JCEM Case Reports, 2023, **1**, 1–3
https://doi.org/10.1210/jcemcr/luac004
Advance access publication 29 November 2022
Case Report

Different Effects of Once-weekly and Once-daily Administered GLP-1RA Semaglutide and Liraglutide on Bile Acid Diarrhea

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Abstract

Bile acid diarrhea (BAD) is a socially debilitating disease. Typical symptoms include loose stools, urgency, and high stool frequency. Recently, we reported the superior efficacy of the glucagon like-peptide 1 receptor agonist (GLP-1RA) liraglutide (administered subcutaneously once daily) in reducing daily bowel movements compared with the traditionally used bile acid sequestrant colesevelam (considered the standard of care). This has generated proposals of testing longer acting and more potent GLP-1RAs for treating BAD. Here, we present a patient with severe BAD who experienced minimal effect of the once-weekly administered GLP-1RA semaglutide, but total remission of BAD symptoms during treatment with liraglutide.

Key Words: bile acid diarrhea, liraglutide, semaglutide, GLP-1-RA, colesevelam

Abbreviations: BAD, bile acid diarrhea; GLP-1, glucagon-like peptide 1; GLP-1RA, glucagon-like peptide 1 receptor agonist.

Bile acid diarrhea (BAD) is a common yet underdiagnosed and underrecognized disease. The primary symptoms are watery diarrhea with high frequency of unpredictable bowel movements, urgency, and fecal incontinence, making BAD a socially debilitating condition. The pathophysiology of BAD involves spillover of bile to the colon, where bile salts irritate the colonic mucosa and cause fluid secretion. Bile acid sequestrants are the most commonly used pharmacological treatment for BAD. These agents bind bile salts and thereby hinder their inexpedient interaction with the colonic mucosa; however, many patients respond poorly, and treatment with the most efficacious bile acid sequestrant colesevelam is associated with hypertriglyceridemia [1].

We previously reported cases of long-term remission of BAD from treatment with the once-daily subcutaneously administered glucagon-like peptide 1 (GLP-1) receptor agonist (GLP-1RA) liraglutide, which is approved for treating both type 2 diabetes and obesity [2]. In our previous publication, a detailed mode-of-action hypothesis was presented based on liraglutide's decelerating effect on small intestinal transit. Recently, these observations were substantiated in a randomized clinical trial showing that liraglutide is superior in reducing stool frequency compared with colesevelam [3]. This has caused a considerable off-label use of liraglutide and speculations about whether longer acting and more potent GLP-1RAs can further improve the management of BAD. The GLP-1RA class has grown considerably since the introduction of liraglutide and now represents a diverse class of drugs with different pharmacokinetic and pharmacodynamic profiles [4] that may interact with BAD pathophysiology in different ways. Semaglutide is a once-weekly subcutaneously administered GLP-1RA approved for treating type 2 diabetes and obesity; it has more potent glucose-lowering and body weight-reducing effects compared with liraglutide [5, 6].

Here, we present a patient with severe BAD who, because of colesevelam-induced hypertriglyceridemia, was changed to semaglutide administered subcutaneously once weekly with minimal effect, but then experienced total remission of BAD symptoms after switching to liraglutide administered subcutaneously once daily.

Case

A 62-year-old man without diabetes but a 5-year history of severe primary BAD diagnosed with 0% retention during a ^{75}selenium-homotaurocholic acid test, with numerous daily bowel movements with loose consistency and bloating experienced colesevelam-induced hypertriglyceridemia (5.1 mmol/L). The managing gastroenterologist discontinued colesevelam and initiated once-weekly subcutaneous administration

Received: 11 September 2022. **Editorial Decision:** 3 October 2022. **Corrected and Typeset:** 29 November 2022

of the GLP-1RA semaglutide (0.5 mg). Two days after the first injection, the patient experienced positive effects on BAD symptoms with lowered stool frequency and firmer stool consistency, but at day 4 after the first injection, these effects waned, and his usual symptoms reemerged. This pattern repeated itself for the next 3 injections (ie, positive effect of semaglutide 2 days after administration and then reappearance of BAD symptoms on day 4 after injection) (Fig. 1). Semaglutide was discontinued and once-daily subcutaneously administered liraglutide was initiated. During the up-titration period (0.6 mg once daily for 1 week and 1.2 mg once daily for the subsequent week), the patient experienced gradual improvement in BAD symptoms and after 1 week on the maintenance dose (1.8 mg once daily) he had 1 bowel movement per day, no bloating, and stools with firm consistency (ie, complete remission of BAD symptoms). After 6 months of treatment, he remained without BAD symptoms and with normal circulating triglyceride concentrations (1.67 mmol/L). Based on the indication of BAD, an application for individual reimbursement for the cost of liraglutide was approved by the Danish Medical Agency, and now, more than 2 years after the introduction of liraglutide, the patient is still experiencing remission of BAD.

