HYPOGLYCEMIA INDUCED BY ANTIDIABETIC SULFONYLUREAS

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HYPOGLYCEMIA INDUCED BY ANTIDIABETIC SULFONYLUREAS (Abstract): Diabetes mellitus is a major health problem due to its increasing prevalence and life-threatening complications. Antidiabetic sulfonylureas represent the first-line drugs in type 2 diabetes even though the most common associated risk is pharmacologically-induced hypoglycemia. In the development of this side effect are involved several factors including the pharmacokinetic and pharmacodynamic profile of the drug, patient age and behavior, hepatic or renal dysfunctions, or other drugs associated with a high risk of interactions. If all these are controlled, the risk-benefit balance can be equal to other oral antidiabetic drugs. Keywords: TYPE 2 DIABETES MELLITUS, SULFONYLUREAS, HYPOGLYCEMIA, SUSCEPTIBILITY FACTORS.

Nowadays diabetes mellitus (DM) has become one of the most challenging health problems due to its remarkable increase in incidence in both developed and developing countries (1, 2). The International Diabetes Federation stated that in 2013 382 million people had diabetes and this number is expected to rise to 582 million in 2035 (3).

At the same time, for researchers DM is still an open subject, both in terms of understanding and elucidating its pathophysiological mechanisms and in developing new drugs for type 2 diabetes with a more advantageous pharmacotoxicological profile.

In terms of biochemistry and pathophysiology, DM is a chronic metabolic disorder characterized by disturbances of carbohydrate, lipid and protein metabolism. This disorder appears to be due to deficiency in insulin secretion by pancreatic β cells, associated or not with insulin resistance in peripheral tissues, leading to elevated blood glucose levels (2, 4, 5).

DM is a silent disease and if undiagnosed or untreated for a long time it can lead to serious macrovascular and microvascular complications. It can be stated that DM has become a life-threatening disease due to its complications, being the fourth leading cause of death in humans (2, 6).

Taking into consideration the fact that an intensive glycemic control is essential in reducing the development and progression of diabetes complications, the pressure to discover new antidiabetic agents has increased and at the moment nine classes of
medications are available for type 2 DM. (4, 7-9). The different mechanisms of action of the various classes of hypoglycemic drugs make combined therapy feasible and give different metabolic and adverse effect profiles (10).

THE PLACE OF SULFONYLUREAS IN THE TREATMENT OF TYPE 2 DIABETES

Hypoglycemic sulfonamides were the first oral antidiabetic agents used in the treatment of type 2 DM (11, 12); they are the first-line medication in patients with moderate diabetes when diet, physical exercise and weight loss do not manage to keep an optimal glycemic control (9, 13).

All these drugs have in common the phenyl-sulfonyl-urea sequence which gives them the hypoglycemic properties; the R and R₁ radicals modulate the pharmacokinetic and pharmacotoxicological profile (14) (fig. 1).

Fig. 1. General chemical structure of hypoglycemic sulfonyleurases

Hypoglycemic sulfonyleurases act by closing ATP-sensitive K⁺ channels with reduction of K⁺ efflux and depolarization of β-cells membrane. Consequently, voltage dependent Ca²⁺ channels are opened, Ca²⁺ influx is increased and phosphorylation reactions are stimulated, leading to the release of insulin from pancreatic β-cells (2, 5, 10, 14, 15).

Despite the extensive use of these drugs, recommendations in official guidelines and pathophysiologic plausibility, there are concerns regarding their safety profile (16); the most troubling adverse effects are hypoglycemia (2, 10, 14) and weight gain (2, 10); other risks are hepatotoxicity (4, 10, 17), hematologic dyscrasias (10, 14), myocardial infarction (10, 13, 15, 18), allergic reactions (2, 10), and gastrointestinal disturbances (10).

SULFONYLUREAS-INDUCED HYPOGLYCEMIA

Pharmacologically-induced hypoglycemia is the major risk in patients using sulfonyleurases for the treatment of type 2 DM and a major barrier in maintaining a good long-term glycemic control (19). If weight gain is a side effect generally accepted and considered „the price to be paid for normalization of blood glucose” (10), hypoglycemia caused by sulfonyleurases is a major concern because of its severe consequences.

It is known that an optimal glycemic control plays an essential role in preventing chronic microvascular complications; achieving this objective without the risk of hypoglycemia is a priority in the early stages of diabetes (8).

Current recommendations advise individualizing the objective of glycemic control based on patient features and diabetes evolution; in young patients without longstanding diabetes and associated comorbidities a strict glycemic control is recommended. This control refers to an HbA1c level less than 6.5%. In older patients with cardiovascular diseases and microvascular complications an HbA1c level of 7% - 8% is considered adequate in order to prevent hypoglycemia (8).

Hypoglycemia can be defined as a condition in which the low blood glucose level exposes the individual to serious damages (8). The most accepted value to define
Hypoglycemia induced by antidiabetic sulfonylureas

Hypoglycemia is 70 mg/dl because this is the threshold for activation of counter regulatory mechanism in non-diabetic individuals and the superior limit at which the counter regulatory response to hypoglycemia changes (20) (tab. I).

