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REVIEW

A Comprehensive Review on the Pharmacokinetics and Drug–Drug Interactions of Approved GLP-1 Receptor Agonists and a Dual GLP-1/GIP Receptor Agonist

Jee Sun Min[1], Seong Jun Jo[1,2], Sangyoung Lee[1], Duk Yeon Kim[1], Da Hyun Kim[1], Chae Bin Lee[3], Soo Kyung Bae[1]

[1]College of Pharmacy and Integrated Research Institute of Pharmaceutical Sciences, The Catholic University of Korea, Bucheon, 14662, Republic of Korea; [2]Department of Pharmaceutical Sciences, State University of New York, Buffalo, NY, 14214, USA; [3]Johns Hopkins Drug Discovery, Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, 21205, USA

Correspondence: Soo Kyung Bae, College of Pharmacy and Integrated Research Institute of Pharmaceutical Sciences, The Catholic University of Korea, Bucheon, 14662, Republic of Korea, Email baesk@catholic.ac.kr

Abstract: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are peptide-derived analogs that were initially investigated to treat type 2 diabetes. Recently, a drug targeting the receptors of both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) (tirzepatide) has been introduced to the market, and its indications have expanded to include treating obesity. Here, we review the pharmacokinetics, pharmacokinetic drug–drug interactions (DDIs), and pharmacokinetic modeling approaches of four currently available GLP-1 RAs (exenatide, liraglutide, dulaglutide, and semaglutide) and tirzepatide. To address the extremely short half-life (2 min) of native human GLP-1, structural modifications have been applied to GLP-1 RAs and a dual GLP-1/GIP RA. These include amino acid sequence substitutions, fatty acid conjugation using a linker, and fusion with albumin or the IgG fragment crystallizable (Fc) region, resulting in minimal metabolism and renal excretion. Due to their diverse structures, the pharmacokinetic profiles vary, and a prolonged half-life may be associated with an increased risk of adverse events. Clinically significant drug-metabolizing enzyme- and transporter-mediated DDIs are yet to be reported. Mechanism-of-action-mediated DDIs are currently limited to those involving delayed gastric emptying, and most studies have found them to be clinically insignificant. However, significant changes in exposure were observed for oral contraceptives and levothyroxine following the administration of tirzepatide and oral semaglutide, respectively, indicating the need for close monitoring in these instances. Thirty models have been developed to predict pharmacokinetics and physiologically based pharmacokinetic modeling can be useful for assessing mechanism-of-action-mediated DDIs. Alterations in the volume of distribution and clearance resulting from other mechanisms of action (eg, reduced fat mass, changes in cytochrome P450 activity, and glomerular filtration rate) are key factors in determining pharmacokinetics. However, the DDIs mediated by these factors remain poorly understood and require further investigation to ensure that GLP-1 RAs can be safely used with concomitant medications.

Keywords: GLP-1, GIP, pharmacokinetics, drug–drug interactions, physiologically based pharmacokinetic model

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are peptide hormone-derived analogs classified as incretin mimetic drugs (Figure 1).[1–5] Incretins are gut hormones released into the bloodstream following food consumption that enhances insulin secretion in pancreatic β-cells and help decrease high blood glucose levels.[6] Therefore, GLP-1 RAs were first investigated as treatments for type 2 diabetes.[7] Compared to other antidiabetic drugs, GLP-1 RAs have the advantage of only being pharmacologically active when blood glucose levels are high.[8] This significantly reduces the incidence of hypoglycemia—a frequently reported adverse drug reaction associated with other antidiabetic drugs like sulfonylureas or insulin.[9,10] Additionally, GLP-1 RAs suppress glucagon secretion from the α-cells in the pancreas, leading to decreased blood glucose levels.[11]

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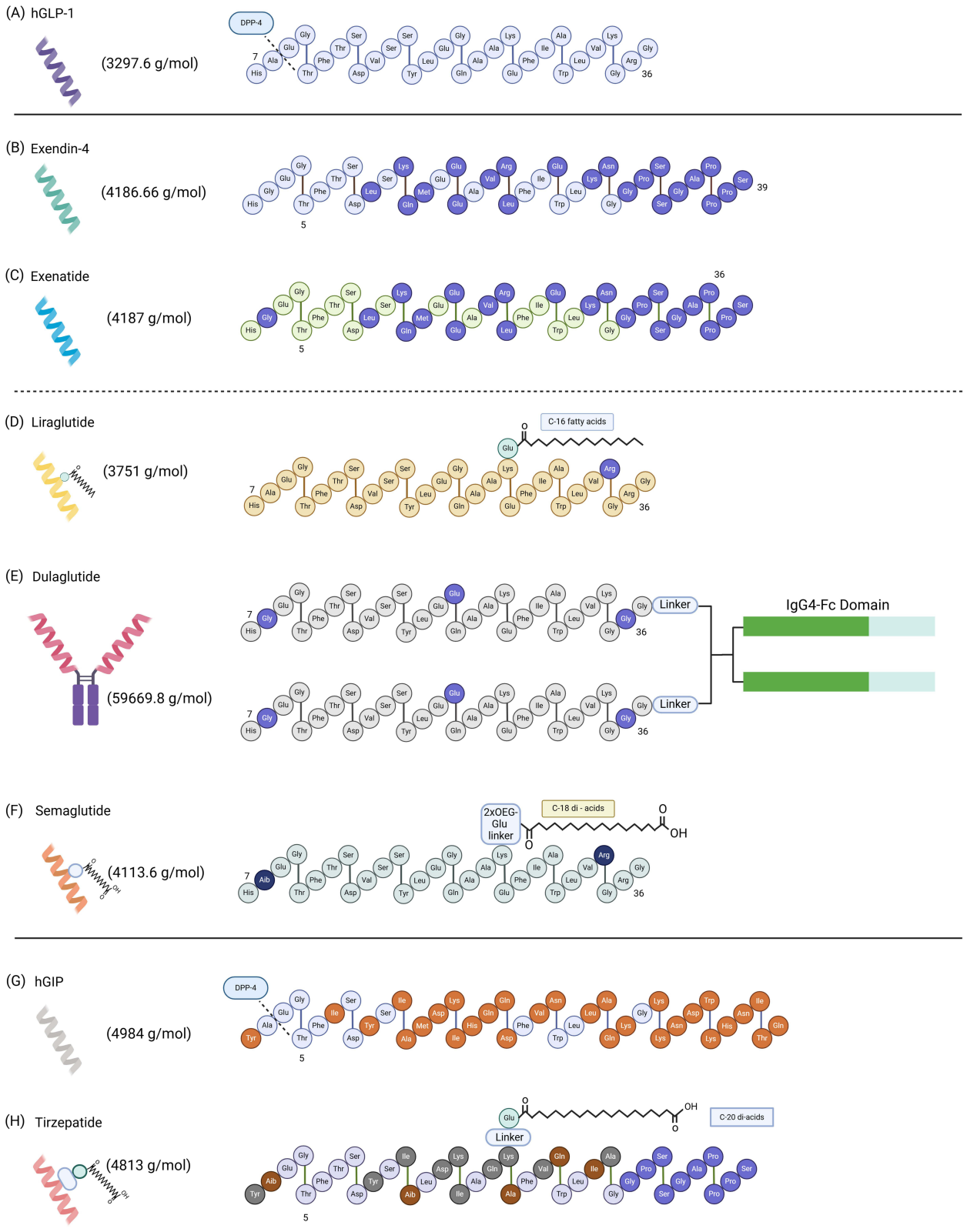

Figure 1 Molecular weights and amino acid sequences of human GLP-1 (**A**), exendin-4 (**B**), exenatide (**C**), liraglutide (**D**), dulaglutide (**E**), semaglutide (**F**), human GIP (**G**), and tirzepatide (**H**), with substituted amino acids marked in different colors. Created in BioRender. Min, J. (2025) https://BioRender.com/o27r742.
Abbreviations: hGLP-1, human glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; IgG4-Fc, immunoglobulin G4 fragment crystallizable; Aib, α-aminoisobutyric acid; OEG, oligoethylene glycol; hGIP, human glucose-dependent insulinotropic polypeptide.

However, a drawback of the native human GLP-1 (Figure 1A) is its extremely short in vivo half-life (2 min) due to fast clearance by dipeptidyl peptidase-4 (DPP-4).[1] Thus, numerous studies have used biotechnology to extend the half-life of GLP-1 RAs, with strategies including amino acid sequence substitution, fatty acid conjugation with a linker, fusion of albumin or the IgG fragment crystallizable (Fc) region (Figure 1).[5,12,13] These efforts have yielded six GLP-1 RAs−starting with the development of exendin-4 (Figure 1B)-based exenatide (Figure 1C), followed by liraglutide (Figure 1D), albiglutide, dulaglutide (Figure 1E), lixisenatide, and semaglutide (Figure 1F)−that have been approved by the United States Food and Drug Administration (US FDA) to treat type 2 diabetes.[14] Among these, albiglutide was pulled from the market in 2017 because of declining sales;[15] likewise, lixisenatide was withdrawn from the US market as of January 1, 2023, for commercial reasons, rather than because of any safety or efficacy issues.[14]

Furthermore, GLP-1 RAs reportedly induce weight loss by reducing appetite and this satiety-promoting effect has recently attracted significant interest.[16,17] The appetite-regulating effects of GLP-1 RAs are primarily mediated by both peripheral (vagal) and central nervous system pathways.[1,18] Food intake causes the stomach to stretch, activating gastro-mechanoreceptors in the intestinal wall, which then transmit satiety signals via the vagus nerve.[19,20] GLP-1 RAs delay gastric emptying and reduce stomach motility in obese patients, contributing to their satiating effect.[21] In addition, intracerebro ventricular administration of GLP-1 decreased food intake in rats, suggesting GLP-1 RAs are involved in a central nervous system pathway.[22] Eight obese women reported reduced hunger following subcutaneous injections of exenatide and it was related with an enhanced functional connectivity of the nucleus tractus solitarius with the thalamus and hypothalamus.[23] Clinical trials also indicated that GLP-1 RA treatment for obese patients presented superior weight loss efficacy compared to other anti-obesity medications.[24] Based on these findings, two GLP-1 RAs were approved by the US FDA to treat obesity so far: liraglutide and semaglutide.

