



The Pharmacokinetic And Pharmacodynamic Profile Of Tirzepatide: A Dual Receptor Affinity Twincretin

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ABSTRACT

A global health issue is the concurrent increase in the widespread presence of obesity and T2DM, sometimes known as “diabesity”. One of the common causes of T2DM and one of the limitations in achieving good glycemic control is obesity. Effectiveness, lack of weight gain or promotion of weight loss with minimal risk of hypoglycemia, and not perturbing cardio-vascular system should all be the characteristics of best glucose-lowering drug. Development of the drug Tirzepatide, which is known as Twincretin by its action has a combined role of GIP and GLP-1 tends to promote weight loss as well with lowering blood glucose level in patients with type 2 diabetes mellitus.

Key words: Pharmacokinetics; Pharmacodynamics; Type 2 Diabetes Mellitus; Glucagon Like Peptide – 1 (GLP-1); Glucose Dependent Insulinotropic polypeptide (GIP); and Weight Loss.

INTRODUCTION

When GIP and a GLP-1 receptor agonist were given together to a healthy person, their combined effects have an additive impact that results in a higher insulin response than when the hormones given separately. Moreover, a single administration of both GIP and GLP-1 did not only reduce glucagon output, also had a strong glucagonostatic effect [1].

Tirzepatide is a glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide 1 (GLP -1) receptor agonist developed by Eli Lilly, which consists of thirty-nine amino acid synthetic-peptide [2]. It has a half-life of about five days, which is due to its conjugation with C20 fatty acid moiety through a hydrophilic linker at the lysine residue present at position twenty, which allows the drug to be once-a-week dose [3].

PHARMACOKINETICS

During the single ascending dose study where forty-one individuals received Tirzepatide, peak plasma concentrations (C-max) of the drug were dose-proportional and ranged between 26 and 826 ng/mL (5.9 and 182.1 nmol/L) and the doses ranging between 0.25 mg and 8.0 mg [4]. After five days of administering Tirzepatide, the maximum concentration (T-max) was reached, and the mean half-life (T_{1/2}) was 116.7 hours, which is five days indicating that once weekly dosing could be efficacious [4]. The time to the highest plasma concentration of Tirzepatide after subcutaneous administration ranges from 8 to 72 hours. It has an 80% absolute bioavailability after subcutaneous injection. Subcutaneous injection of Tirzepatide in the abdomen, thigh, or upper arm resulted in identical exposure [5]. In individuals with T2DM, the mean steady state V_d (volume of distribution) after subcutaneous injection is approximately 10.3 Liters. Tirzepatide therefore has a high (99%) affinity for plasma albumin. Tirzepatide has an estimated average mean clearance of 0.061L/h and an elimination half-life of five days, allowing it as once weekly dosing. The peptide backbone of Tirzepatide is cleaved by proteolytic cleavage, the C20 fatty di-acid moiety is beta-oxidized, and the amide group is hydrolyzed. Tirzepatide metabolites are excreted through urine and feces. There is no evidence that free Tirzepatide in urine or feces. The pharmacokinetics of Tirzepatide are not influenced by renal impairment. In people with varying degrees of renal impairment (mild, moderate, severe, ESRD) with T2DM, the pharmacokinetics of Tirzepatide following a single dose of 5mg were assessed in comparison to persons with normal renal function. The pharmacokinetics of Tirzepatide are unaffected by hepatic impairment. Patients with varying levels of hepatic impairment (mild, moderate, severe) were compared to those with normal hepatic function to determine the pharmacokinetics of Tirzepatide after a single 5mg dosage.[5]

PHARMACODYNAMICS

In individuals with T2DM, Tirzepatide lowers fasting and post-prandial glucose levels, decreases bodyweight, and reduces food consumption. Tirzepatide boosts insulin secretion in the first and second phases of the insulin secretion [6]. Tirzepatide improves insulin sensitivity in studies of hyperinsulinemic euglycemic clamp after 28 weeks of therapy. Tirzepatide reduces glucagon levels in the fasting and postprandial phases due to glucagon secretion. At 15 mg dose, Tirzepatide reduces fasting glucagon levels by 28% and after meal glucagon AUC by 43% after 28 weeks of therapy, compared to no changes in placebo and there was slow emptying of the stomach. The delay is most obvious after the

