Case Report

Combination of Escitalopram and Rasagiline Induced Serotonin Syndrome: A Case Report and Review Literature

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Background: *Serotonin syndrome is a rare but potentially fatal complication of drugs that have effects on central nervous system serotonin. It is characterized by sudden onset of altered mental status, increased neuromuscular activity, and autonomic instability.*
Case Report: *The authors reported a case of serotonin syndrome associated with combined therapy of monoamine oxidase-B inhibitors and selective serotonin reuptake inhibitor. A 77-year-old Thai man had been taking escitalopram for depression for three years. He presented with high-grade fever and confusion two days after taking rasagiline for Parkinson's disease. He also had agitation, hallucination, and behavioral change. Escitalopram and rasagiline were discontinued but his renal function worsened, turning to acute kidney injury. He was diagnosed as serotonin syndrome.*
Conclusion: *This is the first case report of serotonin syndrome due to combination of escitalopram and rasagiline used.*

Keywords: *Escitalopram, Rasagiline, Serotonin syndrome*

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Serotonin syndrome is a life-threatening condition caused by serotonin toxicity, and usually occurs in case of combination of drugs that increase serotonergic transmission[1]. Typically, patients with serotonin syndrome present with an acute symptoms characterized by cognitive/behavioral changes, autonomic instability, and neuromuscular changes either central or peripheral nervous systems[2-4]. A patient who took meperidine and iproniazide was first described as serotonin syndrome in 1955[5]. Currently, the diagnosis is established by the Hunter Serotonin Toxicity Criteria, which fulfill the presence of one of the following classical features or groups of features spontaneous clonus, inducible clonus with agitation or diaphoresis, ocular clonus with agitation or diaphoresis, tremor and hyperreflexia, or hypertonia, temperature above 38 degree Celsius, and ocular or inducible clonus[6]. According to selective serotonin reuptake inhibitors (SSRIs) are increasingly prescribed for management of depression in elderly patients, thus the clinicians have to aware of the risk of this condition especially patients receiving two medications that can increase serotonin level or accelerate the serotonin receptors. The authors described an old man developing serotonin syndrome during combination of escitalopram and rasagiline for treating depression and Parkinsonism.

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Case Report

A 77-year-old man was admitted to our hospital due to high-grade fever, cough, sore throat, abdominal pain, dysuria, shortness of breath and watery diarrhea. He was unclothed, sudden onset of hyperthermia, behavioral change, hallucination, and memory loss (unable to recognize his family) prior to admission. His current medications were ticlopidine 250 mg twice a day, atorvastatin 20 mg once a day, gemfibrozil 300 mg once a day, piribidil 50 mg three times a day, rasagiline 1 mg once a day, rivastigmine patch (10 cm^2) 1 patch once a day, Stalevo® 100 (levodopa 100 mg, carbidopa 25 mg, and entacapone 200 mg) three times a day, pramiprexole 3 mg twice a day, melatonin 2 mg once a day, escitalopram 20 mg once a day, and clonazepam 0.5 mg once a day. His status change began two days after starting rasagiline for Parkinson's disease. At emergency room, his vital signs were, body temperature 38 degree Celsius, blood pressure 129/74 mmHg, respiratory rate 22 breaths/minute, and pulse rate 94 beats/minute. Serotonergic (escitalopram and rasagiline) and dopaminergic agent were discontinued. Creatine phosphokinase enzyme was measured with a high level

(125,700 U/L) Aspartate transaminase was 2,361 U/L and alanine transaminase was 504 U/L. Serum creatinine rose from 4 mg/dl to 8.9 mg/dl. During the development of acute kidney injury, hemodialysis was performed every three days. Moreover, he developed tremor, agitation, and confusion, requiring benzodiazepine treatment (midazolam followed by diazepam). After discontinuation of escitalopram and rasagiline for 16 days, all symptoms recovered. However, his renal function was not improved; therefore, hemodialysis were continued.

Discussion

Serotonin syndrome is often described as a clinical triad of mental-status changes, autonomic hyperactivity, and neuromuscular abnormalities, but not all of these findings are consistently presented in all patients with the disorder[7]. The onset of symptoms is usually rapid, with clinical findings often occurring within minutes after a change in medication or self-poisoning[4]. No laboratory tests confirm the diagnosis of the serotonin syndrome. Instead, the presence of tremor, clonus, or akathisia without additional extrapyramidal signs should lead clinicians to consider the diagnosis, which must be inferred from the patient's history and physical examination[7].

The serotonergic agents that include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, SSRIs, opiate analgesics, over-the-counter cough medicines, antibiotics, weight-reduction agents, antiemetics, antimigraine agents, drugs of abuse, and herbal products; the withdrawal of medications have also been associated with the syndrome[1,8,9]. Commonly, the concomitant use of MAOIs and other serotonergic drugs have to quit MAO inhibitor for at least 14-day before starting another serotonergic agent[10,11]. Escitalopram is a SSRI, for treating depression and generalized anxiety disorder. No single receptor appears to be responsible for development of the serotonin syndrome; although several studies suggest that 5-hydroxytryptamine (5-HT) 1A receptor and 5-HT2A receptors might play important role[12]. Rasagiline is a propargylamine selective irreversible MAO-B inhibitor that exhibits a significant increased serotonin, norephrinephine, and modest dopamine level in brain[13]. This proposed mechanism would be the cause of serotonin syndrome in the present case. Moreover, severe rhabdomyolysis is also defined as set of serotonin syndrome[14]. According to the long half-life of escitalopram and the irreversible enzyme inhibition up to 40 days of rasagiline, these effects could persist longer than one week[15,16] as shown in the present case.