Recently, the newly developed drug tirzepatide, which targets both the GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, was introduced to the market to treat type 2 diabetes and obesity in 2022 and 2023, respectively (Table 1).[25,26] GIP (Figure 1G) is another incretin hormone that triggers insulin secretion when a meal is ingested.[27] Tirzepatide (Figure 1H) was designed to bind GLP-1/GIP receptors by modifying the native amino acid sequence of GIP.[3,28] The combined activation of GLP-1 and GIP receptors more effectively reduces glucose levels and stimulates weight loss compared to the placebo, semaglutide and dulaglutide, or insulin.[29–31]

Several clinical trials and reviews have been conducted to clarify the safety and effectiveness of GLP-1 RAs and a dual GLP-1/GIP RA.[32,33] However, given the lack of comprehensive reviews in the existing literature on the pharmacokinetics and drug-drug interactions (DDIs) of GLP-1 RAs and a dual GLP-1/GIP RA, we produced this review to consolidate current knowledge and provide a thorough analysis of key considerations in clinical practice. The main objective of this review is to examine the pharmacokinetics of five peptide-derived incretin mimetic medications—exenatide, liraglutide, dulaglutide, semaglutide, and tirzepatide—including GLP-1 RAs and a dual GLP-1/GIP RA currently used in the market. First, the structures, indications, and doses of GLP-1 RAs and a dual GLP-1/GIP RA are outlined. Second, their pharmacokinetics, efficacy, and relationship between the pharmacokinetics and adverse events are summarized. Third, the pharmacokinetic DDIs of the medications are examined. Fourth, pharmacokinetic modeling approaches and the applications of GLP-1 RAs and a dual GLP-1/GIP RA are described. Finally, future perspectives of these therapies are briefly discussed.

Structures, Indications, and Dosages of GLP-1 RAs and a Dual GLP-1/GIP RA

Exenatide

Exenatide is the first-in-class incretin mimetic drug.[34] It is a 39 amino acid (aa)-long synthetic peptide drug (Figure 1C), derived from exendin-4 (Figure 1B), a peptide isolated from the saliva of the lizard *Heloderma suspectum*.[4,35] The immediate-release (IR) formulation of exenatide (Byetta®, Amylin Pharmaceuticals, San Diego, CA, USA) was first developed in 2005 to treat type 2 diabetes (Table 1).[34] Initial dosing regimen of Byetta® is 5 μg subcutaneously twice daily and after one month, the dose is increased to 10 μg twice daily based on clinical response (Table 1).[36] In 2012, the extended-release (ER) formulation of exenatide (Bydureon®, Amylin Pharmaceuticals) was approved by the US FDA to

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Table 1 Information on Currently Available US FDA-Approved GLP-1 RAs and a Dual GLP-1/GIP RA

Drug	Brand Name	Approval Date	Indications	Administration Route	Dosage
GLP-1 RAs					
Exenatide	Byetta® (IR)	2005	• T2DM in adults	SC	5,10 μg BID
	Bydureon BCise® (ER)	2017	• T2DM in adults and pediatric patients aged 10 years and older	SC	2 mg QW
Liraglutide	Victoza®	2010	• T2DM in adults and pediatric patients aged 10 years and older • Reduce the risk of MACE in adults with T2DM and established CVD	SC	0.6, 1.2, or 1.8 mg QD
	Saxenda®	2014	• Chronic weight management in adults and pediatric patients aged 12 years and older with obesity[a] • Chronic weight management in adults with overweight[b] in the presence of at least one weight-related comorbid condition	SC	0.6, 1.2, 1.8, 2.4, or 3 mg QD
Dulaglutide	Trulicity®	2014	• T2DM in adults and pediatric patients 10 years of age and older • Reduce the risk of MACE in adults with T2DM and established CVD	SC	0.75, 1.5, 3, or 4.5 mg QW
Semaglutide	Ozempic®	2017	• T2DM in adults • Reduce the risk of MACE in adults with T2DM and established CVD	SC	0.25, 0.5, 1, or 2 mg QW
	Rybelsus®	2019	• T2DM in adults	Oral	3, 7, or 14 mg QD
	Wegovy®	2021	• Reduce the risk of MACE in adults with established CVD and either obesity[a] or overweight[b] • Chronic weight management in adults and pediatric patients aged 12 years and older with obesity[a] • Chronic weight management in adults with overweight[b] in the presence of at least one weight-related comorbid condition	SC	0.25, 0.5, 1, 1.7, or 2.4 mg QW
Dual GLP-1/GIP RA					
Tirzepatide	Mounjaro®	2022	• T2DM in adults	SC	2.5, 5, 7.5, 10, 12.5, or 15 mg QW
	Zepbound®	2023	• Chronic weight management in adults with obesity • Chronic weight management in adults with overweight[b] in the presence of at least one weight-related comorbid condition	SC	2.5, 5, 7.5, 10, 12.5, or 15 mg QW

Notes: [a]Obesity, body mass index (BMI) of 30 kg/m^2 or greater; [b]Overweight, body mass index (BMI) of 27 kg/m^2 or greater.

Abbreviations: IR, immediate-release; T2DM, type 2 diabetes mellitus; SC, subcutaneous; BID, twice a day; ER, extended-release; QW, once a week; CVD, cardio-vascular disease; QD, once a day; MACE, major adverse cardiovascular events.

treat type 2 diabetes mellitus.[37] Bydureon Pen® (AstraZeneca, Wilmington, DE, USA) and Bydureon BCise® (AstraZeneca) were developed later, but currently, only the latter, an enhanced injector pen formulation, is prescribed.[38] The dosing regimen of Bydureon BCise® is 2 mg once weekly subcutaneously (Table 1).[38]

Liraglutide

Liraglutide is a 31 aa-long synthetic peptide drug attached to 16 carbon fatty acids (MW: 3751 g/mol) (Figure 1D).[39] It was approved by the US FDA in 2014 to treat obesity (Saxenda®, Novo Nordisk, Plainsboro, NJ, USA), after first being approved as a type 2 diabetes medication (Victoza®, Novo Nordisk) in 2010 (Table 1). The available doses of liraglutide are 0.6 mg, 1.2 mg, or 1.8 mg for type 2 diabetes, and 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg for obesity, respectively. The initial dosing regimen of liraglutide is 0.6 mg subcutaneously daily, with the dose increased to up to 3 mg for Saxenda® and 1.8 mg for Victoza®, usually after one week at the previous dose.[40,41]

Dulaglutide

Dulaglutide is a recombinant fusion protein consisting of two identical 31-aa chains, each covalently linked to a single Fc fragment derived from a modified human IgG4 heavy chain (MW: 59,669.8 g/mol) (Figure 1E).[42,43] Dulaglutide (Trulicity®, Eli Lilly and Company, Indianapolis, IN, USA) was as a treatment for type 2 diabetes in 2014. It is administered as a subcutaneous injection once weekly, with available doses of 0.75 mg, 1.5 mg, 3 mg, and 4.5 mg (Table 1). The initial dosing regimen of dulaglutide is 0.75 mg subcutaneously weekly, with the dose increased to 4.5 mg, usually one month after the previous dose.[43]

Semaglutide

Semaglutide is a peptide drug composed of 31 amino acids linked with 18 carbon fatty acids (MW: 4113.6 g/mol) (Figure 1F).[44] It was first used to treat type 2 diabetes (Ozempic®, Novo Nordisk) as a subcutaneous injection given once weekly. Subsequently, an oral formulation for once-daily administration (Rybelsus®, Novo Nordisk) was developed in 2019 to treat type 2 diabetes.[45] Oral semaglutide is combined with sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (salcaprozate sodium;SNAC), an absorption enhancer that improves semaglutide's absorption across the gastric mucosa by transcellular mechanisms.[46] By 2021, semaglutide (Wegovy®, Novo Nordisk) administered by subcutaneous injection was also approved by the US FDA as an obesity treatment (Table 1).[47] The doses of semaglutide available for subcutaneous injection are 0.25 mg, 0.5 mg, 1 mg, or 2 mg for type 2 diabetes, and 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, or 2.4 mg for obesity, respectively. The initial dosing regimen of semaglutide subcutaneous injection is 0.25 mg weekly, with the dose increased up to 2 mg for Ozempic® and 2.4 mg for Wegovy®, respectively, usually after one month at the previous dose.[48,49] The available doses of oral semaglutide are 3 mg, 7 mg, and 14 mg (Table 1). The initial dosing regimen of oral semaglutide is 3 mg daily, with the dose increasing to 14 mg daily usually after one month of the previous dose.[45]

Tirzepatide

Tirzepatide is a 39-aa peptide conjugated with C20 fatty acids (MW: 4813 g/mol) (Figure 1H).[3] It was approved by the US FDA in 2023 to treat obesity (Zepbound®, Eli Lilly and Company, Indianapolis, IN, USA) which was initially approved to treat type 2 diabetes in 2022 (Mounjaro®, Eli Lilly and Company) (Table 1). Tirzepatide is available in weekly subcutaneous doses of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg (Table 1).[50,51] The initial dosing regimen of tirzepatide is 2.5 mg weekly, with the dose increased to up to 15 mg weekly usually after one month at the previous dose.[50,51]

Pharmacokinetics of GLP-1 RAs and a Dual GLP-1/GIP RA

Numerous studies have reported the pharmacokinetics of these drugs, with each study showing varying pharmacokinetic parameters based on differences in the clinical study design, pharmacokinetic parameter calculation approaches, or analytical methods. The pharmacokinetic parameters and profiles discussed in this review were primarily derived from clinical pharmacology and biopharmaceutics reviews and prescribing information released electronically by the US FDA.

The pharmacokinetic profiles of GLP-1 RAs and a dual GLP-1/GIP RA vary owing to their diverse structures (Figures 1 and 2).[39,52–58] Due to their large molecular weights and high polarity compared to small-molecule drugs, peptide drugs have low membrane permeability, resulting in a relatively small Vd in general.[59] Compared to human GLP-1 (Figure 1A), the alanine residue at the second position of the N-terminus in GLP-1 RAs and a dual GLP-1/GIP RA (except for liraglutide) has been substituted to prevent metabolism by DPP-4 (Figure 1). Exenatide (Figure 1C) exhibits relatively fast renal clearance and a short half-life (Figure 2A). The ER formulation of exenatide achieves sustained drug concentrations in plasma over time (Figure 2B). Liraglutide (Figure 1D), dulaglutide (Figure 1E), semaglutide (Figure 1F), and tirzepatide (Figure 1H), which incorporate fatty acid conjugation using a linker or an IgG fragment crystallizable (Fc) region, display minimal renal clearance and prolonged half-lives (Figure 2C–G).[60] Detailed information on their pharmacokinetic characteristics is provided below.

