GLP-1 Agonists and Oral Contraceptives: A Review of Tirzepatide and Other Incretin Mimetics

Agonistas de GLP-1 e Contraceptivos Orais: Uma Revisão sobre Tirzepatida e Outros Incretinomiméticos

Agonistas de GLP-1 y anticonceptivos orales: revisión de la tirzepatida y otros incretinomiméticos

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RESUMO

Esta revisão bibliográfica avaliou a interferência dos agonistas do receptor de GLP-1, incluindo tirzepatida, dulaglutida, liraglutida, semaglutida e exenatida, na farmacocinética de anticoncepcionais orais. A tirzepatida, agonista duplo de GLP-1 e GIP, promoveu redução significativa na área sob a curva (AUC) e na concentração máxima (Cmax) de etinilestradiol e norgestimato, além de retardar o tempo para atingir a concentração máxima (Tmax), indicando possível comprometimento da eficácia contraceptiva e necessidade de métodos de apoio durante o início e escalonamento da dose. Os demais agonistas seletivos de GLP-1 não apresentaram alterações clinicamente relevantes na biodisponibilidade dos anticoncepcionais, mantendo sua segurança e eficácia. Os resultados destacam a importância de avaliar as características farmacológicas dos incretinomiméticos ao prescrever terapias combinadas com anticoncepcionais orais.

Palavras-chave: Tirzepatida, GLP-1, GIP, anticoncepcionais orais, farmacocinética, interação medicamentosa.

ABSTRACT

This literature review evaluated the interference of GLP-1 receptor agonists, including tirzepatide, dulaglutide, liraglutide, semaglutide, and exenatide, on the pharmacokinetics of oral contraceptives. Tirzepatide, a dual GLP-1 and GIP agonist, promoted a significant reduction in the area under the curve (AUC) and maximum concentration (Cmax) of ethinyl estradiol and norgestimate, as well as delaying the time to reach maximum concentration (Tmax), indicating possible impairment of contraceptive efficacy and the need for backup methods during initiation and dose escalation. The other selective GLP-1 agonists did not show clinically relevant changes in the bioavailability of contraceptives, maintaining their safety and efficacy. The results highlight the importance of evaluating the pharmacological characteristics of incretin mimetics when prescribing combination therapies with oral contraceptives.

Keywords:Tirzepatide, GLP-1, GIP, oral contraceptives, pharmacokinetics, drug interaction.

RESUMEN

Esta revisión bibliográfica evaluó la interferencia de los agonistas del receptor GLP-1, incluidos tirzepatida, dulaglutida, liraglutida, semaglutida y exenatida, en la farmacocinética de los anticonceptivos orales. La tirzepatida, agonista doble del GLP-1 y el GIP, provocó una reducción significativa del área bajo la curva (AUC) y la concentración máxima (Cmax) de etinilestradiol y norgestimato, además de retrasar el tiempo para alcanzar la concentración máxima (Tmax), lo que indica un posible compromiso de la eficacia anticonceptiva y la necesidad de métodos de apoyo durante el inicio y el escalonamiento de la dosis. Los demás agonistas selectivos del GLP-1 no presentaron alteraciones clínicamente relevantes en la biodisponibilidad de los anticonceptivos, manteniendo su seguridad y eficacia. Los resultados destacan la importancia de evaluar las características farmacológicas de los incretinomiméticos al prescribir terapias combinadas con anticonceptivos orales.

Palabras clave: Tirzepatida, GLP-1, GIP, anticonceptivos orales, farmacocinética, interacción farmacológica. domiciliarias es esencial para el control de lahipertensión y el avance de prácticas de salud centradas en el paciente.

Descriptores: Visita domiciliaria, Hipertensión, Atención primaria de salud.

REVIEW

Introdução

The therapeutic evolution of type 2 diabetes mellitus (T2DM) and obesity has been marked by the development of agents that mimic the action of endogenous incretin hormones, especially glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)[1]. GLP-1 and GIP receptor agonists act directly on pancreatic beta cells, stimulating the cyclic adenosine monophosphate pathway (cAMP), which promotes glucose-dependent insulin secretion, modulation of glucagon release, delayed gastric emptying, and action on hypothalamic centers related to appetite. These mechanisms result in better glycemic control and greater satiety[1,2].

The latest advancement in this class is tirzepatide, a dual agonist of the GLP-1 and GIP receptors, approved by the Food and Drug Administration (FDA) in 2022.[3] Its molecular structure allows prolonged binding to the GLP-1 receptor, enhancing its effect on gastric emptying and extending the duration of incretin action . Although GIP alone does not delay gastric emptying, its concomitant activation with GLP-1 increases the organism's sensitivity to the latter, enhancing its metabolic and anorectic effects. As consequence, superior efficacy is observed in both glycemic control and weight loss, with additional benefits on insulin secretion and sensitivity[4,5].

Tirzepatide also stands out for its tolerability profile, which is superior to that of selective GLP-1 agonists such as semaglutide and dulaglutide.[4] The gradual titration protocol favors gastrointestinal adaptation, minimizing adverse effects such as nausea and vomiting, in contrast to the more rapid escalation regimens of other agonists.[6] Furthermore, its acylation technology, which enables reversible binding to plasma albumin, ensures a prolonged half-life and sustained release, avoiding abrupt peaks in plasma concentrations and providing continuous stimulation of incretin receptors[4].

In the field of drug interactions, the delay in gastric emptying induced by tirzepatide stands out, which can interfere with the absorption of oral drugs, especially hormonal contraceptives[4]. EPharmacokinetic studies showed significant reductions in the area under the curve (AUC), maximum concentration (Cmax) and delay in time to maximum concentration (Tmax) of ethinylestradiol and norgestimate when coadministered with tirzepatide[6]. Such an effect has not been observed to a clinically relevant extent with other GLP-1 agonists[7]. For this reason, it is recommended to use backup contraceptive methods for four weeks after starting or adjusting the dose of tirzepatide, a procedure not necessary for selective GLP-1 agonists.[5,7,8].

