mortality. Although this can be attributed to the long-term complications of T2DM, there has been growing interest in determining whether certain antidiabetic drugs influence this risk. Oral combination therapy with biguanides (metformin) and

sulfonylureas have to be checked. The rationale for the utilization of this mix is predicated on the various sites of action of the 2 sorts of drugs and therefore the possibility for obtaining additive or potentiating effects and reduced drug related problems.

Sulphonylureas is used as monotherapy or in combination with biguanides as well as in combination with other antidiabetic drugs or with insulin. Biguanides (metformin) works by decreasing hepatic glucose production along with enhancing insulin sensitivity in hepatic and peripheral tissues [6]. Whereas sulfonylureas work by stimulating insulin release from the β cells of the pancreas and may moderately improve insulin resistance in peripheral target tissues (muscle, fat cells). On average, this category of drugs reduces glycated haemoglobin A1c (HbA1c) levels by.8-2.0 percent and fasting plasma glucose (FPG) concentrations by 3.3-3.9 mmol/L, with the finest reductions remarked in patients with the highest FPG concentrations at the initiation of therapy [5].

KINETICS AND SIDE EFFECTS

Biguanides work by reducing the assembly of glucose from digestion. Metformin is the only biguanide currently available for treatment of diabetes. Glucophage (metformin) and Glucophage XR (metformin extended-release) are commonly available forms of drugs. Other brands include Fortamet, Glumetza, and Riomet. Metformin is also available in combination with sulfonylureas.

Metformin works by controlling the quantity of sugar in your blood. It has been appear to act via both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent mechanisms; by inhibition of mitochondrial respiration but also perhaps by inhibition of mitochondrial glycerophosphate dehydrogenase, and a mechanism involving the lysosome. There exists another mechanism in which metformin improves glycaemia by acting on the liver via AMPK activation [9]. It doesn't affect the amount of insulin produced, but it increases sensitivity to insulin. This helps cells to take in glucose to use as energy, decreases the production of glucose in the liver, and reduces the concentration of glucose in your bloodstream; thereby decreasing the increased blood sugar levels.

Over time, taking metformin may result in certain drug related problems. The drug on use may block B12 vitamin absorption in the body. It may also cause a serious condition called lactic acidosis with the following symptoms: severe drowsiness, chills, blue / cold skin, muscle pain, fast / difficult breathing, dizziness slow / irregular heartbeat, tiredness, stomach pain with diarrhoea, nausea or vomiting. It is more likely to occur in patients with certain medical conditions like, liver or kidney disease, recent surgery, recent stroke, congestive heart failure, recent heart attack, heavy alcohol use, dehydration, X-ray or scanning procedures that need an injectable iodinated contrast drug and people older than 80 years. Metformin usually does not cause hypoglycaemia; but can cause low blood sugar levels if this drug is used with other anti-diabetic drugs. Hypoglycaemia is more likely to occur with heavy exercise, drinking large amounts of alcohol, or not consuming enough calories from food. Nausea, vomiting, stomach upset, diarrhoea, weakness, or a metallic taste in the mouth may occur rarely. Serious allergic reaction to this drug is rare.

Sulfonylureas apply their hypoglycaemic effects by reviving insulin secretion from the pancreatic beta-cell. Their primary mechanism of action is to lock ATP-sensitive K-channels within the beta-cell cell wall, then initiating a sequence of events which ends up in insulin liberation. Certain recent studies have shown that the beta-cell ATP-sensitive K-channel is a compound of two proteins: a pore-forming subunit (Kir6.2) and a drug-binding subunit (SUR1) which operates as the receptor for sulfonylureas [7].

Sulfonylureas are usually well tolerated drugs as well as the most common

side effect is hypoglycaemia, and is more common with long-acting sulfonylureas such as chlorpropamide and glibenclamide. [8] However, all sulfonylureas may cause hypoglycaemia, usually thanks to an excessive dosage. It is important to remember that hypoglycaemia may persist for many hours and require in-hospital treatment.

