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Adverse effects of GLP – 1 Receptor Agonists

Anna Kasprzak

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

a.kasprzak93@wp.pl

https://orcid.org/0009-0002-1491-245X

Monika Kułaga

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

monikakulaga93@gmail.com

https://orcid.org/0009-0001-3949-2124

Monika Grzybek

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

monika.c@vp.pl

https://orcid.org/0009-0003-2246-800X

Diana Mazur-Lesińska

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

diana_mazur@wp.pl

https://orcid.org/0009-0000-2489-9100

Barbara Szostak

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

barbara.szostak02@gmail.com

https://orcid.org/0009-0000-8035-7584

Sylwia Wielgosz -Biała

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

sylwia.wielgosz@o2.pl

https://orcid.org/0009-0003-0567-5998

Krzysztof Tyszkiewicz

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

tyszkiewicz.krzysztof@wp.pl

https://orcid.org/0009-0005-0208-2286

Borys Łozowski

University Clinical Hospital No 4 in Lublin, Doktora Kazimierza Jaczewskiego 8, 20-954 Lublin

borys.lozowski@gmail.com

https://orcid.org/0000-0002-1990-040X

Małgorzata Kasprzak

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

malgorzata.m.kasprzak@gmail.com

https://orcid.org/0009-0007-3791-1632

Barbara Wilczyńska

University Children's Hospital in Lublin, Profesora Antoniego Gębali 6, 20-093 Lublin

b.machulska@interia.pl

https://orcid.org/0009-0001-4939-7550

ABSTRACT

Introduction and purpose

Glucagon-like peptide-1 receptor agonists (GLP – 1 RAs) are indicated in type 2 diabetes (T2D) and obesity because of their high efficacy in controlling blood glucose levels and inducing weight loss. Patients may develop gastrointestinal adverse effects (GI AEs) such as nausea, vomiting, diarrhoea, constipation and, less commonly, pancreatitis and cholelithiasis. In addition, a recent retrospective cohort study suggested a possible association between nonarteritic anterior ischaemic optic neuropathy (NAION) and the use of one of the GLP – 1 RAs, semaglutide. The aim of this article is to review the side effects associated with GLP – 1 RAs therapy.

Materials and methods

To write this article, data bases such as PubMed and Google Scholar were searched using the following terms: obesity, diabetes, glucagon – like peptide – 1 receptor agonists, gastrointestinal adverse effects, acute pancreatitis, cholelithiasis, hypoglycemia, nonarteritic anterior ischaemic optic neuropathy

Description of the state of knowledge

Pharmacotherapy currently offers a range of treatments for diabetes and obesity. GLP – 1 RAs are increasingly being used to treat these conditions because of their high efficacy compared with other drugs on the market. In addition to lowering blood glucose levels and reducing body weight, they have a number of other beneficial effects, including metabolic, hepatic, renal and cardiovascular benefits. Like all drugs, GLP – 1 RAs can cause adverse effects, most commonly in the gastrointestinal tract. Semaglutide therapy has also recently been shown to be associated with an increased risk of nonarteritic anterior ischaemic optic neuropathy, which can lead to vision loss.

Summary

GLP – 1 RAs can be considered as easy-to-use, highly effective drugs with a good tolerability profile for the treatment of people with obesity or T2D. However, it is important to be aware of the side effects that can occur during treatment with these drugs. The most common side effects are gastrointestinal problems. Much rarer but serious complications include: acute pancreatitis, cholelithiasis, nonarteritic anterior ischaemic optic neuropathy. Patients' awareness of the possibility of these side effects appears to be crucial in ensuring that treatment is not discontinued.

Keywords: type 2 diabetes, obesity, glucagon – like peptide – 1 receptor agonists, hypoglycemia, gastrointestinal adverse effects, nonarteritic anterior ischaemic optic neuropathy

Introduction

GLP – 1 RAs have represented a paradigm shift in the treatment of T2D and obesity. The incretin effect induced by GLP – 1 RAs allows for glycemic control in a glucose – dependent manner more efficiently than other therapeutic classes without increasing the risk of hypoglycemia [1]. Interestingly, some of them are able to cross the blood – brain barrier and act on the brain to stimulate satiety [2], which leads to food intake reduction and, consequently, body weight loss, which occurs at the expense of fat mass. As a result, the risk of progression to T2D decreases, and improvements in lipid profile, blood pressure or sleep apnoea have been

