C-Reactive Protein and Serotonin Syndrome

TO THE EDITOR: Serotonin syndrome is an occasionally fatal medication side effect. Because serotonergic agents, including antidepressant medications, are widely prescribed, identifying risk factors for serotonin syndrome is important. Abnormalities of serovascular serotonergic mechanisms, as occur in angina and hypertension, may increase susceptibility to serotonin syndrome (1). We present a case in which the severity of symptoms of serotonin syndrome fluctuated with serum levels of C-reactive protein.

Mr. A was a 53-year-old hypertensive man who was hospitalized for depression. Mr. A was given a prescription for fluoxetine; his outpatient psychotropics—clonazepam, tramadol, and trazodone—were continued. On hospital day 6, Mr. A became acutely confused and had visual hallucinations, gastrointestinal distress, fever, tachycardia, edema, and a fine petechial rash of the lower extremities. Infection or vasculitis was considered, given the rash and abdominal symptoms. A computerized tomography scan of his head, magnetic resonance imaging, and magnetic resonance angiography were negative for a cerebrovascular accident and vasculitis. An EEG twice gave normal results. Other normal laboratory results included a lumbar puncture, two negative qualitative serum antinuclear antibody levels, a cardiac enzyme level, a CBC, comprehensive serum chemistries, and coagulation studies. However, Mr. A's C-reactive protein was elevated, at 19.2 mg/dl (normal=0 to 0.6 mg/dl). Serotonin syndrome was diagnosed, with symptoms consistent with this and multiple medications with serotonergic activity. Fluoxetine, tramadol, and trazodone were discontinued, and the serotonergic blocker cyproheptadine was begun. By hospital day 22, free of symptoms of serotonin syndrome, Mr. A's C-reactive protein level was 9.6 mg/dl. Three months later, he remained well, and his C-reactive protein level was 1.7 mg/dl.

Serotonin syndrome occurs when an acute increase in extracellular serotonin faces impaired serotonin metabolism. Vascular disease and depression are both linked to elevated C-reactive protein levels (2, 3). The effect of drugs on C-reactive protein levels is just beginning to be investigated; as yet, none of the medications taken by our patient is known to alter C-reactive protein levels. C-reactive protein activates platelets, promotes the release of serotonin, and inhibits endothelial nitric oxide synthase (4). Nitric oxide is an important endogenous "off" signal for the release and action of platelet-derived serotonin (5). C-reactive protein may contribute to the pathophysiology of the serotonin syndrome by perpetuating the release of platelet-derived serotonin and inhibiting endothelial nitric oxide synthase. Our patient's serum C-reactive protein level correlated with the course and severity of serotonin syndrome. C-reactive protein levels may help to predict patients at risk for development of serotonin syndrome.

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Hypophosphatemia in Panic Disorder

TO THE EDITOR: Hypophosphatemia is not listed as a symptom of clinical panic disorder in the literature. In experimentally induced panic attacks, low serum phosphate levels have been described (1). In patients with unipolar depression, serum phosphate correlates inversely with measures of anxiety and somatic symptoms (2).

Mr. A, a 31-year-old man with a positive family history of panic disorder and recurrent panic attacks, experienced a recurrence of panic symptoms. His symptom profile was marked by situation-independent panic attacks with concomitant somatic symptoms (continuous hiccups and paresthesia). Under a combined pharmacological treatment plan (mirtazapine and citalopram) in addition to cognitive behavior therapy, remission developed, but he experienced short relapses. A short while later, he was free of panic attacks. His clinical course was mirrored by normalization of his originally high scores on the Body Sensations Questionnaire (3) and the Agoraphobic Cognitions Questionnaire (3) as well as on the somatization, anxiety, and phobic fear dimensions of the SCL-90-R.

Upon routine laboratory testing, marked hypophosphatemia (normal range=2.5–4.5 mg/dl) was observed (1.7 mg/dl, then 1.3 mg/dl), then 1 month later, it was 1.9 mg/dl. His parathormone level was measured as normal: 31.6 pg/dl (normal range: 12–72 pg/dl). The serum phosphate level returned to normal early the next month (2.8 mg/dl), only to fall below the lower limit of normal soon thereafter (2.3 mg/dl). At the next two measurements (2.8 mg/dl) and (3.0 mg/dl), his serum phosphate level again returned to normal.

Our observation of serum phosphate levels correlating inversely with the severity of panic symptoms is not commonly described in the clinical situation. A possible explanation of the occurrence in our patient is the intensity of the panic attacks with a panic state over hours per day. This state was characterized by continuous hiccups and long-lasting paresthesia indicative of hyperventilation. The latter may cause a decrease in serum phosphate as a secondary metabolic acidosis to compensate a primary respiratory alkalosis. An alternative or additive mechanism may be a β-adrenoreceptor-mediated stimulation of muscle glycogenolysis, which depletes intracellular phosphate, causing a transcellular shift of phosphate from plasma into muscle cells. A similar case of

hypophosphatemia that was not present past remission of anxiety symptoms was reported by Kligler (4).

