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A REVIEW ON NEWLY APPROVED DRUGS FOR TREATMENT OF TYPE 2 DIBETIS AND OBESITY

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ABSTRACT
The occurrence of obesity and diabetes are the most common problems in human beings in nowadays. They are referred as twin epidemics of 21st century. These both conditions are interrelated and are illustrated by using the term "Diabesity. Generally, obesity is the major risk factors for the development of type 2 diabetes. It is necessary to know about various drugs which are used to treat both diabetes and obesity. This review mainly focusses on the describing individual classes of anti-diabetic and anti-obesity drugs and certain newly approved drugs which shows the weight and glycemic control effects.

Keywords: Anti-diabetic, Anti-obesity, Diabesity.

INTRODUCTION

The diabetes and obesity are major public health problems throughout the world and they are considered as twin epidemics of 21st century. some experts call this dual epidemics “Diabesity” [1]. Generally, “diabetes mellitus is a group of metabolic disorders of fat, carbohydrates, protein metabolism that results from defects in an insulin secretion, insulin action or both” [2]. There are different types of diabetes such as type 1; insulin dependent / juvenile onset diabetes, type 2; non-insulin dependent /maturity onset diabetes, gestational diabetes and other specific types of diabetes. Among all type 2 diabetes is mainly associated with obesity. Obesity is defined by the WHO as an ‘’ abnormal or excessive fat accumulation that impair health [2]. As like diabetes mellitus, obesity is also classified into various types based on BMI that means measure of weight for height. If BMI between 25-30 kg /m2 then it is considered as overweight. And BMI of 30 kg /m2 or higher it is considered as obesity [3]. There is a strong association between obesity and type 2 diabetes. About 80 % of adults with type 2 diabetes have obesity. In view of these both conditions, this review mainly describes about some newly approved drugs which are used commonly for treatment of both diabetes and obesity.

SOME NEWLY FDA APPROVED DRUGS FOR MANAGEMENT OF TYPE 2 DIABETES AND OBESITY

SEMAGLUTIDE

Semaglutide is a glucagon like peptide -1 (GLP-1) analogue that is approved, at doses up to 1mg administered subcutaneously once weekly, for the treatment of type 2 diabetes in adults and now, Semaglutide (under brand name Wegovy) is FDA approved for weight loss in obese patients. It can be used by adults with a body mass index (BMI) greater than or equal to 30 mg /kg 2 alone or 27 mg /kg 2 with at least one weight related condition (e.g., hypertension, high cholesterol, type2 diabetes).

GLP-1, a major incretin hormone in humans, acts by numerous mechanisms like insulin secretion (glucose dependent), inhibition of glucose release and suppressed hepatic gluconeogenesis [4].

It also causes delayed gastric emptying, reduced appetite and energy intake. Reduction of HbA1c level along with body weight without any risk of hypoglycemia, provides it is a special status for the treatment of obese type 2 diabetic patients.

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MECHANISM OF ACTION

Semaglutide improves the efficiency of incretin function by activating GLP-1 receptors. It acts by numerous mechanisms like insulin secretion, inhibition of glucagon release and suppressed hepatic gluconeogenesis; there by reducing both fasting as well as postprandial glucose [5] . It is also exhibited improved insulin sensitivity which is likely to be mediated by overall reduction in body weight.

ADVERSE EFFECTS

Although Semaglutide is well tolerated, but it shows dose dependent, mild to moderately severe gastrointestinal adverse effects like vomiting, nausea, constipation, diarrhea and dyspepsia which usually wears off within 2 weeks of treatment initiation [6]. Other infrequent side effects are nasopharyngitis, headache, infection in urinary tract and upper respiratory tract etc.,

DRUG INTERACTIONS

As Semaglutide cause delayed gastric emptying, it can affect the pharmacokinetics of other co-administered drugs. Numerous studies confirm non-interference of oral contraceptives, metformin, furosemide, digoxin etc., co-administration of levothyroxine with oral Semaglutide results in increased exposure of levothyroxine 3 hr after the last meal to avoid unnecessary interactions with Semaglutide.

TIRZEPATIDE.

Tirzepatide, known as a 'twincretin', is a 'first-in-class and the only dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) receptor agonist, that can significantly reduce glycaemic levels and improve insulin sensitivity, as well as reducing body weight by more than 20% and improving lipid metabolism. Tirzepatide, developed by Eli Lilly, was approved, under the brand name Mounjaro, by the United States Food and Drug Administration in May 2022[7]. This started the 'twincretin' era of enormously important and appealing dual therapeutic options for diabetes and obesity Tirzepatide has significantly better therapeutic efficacy than current drugs. It is superior to Semaglutide and insulin degludec.

