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Pharmacologically relevant drug interactions of Glucagon-like peptide-1 receptor agonists

Abstract

Glucagon-like peptide-1 receptor agonists are incretin mimetics and they help to manage the blood glucose of patients with type 2 diabetes mellitus. The gastric emptying is delayed by the administration of Glucagon-like peptide-1 receptor agonists and hence the absorption of orally administered medications such as Acetaminophen, Digoxin, Warfarin, Oral contraceptive pills, Metformin, Statins, Angiotensin Converting Enzyme Inhibitors and Griseofulvin delayed by their concomitant use. It has been observed that the pharmacokinetics of all these drugs did not get altered by the concurrent administration of Glucagon-like peptide-1 receptor agonists. Moreover, the delay in absorption of interacting drugs could be avoided by taking 1 hour before the administration of Glucagon-like peptide-1 receptor agonists.

Keywords: drug interactions, glucagon-like peptide-1 receptor agonists, exenatide, liraglutide, lixisenatide

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Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists are incretin mimetics and they are useful in the treatment of type 2 diabetes mellitus (Type 2 DM). The drugs such as Exenatide, Liraglutide, Lixisenatide, Albiglutide, Dulaglutide and Semaglutide are approved as GLP-1 agonists and administered subcutaneously to manage fasting and postprandial blood glucose.[1] The antidiabetic effect of GLP-1 agonists occurs through many mechanisms including increased glucose-dependent insulin secretion, suppressed glucagon levels, delayed gastric emptying and reduced food intake.[2]

Diabetes affects millions of people around the world and it is one of the leading causes of cardiovascular diseases, blindness, kidney failure, amputations, and others. International Diabetes Federation (IDF) estimated that approximately 5 million global deaths and 850 billion US dollars of healthcare costs were attributed to diabetes in the year of 2017.[3] The patients with diabetes are more prone to develop comorbidities such as cardiovascular diseases, hepatic diseases, renal problems, depression, and others and they may take several medications to manage them all that may result in Polypharmacy.[4]

The rate of drug interactions is enhanced by inappropriate use of multiple medications.[5] Modification of effects of one drug by other drug(s), supplements, food, smoking or alcohol consumption, is termed as Drug interaction.[6] And the drug interaction resulting in elevated risk of adverse effects or decreased therapeutic efficacy is termed Adverse Drug Interaction.[7] GLP-1 agonists may slow down the absorption of certain orally administered medications through delayed gastric emptying.

Acetaminophen (paracetamol)

Acetaminophen has a high permeability and high solubility and hence it is preferably employed to study gastric emptying properties of drugs.[8] The absorption of Acetaminophen was delayed by the concomitant administration of Exenatide,[9] Liraglutide[10] or Lixisenatide.[11] The interaction between Acetaminophen and GLP-1 agonists is minimal and clinically insignificant and no management required. Delayed absorption of Acetaminophen could be avoided by 1 hour prior to the GLP-1 agonists' administration.

Digoxin

Digoxin is a glycoside isolated from Digitalis and it is used as a cardio tonic to treat congestive heart failure and as an antiarrhythmic drug to treat atrial flutter and atrial fibrillation.[12] Concurrent use of Digoxin and Exenatide,[13] Liraglutide,[14] Lixisenatide,[15] Albiglutide,[16] Dulaglutide[17] or Semaglutide[18] resulted in a little delay in the tmax of Digoxin which was clinically insignificant and do not require any dose adjustments.

Warfarin

Warfarin is widely used as an oral anticoagulant and it helps to manage the conditions such as chronic atrial fibrillation, coronary artery disease and others through the prevention of thromboembolic events.[19] The International Normalized Ratio (INR) of patients taking Exenatide,[20] Liraglutide,[21,22] Lixisenatide,[15] Albiglutide,[16] Dulaglutide,[17] or Semaglutide[18] along with Warfarin did not get affected significantly though there was a delay observed in the absorption of Warfarin. Nevertheless, the INR of patients taking GLP-1 agonists and Warfarin concurrently required to be monitored frequently as Warfarin is a drug with narrow therapeutic index.

