

## Fluoxetine Overdose-Induced Seizure

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A 37-year-old woman experienced a witnessed generalized seizure in the Emergency Department three hours after ingesting approximately 1400 mg of fluoxetine in a suicide attempt. Although the majority of fluoxetine ingestions are benign, seizures may occur after large intentional overdoses. [WestJEM. 2008;9:154-156.]

### INTRODUCTION

Fluoxetine (Prozac®, Eli Lilly and Company, Indianapolis IN) is a selective serotonin reuptake inhibitor (SSRI) commonly used to treat depression and for other psychiatric indications. The majority of fluoxetine overdoses result in a benign clinical course. The largest published case series of fluoxetine overdoses found that the most common effects were tachycardia, drowsiness, tremor, nausea, and vomiting, and concluded that such overdoses typically are “minimally toxic”.<sup>1</sup> Despite this suggestion that only mild to moderate symptomatology is to be expected, seizures,<sup>2-8</sup> cardiac conduction abnormalities,<sup>8</sup> and even fatalities<sup>9</sup> have been associated with fluoxetine ingestions, although most of these cases involve co-ingested drugs or other confounding factors. We report the case of a witnessed, generalized seizure occurring three hours after a fluoxetine overdose in an otherwise healthy young woman.

### CASE REPORT

A 37-year-old woman with a history of bulimia nervosa and depression ingested approximately seventy 20 mg fluoxetine capsules and 4-5 cans of beer in a self-professed suicide attempt. Shortly thereafter, she telephoned a friend who activated the EMS system. The patient’s prescribed medications were fluoxetine 20 mg daily and buspirone 15 mg twice daily. The patient stated that she had taken her buspirone only as directed, with the last dose on the morning of the fluoxetine overdose, about six hours earlier. She specifically denied ingesting any additional buspirone or any other medications. She admitted to “purging” herself daily for the last week. Other than some orthopedic surgical procedures, she denied any other significant past medical history, including seizures.

The paramedics arrived approximately 90 minutes post-

ingestion and found the patient to be awake, alert, sitting up, and emotionally upset. The initial blood pressure was 142/ palp and cardiac monitoring showed a sinus tachycardia at 120/minute. In the emergency department (ED) her vital signs were: temperature 37.2°C, pulse 91/min, blood pressure 132/72 mmHg, respirations 20/min, O<sub>2</sub> saturation 99% on room air. The emergency physician noted the patient to be alert and oriented, but with slurred speech and slow verbal response time. The patient had a non-focal neurologic exam without tremor, rigidity, or hyperreflexia, and the remainder of the physical examination was without noted abnormalities. The patient was given 50 g of activated charcoal, and blood and urine samples were obtained for baseline values and for quantitative serum acetaminophen and salicylate measurements. Serum chemistries showed sodium 138 mmol/L, potassium 4.2 mmol/L, chloride 105 mmol/L, bicarbonate 23 mmol/L, BUN 11 mg/dL, creatinine 0.6 mg/dL, glucose 81 mg/dL, salicylate 3.9 mg/dL, acetaminophen <1µg/mL, and ethanol 48 mg/dL. A qualitative urine pregnancy test was negative. An electrocardiogram revealed a normal sinus rhythm of 97 beats per minute with normal intervals (QRS 88 msec, QTc 461 msec).

Approximately three hours after the ingestion, the patient cried out and then experienced a generalized tonic-clonic seizure lasting 30 seconds witnessed by the ED personnel. The seizure resolved spontaneously, and the patient had a post-ictal period lasting five minutes. The patient received an intravenous loading dose of phenobarbital (620 mg [10mg/kg]) and was then transported without incident to a regional toxicology referral center.

On arrival to the intensive care unit, the patient was somnolent but easily arousable. Vital signs were: temperature 36.9°C, pulse 82/min, blood pressure 112/78 mmHg, respirations 24/min. A repeat physical examination was

unremarkable including the neurologic exam. Additional laboratory data obtained upon admission included serum creatinine kinase (140 IU/L), calcium (8.8 mg/dL), and a comprehensive urine drug screen (which combines the enzyme-multiplied immunoassay technique, thin layer chromatography, and gas chromatography/mass spectroscopy to detect over 1500 drugs and metabolites) that showed the presence of only phenobarbital, fluoxetine, ethanol, and caffeine. The laboratory verified that buspirone can be detected by this analysis. Quantitative serum levels of fluoxetine, norfluoxetine, and buspirone were ordered on admission. The fluoxetine level six hours after the ingestion was 922 ng/mL (therapeutic = 50-480 ng/mL) and the norfluoxetine level was 379 ng/mL (therapeutic = 50-450 ng/mL). The quantitative buspirone level could not be determined due to laboratory handling error. The patient was observed overnight without any further seizure activity or other unusual events. The psychiatry consultation and liaison service evaluated the patient the following morning and arranged for outpatient therapy. The patient was then discharged home in stable condition.

