Peripheral Edema Related to Paroxetine Discontinuation: A Case Report

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ABSTRACT:
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Paroxetine is a selective serotonin reuptake inhibitor (SSRI), with antidepressant and anxiolytic characteristics. In association with paroxetine cessation, certain side effects can be observed frequently, including dizziness, vertigo, nausea, vomiting, headache, anxiety, insomnia, and irritability. Paroxetine-induced peripheral edema has been reported. However, there has been no report on peripheral edema related to paroxetine cessation. Here, we report a case who developed peripheral edema related to paroxetine discontinuation and whose peripheral edema disappeared after resumption of the paroxetine treatment.

Keywords: paroxetine, peripheral edema, side effect

INTRODUCTION
Paroxetine is an antidepressant drug of the selective serotonin reuptake inhibitor (SSRI) type having antidepressant and anxiolytic characteristics. It potently inhibits the reuptake of serotonin from the synaptic gap and is used to treat a number of psychiatric disorders such as major depression, panic disorder, obsessive-compulsive disorder, and post-traumatic stress disorder¹. Unlike other SSRIs, it does not have any active metabolites; therefore, it has a shorter half-life². Paroxetine is claimed to be a highly safe medicine in terms of its adverse effects and bioavailability. Its common adverse effects are nausea, somnambulism, asthenia, dizziness, sweating and, much less commonly, tremor, ejaculation dysfunction, loss of appetite, difficulty in urinating, low libido, and yawning³. Certain withdrawal symptoms such as dizziness, vertigo or lightheadedness, nausea, vomiting, headache, anxiety, diarrhea, paresthesia, tremor, weakness, insomnia, irritability and imbalance in walking have been observed following the cessation of treatment with SSRIs, supposedly due to a decrease in the serotonin 5-HT2 receptor density and 5-HT1A and 5-HT2 receptor desensitization. Paroxetine is metabolized by the CYP2D6 enzyme, and this enzyme is at the same time inhibited by paroxetine itself. Thus, upon the discontinuation of paroxetine, the inhibition of the enzyme disappears, and the circulating medicine is rapidly broken down and excreted with the urine. Because of these characteristics, paroxetine and fluvoxamine are the most rapidly excreted SSRIs,
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Peripheral edema may occur with many systemic diseases such as liver cirrhosis, kidney diseases, congestive heart failure, and concomitant use of medications such as non-steroid anti-inflammatory medicines, steroids, and antihypertensive medicines. There are cases of peripheral edema caused by antidepressants such as tranylcypromine, phenelzine, isocarboxazid, escitalopram, sertraline, mirtazapine, and trazodone reported in the relevant literature.

Although there is a case of peripheral edema related to paroxetine use in the literature, there is no peripheral edema case related to its discontinuation has been reported. Here, we report a peripheral edema case developed bilaterally on both legs following the discontinuation of paroxetine in a case having no any other known medical diseases, and which gradually disappeared with the restart of medication.

CASE

G. G. is a 41-year-old, single, female patient. She is a part-time teacher with an associate degree. She came to our psychiatry outpatient clinic with complaints such as swellings and redness on her feet and legs. Her prior history was that she started medication with paroxetine 20 mg/day with a diagnosis of depressive disorder, and the amount of her medication was raised to 30 mg/day after a month. Having regularly used her medicine for a year, she began to discontinue the medication ten days ago due to a decrease of her complaints. She reported that three days after the discontinuation, her feet and legs were swollen to the extent that on the 10th day her walking was effected. During medical examination, pretibial (+++) edema in both lower extremities was detected. There was no redness, ulceration and color change in the skin. The patient’s complete blood count, liver function tests (ALT, AST, GGT, ALP, bilirubin, albumin) and kidney function tests (blood urea nitrogen (BUN), creatinine), electrolytes (Na, K, Cl, Ca), complete urine test, thyroid function tests, and PA chest radiography were normal. The patient was referred to the internal medicine outpatient clinic in order for the cause of edema to be investigated. The patient came again to our outpatient clinic 20 days later because of the continuation of her complaints, after having been seen at the departments of general internal medicine, nephrology, rheumatology, cardiovascular surgery, and orthopedics. No pathology had been detected in her hemogram, electrolytes, BUN, creatinine, B12, albumin, hepatic panel, liver and thyroid function tests, chest radiography, electrocardiography, echocardiography and lower and upper extremity venous Doppler ultrasonography examinations. On the assumption that this case was caused by the discontinuation of paroxetine, a medication of 10 mg/day paroxetine was started, which was raised to 20 mg/day three days later. It was observed that the patient’s complaints began to decrease right after the day of the restart of medication, and on the 7th day, the edema and redness on the legs completely resolved.