Oral contraceptive pills

The peak concentrations of Oral contraceptives were delayed insignificantly by the coadministration of Exenatide,[23] Liraglutide,[24] Lixisenatide,[15] Albiglutide,[16] Dulaglutide[17] or Semaglutide.[25] Though this interaction is not clinically significant, it is recommended to take oral contraceptives at least 1 hour before the administration of GLP-1 agonists.[26]

Metformin

Metformin is a biguanide and it helps to manage many conditions such as Type 2 diabetes mellitus, Gestational diabetes mellitus (GDM), Prediabetes, Obesity, Polycystic Ovarian Syndrome (PCOS),

Cancer, and others.[27] Concomitant use of Metformin and Semaglutide did not result in clinically significant changes in the pharmacokinetics of Metformin.[18] Moreover the coadministration of Metformin with Exenatide[28] or Lixisenatide[29] lead to improved glycemic control and with Liraglutide produced synergistic anti-tumor effect on the pancreatic cancer cells[30] and synergistic protective effects on endothelial function.[31]

Sulfonylureas

Sulfonylureas are oral hypoglycemic agents employed in the treatment of type 2 diabetes mellitus and they include the drugs such as Glibenclamide, Gliclazide, Glipizide and others.[32,33] The risk of hypoglycemia was observed higher in patients taking Liraglutide along with sulfonylurea.[34] The dose of sulfonylurea is recommended to be halved when a GLP-1 agonist is initiated in a patient receiving Sulfonylurea to avoid hypoglycemic episodes.[35]

Insulins

Significant glycemic control and body weight reduction were achieved by the addition of Insulin in patients receiving Exenatide[36] or Liraglutide.[37] To avoid hypoglycemia, the dosage adjustments of Insulin are recommended in patients taking this combination of drugs.[35]

Statins

Statins are the drugs inhibiting cholesterol biosynthesis through the blockade of rate limiting-enzyme 3-hydroxy-methylglutaryl Coenzyme A (HMG CoA) reductase.[38] The bioavailability of Lovastatin slightly changed by the coadministration of Exenatide and did not require a dosage adjustment of Lovastatin.[39] Concomitant use of Atorvastatin and Liraglutide,[14] Lixisenatide,[15] Dulaglutide[17] or Semaglutide[18] resulted in insignificant delay in tmax of Atorvastatin.

ACE Inhibitors

Angiotensin converting enzyme (ACE) inhibitors are preferred as the first line antihypertensive agents to treat patients with Hypertension and Diabetes.[40] The tmax of Lisinopril was delayed by concomitant use of Liraglutide,[14] while Lixisenatide[15] was delaying the tmax of Ramipril insignificantly. However, dosage adjustments for ACE inhibitors is not required.

Hydrocortisone

The administration of Exenatide in a diabetic patient with panhypopituitarism taking hydrocortisone delayed the absorption of hydrocortisone resulting in general fatigue and appetite loss with hypotension.[41]

Griseofulvin

Griseofulvin is an antifungal drug and it shows antifungal activity against dermatophytes.[42] There was a delay in the initial absorption of Griseofulvin when it was coadministered with Liraglutide[43] and this interaction was found clinically insignificant.

Conclusion

GLP-1 agonists delay the gastric emptying through which they interfere with the absorption of interacting drugs. Nonetheless, they do not significantly alter the pharmacokinetics of interacting drugs such as Acetaminophen, Digoxin, Warfarin, Oral contraceptive pills, Metformin, Statins, ACE Inhibitors and Griseofulvin and hence do not require any dosage adjustments. However, GLP-1 agonists may increase the risk of hypoglycemia when coadministered with Sulfonylureas or Insulins and their dose should be adjusted to prevent hypoglycemic episodes. In addition, the delay in absorption of interacting drugs could be avoided by taking 1 hour before the administration of GLP-1 agonists.

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Conflicts of interest

The author declares that there is no conflicts of interest.

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