**CASE REPORT**

**Serotonin Toxicity Caused by Moclobemide Too Soon After Paroxetine-Selegiline**

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Serotonin toxicity is an iatrogenic complication of serotonergic drug therapy. It is due to an overstimulation of central and peripheral serotonin receptors that lead to neuromuscular, mental and autonomic changes. Moclobemide is a reversible inhibitor of monoamine oxidase (MAO)-A, selegiline is an irreversible selective inhibitor of MAO-B, and paroxetine is a selective serotonin reuptake inhibitor. Combined use of these agents is known to cause serotonin toxicity. A 53-year-old woman had been treated with paroxetine and selegiline. After moclobemide was prescribed in place of paroxetine without a washout period, she quickly developed confusion, agitation, ataxia, diaphoresis, tremor, mydriasis, ocular clonus, hyperreflexia, tachycardia, moderately elevated blood pressure and high fever, symptoms that were consistent with serotonin toxicity. Discontinuation of the drugs, hydration and supportive care were followed by remarkable improvement of baseline status within 3 days. This case demonstrates that serotonin toxicity may occur even with small doses of paroxetine, selegiline and moclobemide in combination. Physicians managing patients with depression must be aware of the potential for serotonin toxicity and should be able to recognize and treat or, ideally, anticipate and avoid this pharmacodynamically-mediated interaction that may occur between prescribed drugs. [J Chin Med Assoc 2009;72(8):446–449]

Key Words: drug interaction, monoamine oxidase inhibitor, selective serotonin reuptake inhibitor, serotonin toxicity

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**Introduction**

Serotonin toxicity is a drug-induced toxidrome that is a condition of serotonergic hyperstimulation. It is still commonly referred to as serotonin syndrome. However, it is not a discrete syndrome, but represents a spectrum of serotonergic effects. Serotonin acts centrally as a modulator of exciting neurotransmission. Serotonergic neurons play an integral part in the regulation of wakefulness, affective behavior, food intake, thermoregulation, migraine, emesis, and sexual behavior. In the periphery, serotonin assists in the regulation of vascular tone and gastrointestinal motility. In humans, serotonin is derived from dietary tryptophan, which is converted to 5-hydroxytryptophan and then to serotonin. After transport into cells, serotonin is degraded mainly by monoamine oxidase (MAO). MAO-A is more significant than MAO-B in this process. Serotonergic excess can be caused by drug interactions, overdose of a serotonergic drug, or as a complication of therapy. Serotonergic drug interactions, particularly when 2 drugs increase serotonergic transmission through different mechanisms, are a common cause of serotonin toxicity. It typically results from the combination of MAO inhibitors (MAOI) with other serotonergic agents. The 3 important mechanisms, in relation to severe serotonin toxicity, are inhibition of reuptake, presynaptic release, and MAO inhibition. There have been reports of fatalities from moclobemide alone and in combination with clomipramine, citalopram and paroxetine. Professor Whyte’s research group at the Hunter Area Toxicology Service (HATS) in Australia has maintained a prospective clinical database of all poisonings since 1987. The HATS data indicate that
Serotonin toxicity by moclobemide-paroxetine-selegiline interaction

It is only the higher elevations of serotonin resulting from MAOI plus serotonin reuptake inhibitor (SRI) combinations that are likely to induce hyperpyrexia and death.5 We report a case of serotonin toxicity resulting from the combination of paroxetine, selegiline and moclobemide in therapeutic doses.

Case Report

A 53-year-old woman presented to the emergency department with fever and consciousness disturbance on the day after changing prescriptions. Her past history was significant for multiple system atrophy, secondary Parkinsonism and depression for about 5 years, and neurogenic bladder dysfunction with several episodes of urinary tract infection. Her medications included paroxetine 20 mg qd, selegiline 5 mg bid, midodrine 2.5 mg/1.25 mg bid, biperiden 2 mg tid, and ginkgoflavone 40 mg bid. Because of incomplete response to this regimen, the day before admission, moclobemide (150 mg tid) had been prescribed in place of paroxetine. The patient took paroxetine in the morning and moclobemide after lunch and dinner. A few hours (at 10 pm) after her second dose of moclobemide, she developed stiffness, ataxia and diaphoresis. Hyperthermia and confusion were also noted 2 hours later. She was sent to our hospital 8 hours after the second dose of moclobemide.

In the emergency department, she was confused and disoriented. Glasgow coma scale was E1V2M5. Vital signs were: blood pressure, 154/74 mmHg; pulse, 132 beats/minute; respiratory rate, 20 beats/minute; body temperature, 39.7°C. Mydriasis, ocular clonus, diaphoresis, tremor, neck stiffness, limb rigidity, hyperreflexia and positive Babinski’s sign (left side) were also noted. Biochemical and hematological studies were remarkable, with a leukocyte count of 13,200/mm³ (neutrophils 82%, lymphocytes 15%) and glucose level of 169 mg/dL only. Urinalysis was normal, as were cultures of blood and urine. Brain computed tomography disclosed mild brain atrophy. Cerebrospinal fluid analyses showed normal cell count, protein and glucose, and were negative for microbiological stains and cultures. Chest radiography was normal and electrocardiography confirmed sinus tachycardia. Serotonin toxicity was suspected. The patient’s medications were discontinued, and she was treated with intravenous fluid and supportive care. The fever persisted for only 24 hours, and she achieved complete recovery 3 days later. She had recurrent fever and urinary tract infection on the 4th day of hospitalization but recovered with antibiotic management.

