Case 1

A 43-year-old female patient with a two-year-old history of generalized anxiety disorder, received clinic treatment regularly with daily paroxetine 20 mg, chlorpromazine 100 mg, and clonazepam 2 mg for more than six months. During that time, she visited our clinic numerous times for more prescription drug supplies with complaints of persistent worrying, restlessness, and sleep disturbances. She did not reveal her medication history. She visited different clinics every time and kept asking for more hypnotics. Under the diagnoses of anxiety disorder and depressive disorder, several doctors adjusted her medications as propranolol 10 mg BID, zolpidem 20 mg QHS, quetiapine 50 mg QHS, mirtazapine 30 mg QHS, and trazodone 100 mg QHS. One night, she took all medications from two clinics because of her worsened insomnia. Two hours later, she began to have anxiety, restlessness, sweating, and chill. Therefore, she was sent to our emergency department with the complaints of insomnia, subjective fever, diaphoresis, tremors, and agitation but with a clear consciousness. She denied any serious medical history or substance abuse history.

The patient was normal in physical examination, medical history, neurological examination, and related laboratory work-ups. She was diagnosed as having serotonin syndrome, based on her using several types of serotonergic agents successively and various clinical signs, such as diaphoresis, tremors, and agitation. After an initial therapy of saline infusion and benzodiazepine injection, her chief complaints gradually subsided, and she was discharged home.

The next morning, the patient visited our clinic and reported that hand tremors and sweating had not improved much. After hospitalization, we discontinued all of her psychotropic medications and gave saline infusion and oral lorazepam. Three days later, she improved gradually and was discharged home with lorazepam 1 mg BID, zolpidem 20 mg QHS, and mirtazapine 30 mg QHS. At the clinic follow-up one week later, all her symptoms, including her hand tremors and sweating, had been subsided.

Case 2

A 46-year-old male patient was sent to our emergency department with altered consciousness level for six hours. He was found confused at home, agitated, and was not responding appropriately to verbal stimuli. His family denied any significant past medical history, seizure-like activities, history of head injuries, any recent diseases, drug allergies, or substance abuse history, except having six-year-old dysthymic disorder, treated at a clinic at a medical center. His family reported that he frequently took the combined drugs, including daily doxepin 100 mg, mirtazapine 30 mg, nimetazepam 10 mg, trazodone 100 mg, and flunitrazepam 8 mg. In addition, his family confirmed that he had complained of insomnia recently.
The physical examination showed patient's fever (38.9°C), tachycardia (122 beats/min), muscle rigidity, blood pressure 146/84 mmHg, and his pulse oximetry 97% on a simple mask. The mental status examination showed anxiety, restlessness, agitation, and disorientation to time, place, and persons. He had unclear speech and cogwheel rigidity in his upper extremities. The laboratory findings showed leukocytosis (WBC: 16,240/uL) and serum creatinine phosphokinase (CPK) elevation (2278 U/L) but normal in results of laboratory tests, chest X-ray and a brain computed tomography scan. The patient received midazolam 10 mg IM for sedation. Differential diagnoses included serotonin syndrome, infectious disease, rhabdomyolysis, and neuroleptic malignant syndrome. The family said that the patient typically stayed home all day without significant physical exercise or traveling. His leukocytosis and CPK elevation were considered to be caused by dehydration and persistent agitation. He did not receive any antipsychotic drug. Because he had more than three symptoms of Sternbach's criteria, such as mental status changes, agitation, hyperreflexia, tremor, tachycardia, incoordination and fever [1], the patient was diagnosed as having serotonin syndrome, and received treatment in the intensive care unit.

The patient received intravenous saline infusion, propranolol, cyproheptadine, and benzodiazepine for treating serotonin toxicity. Three days later, his mental status was stabilized and his fever subsided. No neurological abnormality was found. Leukocytosis and CPK were returned to normal ranges. After his becoming alert, he stated that he took all of the above-mentioned medications of one-week supply because of his worsened sleep disturbances. After observation for an additional two days on the general ward, he was discharged home in a stable condition.

Comment

Those two patients in this letter met at least three of the diagnostic symptoms of Sternbach’s criteria for serotonin syndrome after their taking increased doses of serotonergic agents. Patients with serotonin syndrome can appear in various degrees of severity and can be life-threatening [1]. The most common drugs involved in self-poisoning are antidepressants, including tricyclics (TCAs), monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors. TCAs typically have more toxic manifestation within the first six hours after overdose, possibly affecting the patient’s neurological, cardiovascular, and electrocardiography statuses in a life-threatening manner [2]. The most common combinations with serotonergic agonists in patients who die of overdose are TCAs, benzodiazepines, diphenhydramine, and alcohol [3]. In our both patients, we found that the clinical manifestations were worsened because of the patients’ combination of serotonergic antidepressants. The first patient used quetiapine for better sleep, and both patients took 100 mg/day of trazodone which has been warned as not effective as other antidepressants [4]. Quetiapine causes supersensitivity of the 5-HT receptors in an environment of increased synaptic serotonin [5]. Otherwise, no adverse effect was noted between low-dose quetiapine and serotonergic agonists [5]. This observation is to remind doctors to simplify their prescriptions because of possibilities of fatal iatrogenic effects, and not to prescribe trazodone because of its poor efficacy [4].

In serotonin syndrome, the diagnosis is made if the patients uses serotonergic drugs and presence of neurological signs (hyperreflexia and clo-
nus). But muscle rigidity can mask these signs, and laboratory data cannot confirm this diagnosis [1]. Differential diagnoses of serotonin syndrome include CNS infection, anticholinergic syndrome, endocrine disorders, neuroleptic malignant syndrome, trauma, ingestion of toxic agents, and carbon monoxide inhalation [6]. Neuroleptic malignant syndrome is lethal and is frequently confused with severe cases of serotonin syndrome because varied degrees of cognitive, autonomic, and neuromuscular dysfunction characterize both disorders. It is caused by dopamine antagonists, such as haloperidol, chlorpromazine, or antiemetic metoclopramide, and is characterized by a slow onset, an altered mental status, unstable blood pressure, lead pipe rigidity, and hyperthermia [7]. These two urgent disease entities are occasionally misinterpreted by clinicians who lack full clinical information. The therapies for serotonin syndrome are not conclusive. Some investigators have developed new rules that are simpler, more sensitive, and more specific than Sternbach’s criteria [8]. Mild to moderate serotonin syndrome may be self-limiting, and typically subsides within 1-3 days. In severe cases, the patients may have severe hypertension, hypertonia, delirium, and agitation [1]. The first choice of treatment is immediate discontinuation of the implicated medication, providing the patient with supportive care. Specific pharmacologic therapies using serotonin antagonists, such as cyproheptadine, can be beneficial. For severe cases, some physicians believe that administering second-generation antipsychotic drugs with serotonin antagonist activity, sedation, or neuromuscular paralysis is effective [1]. Finally, we strongly suggest that optimized adequate dosages of a single antidepressant are better than the combined use of several antidepressants.

References


Wei-Ting Chen, M.D.1*, Chien-Shu Wang, M.D.1, Ti Lu, M.D., M.S.2
1 Department of Psychiatry, Zuoying Armed Forces General Hospital; 2 Department of Psychiatry, Kaohsiung Veterans General Hospital

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*Corresponding author. No. 553, Junxiao Road, Zuoying District, Kaohsiung City 813, Taiwan

E-mail: Wei-Ting Chen <wt820368@gmail.com>