



Drug-Drug Interactions Between Glucagon-Like Peptide 1 Receptor Agonists and Oral Medications: A Systematic Review

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Abstract

Background Glucagon-like peptide 1 receptor agonists (GLP1RAs) are used in the treatment of diabetes and obesity. Their slowing effect of gastric emptying might change oral drug absorption, potentially affecting pharmacokinetics, particularly in the case of medications with a narrow therapeutic index.

Purpose The purpose of this systematic review is to summarize data on drug-drug interactions between GLP1RAs and oral drugs.

Data Sources The PubMed and EMBASE databases were searched up to November, 1st 2023.

Study Selection We selected pharmacokinetic studies of any injectable GLP1RA given with an oral medication, and product prescribing sheets reporting data without access to the original study.

Data Extraction Two authors independently extracted the data.

Data Synthesis Twenty-two reports and six prescribing sheets were included. Treatment with GLP1RAs resulted in unaffected or reduced C_{max} and delayed t_{max} of drugs with high solubility and permeability (warfarin, contraceptive pills, acetaminophen), drugs with high solubility and low permeability (angiotensin converting enzyme inhibitors), drugs with low solubility and high permeability (statins) and drugs with low solubility and permeability (digoxin). However, the use of GLP1RAs did not exert clinically significant changes in the AUC or differences in clinically relevant endpoints.

Limitations The major limitations of the studies that are included in this systematic review are the enrollment of healthy subjects and insufficient data in conditions that might affect pharmacokinetics (e.g., kidney dysfunction).

Conclusions To conclude, reduced C_{max} and delayed t_{max} of drugs co-administered with GLP1RAs are consistent with the known delayed gastric output by the latter. Nevertheless, the overall drug exposure was not considered clinically significant. Dose adjustments are probably not required for simultaneous use of GLP1RAs with oral medications. Still, results should be carefully generalized to cases of background kidney dysfunction or when using drugs with narrow therapeutic index. The study is registered in PROSPERO: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022332339.

Key Points

Pharmacokinetic and pharmacodynamic studies of GLP1RAs generally reported no clinically significant changes in the absorption or action of co-administered oral medications.

Dose adjustments are probably not needed for simultaneous use of GLP1RAs with oral medications, but careful attention is still recommended when treating patients with background gastroparesis or kidney dysfunction, or when considering drugs with narrow therapeutic index.

1 Introduction

Glucagon-like peptide 1 receptor agonists (GLP1RAs) are widely used in the treatment of diabetes mellitus (DM) and obesity [1, 2]. Beyond glucose control and weight reduction, GLP1RAs were shown to reduce cardiovascular morbidity and mortality and are therefore strongly recommended in early lines of diabetic therapy [3, 4]. Their major mechanisms of action are slowing of gastric emptying, hunger suppression, increased insulin and decreased glucagon secretion from the pancreas.

Glucagon-like peptide 1 receptor agonists do not engage in CYP- or transporter-mediated drug-drug interactions (DDI) [5]. Yet a question remains whether their effect on gastric emptying might modulate the rate of drug

absorption (maximal plasma drug concentration, $[C_{\max}]$, and time to maximal concentration, $[t_{\max}]$). This may be of clinical significance especially for medications with a narrow therapeutic index, where small differences in blood concentration might lead to therapeutic failure or adverse reactions. Gastroparesis caused by non-pharmacologic etiologies is indeed known to affect drug absorption [6, 7]. However, previous studies on the extent of drug absorption (area under the curve [AUC]) in patients with other gastrointestinal motility disorders reported conflicting results [8, 9]. We aimed to review and harmonize the data available on potential DDIs between GLP1RAs and oral medications.

2 Materials and Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [10]. The protocol for this systematic review can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022332339.

2.1 Sources and Search Strategy

The PubMed and EMBASE electronic databases were comprehensively searched up to November 1st, 2023. The PubMed database was searched for the following MeSH terms: “glp1”, “glp 1”, “glucagon like peptide 1 receptor agonist”, “exenatide”, “lixisenatide”, “albiglutide”, “liraglutide”, “semaglutide” or “dulaglutide”, and “drug drug interaction” or “pharmacokinetic(s)”. The EMBASE database was searched for the following terms: ‘glucagon like peptide 1 receptor agonist’ OR ‘exenatide’ OR ‘lixisenatide’ OR ‘liraglutide’ OR ‘albiglutide’ OR ‘dulaglutide’ OR ‘semaglutide’ OR ‘exendin 4’ and ‘drug interaction’ OR ‘pharmacokinetics’. The reference lists of all publications were queried to detect studies not identified during the initial search. GLP1RA prescribing sheets were screened for information about DDI not published elsewhere. There was no restriction on population and language.

2.2 Data Extraction and Study Selection

The databases were scanned by one author (TDC) and selected data were independently extracted by two authors (TDC, BC). Disagreements were solved by consensus or consultation with a third author (ID). We included all the

pharmacokinetic studies conducted in human subjects with any injectable GLP1RA product given concomitantly with an oral medication. Only injectable GLP1RAs were considered eligible (exenatide, lixisenatide, liraglutide, albiglutide, dulaglutide, semaglutide). We excluded studies on drug-drug interactions between GLP1RAs and anti-hyperglycemic medications. Data were extracted from original study manuscripts and from reviews with detailed quantitative results of the pharmacokinetic endpoints of interest. We also extracted pharmacokinetic and pharmacodynamic information that was detailed in the product sheet data of various GLP1RAs. The extracted data included characteristics of the study cohort, study design, details of specific interventions (drugs and dosing) and pharmacokinetic outcomes. Pharmacodynamic outcomes were extracted if available.

