Benign Course in a Child with a Massive Fluoxetine Overdose

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The selective serotonin reuptake inhibitors appear to have a much wider margin of safety than most other classes of antidepressants. Although there is limited experience with acute overdoses of fluoxetine alone, few serious adverse effects have been reported. There has been almost no experience, however, with significant fluoxetine overdoses in children. This report describes the accidental ingestion of as much as 43 mg/kg of fluoxetine by a 4-year-old child. In this case, serum blood levels of the drug and its major metabolite were consistent with a large ingestion and are among the highest reported in the medical literature. Toxic effects were relatively mild and consisted of a brief spell of unresponsiveness, sinus tachycardia, and moderate psychomotor agitation and dyskinesia. Supportive care was provided and the child recovered completely.

Key words. Fluoxetine; overdose; child, preschool.
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Fluoxetine was the first selective serotonin reuptake inhibitor (SSRI) released in this country for the treatment of depression. Since its introduction in 1988, it has been widely used for this purpose, as well as to treat a number of other psychiatric conditions.[1] Four SSRIs are now available in this country and are rapidly replacing the use of the tricyclic antidepressants and related agents. This supplantation may be attributable to the excellent side effect and safety profile of SSRIs compared with that of other available drugs. In particular, SSRIs have proved to be much safer than the highly toxic tricyclics in acute overdosage. Very large ingestions of SSRIs have resulted in relatively minor toxicity in most reported cases. This report describes a child who ingested an extremely large dose of fluoxetine with apparently minimal adverse effects.

Case Report

A 4-year-old girl was brought to the emergency department of a community hospital approximately 4 hours after ingesting an uncertain number of 20-mg capsules of fluoxetine. The child was found with an empty bottle that had previously contained 35 pills prescribed for an older sibling. Although she denied having taken any of the pills, the family was unable to find any of them elsewhere in the house. Because she did not appear to be ill, the family delayed taking her to the emergency department. About 3 hours after the apparent ingestion, she began acting strangely, appearing hypervigilant and nervous, with abnormal jerking movements. She then experienced a spell of unresponsiveness that, according to the mother, lasted several minutes. During this time, she did not respond to verbal or tactile stimuli; however, there were no tonic or clonic movements, breath-holding, automaton-like movements, or incontinence. The child had previously been in apparent good health and her past medical history was unremarkable.

In the hospital emergency department, the child was alert and generally cooperative. She appeared hypervigilant at times, especially when procedures such as venipuncture were performed. Her vital signs included: weight 16.4 kg (36 lb), temperature 37.9°C (100.2°F), respirations 16 per minute, pulse 148 beats per minute, and blood pressure 99/58 mm Hg. In addition to the hypervigilance, she displayed moderate psychomotor agitation, continuously moving on the examination table and around the examination room. Her gross motor movements appeared to be dyskinetic, manifested by erratic jerking with voluntary movement. Her muscle tone

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was within normal limits, however, and deep tendon reflexes were 3+ and symmetrical. Other than these findings and the presence of a regular tachycardia, results of the physical examination were within normal limits.

Admission laboratory results, including complete blood count, multichemistry panel, and urinalysis, were all essentially normal. An electrocardiogram showed sinus tachycardia and right axis deviation that was consistent with her age. A chest radiograph was normal.

After initial evaluation and consultation with a regional poison control center, an attempt was made to give the patient 30 g of activated charcoal slurry by mouth. The commercially prepared suspension contained activated charcoal 25 g and sorbital 48 g per 120 mL. When she refused it by mouth, it was administered through a nasogastric tube. Shortly thereafter, she vomited a large amount, including drug capsule fragments. She was transferred to the intensive care unit for further observation. Charcoal administration was repeated several hours later, this time without vomiting. By this time she was noted to be much calmer and very cooperative with the nursing staff, and the psychomotor agitation was much improved. Repeat physical examinations during the first 24 hours were unremarkable except for a mild tremor and slight dyskinesia.

The results of a repeat complete blood count and a multichemistry panel 48 hours after admission were normal, and electrocardiograms performed 24 and 48 hours after admission showed no significant changes. Serum fluoxetine and norfluoxetine levels obtained at admission were reported as 3080 ng/mL and 459 ng/mL, respectively. Forty hours after admission, these levels were reported as 1302 ng/mL and 423 ng/mL, respectively. Reference ranges for steady-state concentrations of fluoxetine and norfluoxetine in adult patients receiving fluoxetine 20 to 60 mg per day are reported as 47 to 469 ng/mL and 52 to 446 ng/mL, respectively.[2] Close observation was maintained for approximately 72 hours. All psychomotor symptoms and signs resolved during this time; cardiac monitoring demonstrated only sinus tachycardia with rates up to 156 beats per minute. The child was discharged on the fourth hospital day. On follow-up by telephone 10 weeks' postingestion, the child's mother reported that she had gradually returned to her normal state after about 2 weeks of appearing to be "hyped up."

Discussion

Since its introduction in this country in 1988, fluoxetine has been used at a rapidly increasing rate to treat depression and other psychiatric conditions.[1] One reason for its widespread acceptance is that it appears to have a wide margin of safety, especially when compared with tricyclic antidepressants.[3]

There is now limited but expanding literature concerning the effects of fluoxetine overdose. A review of the literature indicates that overdose with fluoxetine alone rarely causes serious problems. Only five fatalities related to fluoxetine overdose have been reported.[4–7] Of these, three involved significant ingestion of other drugs. The role of fluoxetine in the deaths, therefore, is uncertain.[4,7] In another case, a 28-year-old female patient was found dead after apparently ingesting fluoxetine and ethanol[5]; the heart blood ethanol level was 48 mmol/L and the fluoxetine and norfluoxetine levels were 800 ng/mL and 650 ng/mL, respectively. In the fifth case, a 58-year-old woman was found dead after an apparent massive overdose of fluoxetine alone.[6] The only other drug found on toxicologic evaluation was propanolol, which was known to have been prescribed for the woman. The blood propanolol level was well within the usual therapeutic range; however, the blood concentrations of fluoxetine and norfluoxetine found in the patient were 6000 ng/mL and 5000 ng/mL, respectively, higher than any reported elsewhere in the literature. The authors estimated the absorbed (lethal) dose to have been in the range of 1200 to 2000 mg.