DISCUSSION

It was seen in this case that the peripheral edema that had developed in the aftermath of the paroxetine discontinuation disappeared with the restart of medication, and it can be assumed that this edema had developed with the discontinuation of paroxetine, given the absence of any other culprits explaining the edema.

As paroxetine, unlike other SSRIs, does not have any active metabolites, it has a shorter half-life and is more likely to cause withdrawal syndrome. In a meta-analysis by Black et al. on the cases published in the literature until 1997, it was found that out of 46 patients reporting SSRI withdrawal syndrome, 30 (65.2%) developed this syndrome with the discontinuation paroxetine, 8 (17%) with sertraline, 5 with fluoxetine, 3 with fluvoxamine. Price et al. identified that the
withdrawal syndrome frequency of SSRIs is 10 times higher in paroxetine than in sertraline and fluvoxamine, and 100 times higher than in fluoxetine^{10}.

There are rare cases of edema related to the use of antidepressants in the relevant literature. Edema related to the use of escitalopram was reported in two cases. In one of these cases, edema was reported to have developed a month later in both ankles of a 69-year-old female patient who was medicated with escitalopram with the diagnosis of major depressive disorder, and it disappeared a week after the discontinuation of medication^{11}. In the other case, edema developed 13 days later in both feet of a 71-year-old female patient treated with escitalopram with the diagnosis of depressive disorder, and disappeared 10 days after the discontinuation^{12}.

In the literature, there are five cases of edema related to mirtazapine. In one of these cases, a 34-year-old female patient diagnosed with recurrent depressive disorder was using 10 mg/day escitalopram, and upon her complaint of insomnia, she began to be also treated with 15 mg/day mirtazapine. However, a pretibial edema developed a day later. The edema, which began to decrease three days after the discontinuation of mirtazapine, completely disappeared within 10 day^{8}. Kutscher et al. reported that in a 60-year-old male patient diagnosed with hypertension, dyspnea and obesity, who was being treated with gabapentin for neuropathic pain, and with lorazepam for anxiety, began to develop peripheral edema after being medicated with mirtazapine for his depression and anxiety. However, with the discontinuation of mirtazapine, the edema disappeared and did not recur under medication with paroxetine^{13}. Mirtazapine increases cyclic adenosine monophosphate (cAMP) with 5-HT2 receptor blockade and may cause relaxation and edema in vascular smooth muscles. Furthermore, histamine-1 receptor blockade, by inhibiting the increase of inositol 1,4,5-triphosphate (IP3) and decreasing calcium excretion, causes the downregulation of the ATP-dependent calcium pump, and consequently may lead to a decrease in smooth muscle contraction, vasodilatation, and edema^{14}.

Balci et al. report a case of peripheral edema bilaterally developed on both legs which occurred following the use of trazodone, and rapidly decreased and disappeared with the discontinuation of medication. It is thought that trazodone may cause edema by effecting a peripheral 5-HT2 and α-1 receptor blockade with a decrease in vascular resistance and vasodilatation^{7}.

In the relevant literature, there is a case of edema development due to paroxetine use. A 29-year-old female patient was medicated with 20 mg/day paroxetine (10 mg/day for the first four days) with the diagnosis of panic disorder. Three weeks later, a generalized edema occurred in the face, hands and feet of the patient, but recovered 2 weeks after the discontinuation of paroxetine^{9}. In the documented cases, the incidence of edema in women using antidepressants is higher than that of men. The reason for this may be the modifying effect of antidepressants on the sex hormones of females^{15}.

In our case, a peripheral edema occurred not with the use of antidepressants but with the discontinuation of medication. We suggest that this rare condition is idiopathic, since its pathophysiology is unclear.

Clinicians should be careful regarding this adverse effect in patients who discontinue paroxetine. More research needs to be done on the clarification of the mechanism and frequency of this adverse effect.

References:


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