Exenatide

Exenatide IR is absorbed rapidly, with maximum plasma concentrations (C_{max}) usually attained around 2 h following subcutaneous injection (Figure 2A and H).[36,61] However, exenatide ER is encapsulated in microspheres of medical-grade poly-(D,L-lactide-co-glycolide), which ensures the gradual and extended release of the drug (Figure 2B).[62] In the first few hours, <1% of the surface-bound exenatide is released. During the subsequent gradual-release phase, which lasted for

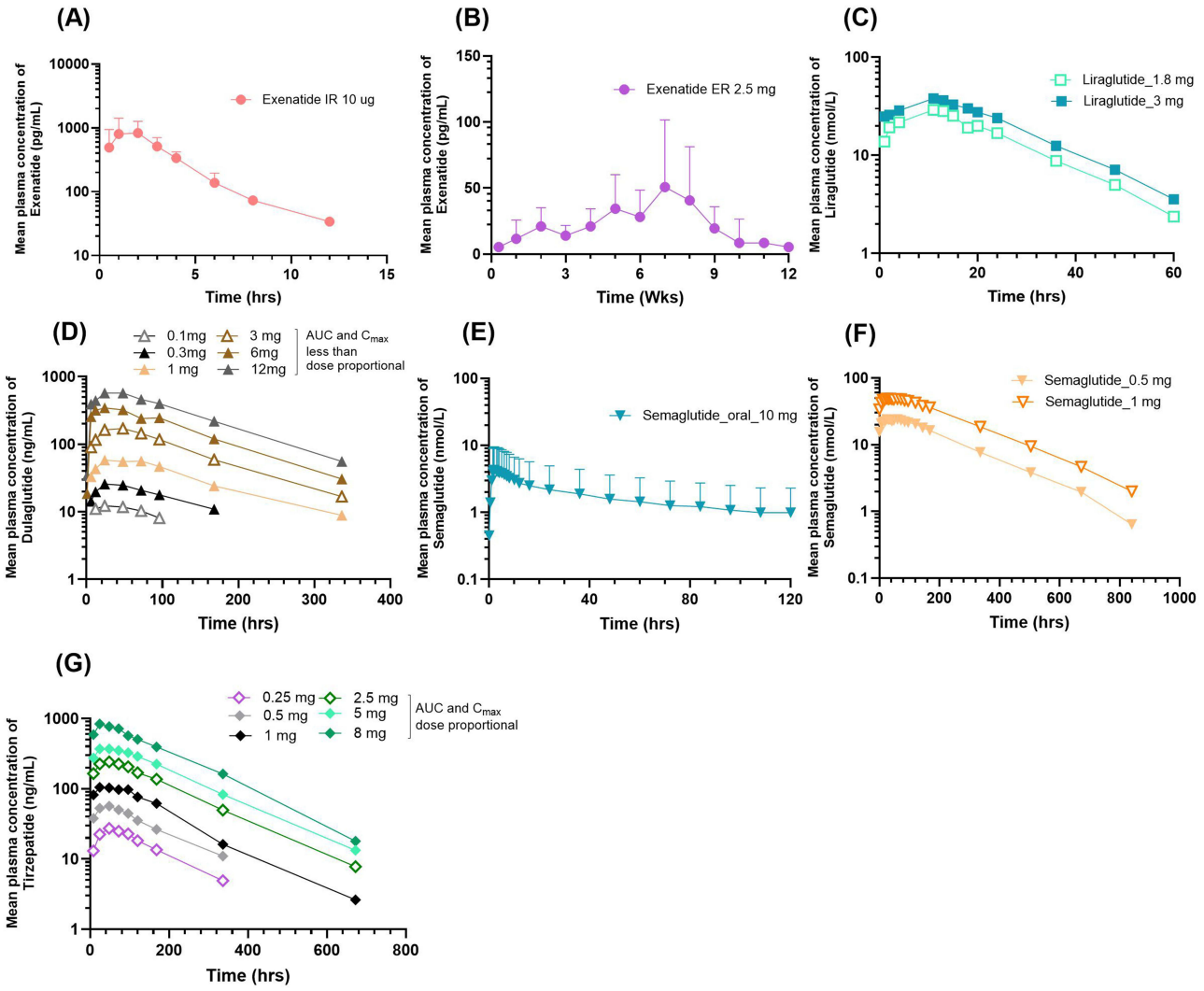

Figure 2 Continued.

(H)

	Exenatide		Liraglutide[63]	Dulaglutide[43,193]	Semaglutide		Tirzepatide[51,73]
	IR[36]	ER[54]			Oral[57,68]	SC[49,56]	
Population	T2DM	T2DM	Healthy, T2DM	T2DM	Healthy, T2DM	T2DM	Healthy, T2DM
C_{max}	less than dose proportional	-	dose proportional	less than dose proportional	dose proportional	dose proportional	dose proportional
AUC	dose proportional	less than dose proportional					
T_{max} (h)	2.1	2.1–5.1, 2 and 7 weeks	12 (7–14)	48 (24–72)	2–2.5	36–59.8	8–72
$t_{1/2}$ (h)	2.4	-	13 (11–15)	112.8	153–161	149–150	120
Vd(L)	-	-	11–24.7	-	8	-	-
CL (L/h)	-	-	0.6–1.2	-	0.04	-	-
F (%)	-	-	55	47–65	0.8	89	80
CL/*F* (L/h)	9.1	-	-	0.107	-	0.05	0.061
Vd/*F* (L)	28.3	-	-	17.4–19.2	-	12.5	10.3

Figure 2 Mean plasma concentration-time profiles (**A**–**G**) and pharmacokinetic parameters (**H**) of GLP-1 RAs and a dual GLP-1/GIP RA. (**A**) Mean + standard deviation (SD) plasma concentration-time profile of exenatide IR following a single dose of 10 µg in healthy participants (n = 39). Data obtained from the US FDA clinical pharmacology biopharmaceutics review of Byetta®.[52] (**B**) Mean + standard deviation (SD) plasma concentration-time profile of exenatide ER following a single dose of 2.5 mg in type 2 diabetes participants (n = 14). Adapted from Fineman M, Flanagan S, Taylor K et al. Pharmacokinetics and pharmacodynamics of exenatide extended-release after single and multiple dosing. *Clin Pharmacokinet*. 2011;50(1):65–74, with permission of Springer Nature.[54] Permission conveyed through copyright clearance center, inc. (**C**) Mean plasma concentration-time profile of liraglutide following 1.8 mg and 3 mg doses at steady state in obese participants (n = 30 and 32, respectively). Data obtained from US FDA clinical pharmacology biopharmaceutics review of liraglutide.[39] (**D**) Mean plasma concentration-time profile of dulaglutide following a single dose of 0.1–12 mg in healthy participants. Data obtained from US FDA clinical pharmacology biopharmaceutics review of dulaglutide.[55] (**E**) Mean + standard deviation (SD) plasma concentration-time profile of oral semaglutide following a single dose of 10 mg in healthy participants (n = 11). Data obtained from US FDA clinical pharmacology biopharmaceutics review of Rybelsus®.[57] (**F**) Mean plasma concentration-time profile of semaglutide following 0.5 mg and 1 mg doses at steady state in healthy participants (n = 8). Data obtained from US FDA clinical pharmacology biopharmaceutics review of semaglutide.[56] (**G**) Mean + standard deviation (SD) plasma concentration-time profile of tirzepatide following a single dose of 0.25–8 mg in healthy participants. Data obtained from US FDA clinical pharmacology biopharmaceutics review of tirzepatide.[58] (**H**) Pharmacokinetic parameters of approved GLP-1 RAs and a dual GLP-1/GIP RA. A power model was used for the statistical analysis of dose proportionality for $AUC_{0-\infty}$ and C_{max}. Data points were digitized using GetData Graph Digitizer (version 2.26) from graphical representations. Created in GraphPad Prism 10 (GraphPad Software, San Diego, CA, USA).

Abbreviations: IR, immediate-release; ER, extended-release; SC, subcutaneous; T2DM, type 2 diabetes mellitus; C_{max}, maximum plasma concentration; AUC, area under the curve; T_{max}, time to reach maximum plasma concentration; $t_{1/2}$, terminal half-life; Vd, volume of distribution; CL, total body clearance; *F*, absolute bioavailability; CL/*F*, apparent clearance; Vd/*F*, apparent volume of distribution.

approximately 10 weeks, exenatide diffused from the deeper parts of the microspheres as the polymer degraded into smaller fragments. This is followed by the final erosion release when the polymer fully hydrolyzes into lactic acid and glycolic acid.[54,62] Plasma concentrations of exenatide after ER formulation injection increased in a dose-dependent manner, but not dose-proportionally, across the 2.5–10 mg dose range.[54] The mean apparent volume of distribution for exenatide after a single dose administered twice daily is 28.3 L, and it is expected to remain the same for exenatide ER (Figure 2H).[38] In nonclinical studies, exenatide was mainly cleared by glomerular filtration, with subsequent proteolytic inactivation occurring in the renal tubules. In humans, exenatide has a dose-independent mean apparent clearance of 9.1 L/h.[38]

Liraglutide

The pharmacokinetics of liraglutide have been well documented in other reviews.[63] In brief, the absolute bioavailability (*F*) of liraglutide is about 55%; furthermore, it has slow absorption (T_{max}: approximately 12 h) (Figure 2C and H).[63,64] The volume of distribution (Vd) and CL estimates from a population pharmacokinetic study ranged between 11.0–24.7 L and 0.6–1.2 L/h, respectively, showing consistency across various populations, including healthy individuals and those with type 2 diabetes, as well as dosage levels.[63] Its half-life ($t_{1/2}$) is approximately 13h (11–15h) (Figure 2H). This prolonged half-life (Figure 2C) can be explained by its structure, being composed of human GLP-1 conjugated with 16-carbon fatty acids, which causes noncovalent binding to serum albumin, reducing renal clearance (Figure 1D).[65] The metabolism of liraglutide is mainly mediated by DPP-4 and neutral endopeptidase.[66] Moreover, unchanged liraglutide was not detected in both urine and feces, implying that it is completely degraded within the body.[66]

