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Updated Insulin Secretagogues (Sulfonylureas and Meglitinides) Treatment for Type 2 Diabetes

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Description

A sulfonylurea drug and meglitinide or glinide (an insulin secretagogue) are two different classes of oral anti-diabetic drugs, but they share a common mechanism of action and both stimulate pancreatic beta cells to stimulate insulin. Sulfonyl ureas are the classic first-line or second-line treatment for patients with type 2 diabetes and have been widely used since their introduction in clinical practice in the 1950s. These are used as a reference to compare the efficacy and safety of other hypoglycemic agents except insulin. Meglitinides stimulate insulin release by a similar mechanism, but they have different subunit binding sites, faster absorption and faster stimulation for insulin secretion. However, more frequent dosing is required.

Mechanism of action

Both sulfonylurea and glinide mechanism of action is based on increased insulin secretion regulated by ATP-sensitive potassium channels (KATP potassium channels) in the membrane of pancreatic beta cells. The binding sites of the sulfonylurea and glinide receptors are different, but both induce channel blockage and cell depolarization, increase cytoplasmic calcium levels, and result in insulin secretion.

Pharmacokinetics

Differences in the pharmacokinetics and binding properties of insulin secretagogues result specific reactions by each drug. Sulfonyl urea agents can be divided into first-generation and second-generation active substances. Glipizide (known in Europe as glibenclamide), glipizide, gliclazide, and glimepiride are second-generation sulfonylureas. The new generations of active ingredients is more effective and have fewer side effects. Second-generation sulfonylureas are equally effective, but differ in absorption, metabolism, duration of action, and effective doses. For example, glybrid has an active metabolite that can prolong its effects.

There are two different glinides i.e. Repaglinide and nateglinide. Repaglinide belongs to the meglitinide family, which is different from sulfonylurea agents. Nateglinide is a derivative of phenylalanine and is structurally different from sulfonylureas and meglitinides. Both have a short half-life and different sulfonylurea receptor binding sites, resulting in less hypoglycemia and less weight gain, and faster absorption and stimulation of insulin secretion. Due to their pharmacokinetics, the main effect of sulfonylureas is to lower fasting plasma glucose levels, and meglitinide primarily lowers postprandial glucose.

Advantages and effectiveness

Sulfonylureas and meglitinides may be effective as monotherapy or in combination with other oral anti-diabetic drugs or insulin. Sulfonylurea is the most cost-effective hypoglycemic agent, has been on the market for a long time, and has a long history of efficacy and safety, low cost, and extensive clinical research data showing excellent hypoglycemic effects. The glucose-lowering effect are said to be high with sulfonylurea agents (expected decrease in HbA1c 1.0% -1.5%) and low with meglitinide (0.5% -1.0%).

Side effects

Loss of efficacy, hypoglycaemia and weight gain represent the main problems related to the use of these drugs. Hypoglycaemia is the most common adverse effect, especially with long acting sulfonylureas (such as glyburide/glimepiride). New generation sulfonylureas have shown to have a significantly lower risk of hypoglycaemia. Meglitinides generally have less risk of hypoglycaemia, thus being useful for individuals in whom the goal of avoiding hypoglycaemic events is important.

Other considerations

Most insulin secretagogues, except meglitinide, undergo significant renal clearance and the risk of hypoglycemia is high in patients with Chronic Kidney Disease (CKD), especially those with glibenclamide/glibenclamide, which has a long duration of action and active metabolites. Sulfonylureas are not particularly contraindicated in patients with liver disease, meglitinide can also be used. In severe liver disease, insulin secretagogues have a high risk of hypoglycemia and should be avoided.

Sulfonylureas are metabolized by cytochrome p450 and therefore have several drug interactions. Repaglinide, including gemfibrozil, is contraindicated due to the high risk of hypoglycemia.