ORIGINAL ARTICLE

SIDE EFFECTS INDUCED BY HYPOGLYCAEMIC SULFONYLUREAS TO DIABETIC PATIENTS - A RETROSPECTIVE STUDY

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Abstract

Sulfonylureas were the first oral hypoglycaemic drugs introduced in therapy and for over 50 years, they represent the first-line treatment for type 2 diabetes mellitus. The most concerning side effects which limit their use are the risk of hypoglycaemia and weight gain. The aim of this study was to analyse the correlation between the side effects induced by the oral hypoglycaemic sulfonylureas and some factors such as drug characteristics, patient's profile and drug interactions. In this study there were enrolled 200 patients treated with sulfonylureas which were monitored for 2 years in terms of side effects. The results showed that 46.5% of the patients have presented one or more side effects; the most frequently reported were weight gain (25.5%), hypoglycaemia (14.5%) and digestive disorders (6.5%). It has been found that the characteristics of drug, the patient's profile and the risk of drug interactions are important factors that contribute to the expression of the reported side effects.

Rezumat

Derivații de sulfoniluree au fost primele hipoglicemiante orale introduse în terapeutică și care, de peste 50 de ani, reprezintă medicația de primă alegere în tratamentul diabetului zaharat de tip 2. Cele mai îngrijorătoare efecte adverse care limitează utilizarea acestora sunt riscul de hipoglicemie și creșterea ponderală. Obiectivul acestui studiu a fost corelarea efectelor adverse induse de către antidiabeticele orale din această clasă cu diferiți factori, precum caracteristicile medicamentului, profilul pacientului și interacțiunile medicamentoase. În cadrul acestui studiu au fost incluși 200 de pacienți tratați cu hipoglicemiante derivați de sulfoniluree care au fost urmăriți pe o perioadă de 2 ani în ceea ce privește efectele adverse. Dintre pacienții urmăriți, 46,5% au prezentat unul sau mai multe efecte adverse, cel mai frecvent raportate fiind creșterea ponderală (25,5%), hipoglicemia (14,5%) și tulburările la nivel digestiv (6,5%). Studiul pune în evidență faptul că tipul medicamentului, profilul pacientului și riscul interacțiunilor medicamentoase reprezintă factori importanți care participă la apariția efectelor adverse raportate.

Keywords: diabetes mellitus, sulfonylureas, side effects, susceptibility factors

Introduction

Diabetes mellitus (DM) is a complex disease which has become one of the most serious public health problems based on its increasing incidence, devastating complications and even concerning the cost of anti-diabetic therapy [12]. Moreover, according to United Kingdom Diabetes Prospective Studies, 40% of patients with type 2 diabetes presented signs or symptoms of microvascular complications at diagnosis, suggesting that the disease was installed many years ago [9, 10].
Considering that the intensive glycaemic control is essential in reducing the incidence of acute and chronic complications, the pressure to find new hypoglycaemic agents is increasing and currently in therapy are available nine classes of drugs [15]. Their different mechanisms of action increase the efficacy, being correlated with different metabolic profiles, but also with several side effects [2, 21].
Hypoglycaemic sulfonylurea drugs were the first oral anti-diabetic agents used in the treatment of type 2 DM. For over 50 years they represent the first choice medication when diet, physical exercise and weight loss did not manage to maintain an optimal glycaemic control [14].
Despite the extensive use of these drugs and their recommendations by the official guidelines, there are concerns regarding their safety profile [6]. The most serious side effects are hypoglycaemia [2, 19] and weight gain [2, 19]. Other risks are hepatotoxicity [2], hematologic dyscrasias [2], myocardial infarction [2], allergic reactions [2, 19] and gastrointestinal disturbances [2].

The aim of this study was to correlate the most common side effects associated with oral hypoglycaemic sulfonylureas with the characteristics of the sulfonylurea drug, the patient's characteristics or behaviours and with the possible interactions with other drugs administered simultaneously.