2.3 Outcomes

The primary pharmacokinetic outcomes were the rate (C_{\max} , t_{\max}) and the extent (AUC) of drug absorption when an oral drug of interest was given concomitantly with versus without a GLP1RA. Other outcomes were pharmacodynamic parameters including the international normalized ratio (INR) of the prothrombin time (warfarin studies), lipid levels (statin studies) and gonadotropins or progesterone levels (combined oral contraceptive [COC] studies).

2.4 Quality Assessment and Risk of Bias

As there are no standard guidelines to assess the risk of bias in pharmacokinetic studies, we applied a previously reported quality rating tool [11].

2.5 Data Analysis

Presentation of the data follows the Biopharmaceutics Classification System (BCS) approach [12]. The BCS approach classifies drugs by their aqueous solubility and intestinal permeability into four groups:

- Class I: high solubility, high permeability.
- Class II: low solubility, high permeability.
- Class III: high solubility, low permeability.
- Class IV: low solubility, low permeability.

The term ‘solubility’ in the BCS report refers to the therapeutic dose of a drug that is soluble in an aqueous media which has pre-specified characteristics (volume, pH and temperature). Assessment of ‘permeability’ in the BCS

report is based on the extent of absorption as determined by absolute bioavailability or mass balance. We followed the BCS approach as it provides a surrogate for in vivo bioequivalence studies.

3 Results

The initial search yielded 5221 potentially relevant references of which 40 records were retrieved for full-text review (Fig. 1). Twenty-two reports were included in the study cohort; these included 15 pharmacokinetic (PK) studies [13–27], one pharmacodynamic (PD) study [28], one review with detailed PK data not elsewhere published [29], three conference abstracts [30–32], one case report [33] and one case series [34] (Fig. 1, Table 1). Prescribing sheets of all GLP1RAs were scanned for PK data not published elsewhere [35–40]. Drug interactions of exenatide were described in eight manuscripts [13, 20–23, 25, 33, 34], liraglutide in five [17, 19, 24, 26, 34], semaglutide in three [16, 18, 27], and lixisenatide, dulaglutide and albiglutide in two each [14, 15, 29–32] and synthetic GLP1 in one manuscript [28]. Three studies enrolled participants

with DM [19, 32, 34], and all others enrolled healthy subjects. Two studies on DDI between GLP1RAs and COCs enrolled post-menopausal women [17, 18] and three studies enrolled pre-menopausal women [14, 15, 21].

Most studies showed good reporting quality implying an overall low risk of bias (Supplementary table). Fair quality of methodology was considered in studies that enrolled only male subjects (“population” category) [14, 22, 25, 26, 28] or when blood sampling did not coincide with a steady state of an investigated drug [13–17, 19, 24]. The number of subjects was small in one study that was rated poor quality for “sample” [26].

3.1 BCS Class I: High Solubility, High Permeability

3.1.1 Warfarin

Warfarin is an anticoagulant with a narrow therapeutic index, assessed by measurement of the INR. The PK and PD studies for assessment of possible DDI between warfarin and GLP1RA were conducted for exenatide [25], lixisenatide [31], albiglutide [14], dulaglutide [15] and semaglutide [16] (Table 2). Specific PK/PD data for liraglutide