Discussion

The typical clinical features of serotonin toxicity in humans, derived from the HATS data, are: (1) neuromuscular hyperactivity: tremor, clonus, myoclonus and hyperreflexia and, in the advanced stage, pyramidal rigidity; (2) autonomic hyperactivity: diaphoresis, fever, mydriasis, tachycardia, moderately elevated blood pressure and tachypnea; and (3) altered mental status: excitement and agitation, with confusion in the advanced stages only.5 The diagnosis of serotonin toxicity is made on a clinical basis. A strong clinical suspicion, known exposure to serotonergic agents, demonstration of specific signs and symptoms, and exclusion of other medical and psychiatric conditions are required for diagnosis. This patient’s symptomology included fever, hypertension, mydriasis, and confusion; therefore, differential diagnoses should include anticholinergic toxicity and sympathomimetic toxicity. Neither anticholinergic syndrome nor sympathomimetic syndrome have features of neuromuscular excitation.6 Our patient had been on medications with anticholinergic and sympathomimetic effects for some time without incident. She presented with tremor, ocular clonus, diaphoresis, hyperthermia, confusion, hypertension, tachycardia, tachypnea and mydriasis rapidly after the second dose of a new serotonergic drug in her regimen. The findings were consistent with the diagnosis of serotonin toxicity.

Serotonin toxicity is a disorder that can be caused by the use of drugs or drug combinations that increase intrasynaptic serotonin. It most often occurs when 2 or more drugs that increase serotonin availability by different mechanisms are used simultaneously. It may develop after therapeutic use or overdose. In our case, there were 3 drugs with the potential to increase serotonin, i.e. paroxetine, moclobemide and selegiline.

Paroxetine is a selective serotonin reuptake inhibitor (SSRI). The effective therapeutic dose range is 10–60 mg daily. The half-life is 15–22 hours, and it is significantly prolonged in older patients. Considerable intersubject variation is observed, as demonstrated by the range of half-lives between 3.8 and 65 hours.7 Paroxetine’s potency is the greatest among the SSRIs. The metabolites of paroxetine, unlike fluoxetine, are not active. Paroxetine and fluoxetine show the greatest inhibition of CYP2D6. If a patient does not respond to paroxetine, 2 weeks should elapse before beginning MAOI therapy.2,3

Moclobemide, an MAOI, is a reversible competitive selective inhibitor of MAO-A, with a wide spectrum of antidepressant activity.8 It is devoid of the major problems that discredited the first generation of
irreversible, mixed inhibitors of MAO-A and MAO-B. However, moclobemide loses selectivity for MAO-A at higher doses. The elimination half-life of moclobemide is rapid, in the range of 1–3 hours. The drug is almost completely metabolized in the liver by 2 enzymes, CYP2C19 and CYP2D6. Moclobemide does not precipitate serotonin toxicity in overdose by itself, nor does it produce serotonergic side effects in clinical use. When switching treatment from moclobemide to SSRI, a washout period of 24 hours is sufficient.

Selegiline, a derivative of methamphetamine, is an irreversible selective MAO-B inhibitor. Selegiline is used for the treatment of early-stage Parkinson’s disease, depression, and senile dementia. It leaves those peripheral mechanisms intact that normally prevent a hypertensive response following tyramine reaction. Dietary restrictions are common for MAOI treatments, but special dietary restrictions for lower doses have been found to be unnecessary. For its selectivity, selegiline has relatively small potential for serotonin toxicity. Selegiline is extensively metabolized to methamphetamine, amphetamine and N-desmethylselegiline. In selegiline overdose, patients may also exhibit clinical effects similar to those of methamphetamine. In the clinical setting, concurrent use of selegiline and paroxetine is not contraindicated. However, concurrent administration of selegiline with antidepressants may produce profound serotonergic toxicity in vulnerable patients.

Both moclobemide and paroxetine are substrates and inhibitors of CYP2D6. Major P450 interaction both ways may occur with expected substantial elevations in the blood levels of both drugs, thereby greatly increasing the likelihood of serotonin toxicity. The risk with combined moclobemide and SRIs is almost certainly much lower than that with older irreversible MAOIs combined with SRIs. However, the combination of moclobemide and SRI still represents a risky approach. The use of such a potentially risky combination therapy must be justified. Ishbister et al’s case series of 106 moclobemide overdoses from the HATS database revealed neither serotonin toxicity nor serotonergic signs in cases of moclobemide alone (32 cases) or moclobemide plus another nonserotonergic drug (52 cases). Eleven (52%) of 21 patients who congeisted a serotonergic drug developed serotonin toxicity, which was significantly more than the 1 (3%) of 33 moclobemide-alone overdoses. Serotonin toxicity occurred even though the other serotonergic drug had often been ingested only in therapeutic quantities, not as an overdose. In 6 of these 21 cases, severe serotonin toxicity developed with a temperature >38.5°C and muscle rigidity requiring intubation and paralysis.

Our patient took both selegiline and paroxetine without the development of side effects before the addition of moclobemide. Because moclobemide is safer than the old irreversible MAOI, some studies have claimed that a washout period is not necessary when switching therapy from an SSRI to moclobemide. In vulnerable patients, the combination of selegiline, paroxetine and moclobemide in therapeutic doses may have the potential to induce moderate serotonin toxicity, as in our patient.

To diagnose serotonin toxicity, the clinician must retain a high index of suspicion and exclude other medical and psychiatric conditions. Serotonin toxicity is a serious and sometimes fatal event. For this reason, combination therapy of any MAOI, including moclobemide, and any potent SRI should be avoided. If a patient does not respond to an SRI, it is prudent to wait for 2 weeks (5 weeks for fluoxetine) before beginning MAOI therapy. Serotonin toxicity should not be viewed as an idiosyncratic reaction, but rather as a predictable one with variability in occurrence and severity among patients. Clinicians who are aware of the potential for serotonin toxicity should be able to recognize and treat or, ideally, anticipate and avoid this pharmacodynamically-mediated interaction that may occur between prescribed drugs.

References
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