Materials and Methods

A retrospective study including 200 diabetic patients was performed. The patients were ambulatory treated with anti-diabetic sulfonylureas, alone or in combination with other oral hypoglycaemic drugs, at the "Providența" Medical Centre – Iași, Romania. The data included in the observation sheets were statistically analysed using MS Excel software and Chi Squared Test of Independence ($p < 0.05$). The profile of the patient was analysed in terms of the demographical characteristics (age, sex, area of origin), the presence of physiological, pathological and behavioural risk factors for diabetes and diabetes related complications (overweight or different degrees of obesity, age, alcohol consumption, smoking), the duration of the disease, associated pathologies and other drugs taken in combination with hypoglycaemic drugs, the presence of microvascular and macrovascular complications and their correlations with the efficiency of the glycaemic control.

The study was focused on the correlation between side effects reported by the patients during the 2 years of monitoring (January 2013 – December 2014) and different parameters such as the characteristics of the antidiabetic drug, patient's condition (in terms of particular characteristics or behaviours that could increase the risk of side effects) and other drugs used (with a risk of interactions leading to a specific side effect).

The study was approved by the "Grigore T. Popa" University Ethics Committee.

Results and Discussion

The age of the patients studied ranged between 37 years and 93 years with an average of 67.29 ± 9.95 years. The group presented a balanced repartition by gender, 48.5% being women and 51.5% being men. Concerning the distribution area, 62.5% of them came from urban areas and 37.5% from rural areas. The most common side effects presented by patients were hypoglycaemia, weight gain and digestive disorders.

Hypoglycaemia

Hypoglycaemia associated with anti-diabetic therapy represents the main risk for sulfonylureas, being a barrier in maintaining an optimal glycaemic control for long term [11]. Hypoglycaemia is defined as a condition when low levels of plasma glucose expose the patient to significant risks. The most widely accepted value to define hypoglycaemia is under 70 mg/dL [3]. This value is considered the threshold for activation of counter regulatory response in non-diabetic individuals and the superior limit at which a response to hypoglycaemia changes occurs [8, 17].

The incidence of hypoglycaemia in type 2 diabetic patients depends on several factors and increases with the evolution of the disease. Data from literature state that 20% of patients treated with sulfonylureas have presented hypoglycaemia compared to the 36.5% value observed for the patients treated with insulin only [6]. Although less frequently, hypoglycaemia induced by sulfonylureas is more prolonged and is associated with a higher rate of mortality than that induced by insulin administration [7].

In this study 29 patients from 200 have presented hypoglycaemia during the monitoring period, which means an incidence of 14.5% (Figure 1).

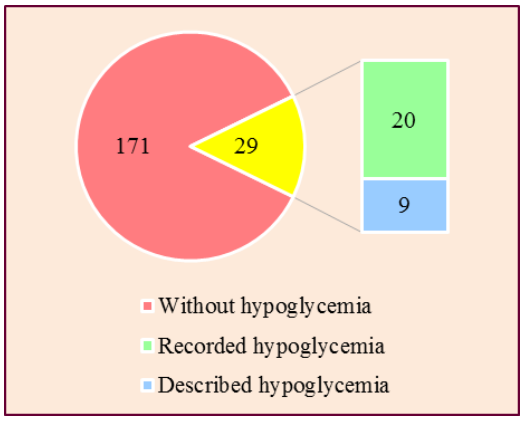

Figure 1.
Incidence of hypoglycaemia in the studied patients

Taking into account that hypoglycaemia is a multifactorial side effect is important to study it in relation with different factors such as drug's characteristics, patient's condition, compliance and drugs interactions.

