Serotonin and yawning: A possible adverse drug reaction during antidepressant therapy

Sérotonine et bâillements : un effet indésirable possible lors d’un traitement par antidépresseur

Yawning is a common but complex stereotyped reflex poorly understood. Different physiologic (hunger, hypoglycaemia, sedation) and pathologic (Eustachian tube disorders, travel sickness, infectious diseases, neurological diseases, iatrogenics) states can induce yawning. Among drugs known to induce yawning, serotoninergic agents are frequently cited, such as selective serotonin reuptake inhibitors antidepressants [1]. Yawning induced by other class of antidepressants, such as noradrenalin and serotonin reuptake inhibitors or imipraminic antidepressants have also been described in literature [2,3]. We report here the case of a young woman who presented repetitive excessive yawning induced successively by paroxetine, a selective serotonin reuptake inhibitor, clomipramine, a tricyclic antidepressant and Saint John’s wort (Hypericum perforatum). Interestingly, the yawns regressed during agomelatine treatment.

Case report

An 18-year-old woman presenting depression was first treated with minalcipran, a noradrenalin and serotonin reuptake inhibitor antidepressant. The treatment was well tolerated but was stopped because of a lack of efficacy and induced insomnia. Then, the patient received a selective serotonin reuptake inhibitor, paroxetine 20 mg daily, but, some days later, she experienced abnormal excessive daytime yawning lasting up to several seconds, associated with contractures of the jaws. These yawns were disturbing, and disabled the patient while working and bothered her to speak. Paroxetine was discontinued and her yawning completely disappeared. Paroxetine was replaced by a tricyclic antidepressant, clomipramine 25 mg daily, which rapidly induced the same symptoms. Clomipramine was stopped and, as previously, yawning rapidly regressed. After one week, this treatment was substituted by Saint John’s wort but yawning reappeared after the first dose, and disappeared the day after discontinuation. Agomelatine, a melatonin receptors agonist, was then introduced, without causing yawning after few weeks of therapy.

Discussion

Yawning is known to be under the control of several neurotransmitters and neuropeptides, such as serotonin, dopamine, acetylcholine, nitric oxide, excitatory amino acids, ACTH and oxytocin [4]. Yawning induced by serotonin reuptake inhibitors antidepressants, such as paroxetine, or tricyclic antidepressants, such as clomipramine, is a rare but known adverse drug reaction. In 2007, Sommet et al. study the observations of yawning in the French Pharmacovigilance Database [1]. Among the 38 reports recorded from 1985 to 2004, 12 involved serotonin reuptake inhibitors (paroxetine \( n = 5 \), fluoxetine \( n = 4 \), sertraline \( n = 3 \)). The delay of occurrence ranged from 1 day to 8 weeks. Drug was withdrawn in 8 cases and the resolution was observed in 9 cases. In this study, the serotonin reuptake inhibitors were the main pharmacological class involved, followed by dopaminergic drugs, confirming the implication of serotonin and dopamine on yawning.

In the other cases reported in literature, yawning appears during the days following the introduction of the treatment, and regresses or disappears after dose reduction [3,5–7]. Some case reports have suggested that yawning behaviour might be dose-dependant. Yawning is considered as an unwanted effect during antidepressant therapy but for few authors, it is considered as beneficial in the regulation of brain homeostasis [8,9]. Indeed, there is a strong connection between yawning and thermoregulation, and a yawn would promote cerebral cooling. Thus, when serotonin, a vasoactive compound implicated in thermoregulation, induces brain and core temperature, it is counterbalanced by excessive yawning.

No case of yawning induced by Saint John’s wort is described in literature, but his mechanism of action passing by the serotoninergic way could explain his involvement in this case. Up to now, no case of yawning induced by agomelatine is reported in literature, probably because no direct action on 5HT increase is associated with this drug. To note, this drug is a melatonin receptor agonist (MT1-MT2) and a 5-HT2C receptor antagonist (but without effect on extracellular serotonin concentrations).

All the treatments inducing yawning in this patient were then acting on the serotonin pathway, which confirms the role of this monoamine in the mechanism of yawning. In addition, the
temporal relationships between the episodes of yawning after the administration of the drugs and especially the regression of the symptoms after drug discontinuation comfort the responsibility of these treatments.

The good tolerance of minalcipran, a noradrenalin and serotonin reuptake inhibitor is however surprising, but the posology (presently unknown) was possibly low.

**Conclusion**

Yawning must be considered as a real disabling adverse event of antidepressant drugs, which could be a strong reason for inobservance.

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**References**