Riddle and colleagues[8] described a 13-year-old boy with Tourette's syndrome and obsessive-compulsive disorder who experienced a generalized tonic-clonic seizure after ingesting an estimated 1880 mg of fluoxetine. Although the seizures resolved spontaneously, the patient was subsequently treated with phenytoin for seizure prophylaxis. He also experienced abdominal pain, nausea, blurred vision, fatigue, headache, and dizziness, and his electrocardiogram demonstrated ST depression. At 90 minutes postingestion, blood levels of fluoxetine and norfluoxetine were 428 ng/mL and 211 ng/mL, respectively. At approximately 15 hours postingestion, levels were reported as 1142 ng/mL and 322 ng/mL, respectively.

Other reported cases have demonstrated relatively benign effects of fluoxetine overdoses. One patient who is believed to have taken 3000 mg during premarketing clinical trials experienced two grand mal seizures that remitted spontaneously. The patient subsequently recovered, but blood levels of fluoxetine were not reported.[7] In the largest series to date, Borys and associates[9] reported 234 cases from four poison control centers. Of the 87 cases in which fluoxetine alone was ingested, 67 patients were adults and 20 were children. In the adult group, the mean dose ingested was 455.4 mg; the maximum dose was 1500 mg. Thirty of these adults remained asymptomatic, including one who had ingested an estimated 1200 mg. The most common symptoms noted were tachycardia, drowsiness, tremor, nausea, and vomiting.

Very few cases of fluoxetine overdosage in children have been reported. Eighteen of the 20 pediatric patients

in the series reported by Borys et al[9] remained asymptomatic. A 2-year-old child who ingested 10 mg was reported to have hyperactivity and diarrhea, and a 23-month-old child who ingested an unknown amount was reported to develop sleepiness. Spiller and co-workers[10] reported a series of 44 fluoxetine overdoses, five of which were in children under the age of 5. Apparently the only one of these individuals who ingested fluoxetine alone and had follow-up information available was a 3-year-old child who ingested 20 mg and remained asymptomatic. Despite the apparent benign course following fluoxetine ingestion in these patients, it is important to note that the maximum dose known to be ingested was only 3.6 mg/kg.

Recommendations for the management of fluoxetine overdoses are the same for both children and adults. These include general supportive care and prompt elimination of the unabsorbed drug from the gastrointestinal tract. Prevention of gastrointestinal absorption of fluoxetine is similar to that of other pharmacologic agents and may be accomplished by any of three methods: (1) gastric emptying by induced emesis or gastric lavage; (2) drug adsorption with activated charcoal; and (3) catharsis using osmotic agents, such as sorbitol or magnesium sulfate. Although gastric emptying may be useful in removing some of the ingested material, there is no conclusive evidence that it significantly improves outcome in drug overdoses.[11] The use of gastric lavage or induced emesis may be contraindicated in overdoses with central nervous system stimulants, since further stimulation may precipitate seizures.[12] Some authorities believe that the use of activated charcoal may be the safest and most effective means of preventing gastrointestinal absorption of most drugs,[11] including fluoxetine (personal communication, Lilly Research Laboratories, Indianapolis, Ind, May 12, 1995). However, there are no published data to strongly support any single or combination approach to elimination of fluoxetine from the gastrointestinal tract. In the case reported here, induced emesis and gastric lavage were not felt to be appropriate for two reasons. First, the relatively long delay between the ingestion and the child's arrival at the emergency department made it unlikely that a significant amount of drug remained in the stomach; second, the patient's psychomotor agitation raised concerns that any additional stimulation might precipitate seizures.

According to the manufacturer (Dista Products Co, a division of Eli Lilly and Co, Indianapolis, Ind), hemodialysis is unlikely to be of any benefit in cases of fluoxetine overdose, and there are no specific antidotes available (personal communication, Lilly Research Laboratories, May 12, 1995). Supportive care in cases of significant overdose includes airway maintenance, supplemental oxygen, and ventilatory support as necessary. Vital signs and cardiac monitoring is recommended, as is observation for seizures. Intravenous diazepam may be useful in the event of seizures.[7]

If the quantity apparently ingested in this case is accurate (approximately 43 mg/kg), this would be the largest childhood ingestion of fluoxetine reported in the literature to date. The serum drug levels are consistent with an ingestion of this magnitude, and are among the highest reported from all previous cases (adults and children). Despite this, the only significant consequences noted were the episode of unresponsiveness before arrival at the hospital, sinus tachycardia, and some degree of psychomotor agitation and dyskinesia, all of which were transient and self-limited. It is interesting to note that the psychomotor agitation and gross motor dysfunction were most severe in the hectic and threatening emergency department setting. Once the child was in a calmer, private intensive care unit room, comforted by her mother, these findings improved dramatically. The relatively benign course of this case is consistent with previous reports suggesting that, in most instances, fluoxetine overdose alone results in minimal acute toxicity. It is important to note, however, that the experience with very large overdoses confirmed with serum drug levels is limited, especially in children. It is also important to remember that multidrug overdoses including fluoxetine are potentially more serious and are more likely to result in serious complications, including death.

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