Hypoglycaemia correlated with the type of sulfonylurea

The pharmacokinetic profile of the drug, especially the half-life, is strongly related with the risk of hypoglycaemia [1]. However it is important to be noticed that the severity of hypoglycaemia is not always related with plasma levels of sulfonylureas. These drugs can increase the sensitivity to insulin which may result in the stimulation of insulin secretion even if their blood concentration is decreased. In this case it is difficult to predict the severity of hypoglycaemia [2, 5]. We found that from 29 patients with hypoglycaemia, 14 of them were treated with glimepiride, 10 with gliclazide, 4 with glibenclamide and 1 with gliquidone (Table I).

Table I

Incidence of hypoglycaemic events related to the type of sulfonylurea

Drug	Number of patients treated with a specific sulfonylurea	Number of patients which presented hypoglycaemia	Incidence (%)
gliclazide	95	10	10.5%
glimepiride	97	14	14.4%
gliquidone	4	1	25%
glibenclamide	4	4	100%

It can be noticed that all patients treated with glibenclamide have presented hypoglycaemia; our results being in agreement with other data from the literature [2]. The high hypoglycaemic risk for glibenclamide could be explained by its pharmaco-kinetic profile. This sulfonylurea has a long half-life and longer duration of action that could be responsible for its accumulation [6].

Gliclazide and gliquidone are drugs with low risk to produce hypoglycaemia, having a short and medium duration of action respectively and their metabolites are inactive or have reduced activity [19]. In our study the incidence of hypoglycaemia for gliclazide was 10.5%, while for gliquidone was 25%. Although glimepiride is a long-acting drug, it is less incriminated in inducing hypoglycaemia, probably due to better modulation of insulin release [6]. In case of glimepiride the incidence of hypoglycaemia in this study was found to be 14.4%. In reference with the literature data [2] the results of our study were higher, and the differences could be explained taking into consideration other factors such as patient's profile and drug interactions.

Hypoglycaemia correlated with the patient's profile

Patient's profile includes characteristics that may represent susceptibility factors for the occurrence of hypoglycaemia. It was found that for elderly patients (over 60 years) treated with sulfonylureas, the risk of hypoglycaemia is with 36% higher than in case of young adults [1]. Taking into account the fact that these drugs are metabolized in the liver and eliminated by the kidney, the damage of these organs can also increase the incidence of hypo-glycaemia [1]. In elderly patients, hypoglycaemia can be difficult to recognize because the specific symptoms may be absent, has lower intensity or is inadequately interpreted.

All 29 patients who have presented hypoglycaemia were over 60 years and 6 of them (20.68%) had different forms of impaired hepatic function (hepatic steatosis, chronic hepatitis) (Figure 2).

Hypoglycaemia can also be the result of some particular conditions related to drug administration including reduced food intake, intense or prolonged physical exercise and alcohol consumption [1, 2]. In our study, of those 29 patients which have recorded hypoglycaemia, 3 cases (10.34%) were associated with intense physical exercise, 4 cases (13.79%) were associated with reduced food intake and 2 cases (6.89%) were associated with chronic alcohol consumption (Figure 2).

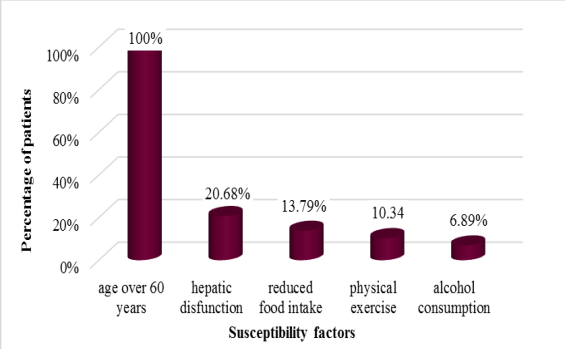

Figure 2.
Incidence of hypoglycaemic events correlated with patient's profile

Hypoglycaemia correlated with potential drug interactions

Another cause which can contribute to the occurrence of hypoglycaemia is represented by drug interactions between sulfonylureas and other drugs that are co-administered. The possible mechanisms involved are: the displacement from the binding sites of plasma proteins and increasing the free fraction responsible for the pharmaco-toxicological effect; increasing of half-life through inhibition of hepatic metabolism or renal excretion; improving the effects of sulfonylureas through own effect of associated drug on the carbohydrate metabolism [1, 2, 13, 20]. Table II summarizes the main drug interactions of the sulfonylureas that can lead to hypoglycaemia.