Cyproheptadine is a 5-HT2A antagonist recommend for therapy of the serotonin syndrome, although its efficacy has not been well established[17,18]. Treatment of the serotonin syndrome in adults may require initially 12 to 32 mg of cyproheptadine during a 24-hour period[19]. Clinicians should consider supportive therapy such as the intramuscular administration of 50 to 100 mg of chlorpromazine. Even though chlorpromazine is an outdated therapy that has been replaced in psychiatric practice by newer agents, its use may be considered in severe cases[17]. Benzodiazepines such as diazepam improve survival in animal models and blunt the hyperadrenergic component of the syndrome[17,20].

However, the differential diagnosis in the present case needed to be clarified, including sepsis with meningitis, delirium tremens, anticholinergic toxicity, heat stroke, sympathomimetic overdose, and neuroleptic malignant syndrome (NMS), especially when serotonergic and dopaminergic agents were used at the same time[21]. History and laboratory data were crucial to rule out other disorders by using Sternbach's criteria[1] and Hunter Serotonin Toxicity Criteria[22].

In conclusion, the authors reported a suspected patient of serotonin syndrome precipitated by combination therapy of escitalopram and rasagiline. The authors would like to caution clinicians of serotonin syndrome as a differential diagnosis in patients who develop symptoms and signs of serotonin syndrome, while being treated with SSRI and MAO-B inhibitor. Discontinuation of suspected medications immediately and initiate supportive therapies are necessary for serotonin syndrome management.

What is already known on this topic?

The previous case report of serotonin syndrome precipitated by using escitalopram with selegiline, as irreversible MOA-B inhibitor[23].

What this study adds?

This was the first case report of serotonin syndrome due to combination of escitalopram and rasagiline used. The present case had investigated the potential of pharmacodynamic and pharmacokinetic interactions between rasagiline and escitalopram in a clinical sequential setting with healthy volunteers. Although results from this study suggest no clinically significant interactions. Carefully monitoring is

recommended when combining rasagiline and escitalopram[24].

Potential conflicts of interest

None.

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การใช้ยาราซาจิลีนร่วมกับยาเอสซิตาโลแพรมกับการเหนี่ยวนำการเกิดภาวะซีโรโตนินซินโดรม:รายงานผู้ป่วย 1 ราย และทบทวนวรรณกรรม

จุฑาทิพย์ สุพรรณกลาง, วิชัย สันติมาลีวรกุล, อุปถัมภ์ ศุภสินธุ์

ภูมิหลัง: *ซีโรโตนินซินโดรมเป็นกลุ่มอาการไม่พึงประสงค์จากการใช้ยาที่มีผลกับซีโรโตนินในระบบประสาทส่วนกลาง ถึงแม้อุบัติการณ์การเกิดได้จะน้อยแต่มีความรุนแรงถึงชีวิตได้ ลักษณะอาการของซีโรโตนินซินโดรมนั้นจะเกิดขึ้นอย่างทันทีทันใดประกอบไปด้วยอาการเปลี่ยนแปลงความรู้สึกตัว การทำงานเพิ่มขึ้นของกล้ามเนื้อร่วมประสาท และอาการระบบประสาทอัตโนมัติไม่คงที่*

รายงานผู้ป่วย: *ผู้นิพนธ์ได้รายงานภาวะซีโรโตนินซินโดรมในผู้ป่วยที่ใช้ยากลุ่มโมโนเอมีนออกซิเดสอินฮิบิเตอร์ร่วมกับยากลุ่มซีเล็กทิฟซีโรโตนินรีอัพเทคอินฮิบิเตอร์ ผู้ป่วยชายไทยอายุ 77 ปี รับประทานยาเอสซิตาโรแพรม เพื่อรักษาโรคซึมเศร้ามาเป็นเวลา 3 ปี มีอาการไข้สูง และสับสน 2 วัน ก่อนมาโรงพยาบาล หลังจากที่เริ่มยาราซาจิลีนเพื่อรักษาโรคพาร์กินสัน ผู้ป่วยมีอาการอยู่ไม่นิ่ง ประสาทหลอน และมีพฤติกรรมเปลี่ยนแปลง จากนั้นจึงหยุดยาเอสซิตาโรแพรมและราซาจิลีนแต่ยังพบว่าการทำงานของไตแย่ลงและนำไปสู่การเกิดไตวายเฉียบพลันในที่สุด ผู้ป่วยได้รับการวินิจฉัยเป็นซีโรโตนินซินโดรม*

สรุป: *รายงานผู้ป่วยรายนี้เป็นรายงานภาวะซีโรโตนินซินโดรมรายแรกจากการใช้ยาเอสซิตาโรแพรมร่วมกับยาราซาจิลีน*