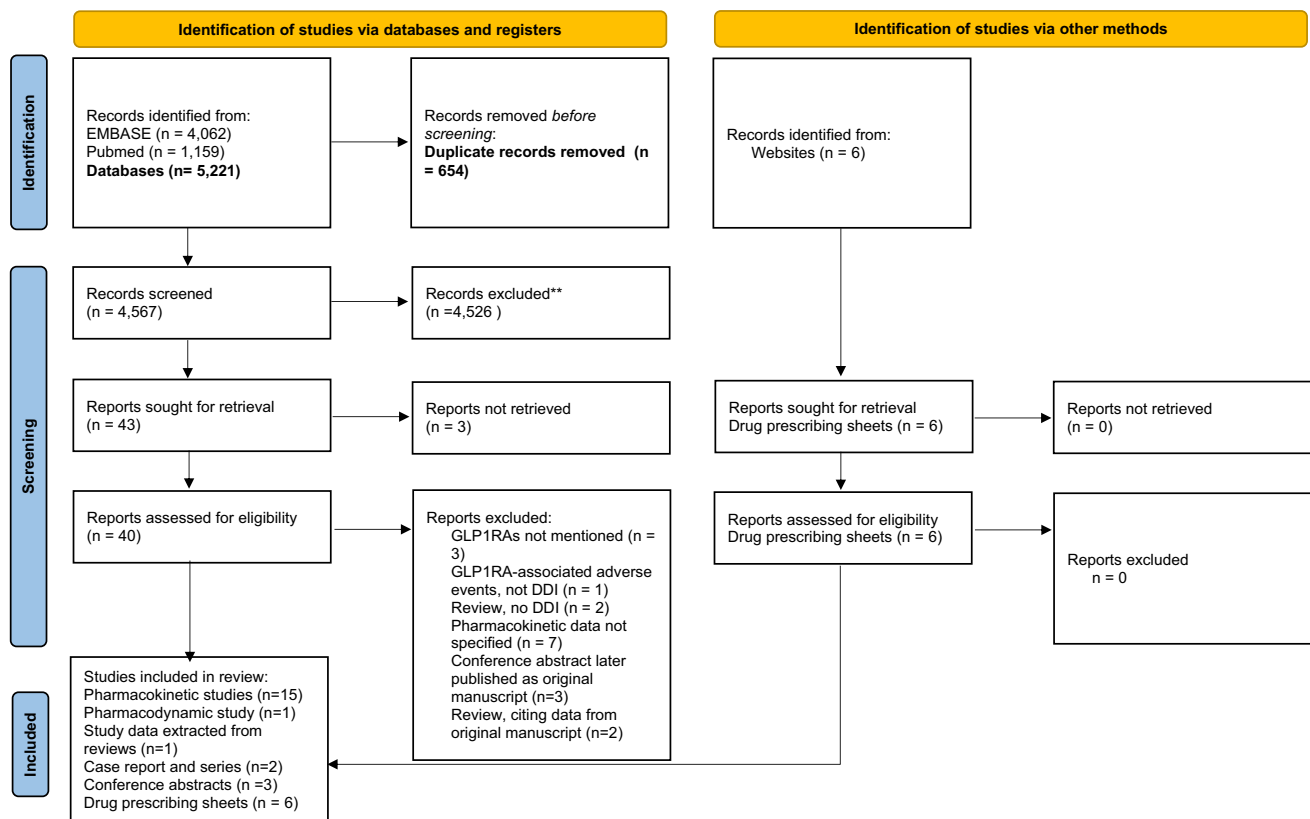


Fig. 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources. From: Page et al. [10]. <https://doi.org/10.1136/bmj.n71>. For more information, visit: <http://www.prisma-statement.org/>

Table 1 Records included in the systematic review

Study type/data source	Study design	Investigated drugs	Investigated GLPIRA – dose	Investigated oral drug – dose	Population	Number, gender and age of subjects
Kothare PA 2005 PK study	Open-label, fixed-sequence	Exenatide – steady state, digoxin – steady state	Exenatide 10 mcg BID	Digoxin 0.25 mg	HS	23 pts, M, 21–42 y
Blase E 2005 PK study	RCT, single-blind, crossover	Exenatide – steady state, acetaminophen – single dose	Exenatide 10 mcg BID	Acetaminophen 1000 mg	HS	40 pts, M+F, 18–65 y
Soon D 2006 PK study	Open label, fixed-sequence	Exenatide – steady state, Warfarin – single dose	Exenatide 10 mcg BID	Warfarin 25 mg	HS	16 pts, M, 22–50 y
Kothare PA 2007 PK study	Open-label, fixed-sequence,	Exenatide – steady state, lovastatin – single dose	Exenatide 10 mcg BID	Lovastatin 40 mg	HS	22 pts, M+F, 18–66 y
Linnebjerg H 2009 PK study	RCT, double-blind, crossover	Exenatide – 2 doses, lisinopril – steady state	Exenatide 10 mcg BID	Lisinopril 5–20 mg qd	HS	22 pts, M+F, mean age 60 ± 6.2 y
Kothare PA 2012 PK study	Open-label, randomized, 3-period, crossover	Exenatide – steady state, COC – steady state	Exenatide 10 mcg BID	COC: EE 30 mcg, LV 150 mcg	HS pre-menopause	38 pts, F, 18–45 y
Fujita Y 2013 Case report			Exenatide	Hydrocortisone		
Liu YH 2010 Conference abstract	Open-label, randomized, crossover	Lixisenatide – steady state, warfarin – single dose	Lixisenatide 20 mcg	Warfarin 25 mg	HS	16 pts, M, age – ND
Dahmen R 2011 Conference abstract	Open-label, randomized, crossover	Lixisenatide and ramipril – steady state	Lixisenatide 20 mcg	Ramipril 5 mg	HS	30 pts, M+F, age – ND
Kapitza C 2011 PK study	RCT, double-blind, 2-period crossover	Liraglutide – steady state, acetaminophen – single dose	Liraglutide 1.8 mg	Acetaminophen 1000 mg	DM2	18 pts, M+F, 48–70 y
Jacobsen LV 2011 PK study	RCT, double-blind, 2-period crossover	Liraglutide – steady state, COC – single dose	Liraglutide 1.8 mg	COC: EE 30 mcg, LV 150 mcg	HS post-menopause	21 pts, F, 51–71 y
Malm-Erjefält M 2015 PK study	RCT, double-blind, 2-period crossover	Liraglutide – steady state, Atorvastatin, lisinopril and digoxin – single dose	Liraglutide 1.8 mg	Atorvastatin 40 mg, lisinopril 20 mg, digoxin 1 mg,	HS	M+F, 18–55 y. Atorvastatin, lisinopril: 42 pts. Digoxin: 28 pts
Pinelli NR 2013 PK study	Open-label, fixed-sequence	Liraglutide, tacrolimus – steady state	Liraglutide 1.8 mg	Tacrolimus various doses for goal trough concentration 5–15 ng/mL	Kidney transplant recipients, non-diabetic	5 pts, M+F, 55.4 ± 8.2 y