In the performed study, 6 patients (20.68 %) from the hypoglycaemia cases didn't have co-administrated drugs. It is important to notice that 4 of them were under treatment with glibenclamide and the other two were under treatment with glimepiride.

The drugs which were co-administered with sulfonylureas were β_1-adrenergic receptor blockers, angiotensin converting enzyme (ACE) inhibitors, fibrates and non-steroidal anti-inflammatory drugs (NSAIDs). From the cases of reported hypoglycaemia 9 patients (31.03%) received as associated drug to sulfonylurea a β_1-adrenergic receptor blocker, 9 patients (31.03%) received an ACE inhibitor and 5 patients (17.24%) received a fibrate.

Table II

Drug interactions between sulfonylureas and other drugs with risk of hypoglycaemia

The drug involved in interaction	Mechanism of interaction
Non-steroidal anti-inflammatory drugs (NSAIDs)	Displacement from plasma proteins, inhibition of hepatic metabolism, reduced renal excretion
Salicylates	Displacement from plasma proteins, reduced renal excretion, own hypoglycaemic effect
Coumarin anticoagulants	Displacement from plasma proteins, inhibition of hepatic metabolism
Lipid-lowering (fibrates)	Displacement from plasma proteins
Allopurinol	Inhibition of hepatic metabolism, reduced renal excretion
β_1-receptor blockers	Acting on carbohydrate homeostasis, masking the symptoms of hypoglycaemia
Angiotensin converting enzyme (ACE) inhibitors	Unknown mechanism
Antibiotics (chloramphenicol)	Displacement from plasma proteins, inhibition of hepatic metabolism
Antimicrobial sulphonamides	Inhibition of hepatic metabolism, displacement from plasma proteins, reduced renal excretion
Antiparkinsonian agents(levodopa)	Acting on carbohydrate homeostasis
H_2-receptor blockers (ranitidine)	Inhibition of hepatic metabolism (probably)
Antifungal agents (miconazole, fluconazole)	Inhibition of hepatic metabolism
Antibiotics (ciprofloxacin)	Inhibition of hepatic metabolism
Loop diuretics (furosemide)	Unknown mechanism
Monoamine oxidase inhibitors (MAOIs)	Unknown mechanism
Peripheral vasodilators (pentoxifylline)	Unknown mechanism
Antihypertensive drugs (clonidine, guanethidine, reserpine)	Inhibition of adrenergic transmission

It should be mentioned that 6 patients were taking at the same time a β_1-adrenergic receptor blocker and an ACE inhibitor, increasing the risk of hypoglycaemia.

The NSAIDs can increase the risk of hypoglycaemia by displacing sulfonylureas from the binding proteins and by reducing the hepatic metabolism or renal excretion, depending on the drug. In the study carried out, chronic administration of NSAIDs was reported in 4 cases (13.79 %), but the number could be higher knowing that NSAIDs are often used without prescription. It should also be noted that for 11 cases of reported hypoglycaemia, the treatment included more than 2 drugs susceptible of interactions.

Concerning the correlation of drug interactions with the risk of hypoglycaemia, a statistically significant dependence was found for chronic administration of NSAIDs (X^2: calculated 13.57 *vs.* theoretical 6.63, with a significance level of 0.01). For β-adrenergic receptor blockers, ACE inhibitors and fibrates, the results showed no statistically significant dependence.

Weight gain

Another barrier in maintaining a long term glycaemic control with sulfonylureas is weight gain, which is estimated to be between 2 and 5 kg, depending on patient's characteristics and patient's effort. This weight gain may induce insulin resistance and consequently the benefits of these drugs are reduced. Even if the weight gain is less severe than hypoglycaemia having a reduced clinical impact, this side effect represents a discouraging factor in a population already prone to obesity or that struggles to lose weight.