Dulaglutide

Dulaglutide is absorbed slowly, with a median T_{max} of 48 h (Figure 2D and H).[43] After a single subcutaneous dose of dulaglutide at 0.75 mg or 1.5 mg, the mean absolute bioavailability values (*F*) were 65% and 47%, respectively.[43] Systemic exposure to dulaglutide did not increase proportionally with doses ranging from 0.05 to 8 mg.[67] The steady state volume of distribution (Vd_{ss}) were 19.2 L and 17.4 L, following the administration of 0.75 mg and 1.5 mg dulaglutide, respectively (Figure 2H).[43] Dulaglutide is expected to be primarily metabolized by general protein catabolism, in which it is broken down into its constituent amino acids. The apparent clearance of dulaglutide at steady state was approximately 0.1 L/h for both the 0.75 mg and 1.5 mg once-weekly doses. The half-life ($t_{1/2}$) of dulaglutide for the 0.75 mg and 1.5 mg once-weekly doses is approximately 5 d, which supports its once-weekly administration (Figure 2D).[43]

Semaglutide

The absolute bioavailability (*F*) of subcutaneously administered semaglutide is 89% (Figure 2H).[48,49] Despite being co-formulated with an absorption enhancer, the absolute bioavailability of orally administered semaglutide was relatively low, at 0.8%.[68] This limited absorption is likely due to semaglutide's large molecular size.[69] Orally administered semaglutide is primarily absorbed in the stomach and is facilitated by an absorption enhancer, with a T_{max} of 2–2.5 h (Figure 2E and H).[57] Conversely, semaglutide administered subcutaneously is absorbed more slowly, with a T_{max} ranging from 36 to 59.8 h. It has a half-life ($t_{1/2}$) of approximately 7 d, which supports its once-weekly administration (Figure 2F).[48] Semaglutide possess a longer fatty acid chain (C-18 fatty acids) (Figure 1F) than liraglutide (C-16 fatty acids) (Figure 1D), which leads to increased albumin binding of the drug.[70] In addition, alanine at the 8^{th} position is substituted with 2-amino isobutyric acid in semaglutide, which increases the drug's resistance to DPP-4 (Figure 1F).[71] Such structure differences between liraglutide and semaglutide may result in a longer half-life and less frequent dosing of semaglutide. The apparent clearance and volume of distribution of semaglutide are 0.05 L/h and 12.5 L, respectively (Figure 2H). Semaglutide is metabolized by proteolysis and fatty acid oxidation and 3.1% of unchanged semaglutide is detected in urine.[72]

Tirzepatide

Tirzepatide has a mean absolute bioavailability (*F*) of 80% and is absorbed slowly, with a T_{max} of 8–72 h in patients with type 2 diabetes (Figure 2G and H).[51,73] The systemic exposure to tirzepatide increased dose-proportionally with doses ranging from 0.25 to 15 mg.[74] The mean apparent steady-state volume of distribution (Vd_{ss}) of tirzepatide in patients with type 2 diabetes is approximately 10.3 L. Metabolism of tirzepatide is primarily mediated by hydrolysis of the peptide and beta-oxidation of the fatty acid (Figure 2H).[51] The apparent clearance (CL/*F*) of tirzepatide is 0.061 L/h, and its half-life ($t_{1/2}$) is approximately 5 d, which supports once-weekly dosing (Figure 2G).[51,75] The metabolites are mainly excreted in urine and feces, while intact tirzepatide is not detected in either.[76] The pharmacokinetics of the drugs were found to be similar between healthy individuals and patients with type 2 diabetes.[77]

Pharmacological Effects and Adverse Events of GLP-1 RAs and a Dual GLP-1/GIP RA

After being absorbed into the bloodstream, both GLP-1 RAs and a dual GLP-1/GIP RA exert their pharmacological effects by interacting with their respective target cell membrane receptors.[78] GLP-1 receptors, class B of seven transmembrane G protein-coupled receptors, are expressed in various organs, including the brain, gastrointestinal tract, pancreas, kidneys, lungs, breasts, and thyroid gland.[79–81] GLP-1 receptors are also found in blood vessels within specific organs, particularly the kidneys and lungs.[79] Recent studies have also reported the presence of GLP-1 receptor mRNA transcripts in both heart chambers and heart muscle cells.[82,83] Similarly, GIP receptors are class B-seven-transmembrane G protein-coupled receptors that are also expressed in various organs. However, their binding affinities and specificities differ from those of GLP-1 receptors because of differences in their amino acid sequences.[84,85]

Their interactions activate various cell signaling pathways, which have been extensively reviewed in previous studies.[86,87] Based on this information, numerous clinical trials have been conducted, and the efficacy and adverse

events of pivotal clinical trials related to the US FDA approval of GLP-1 RAs and a dual GLP-1/GIP RA for the treatment of type 2 diabetes and obesity are summarized in Table 2.[88–96] Among the hitherto developed GLP-1 RAs, semaglutide has shown the highest efficacy with changes in HbA1c (%) and body weight of –1.45−1.55 and −14.85%, respectively, while tirzepatide has demonstrated relatively more effective blood glucose-lowering effects (−1.87−2.07) and weight loss (−15−20.9%) (Table 2).

In addition to the glucose-lowering effect mediated by the insulin secretion of pancreatic β-cells, and the central nervous-mediated delayed gastric emptying and satiety effects, some GLP-1 RAs also reportedly have cardioprotective, renoprotective, and hepatoprotective effects.[97–102] Evidence indicates that GLP-1 RAs either reduce the risk of major adverse cardiovascular events (MACEs) or have no effect on cardiac safety in patients with type 2 diabetes, based on findings from cardiovascular outcome trials.[97,98] Therefore, the indications for liraglutide, dulaglutide, and semaglutide have been expanded to treat patients with type 2 diabetes at risk of MACEs (Table 1). The pharmacological actions mediated by GLP-1 RAs, such as glucose-lowering effects, weight loss, reduced blood pressure, and improved lipid profile, may partially contribute to these cardiovascular outcomes.[87,99]

Table 2 also summarizes the most frequently reported adverse events from the pivotal clinical trials. GLP-1 RAs and a dual GLP-1/GIP RA administration-associated adverse events are primarily related to the gastrointestinal system, with nausea, vomiting, and diarrhea being the most common issues (Table 2).[103] To mitigate these adverse events, the doses of some GLP-1 RAs are carefully titrated (Table 1).[104] The administration of GLP-1 RAs to obese patients has also led to

Table 2 Half-Life, Efficacy, and Adverse Events of Approved GLP-1 RAs and a Dual GLP-1/GIP RA

Drug	Half-Life (h)	Clinical Trial		
		Dose	Endpoint Changes	Adverse Events (% of Number of Patient)
Exenatide (IR)	2.4 h[36]	DURATION-5 (n = 252, 24 wks)[88]		
		5 μg (4 wks) →10 μg (20wks) BID, SC	HbA1c (%) −0.9	Nausea (35.0) Vomiting (8.9) Headache (8.1)
Exenatide (ER)	–	DURATION-5 (n = 252, 24 wks)[88]		
		2 mg QW, SC	HbA1c (%) −1.6	Nausea (14) Diarrhea (9.3) Respiratory tract infection (7)
Liraglutide	13 h[63]	LEAD-6 (n = 464, 26 wks)[89]		
		1.8 mg QD, SC	HbA1c (%) −1.12	Nausea (25.5) Diarrhea (12.3) Nasopharyngitis (11.5)
		SCALE (n = 3731, 56 wks)[90]		
		3.0 mg QD, SC	Change in body weight (%) −8.0	Nausea (40.2) Diarrhea (20.9) Constipation (20.0)
Dulaglutide	112.8 h[43]	AWARD-6 (n = 599, 26 wks)[91]		
		1.5 mg QW, SC	HbA1c (%) −1.42	Nausea (20) Diarrhea (12) Dyspepsia (8)

(*Continued*)

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Table 2 (Continued).

Drug	Half-Life (h)	Clinical Trial		
		Dose	Endpoint Changes	Adverse Events (% of Number of Patient)
Semaglutide	149–161 h[49,56,57,68]	SUSTAIN-1 (n = 388, 30 wks)[92]		
			HbA1c (%)	Nausea (20–24) Diarrhea (11–13) Headache (7–12)
		0.5 mg QW, SC	−1.45	
		1 mg QW, SC	−1.55	
		PIONEER-1 (n = 703, 26 wks)[93]		
			HbA1c (%)	Nausea (5.1–16) Diarrhea (5.1–8.6) Vomiting (2.9–6.9)
		3 mg QD, Oral	−0.6	
		7 mg QD, Oral	−0.9	
		14 mg QD, Oral	−1.1	
		STEP-1 (n = 1961, 68 wks)[94]		
		2.4 mg QW, SC	Change in body weight (%)	Nausea (44.2) Diarrhea (31.5) Vomiting (24.8)
			−14.85	
Tirzepatide	120 h[51,73]	SURPASS-1 (n = 705, 40 wks)[95]		
			HbA1c (%)	Nausea (12–18) Diarrhea (12–14) Dyspepsia (6–9)
		5 mg QW, SC	−1.87	
		10 mg QW, SC	−1.89	
		15 mg QW, SC	−2.07	
		SURMOUNT (n = 2539, 72 wks)[96]		
			Change in body weight (%)	Nausea (24.6–33.3) Diarrhea (18.7–23.0) Constipation (11.7–17.1)
		5 mg QW, SC	−15	
		10 mg QW, SC	−19.5	
		15 mg QW, SC	−20.9	

Note: –, not determined.
Abbreviations: IR, immediate-release; BID, twice a day; SC, subcutaneous; HbA1c, hemoglobin A1c; ER, extended-release; QW, once a week; QD, once a day.

significantly higher risks of pancreatitis, bowel obstruction, and gastroparesis compared to those treated with bupropion-naltrexone.[105] Increased risk of gallbladder disease was also observed in patients with type 2 diabetes.[106] Recent studies have highlighted the association between diabetic retinopathy and GLP-1 RA treatment, indicating the need for further investigation into the underlying mechanisms and more comprehensive evidence.[107]

For GLP-1 RA, it appears that the incidence of adverse events increased as a drug remains in the body longer (Table 2). For example, exenatide IR, which has a short half-life ($t_{1/2}$ = 2.4 h), exhibits relatively fewer adverse events, with the percentages of patients experiencing nausea and vomiting being 35.0% and 8.9%, respectively. In contrast, semaglutide, which has a longer half-life ($t_{1/2}$ = 149–161 h), shows a higher incidence of adverse events (44.2, 31.5, and

24.8% for nausea, diarrhea, and vomiting, respectively) compared to liraglutide ($t_{1/2}$ = 13 h; 40.2, 20.9, and 20.0% for nausea, diarrhea, and constipation, respectively) (Table 2). The ongoing pharmacovigilance studies also report an increased incidence of gastrointestinal or metabolism and nutrition-related disorders as the half-life of GLP-1 RAs increases.[108,109] Traditionally, the relationship between pharmacokinetics and adverse events has been described based on the drug concentration in plasma.[110,111] Therefore, the longer the drug concentration is maintained in the body, the more likely it is to have a pronounced and longer-lasting impact on the affected organs.[112] However, there is evidence showing that GLP-1 RA-induced delayed gastric emptying experiences rapid tachyphylaxis, attenuated over time, and this effect must be taken into account for long-term use.[113] Therefore, findings from real-world evidence studies evaluating the long-term safety of GLP-1 RAs and a dual GLP-1/GIP RA should be carefully considered. There have been emerging reports of an elevated risk of adverse events, such as gastrointestinal and ocular disorders, acute pancreatitis, and thyroid cancer, associated with GLP-1 RA treatment.[108,109,114–116] In the future, large-scale data from these pharmacovigilance studies may enable more comprehensive discussions.