Our case thus supports the notion that hypophosphatemia can be observed as a symptom not only directly after experimental panic attacks but also in the clinical course of severe panic disorder. Serum phosphate levels appear to mirror the clinical course of the disorder.

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Clozapine Treatment of Dimenhydrinate Abuse

TO THE EDITOR: The antinausea medication dimenhydrinate has been recognized as an over-the-counter drug of abuse for years. Dimenhydrinate can cause euphoria, induce pleasant visual and tactile hallucinations, and have anxiolytic effects (1). Patients suffering from schizophrenia may be at an increased risk of dimenhydrinate abuse because of the drug's anticholinergic properties, which may alleviate the extrapyramidal side effects of their neuroleptics (2). While the effects of clozapine on reducing alcohol, nicotine, and even cocaine use have been described (3), we are not aware of published reports of clozapine decreasing dimenhydrinate use. We report two relevant cases.

Ms. A had multiple hospitalizations for schizophrenia from the age of 20. Her first dimenhydrinate abuse was at age 29. Ms. A abused dimenhydrinate repeatedly "to get high" during an 8-year stay in the hospital. At these times, she would be loud and aggressive, with extremely poor self-care. At times, Ms. A ingested 5000 mg of dimenhydrinate, and on more than 10 occasions, she had generalized seizures secondary to overdoses. She stated, "I was relying on [dimenhydrinate] to get me through the day." The ward staff believed that Ms. A's dimenhydrinate abuse would eventually kill her.

We gave Ms. A clozapine when she was 35 years old. At a dose of 700 mg/day of clozapine, her blood level of the drug was 635 ng/ml. Ms. A reported a decreased urge to use dimenhydrinate while taking clozapine. She has since lived in the community, been free of seizures, and worked in a sheltered workshop for more than 3 years. Her dimenhydrinate use dropped to an average of 250 mg/day.

Mr. B explained his dimenhydrinate abuse of up to 3000 mg at a time by saying that it was a cheaper alternative to cocaine. Such ingestions were pleasant, as he reported that they made him "musical" and "creative." He was 36 years old when we first gave him a prescription for clozapine for his schizophrenia. It was difficult to achieve a therapeutic blood level of clozapine. We then gave him fluvoxamine to increase his clozapine blood level. At a clozapine dose of 700 mg/day and a fluvoxamine dose of 25 mg/day, his blood level of clozapine increased to 441 ng/ml. His cravings for dimenhydrinate markedly decreased when clozapine had reached a therapeutic level. Mr. B has been out of hospital for 1.5 years and has continued to use dimenhydrinate at a markedly reduced level.

These are the first reports to our knowledge of clozapine helping to reduce cravings for dimenhydrinate. While neither of these patients ceased to use dimenhydrinate completely, their use was greatly curtailed, thus decreasing problematic behavior and seizures. These changes coincided with therapeutic clozapine levels. More important, the patients themselves reported that clozapine decreased their cravings for dimenhydrinate. Indeed, as Ms. A stated, "Clozapine takes the place of [dimenhydrinate]."

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Suicide Methods From the Internet

TO THE EDITOR: Recent articles have described use of the Internet by individuals to obtain instructions on how to complete a suicide (1, 2). Editorials and discussions have focused on the existence of these sites and the information they provide (3, 4). What is lacking is information on the characteristics of individuals who access these sites. I report the case of another individual who used the Internet to research suicide methods.

Mr. A was a 20-year-old man who was admitted to the hospital after his mother expressed her concerns about his suicidal thoughts. On his initial interview, he reported no symptoms of depression. He had been admitted previously after a suicide attempt in which he overdosed on codeine that was distilled from an acetaminophen-based product. He reported that he found this procedure on the Internet. He was treated with an antidepressant, a mood stabilizer, and a second-generation antipsychotic. He discontinued his medications after discharge and refused to come in for outpatient follow-up. Shortly after the current admission, he left the hospital without permission. During this absence, he purchased the necessary equipment to commit suicide by helium asphyxiation but returned to the hospital without attempting self-harm. He reported that he had identified this method of suicide on the Internet. He subsequently endorsed symptoms of depression and was treated with citalopram. Additionally, he was diagnosed with narcissistic personality disorder by myself, was noted to have a high IQ (superior range), and used a rigid interpretive style characterized by intellectualization and rationalization. He responded to pharmacotherapy but was difficult to engage in a psychotherapeutic rela-