Therapeutic doses of chlorpropamide or tolbutamide prompted a hyponatraemic syndrome similarly with that of inappropriate secretion of Antidiuretic hormone (ADH) (serum Na 117 mEq/1). Hyponatremia was due to negative sodium balance disclosed by metabolic studies. Physicians using sulfonylurea in the management of diabetes mellitus must be alert to the possible issues of hyponatremia. [10]

POSSIBLE DRPS

The most important drug related problem of sulfonylureas is hypoglycaemia. According to certain surveys hypoglycaemia manifest at a frequency of 2 cases per 10,000 treatment years. Mortality is high, i.e., about 10%. During treatment with chlorpropamide the syndrome of inappropriate ADH-secretion has been noticed entirely. Hyponatraemia has been detected in 6-10% of diabetics treated with chlorpropamide. Asymptomatic cases of Syndrome of inappropriate antidiuretic hormone secretion (SIADH)-syndrome are quite often. [11]

Chlorpropamide does not change the elimination of extracellular ADH. The drug has a central activities, either by increasing release of ADH or by controlling the inhibitory effect of water loading on liberation of ADH. The drug apply an antidiuretic activity in man. Water loaded diabetes patients on chlorpropamide treatment were found to have a remarkable minor potential to expel a dilute urine than typical subjects. [12] This indicates the antidiuretic action of chlorpropamide, that patients with an impaired ability to integrate and release ADH are more reactive than normal individuals.

The biguanides, metformin, phenformin, and buformin, comprise a class of anti-diabetes drugs developed in the 1950s, only metformin is approved for use today in most countries. Later phenformin and buformin was withdrawn due to increased risk of lactic acidosis.

Lactic acidosis is the most dangerous side effects of biguanides. Occurrence of lactic acidosis is significantly more frequent during treatment with phenformin compared to metformin. Reports reveal that metformin has been reported to lead to lactic acidosis in 0.4 cases per 10,000 treatment years. Mortality is about 30% and mortality of phenformin-associated lactic acidosis is even higher, 70%. [35]

Oral intake of biguanide is related with an increase in blood lactate levels. The increase in plasma lactate concentration with therapeutic doses of metformin is minor, usually < 2 mmol/L, although higher levels may occur. [13] [14] [15] [23] [17] [18] Mechanism in which metformin increases plasma lactate levels corelate with the inhibition of mitochondrial respiration in tissues accountable for lactate removal which results in both accelerated lactate production and lower lactate metabolism.

Vitamin B12- malabsorption is another drug related problem caused by both biguanides, metformin and phenformin (in about 1/3 of the cases). However, symptomatic vitamin B12-deficiency is extremely rare.

CONCLUSION

Although many new drugs have been developed for T2DM, sulfonylureas and biguanides is yet widely accepted as the first-line therapy in clinical practise because of its low prevalence of microvascular and macrovascular incidences, maybe this is due to their lower cost, to the likelihood of mono-dosing and to the presence of an association with metformin in the same tablet and its favourable outcomes on

plasma lipids and body weight [38]. Some of the available combination of sulfonylureas and biguanides are

- Metformin and glipizide (Metaglip)
- Metformin and gliclazide(Glycinorm M)
- Metformin and glyburide (Glucovance)
- Glipizide and metformin(Metaglip)
- Metformin and repaglinide(PrandiMet)
- Metformin and sitagliptin(Janumet)

We can conclude that sulfonylureas should be used in relatively young patients for a limited period of time, whereas the metabolic tolerance of metformin is satisfactory in elderly type II diabetic patients; it may take 3–6 months, in order to rapidly achieve adequate glycemic control. In this way the use of insulin can be postponed, improving the patient's quality of life and the compliance and reducing the cost of anti-diabetic therapy. After 3–6 months, if adequate glycemic control has not been achieved, insulin treatment can be started. On the other hand, if required lower HbA_{1c} reached, replacement of sulfonylureas with other oral anti-diabetic agents can be done, according to the guidelines.

The combination may provide satisfactory glycemic control in diabetes patients treating with for several years, and possibly insulin therapy can be postponed or even avoided. According to an article no particular safety problem is experienced with the combined use of metformin or sulfonylurea i.e., lactic acidosis and hypoglycemia, respectively [28]. It is concluded that more data and clinical studies are required to assess the full clinical potential and the mechanism of action of oral combination therapy.

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