TABLE I
Classification of hypoglycemia depending on severity (8, 20)

<table>
<thead>
<tr>
<th>Type of hypoglycemia</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypoglycemia</td>
<td>Requires external assistance for recovery</td>
</tr>
<tr>
<td>Documented symptomatic hypoglycemia</td>
<td>Typical symptoms and a measured capillary glucose level &lt; 70 mg/dl</td>
</tr>
<tr>
<td>Asymptomatic hypoglycemia</td>
<td>Capillary glucose level &lt; 70 mg/dl without typical symptoms</td>
</tr>
<tr>
<td>Probable symptomatic hypoglycemia</td>
<td>Typical symptoms of hypoglycemia not accompanied by measurement of capillary glyemia</td>
</tr>
<tr>
<td>Pseudohypoglycemia</td>
<td>Symptoms of hypoglycemia with capillary glyemia values &gt; 70 mg/dl</td>
</tr>
</tbody>
</table>

Symptoms. The symptoms of hypoglycemia vary between individuals and they are generated by activation of the adrenergic system and by the direct effect of glucose deprivation on the brain. The release of counter regulatory hormones (glucagon and adrenaline), the adrenergic symptoms and the development of central nervous system dysfunctions are triggered at specific levels of blood glucose. There are 11 most common symptoms experienced during hypoglycemic episodes: sweating, palpitations, shaking, hunger, confusion, drowsiness, strange behavior, difficulty in speaking, incoordination, headache, nausea (19, 21).

Incidence. The incidence of hypoglycemic events in type 2 DM depends on several factors and increases with disease progression, degree of insulin deficiency, as well as in cases of treatment with sulfonylureas and insulin (8). Sulfonylureas cause much more hypoglycemia than it is recognized, with an annual prevalence of severe episodes of 7% (19). Studies reported that up to 20% of sulfonylurea-treated patients experienced symptoms suggestive of hypoglycemia. During the first year of United Kingdom Prospective Diabetes Study at least 30% of glibenclamide-treated patients experienced hypoglycemia. After a follow-up period of 10 years the annual incidence of patients with at least one hypoglycemic event was 11% with chlorpropamide, 17.7% with glibenclamide, and 36.5 % with insulin therapy (16). However, severe hypoglycemic episodes appear to be more prolonged and associated with greater mortality when induced by sulfonylureas than by insulin (22).

Despite differences between the studies, sulfonylurea-induced hypoglycemia has a significant incidence and it is a major concern because of its considerable economic impact on health care system.

Susceptibility factors. Sulfonylurea-induced hypoglycemia is a multifactorial adverse effect where drug features; patient features and patient behavior are intermingled. It is difficult to establish in which proportion each factor leading to hypoglycemia is involved (5).
which is linked to long-lasting hypoglycemia (23).

It is interesting to note that there is not always a relationship between the duration of action and blood concentrations; sulfonylureas may make the cells more sensitive to insulin and when the concentration is falling, stimulation of insulin secretion can continue and it is difficult to predict for how long the hypoglycemic effect will last (10).

The majority of reported cases of hypoglycemia were on chlorpropamide or glibenclamide (12, 16) which are long-acting sulfonylureas whose metabolism can lead to accumulation. Glipizide, gliclazide and gliquidone are less likely to cause hypoglycemia because they are short-acting drugs and their metabolites are inactive or have minimal hypoglycemic effect (2). Although glimepiride has a long duration of action, there were fewer hypoglycemic reactions compared with glibenclamide, probably due to a better modulation of insulin release (16) (tab. II).

As to patient features, there are several susceptibility factors leading to sulfonylurea-induced hypoglycemia including age, liver, renal and cognitive impairment (5, 24). The risk of hypoglycemia among elderly patients treated with sulfonylureas is 36% greater than in younger adults; in this group of patients glimepiride and glipizide are preferred due to their less hypoglycemic potential (25). In a study of 57 patients with type 2 DM who experienced glibenclamide-induced hypoglycemia, more than 90% were older than 60 years and more than 70% above 70 years (16).

In the elderly patients the elimination half-life is longer for most sulfonylureas and patients older than 60 years are particularly at risk. These drugs are metabolized in the liver and eliminated from the circulation via the kidneys (12); thus, renal and hepatic failures are important contributing factors depending on the drug involved (23).

Hypoglycemia may be difficult to recognize in old patients because the characteristic warning symptoms could be absent or not well interpreted but also in patients on β-adrenergic blockers (10).

Taking these into consideration, the most frequent contraindication for sulfonylureas is the elderly diabetic patient with renal or kidney disease; if prescribed, there are preferred short-acting drugs, with a moderate hypoglycemic effect and without active metabolites (26).
Hypoglycemia induced by antidiabetic sulfonylureas

Not only the sulfonylurea is responsible for hypoglycemia, but also the circumstances of drug administrations; reduced food intake, restricted carbohydrate intake, severe or prolonged physical exercise and alcohol consumption are the most common predisposing factors (10, 23).

Finally, another cause of hypoglycemia which cannot be overlooked is represented by drug interactions. Most drugs have been reported to interact with sulfonylureas; these interactions result from changes in the pharmacokinetic profile of sulfonylureas (absorption, displacement from plasma proteins, alterations in their metabolism) or are caused by drugs that affect blood glucose levels (23, 27).

CONCLUSIONS

The treatment of type 2 diabetes mellitus remains a challenge given the necessity to maintain an optimal glycemic control without the risk of hypoglycemia. Despite their increased risk of hypoglycemia, sulfonylureas still occupy a central position in the recommendations of many guidelines.

However, when choosing a specific treatment for diabetes, it is necessary to take account of patient preferences and comorbidities as well as all conditions that may be associated with a sulfonylurea-induced hypoglycemia. If all these procedures are being followed the risk-benefit balance for sulfonylureas is not worse than for others oral hypoglycemic agents.

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