Moreover, exenatide (Figure 1C), which shares only 53% amino acid sequence homology with human GLP-1 (Figure 1A), has been reported to be associated with increased antibody development and exhibited a broad spectrum of adverse events.[117–119] Therefore, relationship between amino acid sequence of GLP-1 RAs and a dual GLP-1/GIP RA and the incidence of adverse events also need to be considered.

Pharmacokinetic DDIs of Peptide Drugs

Recently, the US FDA has released draft guidance addressing clinical considerations for peptide drugs.[120] The guidance defines a "peptide" as a molecule consisting of 40 or fewer amino acids. It recommends conducting in vitro studies related to cytochrome P450s (CYPs) and transporters if hepatic and/or biliary excretion constitutes >20% of the drug's total elimination or if the drug's primary target organ is the liver. Additionally, if the mechanism of action of the peptide drug can alter the pharmacokinetics of other co-administered drugs, it is recommended that the sponsor evaluate the peptide drug as a perpetrator.

Peptide drugs are mainly eliminated by protease enzymes, while liver uptake is minimal. This allows them to bypass metabolism by hepatic enzymes such as CYPs or UDP-glucuronosyltransferases (UGTs).[121–123] Consequently, drug-metabolizing enzyme-mediated DDIs, typically involving competition for the same CYP binding site with another drug, are uncommon in peptide drug-related DDIs.[124] Moreover, many peptide drugs are not known to be substrates or inhibitors of transporters at present, indicating that transporter-mediated biliary or renal excretion may not be a major pathway for their elimination.[124] Therefore, it was speculated that peptide drugs are unlikely to be involved in the occurrence of transporter-mediated DDIs.[122,124]

However, increasing evidence is reporting the involvement of peptide drugs in the occurrence of CYP or transporter-mediated DDIs.[123] The native glucagon peptide stimulates cAMP production, and elevated cAMP levels in rat hepatocytes indirectly reduce CYP2C11 expression.[125] Moreover, research indicates that growth hormone enhances CYP3A4 expression in human hepatocytes, while synthetic somatostatin analogs like octreotide, which inhibit endogenous growth hormone, may decrease CYP3A4 activity.[126] Co-administration of warfarin (a substrate of CYP1A2, CYP2C9, and CYP3A4) and octreotide led to high INR levels in humans, which may be attributed to the increased warfarin exposure caused by octreotide's inhibitory effect on CYP3A4.[127] Additionally, cyclosporine is an 11 aa-long lipophilic cyclic polypeptide used as an immunosuppressant.[128] Cyclosporine has been identified as a substrate for CYP3A4, P-glycoprotein (P-gp), and organic anion transporting polypeptides (OATPs), while also acting as a potent inhibitor of CYP3A4, multidrug resistance-associated protein 2 (MRP2), OATPs, P-gp, and breast cancer resistance protein (BCRP).[129–131] Cyclosporine was found to inhibit CYP3A4 with a K_i of 1.42 μM in human liver microsomes, and systemic exposure of atorvastatin increased 15-fold in humans with the co-administration of cyclosporine.[132,133]

A recent in vitro DDI study of ATSP-7041, a stapled α-helical peptide being developed as an anticancer agent, revealed minimal CYP inhibition. However, uptake transporter assays indicated that ATSP-7041 acts as both a substrate for OATPs and a potent inhibitor of OATP1B1 (IC_{50}: 0.81 μM), suggesting the potential for clinically relevant DDIs. Furthermore, ATSP-7041 inhibited the P-gp and BCRP-mediated efflux of the substrate.[134] In addition, a clinically significant DDI was reported in a Phase I study of ALRN-6924, an analog of ATSP-7041 and an inhibitor of

OATP1B3.[135] A patient co-administered with telmisartan (an OATP1B3 substrate) presented with hypotension, which may have been caused by increased exposure of telmisartan mediated by ATSP-7041.[135,136] Based on these findings, CYP- and transporter-mediated DDIs involving peptide drugs are not negligible and should be carefully evaluated.

Pharmacokinetic DDIs of GLP-1 RAs and a Dual GLP-1/GIP RA

Drug-Metabolizing Enzyme-and Transporter-Mediated DDIs

GLP-1 RAs and a dual GLP-1/GIP RA are now approved for the treatment of type 2 diabetes and obesity, with patients frequently managing coexisting metabolic diseases that require additional medications.[137] Consequently, using multiple medications can result in DDIs, often leading to adverse drug reactions, making it crucial to assess the DDI potential.[138] To date, there are limited data on clinically significant metabolic enzyme- or transporter-mediated DDIs involving GLP-1 RAs and a dual GLP-1/GIP RA. In vitro DDI studies detailed in clinical pharmacology and biopharmaceutics reviews were not included for exenatide and dulaglutide, but were included for liraglutide, semaglutide, and tirzepatide (Table 3).[39,56–58,139] All the investigated GLP-1 RAs and a dual GLP-1/GIP RA exhibited minimal inhibition or induction of CYP enzymes. However, semaglutide and tirzepatide inhibited OATP1B1/3 activity, despite their relatively large molecular size, in the absence of bovine serum albumin (BSA). In addition, P-gp- and BCRP-mediated efflux was inhibited by tirzepatide. However, plasma concentrations of semaglutide at steady state are estimated to be about 100 times lower than the IC_{50} values for OATP1B1/3 (3.50 μM and 2.95 μM, respectively).[56] Moreover, when BSA was

Table 3 Overview of in vitro Drug-Metabolizing Enzyme and Transporter-Mediated DDI Studies by Approved GLP-1 RAs and a Dual GLP-1/GIP RA

	Enzyme		Transporter	
Drug	**Mediator**	**Mechanism** **Results** **Potential Clinical Outcome**	**Mediator**	**Mechanism** **Results** **Potential Clinical Outcome**
Exenatide	–			
Liraglutide[39]	CYP 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4	Inhibition IC_{50} > 100 μM Low	–	
Dulaglutide	–			
Semaglutide[56,57,139]	CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5	Inhibition * Low	P-gp, and BCRP	Inhibition * Low
	CYP1A2, 2B6, and 3A4/5	Induction * Low	OATP1B1, OATP1B3, OAT1, OAT3, and OCT2	Inhibition OATP1B1 IC_{50}: 3.50 μM OATP1B3 IC_{50}: 2.95 μM (Without BSA) Low

(*Continued*)

Table 3 (Continued).

	Enzyme		Transporter	
Drug	**Mediator**	**Mechanism**	**Mediator**	**Mechanism**
		Results		**Results**
		Potential Clinical Outcome		**Potential Clinical Outcome**
Tirzepatide[58]	CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5	Inhibition	P-gp, and BCRP	Inhibition
		IC_{50} > 100 μM		IC_{50} > 100 μM
		Low		Low
	CYP1A2, 2B6, 2C8, 2C9, C19, 2D6, and 3A4/5	Induction	OCT1, OCT2, OAT1, OAT3 OATP1B1 and OATP1B3	Inhibition
		*		OATP1B1 IC_{50}: 15.65 μM OATP1B3 IC_{50}: 2.81 μM (Without BSA)
		Low		Low
			MATE1 and MATE2-K	Inhibition
				*
				Low

Notes: –, not determined; *, weak or no inhibition/induction.
Abbreviations: DDI, drug-drug interaction; CYP, cytochrome P450; IC_{50}, half maximal inhibitory concentration; P-gp, P-glycoprotein; BCRP, breast cancer resistance protein; OATP, organic anion transporting polypeptide; OAT, organic anion transporter; OCT, organic cation transporter; BSA, bovine serum albumin; UGT, uridine diphosphate-glucuronosyltransferase; MATE, multidrug and toxin extrusion protein.

added, the inhibitory effect disappeared or was diminished, probably due to the binding of the fatty acid residues of GLP-1 RAs and a dual GLP-1/GIP RA to BSA.[70]

In addition, a clinical DDI study was conducted to investigate the inhibitory effect of the absorption enhancer for oral semaglutide (SNAC) on BCRP, OAT1/3, and OATP1B1 based on in vitro data.[140] However, the administration of SNAC alone did not alter the plasma concentrations of furosemide (an OAT1 and OAT3 substrate) or rosuvastatin (a BCRP and OATP1B1 substrate). Therefore, the sponsors concluded that clinically significant DDIs mediated by direct inhibition of CYP enzymes or transporters are unlikely to occur with the administration of GLP-1 RAs and a dual GLP-1/GIP RA.