Stucture and activity

Tirzepatide is a synthetic linear peptide molecule containing 39 amino acids. More specifically, the structure is based on the native GIP sequence and includes C20 fatty diacid moiety (eicosane dioic acid) linked via hydrophilic linkers (γ-Glu-2xAdo, gamma glutamate and bis-aminodiethoxyacetyl) connected to lysine residue at C20 position. The peptide sequence of Tirzepatide contains two non-coded amino acid residues (Aib, αamino isobutyric acid) at position 2 and 13, which are responsible for its long half-life and high affinity to albumin [8]. The C-terminus of the peptide is amidated. The molecular formula of Tirzepatide is C225H348N48O68 and the molecular weight is 4813.45.

Tirzepatide is a gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist. Functionally, it stimulates insulin release from the pancreas and leads to a reduction of hyperglycemia. In addition, Tirzepatide also increases the levels of adiponectin which is a protein hormone produced from fat cells, it is involved in an increasing response of cells to insulin there by shows hypoglycemic action. Its dual agonism ability leads to a more significant reduction of hyperglycemia than GLP-1 agonist agents alone and lowers the user's appetite. Due to reduced appetite it also helps in weight loss [9].

PHARMACOKINETICS [10]

Absorption:

Tirzepatide has a bioavailability of approximately 80%. The time it takes to reach peak serum levels can range from 8 to 72 hours.

Distribution:

The mean apparent steady-state volume of distribution (Vd) of tirzepatide is approximately 10.3 L. Tirzepatide is highly bound to plasma albumin (99%).

Metabolism:

Once injected, the peptide structure undergoes proteolytic cleavage. In addition, the C20 fatty diacid composition undergoes beta-oxidation and amide hydrolysis.

Excretion:

Tirzepatide has a half-life of 5 days, allowing once-weekly dosing, and is cleared in urine and feces in the form of metabolites.

ADVERSE EFFECTS

Decreased appetite,nausea and diarrhea may see in 10% of patients . Constipation has also been reported in some individuals.

Hypersensitivity reactions have been infrequently reported at the injection site, but the occurrence is not higher than those reported by patients using GLP-1 agonist. There are also some other affects have been experienced with tirzepatide they include; sinus tachycardia, pancreatitis upon long term use and chol lithiasis have been reported.

DRUG INTERACTIONS

Patients who are currently using other GLP-1 agents, such as Semaglutide or liraglutide, should not be prescribed Tirzepatide. Patients on insulin therapy can be initiated on Tirzepatide therapy and cautiously have their insulin dose decreased to minimize the risk of hypoglycaemia[11].

Tirzepatide is only approved for those with type 2 diabetes mellitus and should not be used in those with type 1 diabetes mellitus. It is also not directly approved for other forms of diabetes, such as latent autoimmune diabetes in adults [12].

Table 01: PHARMACOKINETICS.

Characteristics	Semaglutide (S.C, injection)	Semaglutide (oral)
Absorption		
Absolute bioavailability	89%	0.4–1%
Steady state plasma concentration	65 ng/ml (0.5 mg weekly once)	6.7 nmol/L (7 mg once daily
	123 ng/ml (1 mg weekly once)	14.6 nmol/L (14 mg once daily)
Time to achieve steady state concentration	4–5 weeks	4–5 weeks
Time to achieve maximum concentration	1–3 days	01 h
Distribution		
Volume of distribution	12.5 Litres	8 Litres
Protein binding	>99%	>99%
Metabolic pathway	Proteolytic degradation followed by fatty acid oxidation	Proteolytic degradation followed by fatty acid oxidation
Elimination profile		
Elimination t ½	01 week	01 week
Rate of clearance	0.05 Litres /Hr	0.04 Litres /Hr

CONCLUSION

The prevalence of obesity and diabetes is an increasing global problem especially in developed countries they are referred as the twin epidemics. The type 2 diabetes mellitus and obesity are strongly related. Obesity is one of the risk factors for type2 diabetes. The alarming increase in the number of patients worldwide requires new scientific developments in order to ease administration reduce the frequency of dosing, and include multiple issues within a single medication.

These both conditions are kept under control by proper application of therapy and incorporating some life style modifications. This review mainly describes certain newly approved drugs such as 'Tirzepatide and Semaglutide' are commonly used drugs for treatment of both, type 2 and obesity. Through this review it was concluded that when compared with Semaglutide, Tirzepatide under the brand name Mounjaro, has become a revolutionary agent for the management and treatment of type2 diabetes and achieving weight loss. Patient compliance and dose adherence are also favored as it has minor side effects and reduced dosing frequency.

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