Table 1 (continued)

Study type/data source	Study design	Investigated drugs	Investigated GLP1RA – dose	Investigated oral drug – dose	Population	Number, gender and age of subjects
Nagai Y 2019	Case series	Liraglutide, exenatide – steady state, dexamethasone – single dose	Liraglutide 0.3–0.9 mg or exenatide 10–20 mcg BID	Dexamethasone 0.5 mg	DM2	7 pts
Bush M 2012	PK study	Open-label, sequential Albiglutide – steady state, Digoxin, warfarin – single dose, COC – steady state	Albiglutide 50 mg	Digoxin 0.5 mg, warfarin 25 mg, and COC: EE 35 mcg, NE 500 mcg	HS pre-menopause	Digoxin: 30 pts, M+F, 18–55 y Warfarin: 16 pts, M, 18–55 y COC: 23 pts, F, 18–40 y
Young MA 2014	Review	Review – data extracted on specific DDI	Albiglutide – steady state, Simvastatin – single dose	Simvastatin 80 mg	HS	ND
de la Peña A 2017	PK study	Digoxin, atorvastatin: fixed sequence Warfarin: randomized, crossover. COC: two treatment periods	Dulaglutide 1.5 mg	Digoxin 0.25 mg, warfarin 10 mg, atorvastatin 40 mg and COC: EE 35 mcg and NG 250 mcg	HS pre-menopause	Digoxin, warfarin: 16 pts, M+F, 18–65 y. Atorvastatin: 24 pts, M+F, 18–65 y. COC: 14 pts, F, 18–45 y
Tham LS 2018	Conference abstract	Population–exposure–response and physiologic–based pharmacokinetics modeling	Dulaglutide 4.5 mg	Digoxin, warfarin, acetaminophen, lisinopril – doses not specified	DM2 and HS	Computerized modeling, no subjects enrolled
Kapitza C 2015	PK study	Open-label, one-sequence, crossover	Semaglutide – steady state, COC – steady state	Semaglutide 1 mg COC: EE 30 mcg, LV 150 mcg	HS post-menopause	43 pts, F, mean age 62.2 ± 6 y
Hausner H 2017	PK study	Open label, one-sequence, crossover	Semaglutide – steady state, warfarin / atorvastatin / digoxin – single dose	Warfarin 25 mg, atorvastatin 40 mg or digoxin 0.5 mg	HS	M+F, 18–55 y. Warfarin: 23 pts. Atorvastatin, digoxin: 31 pts
Langeskov EK 2022	PK study	Acetaminophen: open label, randomized, cross-over Atorvastatin: open-label, one-sequence, crossover	Semaglutide 1 mg	Acetaminophen 1500 mg, atorvastatin 40 mg	Acetaminophen: HS obese (average BMI 33.2 kg/m ²). Atorvastatin: HS	M+F Acetaminophen: 29 pts, M+F, 21–65 y. Atorvastatin: 31 pts, M+F, 25–55 y

Table 1 (continued)

Study type/data source	Study design	Investigated drugs	Investigated GLP1RA – dose	Investigated oral drug – dose	Population	Number, gender and age of subjects
Meier JJ 2005 PD study	Open-label, single-blinded, randomized, crossover	IV GLP 1, erythromycin – steady state? Metoclopramide, domperidone, cisapride – single dose	Intravenous GLP1 0.8 pmol* kg ⁻¹ * min ⁻¹ for 270 min	Oral metoclopramide 10 mg, domperidone 10 mg, cisapride 10 mg, or IV erythromycin 200 mg/100 mL for 15 min	HS	9 pts, M, mean age 25 ± 4 y

BID twice daily, *COC* combined oral contraceptives, *DM2* diabetes mellitus type 2, *EE* ethinylestradiol, *F* females, *GLP1RA* glucagon-like peptide 1 receptor agonists, *HS* healthy subjects, *IV* intravenous, *LV* levonorgestrel, *M* males, *NE* norethindrone, *NG* norgestromin, *PD* pharmacodynamic, *PK* pharmacokinetic, *RCT* randomized controlled trial

and warfarin were not identified [37]. Coadministration of warfarin with a GLP1RA resulted in delayed t_{\max} compared to administration of warfarin alone. This result probably reflects a delay in gastric emptying by the GLP1RA. The 90% confidence intervals (CIs) for the AUC and C_{\max} of warfarin in most studies were generally contained within the pre-specified 0.8–1.25 limits that are used to assess significance of drug-drug interactions. Exceptions were a 19 % and a 22 % reduction in warfarin C_{\max} when administered with lixisenatide or dulaglutide (both doses of 1.5 mg and 4.5 mg), respectively [15, 31, 32] that were not considered to be of clinical importance. The pharmacodynamic studies demonstrated similar INR_{AUC} and INR_{\max} in subjects on warfarin with or without GLP1RAs. This suggests that the observed minor PK changes were not clinically relevant. There seems to be no need for dose adjustment with the co-administration of warfarin and a GLP1RA.

