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Liraglutide induced gastrointestinal disturbance – case report and literature review

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Summary

Background. Around eight million adults in Poland are diagnosed with obesity based on the World Health Organization criteria. In contrast, overweight is diagnosed in almost 19 million individuals, but estimating the incidence of all chronic obesity complications is really difficult due to the lack of reliable data. In case of older adults, obesity is often associated with disability and worsening of chronic metabolic diseases (including type 2 diabetes), cardiovascular disease, and osteoarthritis, as well as sarcopenia, frailty, and dementia. Apart from that, weight gain is frequently the first symptom of hypothyroidism. One of the drugs currently used in the treatment of obesity in Poland is liraglutide. ***Material and methods.*** We describe a case report of a 60-year-old female patient (weight 86 kg, height 1.68 m, BMI = 31.18) suffering from Hashimoto's, who experienced an adverse reaction in the form of nausea and vomiting to liraglutide. ***Results.*** The patient discontinued the medication and was referred to an obesity clinic. ***Conclusions.*** The described case confirms the risk of gastrointestinal adverse drug reactions (GADRs) to liraglutide *Geriatria 2022;16:246-251. doi: 10.53139/G.20221624*

Keywords: *liraglutide, obesity, nausea, vomiting, adverse reaction, Hashimoto's disease*

Introduction

Over 70% of early deaths worldwide result from noncommunicable diseases (NCDs), such as cardiovascular diseases, cancer and diabetes mellitus, which represent the leading cause of mortality and premature disability. A significant risk factor for NCDs is obesity [1,2]. However, organizations such as the World Obesity Federation and the American and Canadian Medical Associations have stated that obesity is not just a risk factor for other diseases but is a chronic progressive disease by itself. This complex multifactorial disease is defined as excessive fat accumulation that might impair health [1,3]. Depending on the severity of the condition and comorbid disorders, being obese may decrease the life expectancy by an estimated 5-20 years. It has been proven that obesity not only may reduce the quality of life, lead to unemployment, lower productivity and social disadvantages, but also significantly contributes to the emergence of metabolic diseases (e.g. type 2 diabetes mellitus, fatty liver disease), cardiovascular diseases including hypertension, myocardial infarction and stroke, osteoarthritis, Alzheimer disease, depression and even some types of cancer (for example, breast, ovarian, prostate, liver, kidney and colon). One of the diagnostic criteria for obesity used in epidemiological studies is BMI (Body Mass Index) ≥30 kg/m^2 [1]. Nevertheless, relying on BMI should not stand as the basis for obesity diagnosis due to the low sensitivity of this indicator (there is a prominent individual variability in the percent body fat attributed to age, sex, and ethnicity), which does not indicate the amount of visceral body fat, which is a factor known to increase the cardiometabolic risk. The obesity rates have increased since 1980 in both sexes of all ages (albeit it is more prevalent among the elderly and women). Nowadays, obesity is one of the most common diseases in the world; nearly a third of the world's population is classified as overweight or obese [3,4]. According to the report of the National Institute of Public Health – National Institute of Hygiene from 2020, there were 54% of overweight and 10% obese people in Poland – overweight was reported in 46% of women and obesity in 8% of women [5].

Rapid changes in socioeconomic status, the adoption of energy- and fat-rich diet and a sedentary lifestyle are the bane of developing countries and undeniably the main culprits behind obesity. Although this trend was similar considering many regions and ethnicities, the absolute prevalence rates of overweight and obesity varied widely across the world- e.g. the prevalence rates of obesity in some developed countries seem to have levelled off during the past few years. In case of older adults, obesity is often associated with disability and worsening of chronic metabolic diseases including type 2 diabetes, cardiovascular disease, and osteoarthritis, as well as sarcopenia, frailty, and dementia. Worse yet, these two sets of conditions tend to potentiate each other [3,4].

Apart from that, weight gain is frequently the first symptom of hypothyroidism. The most common type of thyroiditis and autoimmune endocrinopathy, and the most common non-iatrogenic cause of hypothyroidism is Hashimoto's disease [5]. Under normal circumstances, the immune system protects the body against infections. However, in people with Hashimoto's disease, abnormal immune system stimulation induces the formation of antibodies against the thyroid gland. It leads to chronic painless inflammation of the thyroid gland, slowly (over the years) destroying the thyroid gland and reducing hormone production [6]. Hashimoto's disease is more prevalent in females, and anti-TPO antibodies are more common in women (13.9%) than in men (2.8%). Hypothyroidism is treated mainly pharmacologically, and the therapy's primary goal is to supplement thyroid hormones to normalize TSH levels. However, it has been shown that 82% of women treated are still overweight, and 35% suffer from obesity even when they achieve normalization of thyroid hormones and TSH levels within laboratory norms. According to a meta-analysis by Song et al. covering 22 studies, obesity is statistically significantly correlated with Hashimoto's disease ($p = 0.022$) and high levels of anti-TPO antibodies ($p = 0.001$). Furthermore, the data indicates that it is difficult to achieve effective weight reduction in patients even after treatment with L-thyroxine and achieving euthyroidism [5,7]. Current measures such as lifestyle changes, bariatric surgery or available medications are sometimes not effective in controlling obesity, and the development of antiobesity drugs has often been challenging. However, advances in biology and molecular technology have led to the subsequent development of new drug targets [8]. The treatment guidelines for obesity recommend the use of pharmacologic therapy in adult patients with a BMI of ≥ 30 kg/m^2 or patients with a BMI of ≥ 27 kg/m^2 with at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, insulin resistance, type 2 diabetes mellitus) [9]. Currently, three drugs are applied in treating overweight and obesity in Poland. These include:

