Bleeding gums: Duloxetine may be the cause

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ABSTRACT

Duloxetine is a newly introduced drug. It is being prescribed for the management of diabetic neuropathic pain and major depressive disorder. The most frequently observed adverse events with duloxetine are nausea, dry mouth and somnolence, constipation, diarrhea, decreased appetite, weight loss, feeling of fatigue, dizziness, somnolence, hypohidrosis, decreased libido and erectile dysfunction. One of the patients being prescribed the drug developed bleeding gums on being started with the drug which resolved on stopping it. We hereby report this case.

KEY WORDS: Bleeding gums, depression, duloxetine, serotonin norepinephrine reuptake inhibitors

Duloxetine is a recently introduced drug and is being promoted as an effective antidepressant with significant action on the physical symptoms that commonly accompany depression in the Indian population. It has got additional indications for stress incontinence and fibromyalgia.[1] This case reports highlights an uncommon side-effect of the drug, thereby advising the prescribers to be cautious about the same.

Case History

"My life has become a story of sufferings and my body is the housing for all the possible diseases" is the way Mr. AD would express his anguish and frustration of suffering from a major depressive episode with multiple somatic complaints whose cause could not be ascribed ascertained to any of the body systems in spite of two files full of investigation reports. He used to feel low throughout the day and had lost his interest in pleasurable activities like watching TV, chatting with others or even playing with his newly born daughter. He had difficulty in concentrating and his appetite had decreased. Although he never contemplated suicide, he found his life meaningless. The patient also had multiple somatic complaints in the form of a vague aching sensation in his head, chest and generalized myalgia.

He had been having these problems for over a year and had been on tri cyclic antidepressants (TCA), namely amitryptiline up to 200 mg/ day, nortryptiline up to 175 mg/ day and selective serotonergic reuptake inhibitors (SSRI) group, namely fluoxetine up to 60 mg/ day and escitalopram up to 20 mg/ day, as the patient had chosen pharmacotherapy at the beginning of the treatment. There was only minimal improvement in his symptoms with the medicines.

Following the introduction of duloxetine in the local market, the treating team decided to try it as it acts on both, the noradrenergic and serotonergic systems. He was put on 20 mg/day and the dose was gradually increased to 40 mg/day in two divided doses after two weeks. The patient didn't report any significant side-effect apart from a mild exacerbation of his epigastric pain that responded well to a proton pump blocker that he took for four days. After 10 days of hiking the dose to 40 mg/day he developed bleeding from the gums. He noticed traces of blood in his saliva in the morning while spitting. His gums had become raw and blood oozed from their surface. The bleeding was minimal but was alarming to the patient and his family and they returned for review a week after the onset of bleeding. There was no change in his dietary habits or any new drug intake during this time. He did not consume alcohol and never had any significant medical illness. He never had any problem with his teeth or gums and had never been to a dentist before.

A dental referral did not reveal any local cause of the bleeding. The patient was not taking any other concomitant medications at the time of the development of this side-effect. His bleeding time, clotting time, platelet count, activated partial thromboplastin time (APTT), prothrombin time (PT) were

all within the normal range. Routine hemogram, renal and liver function tests were also within the normal range. Considering the temporal correlation of the bleeding to duloxetine, the drug was withdrawn. Over the next one week the bleeding from his gums resolved and the patient was continued on tricyclic antidepressants. The patient is currently in partial remission of depression and has not reported any further episodes of gum bleeding. A score of four was obtained on Naranjo's algorithm for adverse drug reaction which implicated duloxetine as a possible cause of the event.

Discussion

Duloxetine is a dual reuptake inhibitor of synaptic serotonin and norepinephrine. In contrast to other dual reuptake inhibitor antidepressants, duloxetine appears to exert clinically demonstrable effects on both noradrenergic and serotonergic neurotransmission at starting doses.[2] It is described as an SNRI (selective serotonin norepinephrine reuptake inhibitors). The efficacy of duloxetine for depression has been established in controlled trials using 40-120 mg/day. The most frequently observed adverse events with duloxetine are nausea, dry mouth and somnolence.[3] Other side-effects attributed to the drug are constipation, diarrhea, decreased appetite, weight loss and feeling of fatigue, dizziness, hypohidrosis, decreased libido and erectile dysfunction.

The authors have not come across any reported case of bleeding associated with duloxetine. This side-effect has been reported with drugs having serotonin reuptake inhibition as their main action. The SSRI medications are well known to cause prolonged bleeding after surgery, gastrointestinal and vaginal bleeding. The incidence with each of the antidepressants is not currently available, but it has been reported with fluoxetine, escitalopram, sertraline, paroxetine, venlafaxine and bupropion. The odds ratio of 3 has been suggested for SSRI with higher serotonin reuptake inhibition, while intermediate ones have an odds ratio of 1.7 to cause bleeding. *Weinrieb et al*. in a metanalysis with literature search on MEDLINE from 1966 to 1st September 2004 reviewed seven retrospective analytical studies and 24 case reports of bleeding in 43 different people. Analytical studies supported an association between SSRI consumption and upper gastrointestinal bleeding and perioperative bleeding, although there is little evidence linking SSRI use with intracerebral hemorrhage.[4]

SSRI have been shown to inhibit nitric oxide synthase, which leads to decreased production of nitric oxide from the nitric oxide donor, L-arginine. Nitric oxide is essential to activate guanylate cyclase for stimulating the formation of cyclic guanosine monophosphate (cGMP), which acts to relax smooth muscle and regulate platelet aggregation. This reduced cGMP may be responsible for SSRI-induced bleeding. The exact pathophysiology of duloxetine-induced bleeding is not known but may be associated with the same mechanism.[5] The impairment of the platelet aggregation could be a possible mechanism of occurrence of the event. It may also be advisable to provide ulcer protective agents to old patients and patients who are taking anti-inflammatory agents when SSRI are prescribed to them. Physicians should be aware of this side-effect when prescribing duloxetine to their patients and more cautious postmarketing surveillance is needed to ascertain any new side-effect.

However, the observed side-effects in this particular case might be worth considering as in this case the parameters of platelet count, bleeding time, clotting time, APTT and PTT were within the normal range. Moreover, the absence of the effect with fluoxetine and escitalopram in the past might point to a novel mechanism of the side-effect.

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