3.1.2 Combined Oral Contraceptives

Combined oral contraceptives usually contain estrogen and progesterone. A higher exposure to estrogen and/or progesterone might increase the risk for thromboembolism, and a lower exposure might result in failure of birth control [41]. The Food and Drug Administration (FDA) has issued specific guidance for sponsors of new drugs to encourage evaluation of potential DDI with COCs [42]. Pharmacokinetic studies with exenatide [21], lixisenatide [36], liraglutide [17], albiglutide [14], dulaglutide [15] and semaglutide [18] given concomitantly with COCs are presented in Table 3. Following the FDA guidance, all studies used ethinylestradiol as it is the most commonly used estrogen in COCs [42]. Similarly, norethindrone, norgestimate and levonorgestrel were the progestins of choice for their wide use in the USA. Overall, administration of GLP1RAs resulted in reduced C_{\max} and delayed t_{\max} of the estrogen and the progesterone elements, consistent with a right shift of the concentration-time curve of drug absorption resulting from the expected prolonged gastric transit time. However, the bioequivalence criterion for the AUC was met for ethinylestradiol in all cases, and the AUC for the progestin component was either unaffected or showed approximately 20% higher mean exposure, which is not considered to affect the safety or efficacy of the combined pills. This attests to an overall unchanged bioavailability of the COCs when given with a GLP1 analogue. Moreover, given the right shift of the concentration-time curve with a similar AUC, it is expected that the minimum concentration of the combined contraceptive pills will not be lower. Indeed, direct measurement of the minimum concentration of ethinylestradiol and norethindrone was similar with or without co-administration of albiglutide [14]. This

Table 2 Pharmacokinetic studies with GLP1 receptor agonists and warfarin

	AUC (h·ng/mL) ^a	C _{max} (ng/mL) ^a	t _{max} (h)	INR _{AUC} ^a	INR _{max} ^a
Exenatide 10 mcg BID Soon et al. [25]	S: 1.06 (1.01, 1.11) R: 1.11 (1.06, 1.17)	S: 0.97 (0.93, 1.01) R: 1.05 (1.00, 1.09)	S: W 4 (3–6) W+GLP 6 (4–12) R: W 5 (3–12) W+GLP 6 (5–12)	0.94 (0.93, 0.96)	0.88 (0.84, 0.92)
Lixisenatide 20 mcg Liu [31]	S: 1.03 (0.87, 1.22)	S: 0.81 (0.68, 0.96)	S: W 1 h W+GLP 8 h	No effect	No effect
Albiglutide 50 mg Bush et al. [14]	S: 0.99 (0.95, 1.03) R: 1.02 (0.98, 1.07)	S: 0.93 (0.87, 0.98) R: 0.94 (0.89, 0.99)	S: W 1 h W+GLP 1.5 h R: W 1 h W+GLP 1.5 h	No effect	No effect
Dulaglutide 1.5 mg de la Peña et al. [15]	S: 0.986 (0.959, 1.01) R: 0.989 (0.958, 1.02)	S: 0.783 (0.737, 0.833) R: 0.857 (0.817, 0.900)	S: W 2 (1–4) W+GLP 4 (1–24) R: W 2 (1–4) W+GLP 8 (2–24)	1.02 (1.01, 1.03)	1.02 (0.977, 1.07)
Semaglutide 1 mg Hausner et al. [16]	S: 1.05 (0.99, 1.11) R: 1.04 (0.98, 1.10)	S: 0.91 (0.85, 0.98) R: 0.93 (0.87, 1.00)	S+R: W1 h W+GLP 3 h	1.05 (0.87, 1.28)	1.04 (0.99, 1.10)

BID twice daily, *C*_{max} maximum observed plasma concentration, *GLP1* glucagon-like peptide 1, *INR* international normalized ratio, *INR*_{max} maximum observed level, *R* R-warfarin, *S* S-warfarin, *t*_{max} time to maximum observed plasma concentration, *W* warfarin, *W+GLP* warfarin administered with a GLP1 receptor agonist

^aData are presented as the ratio of the least squares geometric mean (warfarin+GLP1 receptor agonist / warfarin) with a 90% confidence interval for the ratio. The 0.8–1.25 limits are considered for equivalence

is especially important with the use of low-dose contraceptives that are dependent on threshold blood levels for birth control. Pharmacodynamic studies were conducted only for albiglutide; the simultaneous administration with COCs did not affect the plasma levels of gonadotropins or progesterone. Given the above and current knowledge, a clinically significant DDI between GLP1RAs and COCs is probably not expected, and there is no recommendation in any GLP1RA prescription sheet for dose adjustment of COCs in this context.

3.1.3 Acetaminophen

Acetaminophen is a widely used over the counter drug for pain control and antipyretic effects. It has also been used in clinical research as a surrogate measure for gastric emptying [43]. Co-administration of exenatide [13], lixisenatide [36], liraglutide [19], dulaglutide [32, 38] or semaglutide [27, 40] resulted in decreased *C*_{max} and delayed *t*_{max} of acetaminophen (Table 3). However, the AUC showed bioequivalence with and without the GLP1 agonists. Dose adjustment

is probably not needed for the use of acetaminophen in patients treated with GLP1RAs.