- orlistat (gastrointestinal lipase inhibitor)- for patients who have no problems controlling the amount of food intake (the feeling of satiety and appetite is not affected by this drug) and with a preference for fatty foods; however, this drug is considered of marginal importance, regarding the knowledge on the importance of emotions in the regulation of food consumption, and thus, it is not included in the current guidelines;
- a combination drug containing bupropion hydro-chloride and naltrexone hydrochloride- this drug, in turn, increases satiety and inhibits emotional eating; it acts on the neurons of the arcuate nucleus of the hypothalamus, it increases the secretion of proopiomelanocortin of the α-melanotropin precursor (α-MSH) and prolongs its release by blocking the mi opioid receptor- the drug acts on both the biological and emotional mechanisms of food intake.
- liraglutide- a long-acting glucagon-like peptide 1 (GLP-1) receptor analogue known to increase the glucose-dependent insulin secretion from pancreatic β-cells (successfully used in the treatment of type 2 diabetes for several years); moreover, it acts on the centres of satiety and hunger in the hypothalamus, provides the feeling of fullness and inhibits the feeling of hunger, but does not affect appetite [9-12].

The long-acting analogs of the gut hormone, GLP-1, are considered potent antiobesity treatment as weight loss has been well described as an additional benefit of liraglutide therapy. It occurred to be effective in reducing and sustaining body weight loss in clinical trials, and moreover, there were numerous reports on its efficacy in improving glycemic and cardiovascular risk factors indices. Thus, the manufacturer released the higher dose formulation specifically for treating obesity – liraglutide in a dose of 3 mg/day was approved by the FDA for this indication in 2014 [9,13]. The most well-established adverse events from therapy with glucagon-like peptide-1 (GLP-1) receptor agonists

(GLP-1RAs) are gastrointestinal adverse drug reactions (GADRs) which include nausea, vomiting, diarrhea, and constipation (closely related to activation of central and peripheral GLP-1 receptors) and headache. However, most patients tolerate the drug well, and the tolerance improves with its use [14,15]. In this article, we describe a case of an adverse drug reaction (ADR) in the form of nausea and vomiting to liraglutide.

Case report

We describe a case of a 60-year-old female patient (weight 86 kg, height 1.68 m, BMI = 31.18) suffering from Hashimoto's disease from 2020 (treated with levothyroxine 112 μg, Vitamin D3 – 2000 J, bisoprolol 2.5 mg) due to weight gain (approx. 14 kg per year) after unsuccessful attempts to reduce body weight (a diet of 1500 calories/day). After medical consultation and follow-up (normal thyroid profile parameters, normal blood pressure values) due to diagnosed obesity – BMI ≥30 kg/m^2, the patient took the initial dose of liraglutide subcutaneously – 0.6 mg once a day. Approximately 2 hours after the administration of the drug, the patient experienced nausea and vomiting lasting about four days. The patient did not use other products to control her body weight and products that may cause weight gain and did not report any side effects from other medicinal products. After consultation, the patient withdrew from taking another drug dose and was re-referred to an obesity clinic.

Dissusion

Around eight million adults in Poland are diagnosed with obesity based on the World Health Organization criteria. In contrast, overweight is diagnosed in almost 19 million individuals, but estimating the incidence of all chronic obesity complications is difficult due to the lack of reliable data [10]. Obesity is a progressive disease entailing numerous complications. Their development depends on adipose tissue distribution, the stage of the disease, and its duration. Thus, the treatment of obesity should be started as early as possible to avoid the progression of the disease, prevent the development of complications, and improve the overall health and quality of the patient's life [16].