Mechanisms of Action-Mediated DDIs

Furthermore, assessing DDIs for GLP-1 RAs and a dual GLP-1/GIP RA requires additional considerations, including the possible occurrence of DDIs mediated by mechanisms of action that remain poorly understood (Figure 3).[120] Long-acting GLP-1 RAs remain in the body for an extended period (eg, with a mean residence time [MRT] of 224 hours at a steady state after administering 14 mg of oral semaglutide).[141] This prolonged duration may be driven by albumin binding to the fatty acid residues of GLP-1 RAs and their ability to escape protease metabolism due to amino acid substitutions (Figure 1).[141] They remain in the body, interacting with GLP-1 receptors in various organs, which could lead to DDIs through mechanisms of action such as slowing gastric emptying, reducing fat mass and inflammation, and increasing glomerular filtration rate (GFR) and renal plasma flow, consequently altering the pharmacokinetics of the victim drug (Figure 3).[124,142] Investigations into mechanism of action-mediated pharmacokinetic DDIs are currently limited to those mediated by the slowing of gastric emptying, with examples summarized in other reviews.[124,143]

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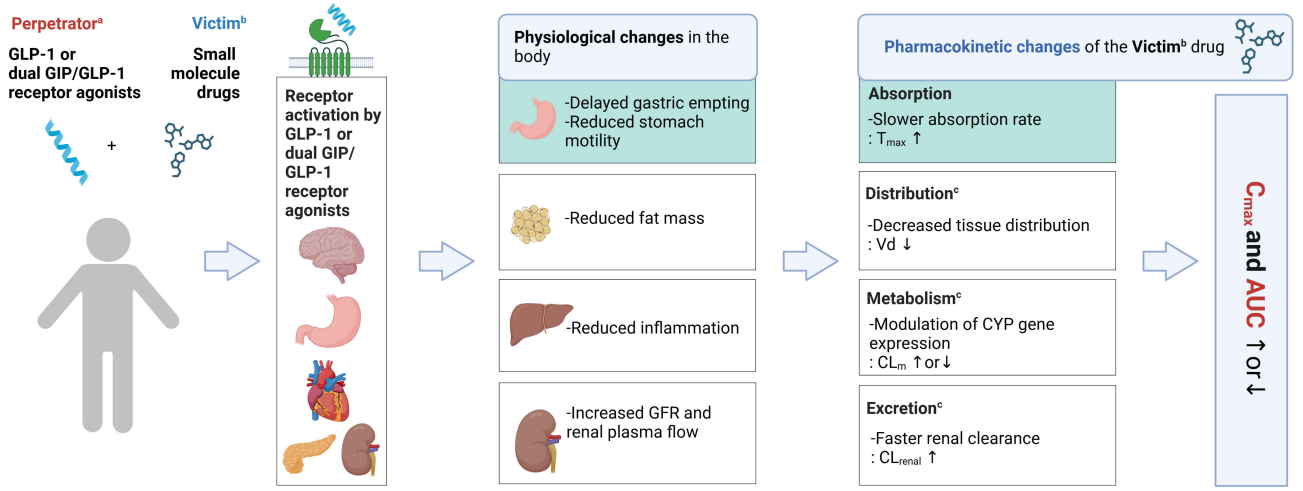

Figure 3 Flowchart illustrating the process of pharmacokinetic DDIs mediated by the mechanisms of action of approved GLP-1 RAs and a dual GLP-1/GIP RA; 1) GLP-1 RAs or a dual GLP-1/GIP RA (perpetrator) administration triggers receptor activation in GLP-1 receptor-expressing organs, leading to drug efficacy → 2) Physiological changes in the human body due to the drug effect → 3) Pharmacokinetic changes of small-molecule drugs (victim) influenced by these physiological changes. Created in BioRender. Min, J. (2025) https://BioRender.com/g44y018.

Notes: [a]Perpetrator, the drug that influences the pharmacokinetics of another drug; [b]Victim, the drug altered by the DDIs; [c]Mechanism of action-mediated pharmacokinetic changes requiring additional validation through follow-up studies.

The pharmacokinetic DDI are commonly expressed in terms of "victim drug" and "perpetrator drug". The perpetrator drug is the drug which affects the pharmacokinetics of the other drug; the victim drug is the drug affected by the DDI.[144] GLP-1 RAs or a dual GLP-1/GIP RA as perpetrator drugs in combination with a victim drug, a number of clinical trials have been conducted to evaluate DDI potentials (Table 4 and Table 5). The regulatory guidance for DDI studies emphasizes that "perpetrators" must attain systemic exposure consistent with the highest therapeutic dose administered under steady-state conditions.[144,145] Therefore, the effect of GLP-1 RAs or a dual GLP-1/GIP RA at steady-state conditions on the victim drug was generally investigated in the studied DDIs. Currently, an exact standard for determining pharmacokinetic changes caused by DDIs that may have a clinically significant impact has not been established. However, regulatory guidance states that when the ratio of the area under the concentration-time curve (AUC) of the victim drug with and without the perpetrator drug falls outside the range of 0.8–1.25, there is a potential risk of a clinically significant impact, necessitating further investigation.[146] The rationale for selecting the victim drugs was based on their being commonly used or a narrow therapeutic index, with different Biopharmaceutics Classification System (BCS) classifications.[124] The list of victim drugs that have been investigated to confirm the magnitude of DDIs caused by delayed gastric emptying is as follows: acetaminophen, metoprolol and oral contraceptives (BCS Class I); statins and griseofulvin (BCS Class II); levothyroxine, lisinopril, metformin, and sitagliptin (BCS Class III); digoxin and furosemide (BCS Class IV).[124,140,143,147–163]

In general, the administration of GLP-1 RAs delayed the absorption of the tested drugs by decreasing C_{max} and/or delaying t_{max}. However, the AUC of the victim drugs were not altered by GLP-1 RA administration in most cases, suggesting that clinically significant DDIs are unlikely to occur.[124] Conversely, both the C_{max} and AUC of statins decreased by 28–70% and 0–40%, respectively, after GLP-1 RA subcutaneous administration.[140,147,153,155,159] However, statins are known to exhibit high interindividual variability in terms of pharmacokinetics, and GLP-1 RA administration did not affect the lipid-lowering effect of statins in clinical studies, indicating minimal clinical significance.[147,164] Moreover, the AUC of metformin increased by 32%, while the C_{max} of metformin remained unchanged following oral semaglutide administration.[158] In addition, the C_{max} and AUC of furosemide were decreased by 34% and increased by 28%, respectively.[140] Due to metformin and furosemide's wide therapeutic index, the risk of clinically significant DDIs is low.[140,158]

Administration of SNAC, the absorption enhancer for oral semaglutide, did not alone alter exposure to lisinopril, warfarin, digoxin, or metformin. The AUC and C_{max} ratios with or without SNAC administration remained within the 0.8–1.25 range.[158]

DDIs with Oral Contraceptives

Some GLP-1 RAs and a dual GLP-1/GIP RA altered the exposure of oral contraceptives, implying the potential for clinically significant DDIs (Table 4).[55,57,148,155,157,161,163] About 25% of women between the ages of 15 and 44 use oral contraceptives, highlighting the importance of studying their potential DDIs.[165,166] The C_{max} and AUC values of ethinylestradiol and levonorgestrel were not affected by the administration of 14 mg oral or 1 mg subcutaneous semaglutide, indicating that it is not clinically relevant (Table 4).[56,157] Notable changes in the C_{max} ratios of oral contraceptives after the administration of 10 µg exenatide twice daily seem to be caused by their administration 30 min after exenatide, when the delayed gastric emptying effect was at its peak. Therefore, it was concluded that clinically significant pharmacokinetic changes are unlikely to occur.[148,167] Similarly, alterations in the pharmacokinetics after 1.8 mg liraglutide and 1.5 mg dulaglutide administration have also been shown to have minimal clinical significance.[161,168]

The most significant pharmacokinetic alterations were reported following the administration of a single 5 mg dose of tirzepatide, with the C_{max} and AUC values of ethinylestradiol decreasing by 59% and 21%, respectively, and those of norelgestromin by 55% and 22%, respectively (Table 4).[161] However, the pharmacokinetic /pharmacodynamic relationship of oral contraceptives is not yet fully defined; therefore, additional studies are required to explore how changes in exposure influence their effectiveness.[166] Moreover, this implies that tirzepatide more strongly affects the absorption of oral contraceptives and that this increased impact may be driven by rapid dose escalation.[161] Unlike other pharmacodynamic effects, such as lowering blood glucose or reducing appetite, the delay in gastric emptying shows tachyphylaxis, with the effect gradually decreasing over time.[169] Therefore, the investigators have suggested switching to a non-oral

Table 4 Changes in Oral Contraceptive Pharmacokinetics without and with Treatment with Approved GLP-1 RAs or a Dual GLP-1/GIP RA

Victim[a]			Perpetrator[b]				
			Exenatide[148]	Liraglutide[163]	Dulaglutide[55,155]	Semaglutide[140]	Tirzepatide[51,161]
Ethinylestradiol	T_{max} difference (h)		+ 4.5	+ 1	+ 0.3	–	+ 4.99
	C_{max} (ratio)	w/wo	↓ (0.55)	↔ (0.88)	↔ (0.87)	↔ (0.97)	↓ (0.41)
	AUC (ratio)		↔ (0.96)	↔ (1.06)	↔ (1.03)	↔ (1.06)	↓ (0.79)
Levonorgestrel	T_{max} difference (h)		+ 3.75	+ 1	ND	–	ND
	C_{max} (ratio)	w/wo	↓ (0.73)	↔ (0.87)		↔ (0.95)	
	AUC (ratio)		↔ (1.05)	↔ (1.15)		↔ (1.06)	
Norelgestromin	T_{max} difference (h)		ND	ND	+ 2	ND	+ 4.5
	C_{max} (ratio)	w/wo			↓ (0.74)		↓ (0.45)
	AUC (ratio)				↔ (0.97)		↓ (0.78)

Notes: [a]Victim, the drug altered by the DDIs; [b]Perpetrator, the drug that influences the pharmacokinetics of another drug; +, delayed; –, no difference; ↓, decreased (ratio<0.8); ↔, no change (ratio 0.8−1.25).

Abbreviations: T_{max}, time to reach maximum plasma concentration; C_{max}, maximum plasma concentration; AUC, area under the curve; w/wo, with/without; ND, not determined.