3.2 BCS Class II: Low Solubility, High Permeability

3.2.1 Statins

Statins and GLP1 analogues are often simultaneously prescribed, as dyslipidemia and obesity or diabetes are commonly encountered in the same patient. The PK studies with lixisenatide [36], liraglutide [24] and semaglutide [16, 27] demonstrated reduced *C*_{max} and delayed *t*_{max} of atorvastatin, but overall minor changes in the AUC were not considered to be of clinical importance (Table 3). Notably, the efficacy of atorvastatin is poorly correlated with *C*_{max} [44], probably due to complex pharmacokinetics of drug metabolites with longer half-life compared to the parent compound. Treatment with dulaglutide showed similar inhibitory effects on *C*_{max} and *t*_{max}, but the AUC of atorvastatin was reduced (0.786, 90% CI 0.752–0.821) [15], as with co-administration of albiglutide [29]. The reduction in AUC was contained within the known

Table 3 Pharmacological studies with GLP1 receptor agonists and oral medications

GLP1 agonist	Investigated drug	AUC (h·ng/mL)	C _{max} (ng/mL)	t _{max} (h)	Clinical significance
Exenatide	Ethinylestradiol	↔	↓	Delayed	NS
Lixisenatide	Ethinylestradiol	↔	↓	Delayed	NS
Liraglutide	Ethinylestradiol	↔	↓	Delayed	NS
Albiglutide	Ethinylestradiol	↔	↔	ND	NS
Dulaglutide	Ethinylestradiol	↔	↓	Delayed	NS
Semaglutide	Ethinylestradiol	↔	↔	Delayed	NS
Exenatide	Levonorgestrel	↔	↓	Delayed	NS
Lixisenatide	Levonorgestrel	↔	↓	Delayed	NS
Liraglutide	Levonorgestrel	↑	↓	Delayed	NS
Albiglutide	Norethindrone	↔	↑↔	ND	NS
Dulaglutide	Norelgestromin	↔	↓	Delayed	NS
Semaglutide	Levonorgestrel	↑↔	↔	↔	NS
Exenatide	Acetaminophen	↓↔	↓	Delayed	NS
Lixisenatide	Acetaminophen	↔	↓	Delayed	NS
Liraglutide	Acetaminophen	↔	↓	Delayed	NS
Albiglutide	Acetaminophen	ND	ND	ND	NS
Dulaglutide	Acetaminophen	↔	↓	Delayed	NS
Semaglutide	Acetaminophen	↔	↓	ND	NS
Exenatide	Lovastatin	↓	↓	Delayed	NS
Lixisenatide	Atorvastatin	↔	↓	Delayed	NS
Liraglutide	Atorvastatin	↔	↓	Delayed	NS
Albiglutide	Simvastatin	↓	↔	↔	NS
Dulaglutide	Atorvastatin	↓	↓	Delayed	NS
Semaglutide	Atorvastatin	↔	↓	Delayed	NS
Exenatide	Lisinopril	↔	↔	Delayed	NS
Lixisenatide	Ramipril	↑	↓	Delayed	NS
Liraglutide	Lisinopril	↓	↓	Delayed	NS
Albiglutide	Lisinopril	ND	ND	ND	NS
Dulaglutide	Lisinopril	↔	↔	Delayed	NS
Exenatide	Digoxin	↔	↓	Delayed	NS
Lixisenatide	Digoxin	↔	↓	Delayed	NS
Liraglutide	Digoxin	↓	↓	Delayed	NS
Albiglutide	Digoxin	↔	↑↔	Delayed	NS
Dulaglutide	Digoxin	↔	↓	Delayed	NS
Semaglutide	Digoxin	↔	↔	↔	NS

AUC area under the curve, C_{max} maximum observed plasma concentration, GLP1 glucagon-like peptide 1, ND not determined, NS not significant t_{max} time to maximum observed plasma concentration

>30% PK variability of atorvastatin [45], and was therefore interpreted as non-clinically significant. Likewise, exenatide resulted in reduced C_{max}, delayed t_{max} and reduced AUC of lovastatin [20]. However, an analysis of 966 subjects who received statins in Phase 3 trials of exenatide (51% atorvastatin, 31% simvastatin, 11% pravastatin, 5% lovastatin, 3% fluvastatin) showed comparable lipid-lowering statin effects compared to placebo [20]. The groups also did not differ in the number of subjects who increased their statin dosage. It was concluded that dose adjustments are not expected to be required when prescribing statins with GLP1RAs.

3.2.2 Tacrolimus

Post-transplant DM is seen in 30% of solid organ transplant recipients. Data on the use of GLP1RAs in transplanted patients is scarce. Coadministration of liraglutide and tacrolimus in five kidney transplant recipients resulted in reduced AUC of the latter, but trough levels remained unaltered [26]. There was no change in prescribed doses of tacrolimus or graft rejection. These preliminary results, though reassuring, need validation in larger cohorts, especially due to the narrow therapeutic range of tacrolimus and the risk for

graft rejection in undertreatment. Monitoring of drug levels is best advised until further data are published.