first dose and gradually fell. It also lowers post-prandial hyperglycemia by decreasing glucose absorption after meals [7]. One of the key elements influencing postprandial glycaemia and food intake is gastric emptying (GE), which is a complex interaction involving gastric, intestinal, central, neuronal, and humoral systems. Research done on GLP-1's function on GE and there has not been much study done on GIP and how it affects GE. GIP receptor agonists and native GIP that mimic postprandial GIP blood levels did not show any effects on GE. After the first dose of 5mg of Tirzepatide in people with T2DM, GE delay was seen. However, after 4 weeks of recurrent treatment, there was evidence of tachyphylaxis. The GE delay was still noticeable after the final dose after four weekly administrations of 5/5/10/10 or 5/5/10/15 mg [8]. Even though the 5mg dose develops tachyphylaxis in the GE effect, the impact on postprandial glucose persisted even after subsequent 5-mg doses. Furthermore, it has been demonstrated that the effects of the 5mg dose on weight reduction last for longer with that for 4 weeks (4.8 kg at 26 weeks vs. 2.5 kg at 4 weeks). This effect shows that in addition to diminishing effects on GE, must contribute to the reduction of postprandial glycaemic increases in the long haul. It is evident that GLP-1 regulates metabolism differently, since its impact on GE develops the tachyphylaxis with prolonged treatment. But does not directly result in a loss of glucose control or body weight effect [8].

MECHANISM OF GLP-1R

Uncertain processes including interaction between membrane I on channel, cyclic AMP (cAMP)-

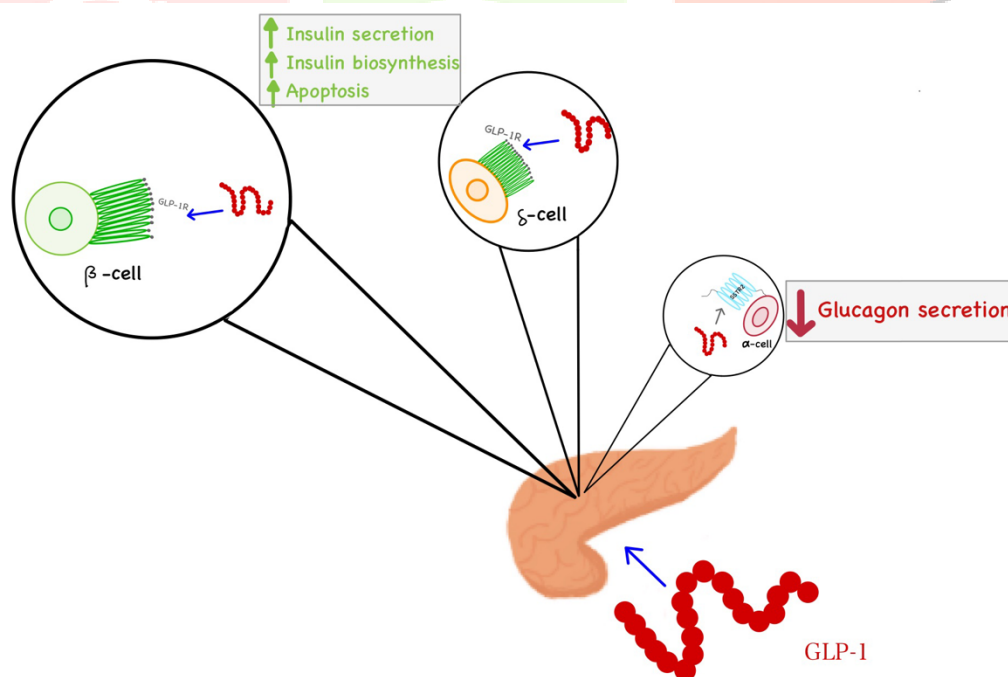


Figure 1[9] : GLP-1's effect on islets and acinar cell through the pancreas' endocrine and exocrine systems.

