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Can Sertraline Induced Constipation be Sigma 1 Receptors Mediated and Dose Depended?

Ali Tarık ALTUNÇ,[1] Yasin KAVLA,[1] Şenol TURAN[2]

[1]M.D., [2]Assoc. Prof., Istanbul University-Cerrahpasa, Cerrahpasa Medical School, Department of Psychiatry, Istanbul, Turkey

Corresponding Author: Ali Tarık ALTUNÇ, Istanbul University-Cerrahpasa, Cerrahpasa Medical School, Department of Psychiatry, Fatih, Istanbul, Turkey.

Phone: +90 212 414 3000
Fax: +90 212 632 0025
E-mail: dralitarik@gmail.com

Ali Tarık ALTUNÇ ORCID No: https://orcid.org/0000-0002-0092-6386

Yasin KAVLA ORCID No: https://orcid.org/0000-0002-2491-6270

Şenol TURAN ORCID No: https://orcid.org/0000-0002-8684-2617

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LETTER

Gastrointestinal reactions are among the common side effects of selective serotonin reuptake inhibitors (SSRIs). It is known that diarrhea is a more common gastrointestinal side effect due to SSRIs, but constipation may develop in some patients.[1] According to U.S. Food and Drug Administration (FDA) open access data, the constipation side effect frequency of SSRIs is as follows: paroxetine (%14)> fluvoxamine (%10) > sertraline (%6) > fluoxetine (%5) > escitalopram (%3) > citalopram (no report).[2] There is insufficient information in the literature to explain this difference between the SSRIs in terms of developing constipation. In this report, we present a patient that developed dose-dependent constipation under treatment of sertraline. Besides, we will discuss the possible mechanism of SSRI-mediated constipation based on the effects of SSRIs on different receptors other than serotonin.

CASE

A 55-year old female patient applied to our psychiatry outpatient clinic with complaints of unhappiness, cheerless, loneliness feelings and crying. She described having anhedonia, depressed mood, loss of energy and feelings of worthlessness for about three months. The middle aged female patient presented herself during her mental examination as age appropriate in appearance, yet with reduced selfcare. Her psychomotor activity was normal, mood was depressed and she had a restricted affect. There was worthlessness ideas in her thought content. There was no perceptual pathology. Memory, attention, judgment and other executive functions were preserved. Her insight was intact and there was no alteration in her appetite. This was her first psychiatric appointment and she had no chronic diseases other than rheumatoid arthritis which was in remission. Based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), she was diagnosed with moderate major depressive disorder and 50 mg sertraline per day was started. After four week, sertraline dose was increased to 100 mg per day because the patient's depressive symptoms did not improve sufficiently. Two days after increasing the dose of the drug, the patient developed constipation and 30 ml of lactulose was started to be used daily, but it was not effective. The other constipation reasons that diabetes mellitus, hypothyroidism, electrolyte imbalances, infectious diseases, dietary factors were excluded. Although she developed constipation from time to time and had anal fissure related with constipation episodes, there was no constipation history just before initiating sertraline treatment and anal fissure was in remission. She stated that the fissure started bleeding due to constipation. At the appointment one month later, the patient's depressive symptoms decreased, but the patient complained of severe constipation. Therefore, the sertraline dosage was reduced to 50 mg per day. Two days later, the patient stated that her constipation had completely disappeared. In the 3-month follow-up of the patient, her constipation complaints did not recur. Depressive symptoms were under control at 50 mg of sertraline.

DISCUSSION

SSRIs are psychotropic agents used in the treatment of many psychiatric illnesses, including depression. SSRIs are known to act on various receptors other than the serotonin receptor. For sertraline, these receptors are dopamine and sigma receptors.[3]

Sigma receptors, like mu and kappa receptors, were discovered as opioid receptors in 1976 but soon, it became clear that the sigma receptors has different structural properties from opioid receptors.[4] There are two subtypes of sigma receptors currently known: Sigma-1 and sigma-2 receptors.[5] The frontal cortex, hypothalamus and hippocampus contain a large amount of sigma-1 receptors.[6] Also known that gastrointestinal tract cells, especially in submucosal layer, express sigma 1 receptors. These receptors are found in stomach, duodenum, ileum, colon and they regulate gastrointestinal motility.[7]

It has been known for a while that some SSRIs bind to the sigma-1 receptor.[8] Despite the therapeutic role of this binding is not clear, SSRIs' extra anxiolytic effects are thought to be depended on the binding of sigma-1 receptors.[3] In addition, it is known that it causes neuromodulation in various parts of the brain, especially in the hippocampus, by stimulation of sigma-1 receptors.[9]

As paroxetine is excluded for its well-known anticholinergic activity, the constipation side effect frequency of SSRIs is parallel to their sigma-1 receptor affinity: fluvoxamine > sertraline > fluoxetine > escitalopram > citalopram.[10] When this parallelism is considered together with our case, it can be suggested that the constipation side effect of SSRIs is related to sigma-1 receptor affinity. In this case, we would like to point out that sigma-1 receptors may have a role in the constipation side effect of SSRIs and the relation between sigma receptors and constipation may be dose-dependent.

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