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CLINICAL PHARMACOLOGY OF HYPOGLYCEMIC DRUGS

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ANNOTATION

In patients with diabetes mellitus type 2, non-insulin antihyperglycemic therapy is aimed to control symptoms of hyperglycemia and to limit microvascular complications. It is introduced early after diagnosis of the disease. Antihyperglycemic agents may predominantly act through one of four ways. The involved mechanisms are: enhancement of insulin secretion, through which act sulfonylureas, meglitinides and two types of incretin mimetics - glucagon-like peptide-1 (GLP-1) receptor agonists and inhibitors of dipeptidyl peptidase-4 (DPP-4) activity -gliptins; suppression of hepatic glucose production - biguanides; enhanced sensitivity to insulin - thiazolidinediones, and decrease of the rate or extent of glucose absorption: islet amyloid polypeptide (amylin) analogs and α-glucosidase inhibitors. With exception of GLP-1 receptor agonists and pramlintide, a synthetic form of amylin, all these drugs are administered orally.

Keywords: complex, diabetes, pharmacogical, insulin,Glucose-lowering agent Guidelines, Pharmacotherapy, Type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex disease that progressively aggravates with time, is associated with diverse comorbidities, can lead to a variety of complications, may result in premature death, and ultimately represents a huge burden for both individuals and society [1]. Choices for the pharmacological treatment of T2DM have multiplied as our understanding of the underlying pathophysiological defects of the disease improved. Treatment of hyperglycaemia should target multiple organ defects (impaired pancreatic insulin secretion, hepatic and muscular insulin resistance, reduced intestinal-driven incretin effect, increased glucose renal threshold) [2]. Thus, a combination of glucose-lowering agents with complementary modes of action is commonly required to reach optimal glucose control in T2DM. Furthermore, a new paradigm has emerged during the last two decades. Optimal management of patients with T2DM should consider other risk factors beyond glycaemic control, including body weight excess, cardiovascular (CV) risk, heart failure, and renal disease [3]. Overall, a patient-centered approach is recommended, with a shift from a "glucocentric" view to an "organ-disease" approach [4,5].

Oral Hypoglycemic Medications

Sulfonylureas (glipizide, glyburide, gliclazide, glimepiride)

Meglitinides (repaglinide and nateglinide)

Biguanides (metformin)

Thiazolidinediones (rosiglitazone, pioglitazone)

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α-Glucosidase inhibitors (acarbose, miglitol, voglibose)

DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin)

Insulin

FDA-approved indications for the use of oral hypoglycemic drugs primarily focus on type 2 diabetes mellitus.

Non-FDA approved indications of oral hypoglycemic drugs, such as metformin, are for the prevention of type 2 diabetes mellitus, treatment of gestational diabetes mellitus, treatment of polycystic ovary syndrome (PCOS) with menstrual irregularities, and prevention of ovarian hyperstimulation syndrome in PCOS patients undergoing intracytoplasmic sperm injection (ICSI) or in vitro fertilization (IVF), and management of antipsychotic-induced weight gain.

Mechanism of Action

Sulfonylureas-bind to adenosine triphosphate-sensitive potassium channels (K-ATP channels) in the beta cells of the pancreas; this leads to the inhibition of those channels and alters the resting membrane potential of the cell, causing an influx of calcium and the stimulation of insulin secretion.

Meglitinides- exert their effects via different pancreatic beta-cell receptors, but they act similarly to sulfonylureas by regulating adenosine triphosphate-sensitive potassium channels in pancreatic beta cells, thereby causing an increase in insulin secretion.

Metformin- increases hepatic adenosine monophosphate-activated protein kinase activity, thus reducing hepatic gluconeogenesis and lipogenesis and increasing insulin-mediated uptake of glucose in muscles.

Thiazolidinediones- activate peroxisome proliferator-activated receptor gamma (PPAR-γ), a nuclear receptor, which increases insulin sensitivity and resultant peripheral uptake of glucose and increases the level of adiponectin, a fat tissue-secreted cytokine, that increases not only the number of insulin-sensitive adipocytes but also stimulates fatty acid oxidation.

Alpha-glucosidase inhibitors- competitively inhibit alpha-glucosidase enzymes in the intestinal brush border cells that digest the dietary starch, thus inhibiting the polysaccharide reabsorption and the metabolism of sucrose to glucose and fructose.

DPP-4 inhibitors- inhibit the enzyme dipeptidyl peptidase 4 (DPP- 4). These deactivate glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), among others. Therefore, these influence glucose control through multiple effects, such as decreasing glucagon release and increasing glucose-dependent insulin release, decreasing gastric emptying, and increasing satiety.

Insulin

Even if insulin therapy may be considered at all stages of T2DM, in clinical practice it is most commonly used after failure of a combination of oral antidiabetic agents. The classical approach for a long time was the addition of a bedtime basal insulin [107]. The dose should be up-titrated in order to control overnight plasma glucose according to the so-called “fixing the fasting first” strategy [108]. However, because of the presence of insulin resistance, insulin dose should be markedly increased in some patients, especially if obesity is present, which exposes to nocturnal hypoglycaemia and further weight gain. In a meta-analysis of 7 RCTs with 1119 patients assigned to insulin therapy and 1080 to a GLP-1 analogue, GLP-1RAs and basal insulin were equally effective in lowering HbA1c; however, GLP-1RAs had additional non-glycaemic benefits (reduction in body weight and arterial blood pressure) and were associated with a lower risk of hypoglycaemia [98].

Conclusion

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The landscape of T2DM treatment is constantly changing as new therapies emerge and the understanding of currently available agents deepens. The personalization of T2DM management has gained precedence in more recent guidance and should account for several medical factors that include the patient phenotype (age, body weight, disease duration, life expectancy …), available biomarkers of insulin secretion/resistance (insulin/C-peptide, …), risk of treatment-related adverse effects (hypoglycaemia, gastrointestinal intolerance) and the presence of comorbidities/complications (cardiovascular and renal diseases, …). Diabetes precision medicine offers plenty of potential but is not yet ready for prime time [118,119],

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