Discussion and Conclusion

Compared with the longer acting and more potent GLP-1RA semaglutide, the present patient with BAD experienced superior effects on BAD symptoms with the shorter acting and less potent GLP-1RA liraglutide. We believe that this seemingly paradoxical observation may be explained by the different pharmacokinetics and pharmacokinetics-related pharmacodynamics of the 2 compounds.

Colesevelam-induced hypertriglyceridemia occurs in 4% to 5% of patients and severe hypertriglyceridemia in only <1% of patients [7] and, thus, does not represent a common limiting factor for colesevelam treatment.

In addition to its glucose-lowering and satiety-promoting effects, the gut-derived hormone GLP-1 is a humoral mediator of the inhibitory feedback mechanism that controls meal transit through the gastrointestinal tract and optimize nutrient assimilation [4]. Endogenous GLP-1 has a very short circulating half-life (~1 minute), and GLP-1RAs with half-lives ranging from ~2.5 hours to more than a week have been developed for type 2 diabetes and/or obesity treatment [4]. The intermittent exposures seen with short-acting GLP-1 receptor agonists (lixisenatide and exenatide, administered once and twice daily, respectively, with meals) result in sustained inhibitory effects on gastrointestinal motility. In contrast, the continuous exposure of long-acting GLP-1 receptor agonists administered once daily (liraglutide) or once weekly (dulaglutide and semaglutide) results in tachyphylaxis with regard to deceleration of gastric emptying. However, despite the continuous exposure seen with liraglutide, its intermediate half-life (~13 hours) and once-daily administration is associated with significant peaks and troughs (Fig. 1), which may explain the incomplete tachyphylaxis regarding its decelerating effect on gastrointestinal motility and small intestine transit time [8].

We previously speculated that any positive and sustained effect of liraglutide on BAD symptoms may rely on liraglutide-induced prolongation of small intestinal transit time allowing a greater degree of passive and active bile acid

