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Letter to the Editor (Case report)

Tardive dyskinesia associated with long-term administration of escitalopram and itopride in major depressive disorder

1. Introduction

Tardive dyskinesia (TD) is characterized by involuntary abnormal movements which develop as a result of antipsychotics exposure. However, other classes of drugs related to dopamine system have the potential to cause TD (Kennedy et al., 2008).

Itopride, a kind of prokinetics, blocks dopamine D2 receptors and inhibits acetylcholinesterase to increase the acetylcholine level and thereby stimulate GI motility. The high polarity of itopride means that it does not readily cross the blood-brain barrier, resulting in a low risk of extrapyramidal effects and there are also no reports of itopride-associated TD, which is quite unlike the effects of metoclopramide (Stevens et al., 2008). However, it is possible that itopride can induce TD due to its blocking of D2 receptors.

It has been theorized that SSRIs exert an indirect dopamine blocking effect. Experiments on monkeys have demonstrated that SSRIs can induce dyskinetic movements (Korsgaard et al., 1985). In addition, many clinicians have reported fluoxetine-induced TD in humans (Baldessarini and Marsh, 1990; Bouchard et al., 1989; Dubovsky and Thomas, 1996; Mander et al., 1994; Sandler, 1996).

To our knowledge, there is no previous report on whether itopride, a peripheral dopamine D2 receptor antagonist, and escitalopram can induce or aggravate TD, as can other dopamine D2 receptor antagonists (Ganzini et al., 1993; Kennedy et al., 2008). We report here on a patient with major depressive disorder and dyspepsia who developed TD after the long-term administration of escitalopram and itopride.

2. Case report

Mrs. K, a 66-year-old Korean female with a 2-year history of depressed mood, visited a day- clinic in April, 2005. The presenting symptoms were depressed mood, fatigue, lack of drive, loss of appetite, and somatic symptoms including dyspepsia. She was initially treated with citalopram and itopride at 20 and 50 mg, respectively, once daily. She complained of heartburn and anxiety after 1 week of treatment, and hence itopride was replaced with cimetidine and alprazolam at 300 and 0.25 mg, respectively, twice daily, with citalopram at 40 mg once daily. After 1 year of relative stability, she complained of GI symptoms including dyspepsia and nausea in April, 2006. Her medication was changed to itopride and escitalopram at 50 and 20 mg once daily at bed-time, which was continued for 18 months, without the appearance of involuntary movements. In October, 2007, she presented with repetitive buccolingual movements and also developed bilateral upper extremity resting and postural tremor, which increased in severity over the following several weeks. The results of a neurologic examination and laboratory test were normal although we did not perform MRI. Her score on the Abnormal Involuntary Movement Scale (AIMS) was 8 points. We stopped administering itopride and escitalopram, and maintained her on 1.0 mg of lorazepam daily. We also added 150 mg of bupropion. Several months later her TD symptoms had improved to mild (4 points on AIMS).

3. Discussion

Several risk factors have been associated with susceptibility to TD. Older age is the most robust risk factor for TD. Other factors, including female sex, brain damage, dementia, presence of major affective disorder and longer exposure to antipsychotics, have been tentatively associated with greater prevalence of TD (Talsy and Baldessarini, 2006).

Our patient had no neurological disorder or brain damage. In addition, she did not have prior exposure to antipsychotics, which might have increased her higher vulnerability to the effects of altered serotonergic input from the raphe nuclei (Brod, 1989). However, she had other risk factors such as a major depression, older age, and being female.

After the discontinuation of itopride and escitalopram, her TD symptoms had improved. Thus, this might be the first case supporting the hypothesis that the long-term combined administration of itopride and escitalopram is related to the onset of TD. It is also possible that itopride alone is responsible for the onset of TD because citalopram alone, when administered from April 2005 to April 2006, did not cause any TD. However, there have been no reports of TD even when itopride is administered at 200 mg three times daily (Holtmann et al., 2006), and our patient was treated with itopride at only 50 mg, once daily.

Several biological mechanisms of TD have been hypothesized, including dopamine receptor supersensitivity, the dysfunction of the serotonergic system, gamma-aminobutyric acid insufficiency, and disturbances in antioxidative protection (Andreassen and Jorgensen, 2000; Casey et al., 1980). Recently, it has been suggested that an increase in the effectiveness of somatodendritic as well as postsynaptic 5HT1A receptors is a major contributing factor in the pathophysiology of TD in animal study (Samad et al., 2007).

Our patient had received the long-term administration of itopride and escitalopram with 50 and 20 mg once daily, at bed-time. Therefore, it is possible that the long-term and/or synergistic effects of itopride and escitalopram are responsible for TD. This might be more likely when it is considered that there has been no reported association of TD with each of these drugs in isolation. However, it remains open as to whether the combination or even itopride alone is responsible for TD.

4. Conclusion

In conclusion, the long-term administration of escitalopram and itopride might induce TD. However, the limitations of this single case report must be acknowledged. Although the cause of TD in this case remains unclear, clinicians should carefully monitor for the potential induction of TD associated with SSRIs and prokinetics. Further investigations with a larger sample size are needed. In addition, it is

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necessary to evaluate the possible involvement of as-yet-uncovered gene(s) that influence susceptibility to medication-induced TD as well as the possibility of gene–gene interaction.

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