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contraceptive option or adding a barrier method of contraception for 4 weeks after tirzepatide administration is initiated or if the dose is substantially increased.[50,51]

DDIs with Narrow Therapeutic Index Drugs

Other clinical studies on DDIs have investigated the delayed gastric emptying effect of GLP-1 RA on the pharmacokinetics of drugs with narrow therapeutic index (Table 5). It was concluded that the C_{max} and AUC changes of digoxin after GLP-1 RA administration may not be clinically significant.[55,56,58,150,153] Likewise, the pharmacokinetics of warfarin were not altered by semaglutide administration.[158,159] The AUC of S- and R-warfarin was not affected by dulaglutide and tirzepatide administration.[55,58] However, postmarketing data on exenatide indicate an increase in INR, which is sometimes associated with bleeding events, highlighting the need for close INR monitoring after GLP-1 RA treatment.[36]

Furthermore, DDIs between levothyroxine and oral semaglutide, caused by delayed gastric emptying, have been explored (Table 5).[160] Levothyroxine, a synthetic form of the thyroid hormone thyroxine, is an orally administered narrow therapeutic index drug used to treat hypothyroidism.[170] It has been reported that gastrointestinal motility may affect its bioavailability, and reduced absorption is a leading contributor to refractory hypothyroidism.[171,172] Therefore, it is recommended to administer levothyroxine at least 1 h before meals.[173] Based on this information, the influence of gastric emptying effect by oral semaglutide administration on pharmacokinetics of levothyroxine was investigated.[160] After multiple oral doses of 14 mg oral semaglutide, the T_{max} of levothyroxine was delayed by 2 h, with a 12% decrease in the C_{max} and a 33% increase in the AUC, indicating potential clinical relevance (Table 5). Therefore, monitoring thyroid parameters is advised when oral semaglutide is co-administered.[45,160]

Table 5 Changes in Narrow Therapeutic Index Drug Pharmacokinetics without and with Treatment with Approved GLP-1 RAs or a Dual GLP-1/GIP RA

Victim[a]			Perpetrator[b]				
			Exenatide[149,151]	Liraglutide[153]	Dulaglutide[55,155]	Semaglutide[158–160]	Tirzepatide[c58]
Digoxin	T_{max} difference (h)		+ 2.5	+ 1.12	+ 0.5	–	ND
	C_{max} (ratio)	w/wo	↔ (0.82)	↓ (0.69)	↓ (0.78)	↔ (0.98)	↓ (0.78)
	AUC (ratio)		↔ (0.95)	↔ (0.84)	↔ (0.96)	↔ (1.03)	↔ (1.0)
Levothyroxine	T_{max} difference (h)		ND	ND	ND	+ 2	ND
	C_{max} (ratio)	w/wo				↔ (0.88)	
	AUC (ratio)					↑ (1.33)	
R-Warfarin	T_{max} difference (h)		+ 1	ND	+ 5.5	+ 2	ND
	C_{max} (ratio)	w/wo	↔ (1.05)		↔ (0.86)	↔ (0.93)	
	AUC (ratio)		↔ (1.11)		↔ (0.99)	↔ (1.04)	
S-Warfarin	T_{max} difference (h)		+ 2	ND	+ 4.02	+ 2	ND
	C_{max} (ratio)	w/wo	↔ (0.97)		↓ (0.78)	↔ (0.91)	↔ (0.82)
	AUC (ratio)		↔ (1.06)		↔ (0.99)	↔ (1.05)	↔ (1.0)

Notes: [a]Victim, the drug altered by the DDIs; [b]Perpetrator, the drug that influences the pharmacokinetics of another drug; [c]Predicted by physiologically based pharmacokinetic modeling; +, delayed; –, no difference; ↔, no change (ratio 0.8–1.25); ↓, decreased (ratio<0.8); ↑, increased (ratio>1.25).

Abbreviations: T_{max}, time to reach maximum plasma concentration; C_{max}, maximum plasma concentration; AUC, area under the curve; w/wo, with/without; ND, not determined.

In summary, most of the studied drugs did not show clinically significant DDIs related to delayed gastric emptying caused by GLP-1 RAs or a dual GLP-1/GIP RA administration. However, oral contraceptives and levothyroxine, showed notable changes in AUC following the administration of tirzepatide and oral semaglutide, respectively, implying a potential risk of a clinically significant DDIs (Table 4 and Table 5). This indicates the need for close monitoring when GLP-1 RAs and a dual GLP-1/GIP RA are co-administered, especially when starting treatment or increasing the dose. For a more accurate assessment, large-scale pharmacokinetic/pharmacodynamic (PK/PD) studies need to be conducted. Delayed gastric emptying may undergo tachyphylaxis, potentially reducing the impact of DDIs with repeated dosing.[169,174] Moreover, delayed absorption of the concomitant drug due to delayed gastric emptying can be minimized by administering the drug 1 h before GLP-1 RAs or a dual GLP-1/GIP RA administration.[168] However, the possibility of DDIs related to delayed gastric emptying cannot be excluded,[175] so investigators recommend monitoring when oral drugs are co-administered with GLP-1 RAs and a dual GLP-1/GIP RA.

The Developed Pharmacokinetic Models for GLP-1 RAs and a Dual GLP-1/GIP RA

Pharmacokinetic models of GLP-1 RAs and a dual GLP-1/GIP RA have been developed as clinical support tools, enabling the prediction of their pharmacokinetic behavior across different clinical scenarios (Table 6). The developed pharmacokinetic models of GLP-1 RAs and a dual GLP-1/GIP RA were searched in the PubMed electronic database. The search terms were "exenatide", "liraglutide", "dulaglutide", "semaglutide", or "tirzepatide", along with "pharmacokinetic model". A total of 26 articles were identified as of October 8, 2024. Clinical pharmacology and biopharmaceutics reviews released electronically by the US FDA were also examined for information on the pharmacokinetic models of GLP-1 RAs and a dual GLP-1/GIP RA.[39,52,55–58,139,176] Thirty pharmacokinetic models were developed to predict the pharmacokinetics of GLP-1 RAs and a dual GLP-1/GIP RA. Among the GLP-1 RAs and a dual GLP-1/GIP RA, exenatide has the most developed pharmacokinetic model (9 of 30),[61,177–184] followed by semaglutide (8 of 30),[68,162,182,185–189] liraglutide and dulaglutide (each 5 of 30),[156,177,182,189–194] and tirzepatide (3 of 30).[58,73,195] The developed pharmacokinetic models were used either

Table 6 The Developed Pharmacokinetic (PK) and Pharmacokinetic/Pharmacodynamic (PK/PD) Models of Approved GLP-1 RAs and a Dual GLP-1/GIP RA

Drug	Model Type	Software	Application
Exenatide IR	Pop PK	NONMEM	: PKs of exenatide IR formulation across various concentration levels and different population[61]
		NONMEM	: PKs of twice daily exenatide in subjects with T2DM[177]
	TMDD	MATLAB® R2009a	: Interspecies scaling[178]
	PK/PD	IQM Tools, MATLAB® R2013b	: Exposure-response relationship; gastric emptying rate, glucose rate of appearance in plasma[179]
Exenatide ER	PBPK	Simcyp™	: PKs of exenatide with once-monthly dosing[180]
	Pop PK	NONMEM	: PKs of exenatide ER formulation[181]
	Pop PK PK/PD	NONMEM	: Exposure-response relationship; HbA1c reduction and weight loss[182]
	TMDD/PD	Monolix®	: Exposure-response relationship; FPG and HbA1c reduction[183]
Exenatide (IR, ER)	Pop PK PK/PD	NONMEM	: Exposure-response relationship; QT interval change[184]

(*Continued*)

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Table 6 (Continued).

Drug	Model Type	Software	Application
Liraglutide	Pop PK	NONMEM	: PKs in pediatric and adult with T2DM[190]
		NONMEM	: PKs in subjects with overweight and obese[191]
		NONMEM	: PKs in subjects with T2DM[177]
	Pop PK/PD	NONMEM	: Exposure-response relationship; weight loss[192]
	Pop PK PK/PD	NONMEM	: Exposure-response relationship; HbA1c reduction and weight loss[182]
Dulaglutide	PBPK	Simcyp™	: DDI; assess the effects of delayed gastric emptying caused by dulaglutide on the PKs of atorvastatin[156]
	Pop PK	NONMEM	: PKs in subjects with T2DM[193]
	Pop PK PK/PD	NONMEM	: Exposure-response relationship; nausea and vomiting events[194]
		NONMEM	: Exposure-response relationship; HbA1c reduction and weight loss[189]
		NONMEM	: Exposure-response relationship; HbA1c reduction and weight loss[182]
Semaglutide	PBPK	Gastroplus®	: PKs in pediatrics with normal and obese body weights[185]
	Pop PK	Phoenix NLME™	: DDIs; assess the effects of delayed gastric emptying caused by semaglutide on the PKs of acetaminophen and atorvastatin[162]
		NONMEM	: PKs after oral administration and in subjects with T2DM[68]
		NONMEM	: PKs in subjects with T2DM[186]
		NONMEM	: PKs in subjects with T2DM[187]
	Pop PK PK/PD	NONMEM	: Exposure-response; weight loss[188]
		NONMEM	: Exposure-response; HbA1c reduction and weight loss[182]
		NONMEM	: Exposure-response; HbA1c reduction and weight loss[189]
Tirzepatide	PBPK	PK-Sim® and MoBi®	: Pediatric dose[195]
		Simcyp™	: DDIs; assess the effects of delayed gastric emptying caused by tirzepatide on PKs of atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin, S-warfarin[58]
	Pop PK	NONMEM	: PKs in in different population[73]

Abbreviations: IR, immediate-release; Pop PK, population pharmacokinetics; NONMEM, NONlinear mixed-effects modeling; T2DM, type 2 diabetes mellitus; TMDD, target-mediated drug disposition; PD, pharmacodynamics; ER, extended-release; PBPK, physiologically based pharmacokinetics; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; DDI, drug–drug interaction.

solely to predict pharmacokinetics (18 of 30) or integrated with pharmacodynamic models to evaluate responses (12 of 30). Most of the developed pharmacokinetic models were population pharmacokinetic models utilizing nonlinear mixed effect modeling (22 of 30). The models have been used to predict pharmacokinetics in special populations, including those with hepatic or renal impairment, as well as in disease states such as type 2 diabetes and obesity. Additionally, pharmacokinetic differences were predicted in subjects based on factors such as age, body weight, sex, race, ethnicity, and injection site, with most GLP-1 RAs and a dual GLP-1/GIP RA exhibiting only minor variations.

Physiologically based pharmacokinetic (PBPK) models have been developed for exenatide (1 of 30), dulaglutide (1 of 30), semaglutide (1 of 30), and tirzepatide (2 of 30). The developed models were used to investigate the initial dose for

pediatric patients (2 of 30), the potential for DDIs caused by delayed gastric emptying (2 of 30), and the pharmacokinetics of once-monthly dosing (1 of 30) (Table 6).