It is considered that weight gain appears as consequence of the increased plasma insulin levels [4]. Another mechanism involved is the direct metabolic effect of sulfonylureas on adipocytes, which are expressing specific receptors; their activation lead to increasing of intracellular Ca^{2+} levels and consequently the lipogenesis is stimulated [18].

In our study, weight gain was recorded in 25.5% of cases (51 patients). Referring to the correlation between the type of sulfonylurea and weight gain, more than a half of these patients (32 cases) were treated with glimepiride (3 - 4 mg daily), 18 cases were associated with gliclazide (60 mg daily) and 1 case with gliquidone (30 mg daily) (Figure 3).

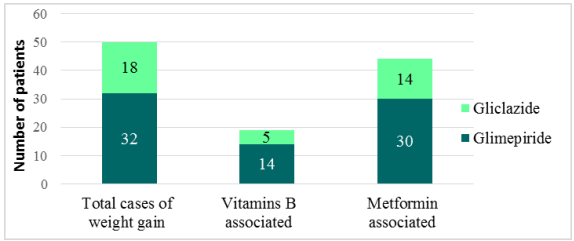

Figure 3.

Incidence of the cases of weight gain correlated with the sulfonylureas and drugs associated

The statistical analysis showed a more significant dependence between the treatment with glimepiride (X^2: calculated 5.56 *versus* theoretical 3.84, with a significance level of 0.05) than with gliclazide

(X^2: calculated 4.08 *versus* theoretical 3.84, with a significance level of 0.05) and weight gain.

It is also important to notice that 19 patients (37.25%, 14 patients treated with glimepiride and 5 patients with gliclazide) from those 51 cases received vitamins of the B group (B_1, B_6, B_{12}) as associated drugs. These drugs were indicated to ameliorate the symptoms of diabetic neuropathy and are known to increase appetite and to induce weight gain. Also, 44 patients (86.27%) from those 51 cases received metformin as associated drug which is known to promote the weight loss [4]. The co-administration of vitamins from the B group and metformin was found to have no statistically significant dependence related to weight gain.

Digestive disorders

The literature data support that sulfonylureas are also associated with digestive disorders [2]; more frequently this side effect is reported by patients treated with metformin, with a frequency of 10 - 15% [4]. In the studied group digestive disorders were reported in 6.5% of patients (13 cases) described as abdominal discomfort, epigastric pain, nausea and diarrhoea. All these patients received metformin in association with a sulfonylurea and in 6 cases acarbose, an α-glucosidase inhibitor, with risk of gastrointestinal side effects. No statistically significant dependence between a specific drug associated to sulfonylureas and digestive disorders was observed.

Other side effects

In the group of the studied patients there were reported other side effects as insomnia, associated with B vitamins and headache, associated with metformin. Liver damage is a problem that is difficult to quantify and to correlate with sulfonylureas due to the presence of chronic liver diseases as associated pathologies and the co-administration of drugs potentially hepatotoxic, in particular statins. The liver toxicity of statins is controversial, there are studies that support a favourable evolution of the hepatic function under treatment with statins, even for patients with C hepatitis [16, 22].

Conclusions

A retrospective study including 200 diabetes patients treated with sulfonylureas was performed. The patients were monitored during January 2013 - December 2014, in terms of side effects and their correlation with several susceptibility factors such as the type of sulfonylurea, patient's profile and the drugs associated.

The results showed that 53.5% of patients reported no side effect while 46.5% of patients presented one or more side effects. The most frequently reported was the weight gain (25.5%), followed by hypoglycaemia (14.5%) and digestive disorders (6.5%). Sulfonylureas are considered drugs with low therapeutic index because of their pharmaco-toxicological profile. But it is important to highlight that several factors, as patient's profile and drugs associated, can contribute to the side effects associated with sulfonylureas.

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