GLP-1 controls insulin and somatostatin (SMS) production through the GLP-1 receptor, which is expressed on islets β cells and α cells, respectively. Through the somatostatin-2 receptor, SMS in turn prevents islets α cell

dependent signaling, and intracellular glucose metabolism are likely involved in the fast restoration of glucose sensitivity to failed diabetic human pancreatic beta cells by GLP-1R signaling [9]. The restoration or deletion of mouse's beta cell GLP-1R has shown the physiologic significance of this receptor. Succeeding oral and intraperitoneal glucose challenge, GLP-1R deficient mice had improved glucose tolerance and glucose-stimulated insulin production because of transgenic targeting of GLP-1R expression to GLP-1R deficient mouse's beta cells under the control of the Pdx1 promoter. It is noteworthy that the activation of GLP-1R signaling increases insulin production and secretion and at the same time reduces the onset of ER stress in beta cells via cAMP-dependent potentiation of ATF-4 translation. The hypothesis that maintained GLP-1R activity could result in disease-modifying activity through preservation or enhancement of functional β cell mass in human subjects with T2DM was supported by these findings [9].

GLP-1 also regulated glycemic index by inhibiting α cell glucagon secretion. Insulin, zinc, and GABA are just a few of the secondary metabolites produced by β cells and that in theory may contribute to the GLP-1R-dependent suppression of cell's secretory activity. These substances also dock the release of glucagon. The concept of direct GLP-1R-mediated regulation of glucagon secretion is supported by studies that have shown GLP-1R expression in a subset of cells [9]

DOCKING-RECEPTOR BINDING

The affinity of Tirzepatide towards GIPR resembles native GIP and towards GLP-1 is 5-fold lower than native GLP-1 and the drug's potency towards GIP is 13-fold weaker than native GLP-1[4]. Tirzepatide stimulates insulin secretion either by binding to the GIPR or the GLP-1R[4]. During a 26-week phase 2b clinical trial, Tirzepatide showed significant efficacy in reducing glucose levels as well as body weight in subjects with T2DM [10].

Structure

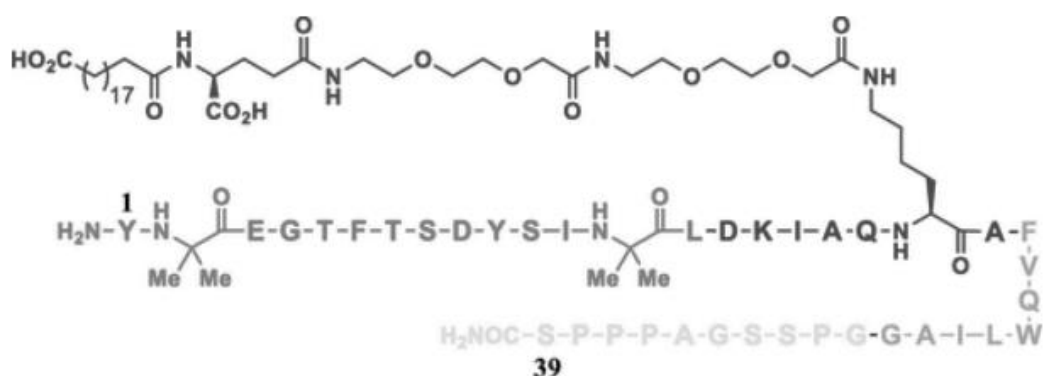


Figure 2 : Tirzepatide

STRUCTURAL ACTIVITY RELATIONSHIP

The structure is constructed on the native GIP sequence and comprises a C20 fatty-diacid moiety coupled through hydrophilic linkers to a lysine residue at the C20 position. Tirzepatide's peptide sequence comprises two non-coded amino acid residues at positions 2 and 13, which are responsible for its long half-life and strong affinity to albumin. The peptide's C-terminal is amidated. C₂₂H₃₄N₄O₆S and 4813.45 are the Molecular formula and molecular weight the drug respectively [11]

SAFETY PROFILE OF TIRZEPATIDE

The common adverse events observed are gastrointestinal (nausea, vomiting, diarrhea and decreased appetite and others include hypoglycemia, pancreatitis, cholecystitis, altered heart rate, hypersensitivity, and anti-drug antibody formation.[12]

CONCLUSION

Amongst many upcoming anti-diabetic medications, Tirzepatide possesses significant efficiency towards treating type 2 diabetes mellitus. The combined effect of Tirzepatide makes it a more potent drug in treating patients with T2DM and once weekly dosing can also be done due to its pharmacokinetic effects. What's more is that it has shown weight loss in healthy as well as type 2 DM patients within 4 weeks course of treatment.

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