One of the drugs advised during the treatment of obesity is liraglutide (Saxenda). It is a glucagon-like peptide-1 (GLP-1) receptor agonist, structurally homologous to endogenous human GLP-1 in 97% [9]. The mechanism of action of endogenous GLP-1 and its analogues on body weight is complex. GLP-1 is secreted in the intestinal mucosa, primarily in the ileum and distal colon; however, it is also present in the central nervous system. GLP-1 receptor mRNA is distributed in many brain areas (including the area postrema (AP), the dorsal motor nucleus of the vagus, and the nucleus of the solitary tract (NTS)) associated with food intake, energy homeostasis and body weight [13,17]. GLP-1 released from L cells within the gut may reduce the feeling of hunger through vagal sensory afferent nerves signalling to the brain as well as acting directly on the stomach by delaying gastric emptying, which results in satiety [9]. GLP-1 analogues act by mimicking the action of the endogenous GLP-1. The studies performed mainly in rodent models have shown that GLP-1 analogues act by stimulating insulin secretion, reducing glucagon release, reducing insulin resistance, inhibiting gastric emptying and postprandial gastric secretion, and activating brown adipose tissue and the hypothalamic satiety center and inhibition of the hunger center [18]. The endogenous GLP-1 has a short elimination half-life of 1-2 minutes as it is rapidly degraded by dipeptidyl peptidase-4 (DPP-4). In contrast, liraglutide is stable against metabolic degradation by the abovementioned enzyme and has a half-life of 13 hours after subcutaneous administration, allowing for once/day dosing [9]. The only GLP-1 analog registered in Poland for the treatment of obesity is liraglutide at a maximum dose of 3.0 mg [15]. Nevertheless, all over the world (and in our country, on an off-label basis), other drugs from this group such as semaglutide or dulaglutide are also used. Liraglutide was first approved for the treatment of type 2 diabetes. The outcomes of the studies performed in a large population exposed that liraglutide improved glycemic control and produced significant body weight loss with limited side effects [13]. It has been shown to effectively lower hemoglobin A1C (HbA1C) at daily doses of 1.2 and 1.8 mg [9]. A study comparing the effects of orlistat and liraglutide has shown, that the latter induced greater weight loss and lowered systolic and diastolic blood pressure to a greater extent (after the two-year treatment period). There were self-reported cases of symptomatic hypoglycemia in the primary outcome measures of safety and tolerability [13,19,20]. About one in four patients with type 2 diabetes may experience symptomatic hypoglycemia at least once over the course of one year [21]. Nevertheless, the overall risk of hypoglycemia after therapy with GLP-1 receptor

agonists is low, as these agents stimulate insulin release and inhibit glucagon secretion in a glucose-dependent fashion. Thus, it seems beneficial for patients without diabetes, in whom the risk of low blood glucose levels is not desired [9]. The majority of adverse effects of liraglutide reported in the studies by Astrup et al. and Lean et al. were transient nausea and vomiting; however, the drug was well tolerated over extended treatment periods and was effective in sustaining weight loss and improving cardiovascular risk factors [19,20]. The analogous results were obtained in a study by Inoue et al. which aim was to scrutinize the long-term impact of liraglutide on body weight and glycemic control in Japanese type 2 diabetic subjects, and in a study performed by Wadden et al. that proved that in overweight and obese adults with type 2 diabetes a combination of a low-calorie diet, physical activity and liraglutide (3.0 mg/day) resulted in significantly greater weight loss than in those receiving placebo [22,23]. Another adverse reaction to GLP-1 agonists may be small (2–4 beats/min) but sustained increase in heart rate [13]. However, liraglutide is considered suitable for patients with type 2 diabetes with or without a history of heart failure (NYHA functional class I to III), and even it may reduce cardiovascular outcomes in patients with myocardial infarction (MI) and/or stroke and in those with established atherosclerotic cardiovascular disease without MI/stroke [24,25]. Another issue is probable pancreatic injury due to the long-term use of GLP-1 receptor agonists since these drugs induce pancreatic beta-cell proliferation. [13,26]. In clinical trials, including approximately 4,500 patients, pancreatitis was reported in seven cases that were as not beyond expected rates for this population. Reviews of clinical data by the EMA concluded that GLP-1 agonist treatments did not pose an increased risk for the development of pancreatitis [27]. Cao et al. performed a meta-analysis aiming to collect data from large-scale cardiovascular outcome trials (CVOTs) and assess the effect of GLP-1 receptor antagonists on the incidence of acute pancreatitis and pancreatic cancer. From seven CVOTs enrolling 56,004 patients with type 2 diabetes (with a median follow-up time ranging from 1.3 to 5.4 years), a total of 180 cases of acute pancreatitis and 108 cases of pancreatic cancer were reported. The analysis of CVOTs did not suggest any increased risk of either acute pancreatitis or pancreatic cancer in T2DM patients treated with GLP-1 receptor antagonists [28]. Thus, pancreatitis is considered a rare ADR to GLP-1 receptor antagonists [27,28]. There are also some concerns raised about the potential risk of thyroid cancer due to GLP-1 analogues based on studies in rodents demonstrating the proliferation of thyroid C-cells and tumor formation following long-term treatment with GLP-1 agonist compounds. Nevertheless, these results were not consistent with those obtained from nonhuman primates which, similarly to humans, are characterized by a much lower density of GLP-1 receptors on thyroid C cells. Mali et al. conducted a research to detect a signal of thyroid cancer during treatment with GLP-1 analogues in patients with diabetes from the European pharmacovigilance database (EudraVigilance). Unfortunately, spontaneous reports indicate that GLP-1 analogues are associated with thyroid cancer in patients with diabetes [29]. Nevertheless, the effects of prolonged use of higher doses of liraglutide, such as those used for weight loss treatment, have not been determined in humans [13]. Returning to nausea, the most frequent ADR of GLP-1 agonists, it is more problematic in the early stages of treatment and with shorter-acting agonists (e.g. exenatide) due to higher peak concentrations. Vomiting (11-15%), diarrhea (20-28%) and constipation (20-23%) have also been reported by the patients during the therapy with liraglutide, but less frequently than nausea (39-45%), [13,21,30]. A study by Wadden et al. aimed to evaluate the effects of intensive behavioral therapy (IBT) alone and with liraglutide 3.0 mg in 150 obese adult individuals (randomized into three groups: IBT-alone, IBT combined with liraglutide and IBT-liraglutide + replacement diet). Additional pharmacological and behavioural therapies were beneficial and resulted in better weight loss in the two latter groups; however, researchers reported few ADRs within groups with liraglutide. Cases of nausea, constipation, upper respiratory infection, and gastroenteritis were ten or more percentage points higher in both liraglutide-treated groups than in the IBT-alone group. A total of six serious ADRs were reported, including asthma, bile duct stones, gastroenteritis, pneumonia, and wound infection, all of which resolved fully [31]. Zhang et al. performed a meta-analysis to assess the efficacy and safety of liraglutide in obese, non-diabetic individuals based on randomised control trials published in the following databases: EMBASE, MEDLINE and the Cochrane Controlled Trials Register. Five publications involving a total of 4,754 patients that compared liraglutide with placebo were included. Liraglutide was an effective and