observed [3]. GLP – 1 RAs also exert pleiotropic actions with metabolic, hepatic, renal and cardiovascular beneficial effects [4,5]. Of note, a recent meta – analysis encompassing those clinical trials focused on the cardiovascular safety of GLP – 1 RAs found significant reductions in MACE3 (a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke), hospitalization for heart failure and progression of chronic kidney disease [6]. Numerous clinical studies highlight that the most frequent adverse effects (AEs) associated with GLP – 1 RA are those of a gastrointestinal (GI) nature, namely nausea, vomiting, diarrhoea and constipation. According to the literature addressing clinical trials, GI AEs usually develop in 40–70% of treated patients, although they have sometimes been reported in up to 85% [7,8,9,10]. Gastrointestinal side effects occur regardless of the half-life (long/short acting) or route of administration (subcutaneous/oral) of the selected GLP – 1 RA. They are usually transient, usually begin during the dose escalation period and usually subside soon after reaching the maintenance dose, and in most cases are mild to moderate in severity. A recent report summarizing the results of several studies concluded that the majority (99.5%) of documented gastrointestinal adverse events in obese subjects treated with GLP – 1 RAs were not serious [11]. A substantial body of real-world evidence supports these observations [12,13]. Nevertheless, it is important for patients and health care professionals (HCPs) to be aware of these AEs in order to mitigate their effects and improve adherence and persistence with treatment. GI AEs may lead to the temporary or permanent discontinuation of GLP – 1 RA treatment. Although interruption has been reported to occur in up to 12% of GLP – 1 RA – treated patients (vs. ~2% in those treated with placebo) [7,8.9,10], permanent discontinuations range between 1.6–6% of treated patients (vs. <1% with placebo), according to clinical trial programs [7, 11]. In the real-world setting, persistence with GLP – 1 RA therapy has been found to range between 40% and 60% and between 34% and 67% at 180 and 360 days, respectively [14,15]. The results seem to be better with once-weekly administered GLP – 1 RAs compared to those requiring once-daily injections [16,17].

Adverse Effects Associated with GLP – 1 RAs

Gastrointestinal disorders

As previously mentioned, the most common AEs associated with GLP – 1 RAs are those of a gastrointestinal nature. Among the most frequently GI side effects are nausea, vomiting, diarrhoea and constipation, nausea appears systematically as the most frequent event in all

clinical trials. The prevalence of the other GI AEs is lower. Overall, the onset of GI AEs are slightly higher in those trials designed to assess the efficacy and safety of GLP – 1 RA in people with obesity, which may be due to the fact that doses are higher than those used in clinical trials in people with T2D. Interestingly enough the long-acting agents have been associated with less nausea and vomiting but with more diarrhoea [18], which might be explained by a more sustained effect of these compounds on GLP – 1 intestinal receptors [19]. Furthermore, it is worth mentioning that flatulence may occasionally appear, although studies reporting its frequency are lacking. Patient education in terms of how to take and deal with satiety once GLP – 1 RAs are started is crucial for ensuring treatment compliance. It is accepted that persistence improves when weight is adequately managed and safe, straightforward treatments are used [20,21].

Pancreatobiliary complications

Pancreatobiliary complications have been documented, althought seldom. A comprehensive review encompassing 30 trials focusing on GLP – 1 RA safety in people with T2D concluded that the risk of gallbladder complications or acute pancreatitis (AP) associated with this treatment was generally low [22]. In people with obesity, the incidence of gallbladder – related events were always <3% [8,23]. Cholelithiasis was reported in <1% patients in the majority of cohorts, regardless of having T2D or obesity [7,8,9,10]. Its association with GLP – 1 RA use, although unusual, has been linked to a combination of factors. Among these, the relevant weight loss often experienced by people with obesity may promote biliary lithogenicity, such as after bariatric surgery. Other explanations might be a direct action of the drug on biliary secretion and the change of gallbladder motility [24]. Whereas cholecystitis episodes were anecdotal [7,8,9,10]. Finally, although higher circulating levels of lipase and amylase were reported in patients on GLP – 1 RA therapy in many trials, the increases were rarely higher than three or five – fold the upper limit of normal, respectively [7,8,34,36], returned to normal levels after dechallenge, and were poor predictors of AP [23]. A meta – analysis that included studies lasting for ≥24 months, with more than 9000 patients treated with GLP-1 RA during such period, did not find an association between GLP – 1 RA therapy and AP either [25]. Another one covering 55 randomized controlled trials and five observational studies with more than 300,000 participants, drew the same conclusion. Nevertheless, a recent meta – analysis encompassing up to 76 randomized controlled trials concluded that GLP – 1 RA treatment was associated with