## DISCUSSION

Data from human and animal trials show fluoxetine to be generally safe and with few drug interactions.<sup>10-12</sup> Fluoxetine overdose typically results in a benign clinical course, with the most common symptoms being tachycardia, drowsiness, tremor, nausea, and vomiting, and has therefore been identified as “minimally toxic in doses up to 1,500 mg and with combined plasma levels [fluoxetine plus norfluoxetine] up to 1390 ng/mL.”<sup>11</sup> With regard to potential neurotoxic effects, considerable evidence exists that fluoxetine has an anticonvulsant effect at therapeutic doses in humans and animal models.<sup>13</sup> Antidepressants may display both anticonvulsant and pro-convulsant properties, with the most important determining factor being the dose.<sup>14</sup> In a study of five different SSRIs taken in overdose, fluoxetine had the lowest incidence of inducing seizures (1%, vs. 2% for sertraline, paroxetine, and citalopram, and 4% for fluvoxamine).<sup>15</sup> Not surprisingly then, there are few reports of seizures associated with fluoxetine in the medical literature. Many of these reports are confounded by co-ingestants and/or underlying brain disease.<sup>2-5,8</sup> Only a few cases of seizure after isolated fluoxetine overdose in normal subjects have been reported,<sup>6,7</sup> and there is also a case occurring after escalation of therapeutic dosing up to 60 mg/day.<sup>16</sup>

Evidence in the patient presented here for an acute fluoxetine overdose is supported not only by history, but also from the relatively high ratio of the parent substance compared to norfluoxetine, its *N*-desmethylated metabolite. The seizure does not appear to be related to serotonin syndrome, because the patient did not exhibit autonomic instability, muscular rigidity, or abnormal mental status (excluding the seizure

itself and a brief post-ictal period) as typically occur in that disorder.<sup>17</sup> The patient also consumed some ethanol during her suicide attempt, but it is very unlikely that ethanol contributed to her seizure. Firstly, she was only an occasional ethanol consumer without a history of dependence or prior episodes of withdrawal; in such a case, the presence of ethanol would, if anything, act as an anticonvulsant. Secondly, she did not exhibit signs of autonomic instability (e.g., diaphoresis, hypertension) or tremor consistent with ethanol withdrawal. She was initially tachycardic, but this is also commonly found in cases of significant SSRI overdose.

Although acute fluoxetine overdose is believed to cause the seizure in this patient, buspirone might potentiate fluoxetine's neurotoxicity. A seizure has been reported in a patient receiving therapeutic doses of fluoxetine and buspirone for obsessive-compulsive disorder.<sup>18</sup> In contrast, a case series of 11 patients on fluoxetine and buspirone does not describe any seizures or other neurotoxicity.<sup>19</sup> Caffeine overdoses have also been reported to cause seizures,<sup>20</sup> and caffeine was detected in our patient's urine. When questioned about this finding, she reported that she consumed caffeine-containing beverages (e.g. tea, soft drinks), but denied excessive use. Although a serum caffeine level is not available for this patient, she was not exhibiting symptoms of caffeine intoxication such as tremor, agitation, hyperglycemia or hypokalemia.<sup>20</sup> She did have a mild tachycardia initially, but this spontaneously resolved prior to the seizure. In order for caffeine to be responsible for this seizure, one would expect the patient to exhibit prominent symptoms of caffeine toxicity. Thus, although the patient's ingestion was not a completely isolated fluoxetine overdose, since other xenobiotics were detected, there is no evidence that any other drug contributed significantly to her seizure.

## CONCLUSION

We report the clinical course of a patient who had a witnessed seizure following an acute fluoxetine overdose. While the medical literature strongly suggests that most fluoxetine overdoses are benign, emergency physicians need to remain cognizant that intentional, high-dose fluoxetine ingestions may induce seizures.

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