safe treatment for weight loss in individuals without diabetes. Four randomised control trials included the proportion of individuals who withdrew due to adverse events data representing a cohort of 4,703 participants (2,972 in the liraglutide group and 1,731 in the placebo group); liraglutide and placebo were similar in terms of the incidence of withdrawn due to adverse events. Liraglutide administration was generally well-tolerated. However, nausea occurred more common among patients treated with liraglutide as compared to those treated with placebo, but these adverse events were of mostly mild or moderate severity, and discontinuation due to them occurred no more frequently with liraglutide use than with placebo [32]. The therapeutic effect of liraglutide has also been scrutinized in adolescents with obesity and a poor response to lifestyle therapy alone. A total of 125 participants were assigned to the liraglutide group (3.0 mg) and 126 to the placebo group subcutaneously once daily, in addition to lifestyle therapy. 64.8% of patients from the liraglutide group had gastrointestinal adverse events, while in the placebo group, it was 36.5%. Adverse events that led to discontinuation of the trial treatment were 10.4% in the liraglutide group vs 0 in the placebo group. Serious adverse events occurred in both groups (liraglutide-2.4% vs. placebo – 4.0%) and there was one suicide in the liraglutide group, but the investigator assessed it as unlikely to be related to the trial treatment [33]. Gastrointestinal ADRs, such as nausea and vomiting, are the most common adverse effects of liraglutide and have been shown to be transient over time due to tolerance development. Although GADRs are very frequent during the therapy with liraglutide and generally do not represent serious health issues, they may contribute to premature discontinuation of the therapy by many patients [34,35]. What may help reduce the gastrointestinal adverse effects is gradual dose escalation for most GLP-1Ras. Patients should be counselled about the possible adverse effects of GLP-1 receptor antagonists and that they are mostly mild to moderate, and nausea typically subsides after dose escalation is complete. Also, they should be advised on how to manage this kind of GADR, e.g. reducing meal size, mindfulness to stop eating once full, avoiding eating when not hungry, avoiding high-fat or spicy food, and moderating intake of alcohol and fizzy drinks could be helpful [36].

Conclusion

The treatment of obesity is multifaceted. It should be individualized and not limited only to nutritional and physical activity education. Each patient suffering from obesity or overweight should be offered complex support- appropriately selected pharmacotherapy, diet, and, if necessary, psychotherapy. Liraglutide is a medicinal product subject to additional monitoring for rapid identification of new information on its safety. The described case confirms the risk of a very common gastrointestinal adverse effect which is nausea.

Conflict of interest
None

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