a significant, although low, increased risk of gallbladder or biliary diseases (relative risk (RR) 1.37). In the group of patients with obesity, the risk was nearly twice as high (RR 2.29) compared to that observed in studies on the treatment of T2D or other diseases (RR 1.27). Higher GLP – 1 RA doses and, especially, the duration of treatment influenced the risk [26]. Acute pancreatitis was always experienced by less than 1% of patients treated with GLP – 1 RAs. Furthermore, many of the cases were reported in subjects with a previous history of pancreatitis or gallbladder disease. Thus, caution must be exercised in patients with these antecedents. Ursodeoxycholic acid may be recommended for patients with a history of cholelithiasis alongside GLP – 1 RA therapy. HCPs must be aware of the possibility of these rare side effects to act early and avoid the complications related to dehydration, such as severe renal failure [17]. A study performed to assess whether there was a direct association between GI AEs and the extent of weight loss concluded that weight loss was largely independent of GI AEs [28, 29].

Hypoglycemia

The risk of hypoglycemia is small when a GLP – 1 RA is used in combination with metformin. Hypoglycemic events may occur, however, when GLP – 1 RAs are given in conjunction with diabetes medications known to cause hypoglycemia like basal insulin, sulfonylureas. For the majority of patients in whom the addition of GLP – 1 RA is prompted by insufficient glycemic control, a reduction in the dose of basal insulin, sulfonylureas is not typically necessary, neverthereless all patients should be informed of the possibility of hypoglycemia.

Nonarteritic anterior ischaemic optic neuropathy

Anecdotal experience raised the possibility that one of the GLP –1 RAs, semaglutide is associated with nonarteritic anterior ischaemic optic neuropathy (NAION). NAION is a rare (2.5–11.8 per 1,00,000 cases in men above 50 years) but serious condition that causes sudden painless loss of vision due to ischaemia of the optic nerve.[30] It is more common in Caucasians compared with Asians and is associated with various risk factors such as hypertension, T2D, smoking, hyperlipidemia, obesity, obstructive sleep apnea, small optic nerve cup, optic nerve drusen, and certain drugs, especially phosphodiesterase type 5 inhibitors, amiodarone, and

cabergoline. Although the clinical development programs and real – world studies of semaglutide did not report any significant increase in the risk of NAION, a recent retrospective cohort study suggested a possible link between NAION and semaglutide. [31] Hathaway et al conducted a retrospective cohort study to evaluate the association between semaglutide use and the development of NAION over a 6 – year period. The study, published in JAMA Ophthalmology on 3 July 2024, used a centralised clinical data registry that included patients without a history of NAION. Both patients with diabetes (hazard ratio (HR) 4.28) and obesity (HR 7.64) receiving semaglutide had an increased risk of NAION. These findings translate into an increased absolute risk of NAION of 7.5% in people with T2D and 7.0% in people with obesity.[32] Given the large number of participants in randomised clinical trials and the large global population using GLP – 1 RAs, any confirmed absolute risk of developing NAION with semaglutide is likely to be very low. Therefore, the potential risk of NAION should not currently discourage the prescribed use of GLP – 1 RAs in the treatment of T2D or obesity

Conclusions

GLP –1 RAs can be considered as easy – to – handle, highly effective drugs with a good tolerability profile for the treatment of people with obesity or T2D. Patients should be informed that they may experience GI AEs and that these are likely to be mild to moderate in intensity and transient. HCPs need to be aware that comprehensive dietary education, flexibility during the dose – escalation phase and appropriate symptomatic management of persistent GI AEs are factors of paramount importance in minimising the GI side effects associated with GLP – 1 RA use. Whereas the data on the risk of NAION associated with semaglutide therapy require further research to confirm or refute the robustness of the association and mechanistic studies to explore the biological plausibility. Nevertheless, the possibility of this serious complication occurring during GLP – 1 RAs therapy should be kept in mind.

Author's contribution

Conceptualization: Anna Kasprzak

Methodology: Monika Kułaga

Software: Krzysztof Tyszkiewicz and Sylwia Wielgosz

Check: Monika Grzybek, Małgorzata Kasprzak and Borys Łozowski

Formal analysis: Barbara Szostak and Barbara Wilczyńska

Investigation: Monika Kułaga and Diana Mazur – Lesińska

Resources: Małgorzata Kasprzak and Monika Kułaga

Data curation: Borys Łozowski

Writing - rough preparation: Anna Kasprzak and Sylwia Wielgosz – Biała

Writing - review and editing: Diana Mazur – Lesińska and Monika Grzybek

Visualization: Barbara Wilczyńska

Supervision: Krzysztof Tyszkiewicz

Project administration: Anna Kasprzak

Receiving funding: Barbara Wilczyńska and Małgorzata Kasprzak

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