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Case Report

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Linaclotide and vasomotor symptoms

Abstract

Objective: To report a case of a peri-menopausal woman with acute onset vasomotor symptoms following initiation of Linaclotide.

Study Design: The study was carried out by a case report.

Results: A 52- year-old woman with acute onset of hot flushes and night sweats following initiation of Linaclotide for irritable bowel syndrome/constipation. The symptoms slowly improved and stopped after 4 months of Linaclotide use.

Conclusions: The fundamental pathophysiology of menopausal vasomotor symptoms remains enigmatic. Side effects of phosphodiesterase 5 inhibitors, such as Sildenafil, which increases cGMP, include hot flushes. Linaclotide is a potent guanylate cyclase-C agonist which elevates cyclic GMP primarily in the intestine with minimal absorption. Even minimal absorption may be enough to cause vasodilatation and in the peri-menopausal patient, trigger vasomotor symptoms.

Keywords: vasomotor symptoms, linaclotide, menopause

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Introduction

Vasomotor symptoms or hot flushes are periods of intense heat, sweating and peripheral vasodilation. Hot flushes and night sweats are the most commonly reported symptoms in menopausal women, affecting approximately 73% of women.[1] It has been suggested that vasomotor symptoms are triggered by a small elevation of core body temperature above the narrowed thermoneutral zone.[2] This central mechanism is not fully understood and may include peripheral vascular responses. Menopausal women who experience flushing have been shown to have significantly increased peripheral vascular reactivity as compared to women who do not.[3] The narrowed regulatory zone responds to small elevations in body temperature by dilating the already overly reactive peripheral vasculature to dissipate excess heat.[4]

Linaclotide was approved for treatment of chronic constipation and constipation predominate irritable bowel syndrome (IBS) in 2012. IBS is a functional gastrointestinal disorder that involves abdominal discomfort or pain associated with disturbed defecation.[5] Patients may experience predominately constipation, diarrhea, or a mixture of both. The treatment for IBS is mainly directed at symptom control and many patients suffer significant morbidity. Linaclotide is a promising treatment for patients with chronic constipation and constipation predominant IBS.[6]

Linaclotide is an oral medication used to increase intestinal enterocyte fluid secretion, improving colonic transit times and complete spontaneous bowel movements.[6] Linaclotide and its metabolites act as guanylate cyclase-C agonists activating the cyclic 3,5-monophosphate (cGMP) signaling pathway, leading to increased chloride and bicarbonate secretion into the intestinal lumen. Anion secretion results in diffusion of sodium and water into the lumen decreasing transit time of contents.[7] Linaclotide primarily affects the bowel since it has minimal absorption when taken orally.

The purpose of this manuscript is to discuss a potential side effect of Linaclotide in a perimenopausal woman. This patient experienced sudden onset of vasomotor symptoms with initiation of Linaclotide for treatment of chronic constipation. Informed consent was obtained from the patient described in this case report.

Case presentation

A 52-year-old Caucasian woman with long history of constipation predominant IBS presented with acute onset of vasomotor symptoms after starting Linaclotide. The patient had a previous extensive evaluation for IBS, including colonoscopy. Different trials of medications for constipation were unsuccessful with no improvement of symptoms. She was started on Linaclotide orally once per day with significant improvement in symptoms.

After initiating Linaclotide, she noted the immediate onset of hot flushes and night sweats, which significantly disturbed sleep. Prior to starting Linaclotide, she denied hot flushes, night sweats, mood changes, vaginal dryness or weight gain. Patient was status post hysterectomy at age 38 for heavy menses. Physical exam was benign and showed vagina with normal rugae and vaginal cuff. LH and FSH were collected and found to be elevated at 31.1IU/L and 56.2IU/L respectively.

The new onset flushing, night sweats and exhaustion were temporally related to Linaclotide. An option was to stop Linaclotide to determine if the vasomotor symptoms improved. She refused to stop taking the medication due to the vast improvement of her constipation/IBS. The patient noted slow improvement with complete amelioration of her vasomotor symptoms after four months of Linaclotide therapy.

Discussion

Vasomotor symptoms are the most bothersome and commonly reported symptoms in menopausal females.[1] Due to loss of sleep, interruption of social life and ability to work; many menopausal women will seek medical care related to vasomotor symptoms. The combination of a narrowed hypothalamic thermoregulatory zone and increased vascular reactivity make the menopausal woman more vulnerable to hot flushes and night sweats.[3] Minimal changes in temperature from things like hot drinks, stress, and medications

can induce a hot flush.[4] Vasomotor symptoms have been reported as side effects with medications like Sildenafil, and in this case report, Linaclotide (Linzess).

Cyclic-GMP, the main regulator of smooth muscle relaxation, plays an important role in vascular reactivity.[8] Medications such as Sildenafil and Linaclotide increase the amount of available cGMP. Sildenafil, a phosphodiesterase 5 inhibitor, results in penile vascular smooth muscle relaxation by increasing available cGMP in the penis.[9] Linaclotide is a peptide molecule which binds to the guanylate cyclase C receptor and acts as an agonist increasing cGMP. Linaclotide is poorly absorbed and so it primarily affects intestinal enterocytes.[6,7] One of the side effects of Sildenafil is flushing and night sweats, which are thought to be related to elevated systemic cGMP levels altering vascular reactivity.

In this peri-menopausal female there may be sufficient vascular reactivity that even small increases in cGMP, due to minimal systemic absorption of Linaclotide, could result in hot flushes. The sudden onset and correlation of hot flushes to Linaclotide use and lack of other traditional menopausal symptoms, favor a medication side effect rather than vasomotor symptoms associated with menopause. The improvement in symptoms and complete halting of vasomotor symptoms within 4 months of therapy may be related to tachyphylaxis or due to decreased systemic levels due to even less time for absorption due to increased bowel motility.

Acknowledgments

None.

Conflicts of interest

The authors declare there is no conflict of interests.

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