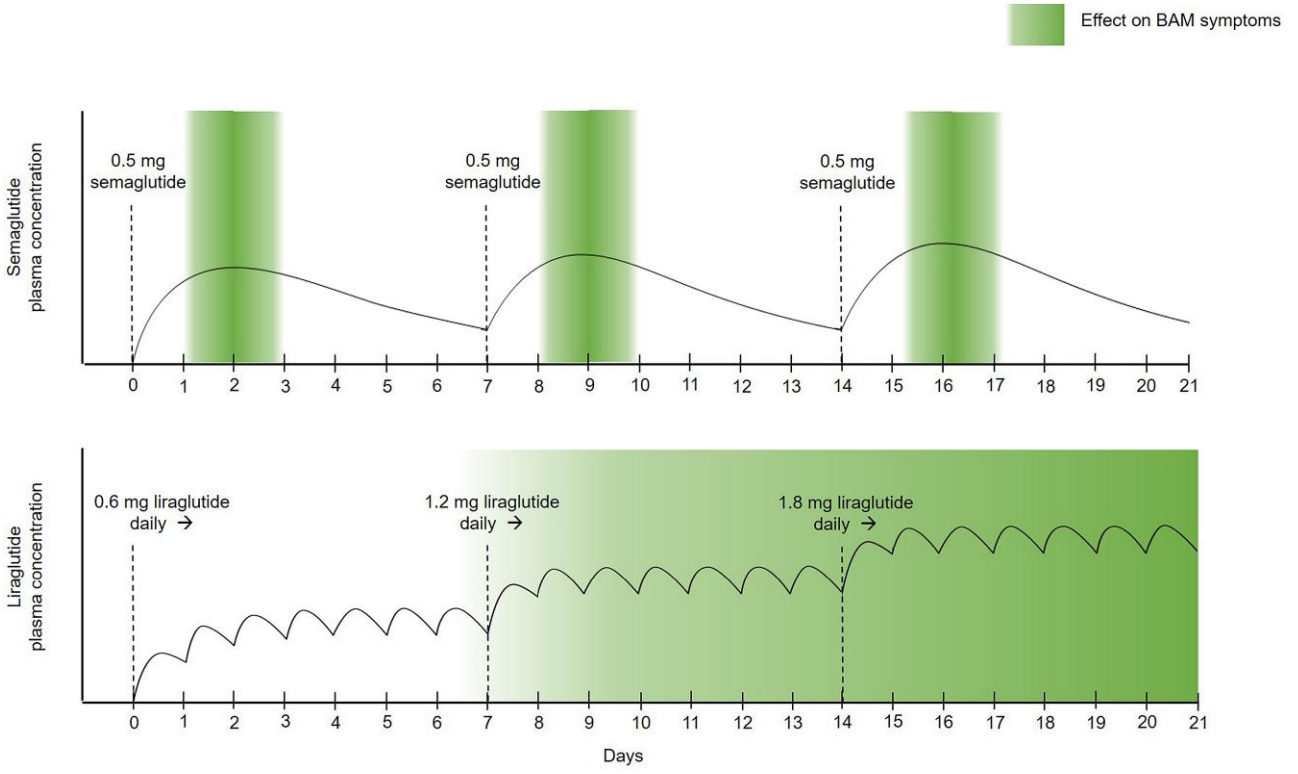

Figure 1. Schematic overview showing theoretical time- and drug exposure-dependent effects of the once-weekly subcutaneously administered glucagon-like peptide 1 receptor agonist (GLP-1RA) semaglutide (top) and the once-daily subcutaneously administered GLP-1RA liraglutide (bottom), respectively, on bile acid diarrhea (BAD) symptoms in a 62-year-old man with BAD. Plasma semaglutide and liraglutide concentrations are based on their circulating half-lives and thus are theoretical.

reabsorption through the small intestine and thereby reducing spillover of bile acids to the colon [2]. Furthermore, enhanced reabsorption may contribute to attenuate BAD symptoms by reducing hepatic bile acid synthesis [2]. These speculations were recently substantiated by findings showing that liraglutide compared with colesevelam increases reabsorption of bile acids and decreases bile acid synthesis. Contrary to the peaks and troughs characterizing the pharmacokinetic profile of liraglutide, plasma levels of once-weekly semaglutide are more plateau-like (Fig. 1), which, combined with its greater potency, may cause a higher degree of tachyphylaxis when it comes to GLP-1R-mediated deceleration of gastrointestinal motility. This is indicated by a 12-week study showing no overall effect of once-weekly subcutaneously administered semaglutide on gastric emptying compared with placebo [9]. We cannot exclude that a higher dose of semaglutide would have resulted in more pronounced effects on BAD symptoms. To our knowledge, no studies evaluating the long-term effect of once-weekly subcutaneously administered semaglutide on small intestinal transit time exist.

In conclusion, the present case with BAD benefitted only 2o days per week from treatment with the once-weekly and potent GLP-1RA semaglutide, whereas the once-daily and less potent GLP-1RA liraglutide caused complete and sustained remission of BAD symptoms. We propose that this difference may be explained by differential pharmacokinetics, with the daily plasma liraglutide peak and troughs resulting in less tachyphylaxis of the decelerating effect of GLP-1 receptor activation on gastrointestinal motility and therefore allowing a greater degree of bile acid absorption.

Colesevelam, semaglutide, and liraglutide are not labeled for the treatment of BAD.

Learning Points

1. The once-daily subcutaneously administered glucagon-like peptide 1 receptor agonist (GLP-1RA) liraglutide was recently shown to be superior in treating bile acid diarrhea (BAD) compared with the current standard of care, the bile acid sequestrant colesevelam
2. Off-label use of newer, longer acting, and more potent GLP-1RAs are now being considered for BAD treatment, but their pharmacokinetics and pharmacokinetics-related pharmacodynamics may influence how they affect BAD
3. The present BAD patient benefitted only 2 days per week from treatment with the once-weekly subcutaneously administered and potent GLP-1RA semaglutide, whereas liraglutide caused complete and sustained remission of BAD symptoms
4. The relatively short half-life of liraglutide and its daily peak and troughs in circulation may result in less tachyphylaxis of its decelerating effect on gastrointestinal motility, allowing a greater degree of bile acid absorption and making liraglutide a perfect GLP-1RA for BAD treatment

Author Contributions

M.L.K. and F.K.K. wrote the manuscript. E.K. reviewed and edited the manuscript.

Disclosures

The authors have nothing to disclose.

Data Availability Statement

All data are presented in the manuscript.

Informed Patient Consent for Publication

Signed consent obtained directly from the patient.

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