Given this scenario, it is essential to understand in depth the impact of tirzepatide and other GLP-1 receptor agonists on the pharmacokinetics of oral contraceptives, the central theme of this review. Thus, the objective of this study is to evaluate the interference of GLP-1 receptor agonists, with an emphasis on tirzepatide, on the pharmacokinetics and efficacy of oral contraceptives, comparing them to other available incretin mimetics.

Method

A systematic bibliographic review was carried out in the PubMed, Google Scholar and ScienceDirect databases, covering publications from January 2020 to January 2024. The focus was to gather clinical trials and reviews on the interaction between GLP-1 receptor agonists and oral contraceptives.

In PubMed, MeSH descriptors related to tirzepatide and other GLP-1 agonists (semaglutide, liraglutide, dulaglutide, and exenatide) were used, combined with terms about hormonal contraceptives, with the following combinations: “tirzepatide AND

contraceptives," "semaglutide AND contraceptives," "liraglutide AND contraceptives," "dulaglutide AND contraceptives," and "exenatide AND contraceptives".

Articles published between 2020 and 2024 that addressed: (1) the functions of GLP-1 and/or GIP agonists; (2) drug interactions with oral contraceptives were included. Duplicate publications, abstracts without full text, isolated reports, and articles not relevant to the study objectives were excluded.

After screening, 24 articles were read in full, and 8 were selected based on relevance, methodological clarity, and specific discussion of the GLP-1/GIP–contraceptive interaction. This study, as it is based exclusively on a literature review, does not require submission to a Research Ethics Committee.

Results

Pharmacokinetic studies have shown that coadministration of tirzepatide with oral contraceptives resulted in significant reductions in hormone bioavailability parameters.[6] In women on stable contraceptive use, a single 5 mg dose of tirzepatide reduced mean AUC by 16.06% for ethinyl estradiol (EE) and 26.63% for norelgestromin (NGM). Cmax showed even more pronounced reductions (58.28% for EE and 56.83% for NGM). Tmax was delayed by 2.5 to 4.5 hours.[6,8].

In contrast, studies with other GLP-1 receptor agonists, such as dulaglutide, liraglutide, semaglutide, and exenatide[7], have not demonstrated a clinically relevant impact on the AUC of oral contraceptives, presenting modest reductions in Cmax and delays in Tmax without clinical relevance[7,8]. The maintenance of AUC and minimum plasma concentrations in these cases suggests that contraceptive efficacy is not compromised by coadministration with conventional GLP1RAs[7].

The comparative graphical analysis (Table I) illustrates that only tirzepatide promoted clinically relevant reductions in the AUC and Cmax of the contraceptives, while the other agonists maintained systemic exposure within the bioequivalence limits.

Table 1– Pharmacological studies with GLP1 receptor agonists, tirzepatide and oral contraceptives.

Incretin agent	Effect on AUC	Clinically relevant?	Effect on Cmax	Clinically relevant?	Effect on Tmax	Clinically relevant?
Dulaglutide	Levels have not been reduced.	N / A	26% reduction in NGMN and 13% in EE.	No	Late by 1 hour.	No
Liraglutide	Levels have not been reduced.	N / A	12% reduction in EE and 13% in LNG.	No	Delayed by 1.5 hours.	No
Semaglutide	EE levels were not reduced; LNG levels increased by 20%.	No	Levels were not reduced.	N / A	EE delayed by 1 hour, LNG not delayed.	No
Tirzepatide	Reduced	Yes	58%	Yes	Delayed	Yes

	by 16% EE and 27% NGM.		reduction in EE and 57% in NGM		from 2.5 to 4.5 hours.	
Exenatide	Levels have not been reduced.	N / A	45% reduction in EE and 27% in LNG.	No	EE was delayed 3 hours LNG was delayed 3.5 hours.	No
Semaglutide (oral)	Levels have not been reduced.	N / A	Levels were not reduced.	N / A	The levels were not delayed.	N / A

Source: Adapted from the Journal of the American Pharmacists Association, 2024.

Discussion

The results demonstrate that tirzepatide, a dual GLP-1 and GIP receptor agonist, has a significantly superior pharmacokinetic impact on oral contraceptives compared to selective GLP-1 agonists.[8] The magnitude of the observed changes suggests a decrease in the maximum exposure of the contraceptive hormones, reflecting slower absorption due to the delayed gastric emptying induced by tirzepatide[4].

This characteristic justifies the recommendation of backup contraceptive methods during the first four weeks of use or after dose escalation, according to current guidelines [3,4,6,8]. These findings reinforce the need for an individualized approach in choosing the contraceptive method for patients using tirzepatide, considering the potential for drug interactions and the risk of contraceptive failure.

The importance of clinical monitoring and appropriate patient guidance is also highlighted, especially during treatment initiation or dose adjustments. Further studies are needed to evaluate the impact of prolonged and escalated use of tirzepatide on the pharmacokinetics of oral contraceptives, as well as to define safer contraceptive strategies in this context.

Final Considerations

Tirzepatide represents a significant advance in the treatment of T2DM and obesity, thanks to its dual GLP-1/GIP mechanism and differentiated pharmacokinetic profile. However, its effects on gastric emptying may reduce the absorption of oral contraceptives, especially in the initial phases or during dose titration.

Therefore, it is essential to guide patients regarding the use of backup contraceptive methods during this period, ensuring a personalized and safe approach. Future studies should clarify the effects of prolonged use of tirzepatide on contraceptives and explore more effective contraceptive strategies in this context.

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