Delayed gastric emptying-mediated DDIs have been investigated using both PBPK models (2 of 30) and population pharmacokinetic models (1 of 30). For example, increased gastric emptying time due to the mechanism of action of dulaglutide was described in the developed PBPK model by modulating the default gastric MRT.[156] Administering 1.5 mg of dulaglutide reportedly decreased gastric emptying by roughly threefold, with the initial MRT (0.27 h) increasing to 0.84 h.[196] The refined model successfully described the pharmacokinetic profiles of the affected drug, atorvastatin acid and lactone, after dulaglutide administration in Simcyp™ (Certara UK Limited, Sheffield, United Kingdom).[156] It appears that clinically significant DDIs caused by delayed gastric emptying affecting the pharmacokinetics of the victim drugs are unlikely to occur.[58,156,162]

Future Perspectives

GLP-1 RAs Currently Under Development

Based on previous findings, dosages that enable longer durations and less frequent administrations have been investigated. For example, efpeglenatide, a long-acting GLP-1 RA and an exendin analog linked to an IgG4 Fc fragment, has been explored for once-monthly administration to treat type 2 diabetes.[197,198] Additionally, efforts have been made to develop oral formulations with improved bioavailability (*F*). Orforglipron, a nonpeptide GLP-1 RA administered once daily, showed dose-dependent efficacy on weight loss in a Phase II trial.[199]

Currently, investigations into GLP-1 RAs and similar drugs are underway to obtain approval for additional indications based on their diverse pharmacological effects. Liraglutide and semaglutide have beneficial effects on non-alcoholic steatohepatitis.[200,201] Additionally, incretin mimetic drugs targeting multiple receptors for greater efficacy, including glucagon and GIP receptors, are under development.[202] A Phase 2a study of efocipegtrutide (HM15211), a new long-acting triple GLP-1/GIP/glucagon RA is currently being conducted to assess its use to treat non-alcoholic steatohepatitis.[203] Survodutide, a novel dual GLP-1/ glucagon RA, significantly reduced body weight and improved metabolic dysfunction-associated steatohepatitis compared to the placebo in phase II trials.[204] Mazdutide, a dual GLP-1/ glucagon RA, and retatrutide, a triple GLP-1/GIP/glucagon RA, also have both shown significant weight loss effects in Phase 2 trials.[205,206]

Among the drugs discussed, including US FDA-approved GLP-1 RAs, tirzepatide was reported to achieve the most significant reduction in blood glucose levels. This weight loss effect was most potent in the CagriSema (cagrilintide and semaglutide combination therapy)-treated group, followed by tirzepatide and retatrutide.[97] These new GLP-1 RAs, including dual and triple agonists, are now in Phase 3 trials, and the clinical use of more potent GLP-1 RAs with additional indications is expected.

Drug-Metabolizing Enzyme- and Transporter- Mediated DDIs of GLP-1 RAs and a Dual GLP-1/GIP RA

To date, no clinically relevant drug-metabolizing enzyme- or transporter-mediated DDIs involving GLP-1 RAs or a dual GLP-1/GIP RA have been reported (Table 3). However, some transporters, including OATP1B1/3 and OAT3, demonstrated inhibition following treatment with GLP-1 RAs and a dual GLP-1/GIP RA in vitro, suggesting that the assessment of transporter-mediated DDI by GLP-1 RAs may be necessary (Table 3). Moreover, glucagon treatment in human hepatocytes leads to the downregulation of CYP gene expression, and the underlying mechanism may be driven by the activation of glucagon receptors expressed in the liver.[125,207,208] Drugs targeting both GLP-1 and glucagon receptors are currently under development, and it is vital to examine their indirect effects on CYP gene expression. Currently, in vitro studies on peptide-mediated DDIs, which would provide better in vitro to in vivo extrapolation, remain poorly established.[207] A recent study introduced new experiment designs using HepatoPac® (Hepregen Corporation, Medford, MA, USA), spheroids or liver-on-a-chip models to assess the modulation of CYPs and transporter gene expression by peptides, but further large-scale experiments are still needed.[209]

Pharmacokinetic DDIs Caused by Mechanisms of Actions Following GLP-1 RAs or a Dual GLP-1/GIP RA Treatment

GLP-1 RAs are currently attracting significant attention because of their remarkable weight loss-promoting effects. From a pharmacokinetic perspective, besides increased gastric emptying, obesity has been suggested to modulate CYP gene expression, and increased fat mass may result in an increased Vd of lipophilic drugs.[210,211] The weight loss effects from GLP-1 RA treatment may reverse these changes and alter the pharmacokinetics of co-administered lipophilic drugs by decreasing the Vd (Figure 3). For example, the Vd of diazepam, lorazepam, and nitrazepam decreased by 3.2-, 1.7-, and 2.1-fold, respectively, in non-obese participants, and their CL and $t_{1/2}$ were altered, indicating the need for dose adjustment.[212]

Furthermore, the anti-inflammatory properties of GLP-1 RAs constitute another notable effect. They can reduce levels of inflammatory biomarkers, such as C-reactive protein and inflammatory cytokines (eg, tumor necrosis factor-alpha and interleukin-6).[100,101] This positively impacts various pathophysiological conditions, including type 2 diabetes, obesity, and non-alcoholic fatty liver disease.[100–102] In addition, inflammatory cytokines are reportedly involved in CYP gene expression, with the reduced cytokine levels-mediated by GLP-1 RA administration may alter CYP gene expression, potentially leading to changes in the pharmacokinetics of co-administered drugs (Figure 3).[213]

Finally, cardiovascular outcome trials have demonstrated that GLP-1 RAs offer beneficial effects on kidney function in type 2 diabetes and decrease the risk of major adverse kidney events in patients with type 2 diabetes and acute kidney disease.[99,214] These renoprotective effects are expected to be driven by both direct and indirect mechanisms including reducing albuminuria, reducing inflammation, natriuresis and diuresis induction, and antioxidative effects.[215] Moreover, GLP-1 RA treatment reportedly increased renal plasma flow and GFR in rats, leading to natriuresis and diuresis.[216] It is known that changes in GFR can affect the elimination of many drugs including narrow therapeutic index drugs (aminoglycosides, lithium, digoxin), diuretics, and nonsteroidal anti-inflammatory drugs.[217–221] Therefore, pharmacokinetic changes in drugs mediated by increased GFR and renal plasma flow following GLP-1 RA administration may occur, and the impact of its mechanism of action need to be investigated in the future. Moreover, as these mechanisms of action may occur concurrently, it is important to investigate alterations in drug exposure when multiple mechanisms are considered simultaneously.

Utilization of PBPK Modeling Approaches to Assess DDIs Caused by Mechanisms of Actions

Evaluating the mechanism of action (eg, delayed gastric emptying, reduced fat mass and inflammation, and changes in GFR)-mediated DDIs of GLP-1 RAs and a dual GLP-1/GIP RA is often challenging to control for and clinical studies are costly. Therefore, modeling approaches can be valuable for examining the extent of pharmacokinetic DDIs driven by these mechanisms. Among various modeling techniques, PBPK modeling appears to be particularly promising. Notably, the US FDA submission documents for tirzepatide include predictions of DDIs mediated by delayed gastric emptying using PBPK modeling, rather than conducting clinical DDI studies for certain drugs (Table 6).[58] PBPK modeling is a mathematical approach that uses differential equations to predict pharmacokinetics in humans and other species. It has become a valuable tool in various stages of drug development, including first-in-human dose calculation, predicting DDI potential, and assessing pharmacokinetic profiles in special populations such as pediatrics and patients with renal or hepatic impairment.[222,223] In particular, it is widely used to predict potential pharmacokinetic DDIs of small molecules.[224] Physiological properties of the body, including organ mass and volume, blood flow rate, plasma protein levels, and the abundance of enzyme and transporter expression, are mathematically described within the model.[225,226] Therefore, the mechanism of action of GLP-1 RAs and a dual GLP-1/GIP RA can be characterized by modulating physiological properties within the model, enabling the prediction of altered pharmacokinetics for the affected drug. To effectively develop a PBPK model for studying mechanism-of-action-mediated DDIs, it is essential to carefully assess the extent to which these mechanisms impact pharmacokinetics. After the validation process, the developed PBPK model can be used to assess the impact of the mechanism of action on the pharmacokinetics of various victim drugs.[58,156]

Conclusion

In this review, pharmacokinetics, pharmacokinetic drug−drug interactions (DDIs), and pharmacokinetic modeling approaches of four currently available GLP-1 RAs (exenatide, liraglutide, dulaglutide, and semaglutide) and a dual GLP-1/GIP RA (tirzepatide), are discussed. Substitutions in amino acid sequences, fatty acid conjugation using a linker, and fusion with albumin or the IgG fragment crystallizable (Fc) region in GLP-1 RAs and a dual GLP-1/GIP RA have minimized metabolism and renal excretion. The pharmacokinetic profiles vary due to their diverse structures and prolonged half-life appears to be associated with an increased risk of adverse events. To date, there have been no reports of pharmacokinetic DDIs involving metabolic enzymes or transporters. However, there is the potential for DDIs of GLP-1 RAs to occur through their mechanisms of action. Among the possible mechanisms underlying DDIs, those related to delayed gastric emptying have been most extensively studied. The pharmacokinetics of most victim drugs were not affected by GLP-1 RAs. However, clinically significant DDIs were observed with oral contraceptives after tirzepatide administration and with levothyroxine after oral semaglutide administration. Therefore, close monitoring is recommended when oral drugs are co-administered with GLP-1 RAs or a dual GLP-1/GIP RA. Drug-metabolizing enzyme- and transporter-mediated DDIs involving GLP-1 RAs and a dual GLP-1/GIP RA require careful evaluation. Thirty pharmacokinetic models were developed to predict the pharmacokinetics of GLP-1 RAs and a dual GLP-1/GIP RA. Among these models, PBPK modeling can be useful for assessing DDIs caused by different mechanisms of action. Alterations in Vd resulting from reduced fat mass and alterations in clearance resulting from changes in CYP activity and GFR are key factors in determining pharmacokinetics. These mechanisms may accelerate the pharmacokinetic changes in the affected drug and lead to clinically relevant DDIs, particularly in drugs with a narrow therapeutic window. However, the DDIs mediated by these factors remain poorly understood and will require further investigation to ensure the safe use of GLP-1 RAs with concomitant medications.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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