3.3 BCS Class III: High Solubility, Low Permeability

3.3.1 Angiotensin-Converting Enzyme Inhibitors (ACEI)

Obesity, DM and hypertension constitute three of the criteria for metabolic syndrome. Angiotensin-converting enzyme inhibitors (ACEIs) are widely used as anti-hypertensives and for treatment of diabetic nephropathy. Co-administration of ACEI and GLP1RAs is therefore expected to be highly prevalent. The PK data on ACEI and GLP1 agonist co-treatment showed different effects by different GLP1RAs (Table 3); Still, all changes were interpreted as minor and non-clinically significant [23, 24, 30, 32, 38]. Moreover, the pharmacodynamic response was assessed by a 24-h ambulatory mean blood pressure and was unaffected [23]. Dose adjustment of ACEI in patients treated with GLP1RAs is probably not required; however, blood-pressure monitoring is recommended.

3.4 BCS Class IV: Low Solubility, Low Permeability

3.4.1 Digoxin

Diabetes and obesity are risk factors for heart diseases such as atrial fibrillation and congestive heart failure; therefore, digoxin may be given with a GLP1RA in the same individual. Slowing of gastric motility was expected to increase solubility and therefore potentially drug absorption. Accordingly, co-treatment with albiglutide did result in mildly increased C_{max} ; yet the digoxin blood concentration remained within therapeutic levels and the AUC did not change [14]. The rate or extent of digoxin's absorption was not affected by co-administration of oral or subcutaneous semaglutide [16]. All other GLP1 agonists resulted in a lower C_{max} and a delayed t_{max} , but the AUC remained unaffected [15, 22, 32, 36]. Liraglutide was an exception as it also decreased the AUC [24]. Nevertheless, in all studies the digoxin concentrations remained within the therapeutic range. Current evidence does not support a need for dose adjustment in coadministration of digoxin and GLP1RAs. However, digoxin is one of the most prevalent pharmacologic causes for hospital admissions for toxicity due to the narrow therapeutic range. We therefore suggest monitoring drug levels at least at the start of cotreatment with GLP1RAs, especially in patients with kidney dysfunction who are at risk for drug accumulation to toxic levels.

3.4.2 Erythromycin

Meier et al. explored a possible pharmacodynamic interaction between GLP1 that decelerates gastric emptying

and the prokinetic drugs metoclopramide, domperidone, cisapride and erythromycin in nine healthy males [28]. Erythromycin counteracted the effect of GLP1 on the velocity of gastric emptying and lowered the post-prandial anti-hyperglycemic effect of GLP1. The other prokinetic drugs did not show interaction with GLP1 action.

4 Discussion

The clinical importance of DDI cannot be overemphasized; DDI that result in drug overdose are responsible for serious and sometimes fatal adverse events. Nonetheless, even a minor adverse event might cause inconvenience and non-adherence or drug discontinuation. Drug-drug interactions that lower drug exposure might result in treatment failure. The FDA and EMA have issued specific guidance to encourage sponsors from the medical industry to assess potential DDI [46, 47]. The studies reviewed in this manuscript align with this guidance.

Only a few cases resulted in reduced C_{max} with delayed t_{max} of the investigated oral drug, findings that are consistent with the known effect of delayed gastric output by GLP1RAs. However, most of the PK studies demonstrated that the absorption characteristics of the oral drugs were not affected, therefore unsurprisingly, the co-exposure to a GLP1RA did not alter the AUC. Moreover, no clinically significant impact was detected even in cases of a decrease in the AUC. Accordingly, PD studies showed no difference in clinically relevant endpoints, further supporting the similar bioavailability of drugs when simultaneously prescribed with a GLP1RA.

Gastric emptying is frequently evaluated by the simple and inexpensive paracetamol absorption test; yet the use of the paracetamol test has been criticized, particularly since it cannot assess gastric emptying of solid foods [48, 49]. Scintigraphy is the gold standard technique for measurement of gastric emptying, and the stable isotope breath test is a simpler, less expensive, and well-validated alternative. Studies that used these tests have shown that both short- and long-acting GLP1RAs decelerate the gastric emptying. The slowed gastric motility lowers the duodenal glucose load after a meal, thereby reducing post-prandial plasma glucose excursions [50]. Still, the total glucose uptake remains unchanged [51]. This food kinetic is similar to the drug kinetics described in this review when an oral drug is co-administered with GLP1RAs. Of note, many of the studies used a single-dose administration of GLP1RAs. An open question remains whether chronic use of GLP1RAs will result in tachyphylaxis of the gastric slowing effect, which will mitigate the risk of DDI [51–53]. On the other hand, some data on chronic administration of long acting GLP1RAs have established that deceleration of gastric

emptying does continue – albeit less compared to short-acting GLP1RAs. In the same line, many of the drugs that were given simultaneously with the GLP1RAs were administered in a single dose, again raising the question of whether the results can be inferred to the context of chronic use with multiple doses.

The studies on potential DDI with GLP1RAs showed absence of clinically significant effects on the PK and PD of drugs from the four BCS classes. These reassuring results can probably be extrapolated to other drugs from all BCS classes. Nonetheless, the slowed rate of absorption seen in several cases may be important in several scenarios; the first is when a rapid pharmacological effect is required, such as with anti-hyperglycemic drugs that affect immediate post-prandial glucose excursions [48, 54]. Inter-individual variation in gastric emptying is common and is even greater in diabetic patients. Gastroparesis is in fact a major determinant of post-prandial glucose excursions, and a cause for upper gastrointestinal symptoms. Administration of short-acting insulin aims to prevent post-prandial hyperglycemia; its PK characteristics should match the rate of carbohydrate delivery since a mismatch might result in hypoglycemia. Pharmacologically induced slowing of gastric emptying by GLP1RAs should be considered in patients treated with short-acting insulin for appropriate timing of administration of the insulin drug and probable use of rapid rather than ultra-rapid insulin analogues. The rate of gastric emptying is also of clinical importance in the context of advanced bolus programs in insulin pumps. Another example is a potential interaction between dexamethasone and GLP1RAs [34], yielding false positive results of dexamethasone-suppression test. This interaction was reported by Nagai et al in two of seven patients, all presented with no clinical manifestation of Cushing's syndrome. After switching the GLP1RA therapy to insulin administration, a repeat dexamethasone suppression test resulted in an adequate decrease of endogenous cortisol levels. It is suggested that positive dexamethasone suppression test in a patient without high pre-test probability for Cushing's syndrome be repeated without coadministration of GLP1RA or be supported by additional screening tests for Cushing's syndrome. In the same line, Fujita et al described a patient on chronic hydrocortisone who manifested symptoms of hypocortisolism after the start of exenatide therapy [33]. Pharmacokinetic assessment revealed a decrease in C_{max} and delayed t_{max} of hydrocortisone when administered after a dose of exenatide compared to postprandial administration of hydrocortisone without exenatide. The PK measurements normalized when hydrocortisone was given before a meal and exenatide 1.5 h after that meal. The prolonged retention of drugs in the stomach should also be considered in the context of intoxication; for example, gastrointestinal decontamination with active charcoal is usually recommended if a patient presents within four hours after toxic ingestion of acetaminophen. This timeline may be

longer if the patient also receives a GLP1RA. Finally, even minor changes in drug absorption may be clinically significant in the context of drugs with a narrow therapeutic index. The studies on digoxin did not show an effect on time in therapeutic range; but the small study on tacrolimus implied that there might be an effect on the extent of absorption. Special attention and careful monitoring are obviously required in such cases.

Notably, one should also consider PD DDI, as demonstrated in the example of the prokinetic drug erythromycin. Patients who need pro-kinetics are probably not good candidates for GLP1RAs due to potential counteraction of their effect.

One limitation of most PK and PD studies is the enrollment of healthy subjects, whereas the major target population for use of GLP1RAs are patients with diabetes and obesity who may have co-morbidities that might affect the PK results. Kidney dysfunction is one example, as it requires longer duration of PK measurements. Increased prevalence of gastroparesis in diabetic and obese patients is another example [7, 55]. Exenatide prolonged the gastric half-emptying time in all diabetic patients without gastroparesis ($n = 20$) and worsened the gastric emptying in two of ten diabetics with pre-existing mild gastroparesis [56]. The patients' reported perception of exenatide's therapeutic effects was similar in diabetic subjects with versus without gastroparesis at start of exenatide therapy. However, more data are needed to assess whether gastric emptying will be more affected by GLP1RAs in patients with pre-exposure gastric motility disorders, and whether it might result in clinically significant PK changes. Another limitation is the focus on change in drug absorption, whereas other PK parameters can be considered. For example, GLP1RAs-induced weight loss might affect drug distribution; accordingly, Bourron et al reported a case of amiodarone-induced thyrotoxicosis in a patient with 45 % weight loss following Roux-en-Y gastric bypass [57]. We are not aware of similar reports in patients treated by GLP1RAs. However, considering the ongoing development of more potent GLP1RAs and combined GLP-GIP drugs, which will probably induce massive weight losses, awareness should be increased for possible DDI at level of drug distribution.

5 Conclusion

The known effect of GLP1RAs to slow gastric motility has raised concerns regarding a possible change of the absorption of oral drugs. To date, no clinically significant effect has been observed in any of the investigated oral drugs co-administered with any of the GLP1RAs. These reassuring results underlie the statement in all of the GLP1RAs' prescribing sheets that dose adjustments are not needed for simultaneous use with oral medications. Still,

this recommendation should be carefully generalized to other medicinal products, especially when treating patients with background gastroparesis or kidney dysfunction, or when considering drugs with narrow therapeutic effects.

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Conflict of Interest BC declares that there are no relationships or activities that might bias, or be perceived to bias, her work. ID has received fees from Astra Zeneca, Novo Nordisk, Abbott, Boehringer Ingelheim, Elli Lilly and Sanofi for educational lectures, and participated in advisory boards of Novo Nordisk, Boehringer Ingelheim, Sanofi and Novartis that are outside the scope of this work. ID reports a grant from Astra Zeneca that is outside the scope of the submitted work. DS declares that there are no relationships or activities that might bias, or be perceived to bias, his work. AL declares that there are no relationships or activities that might bias, or be perceived to bias, his work. TDC has received fees from Astra Zeneca for educational lectures that are outside the scope of this work.

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