Case Report

Fatal Fluoxetine Intoxication with Markedly Elevated Central Blood, Vitreous, and Liver Concentrations

F. Lee Cantrell1, Chris Vance2, Bethann Schaber2, and Iain McIntyre2
1California Poison Control System—San Diego Division, 200 W. Arbor Dr., San Diego, California 92103-8925 and
2San Diego County Medical Examiner’s Office, Toxicology, 5555 Overland Ave., San Diego, California

Abstract

Since being introduced into clinical practice 20 years ago, fluoxetine, a serotonin-reuptake inhibitor, has remained one of the most popular antidepressants prescribed in the United States. Upon reviewing the literature, the highest reported postmortem central blood fluoxetine and norfluoxetine concentrations are 22 and 6.8 mg/L, respectively, and reported liver fluoxetine and norfluoxetine concentrations are 29–128 and 17 mg/kg, respectively. A 31-year-old female with convulsive activity was found at home by her husband. Emergency services was contacted, and responders found the patient unresponsive with agonal respirations, a pulse of 20 bpm, and no measurable blood pressure. Despite all resuscitative efforts, the patient expired. Postmortem analyses revealed concentrations of 33 mg/L fluoxetine and 12 mg/L norfluoxetine in central blood and 400 mg/kg fluoxetine and 460 mg/kg norfluoxetine in liver. Vitreous fluoxetine and norfluoxetine concentrations were 5.2 and 2.2 mg/L, respectively. Utilizing a sensitive and specific analytical procedure, we report the highest recorded central blood and liver fluoxetine and norfluoxetine concentrations.

Introduction

Since being introduced into clinical practice 20 years ago, fluoxetine, a serotonin-reuptake inhibitor (SSRI), has remained one of the most popular antidepressants prescribed in the United States (1). Because patients afflicted with mood disorders have a higher risk for attempting suicide (2), it is not surprising that more than 7000 cases of intentional self-poisoning with SSRIs were reported to U.S. poison control centers in 2006 (3). Despite this large number of exposures, only 23 reported fatalities where fluoxetine was detected during postmortem analysis occurred. Upon reviewing the literature, the highest reported postmortem central blood fluoxetine and norfluoxetine concentrations are 22 and 6.8 mg/L (4), respectively, and reported liver fluoxetine and norfluoxetine concentrations are 29–128 mg/kg and 17 mg/kg (5), respectively. We report the highest central blood and liver fluoxetine and norfluoxetine concentrations on record.

Case History

A 31-year-old female with what was described as convulsive activity was found at home by her husband. Her past medical history included depression, anorexia, suicidal ideations, mild obsessive compulsive disorder, chronic constipation, and anemia. She had no history of illicit drug or ethanol abuse, and her only current medication was fluoxetine. Emergency services was contacted, and responders found the patient unresponsive with agonal respirations, a pulse of 20 bpm, and no measurable blood pressure. Despite all resuscitative efforts, the patient expired. An autopsy was performed and documented a well-developed woman with no evidence of traumatic injuries. Tissue recovery occurred prior to autopsy. Internal examination documented pulmonary congestion and edema (right lung 800 g, left 830 g) and urine retention (220 mL). Her liver weighed 900 g and microscopically showed no necrosis, steatosis, inflammation, or fibrosis. Microscopic examination of the lungs showed vascular congestion without pneumonia. Examination of the remaining viscera found no significant natural disease.

Experimental

Specimens

All specimens analyzed were collected at autopsy at the San Diego County Medical Examiner’s Office. Central blood was collected from the heart and stored in a glass tube containing sodium fluoride (25 mg) and potassium oxalate (20 mg). Peripheral blood was not available. A liver specimen was collected in a sterile 4-oz container without preservative. A vitreous humor specimen was also collected in a glass tube without preservative, and gastric contents were collected in...
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250°C and the detector set at 280°C.

Materials

Fluoxetine and norfluoxetine standards and controls were purchased from Alltech (State College, PA) and Cerilliant (Austin, TX) in methanol dissolved stock at a concentration of 1 mg/mL, and separate lot numbers were used for calibrators and controls. The internal standard used was cyclizine (Burroughs-Wellcome, Kirkland, QC, Canada). Cyclizine was prepared in 1.0 mg/mL stock in methanol. Working stock solutions of fluoxetine and norfluoxetine were prepared in deionized (DI) water at a concentration of 1.0 mg/L for both the standard and control. The cyclizine was diluted with DI water to 5.0 mg/L working solution. 1-Chlorobutane and ethyl acetate are manufactured by OmniSolv. Concentrated hydrochloric acid is manufactured by Aristar, and the concentrated ammonium hydroxide is from EMD. Sodium sulfate (anhydrous, granular ACS grade) was obtained from Sigma-Aldrich Chemical (St. Louis, MO).

Fluoxetine analysis

Fluoxetine and norfluoxetine were first detected in a basic drug screen by GC–MS using a liquid–liquid extraction for blood. Fluoxetine and norfluoxetine was then quantitated on a GC with a selective nitrogen-phosphorus detector (NPD). Five-point calibration curves were obtained by making calibrators from the working fluoxetine and norfluoxetine solutions in the concentration of 0.25, 0.50, 1.0, 2.0, and 3.0 mg/L. Two controls were made from a separate working stock with a different lot number than the calibrators in concentrations of 0.5 mg/L each. A blood curve was used for blood and gastric samples containing blank porcine blood as the matrix. A liver curve was constructed using porcine liver homogenate for the matrix of liver specimens. A vitreous curve was constructed using DI water for the matrix of vitreous specimens.

Fluoxetine and norfluoxetine specimens were analyzed using an HP 5890 series II Plus GC using a DB-1 (15 m × 0.252 mm × 0.25 µm) column and a nitrogen-phosphorus bead detector from Agilent. Helium was the carrier gas and had a flow rate of 1.2 mL/min. For all samples, the inlet temperature was set to 250°C and the detector set at 280°C. For blood and liver samples, 1 µL of sample was injected on the column, and after 30 s, the GC started its oven ramp. The oven started at 50°C, and the ramp was an increase of 35°C/min for 4.5 min. After 4.5 min, the oven temperature remained constant at 275°C until the end of the run. Total runtime after injection was 11.4 min. The cyclizine internal standard was seen at 5.690 min. Fluoxetine had a retention time of 5.177 min within a window of 1% and a relative retention time of 0.910. Fluoxetine had a retention time of 5.501 min within a window of 1% and a relative retention time of 0.967 min.

Samples were all extracted using a modified Foerster-Garratt procedure (6). For all samples, a minimum of two separate unknown sample dilutions of different volumes were used and placed in separate tubes. Volumes used were those that would bring sample response into the calibration curves response range. Any sample added that was less than 1 mL had its difference in volume made up with DI water. Liver specimens were homogenized by taking 15–20 g of liver specimen and blending it with an equal amount of DI water to create a 0.5 g/mL homogenate. One milliliter of this homogenate was then pipetted into a tube and diluted to 10 mL with DI water to create a 0.05 g/mL liver homogenate. All blood specimens were run on a blood curve with its own calibrators and controls, blank, and negative, and all liver samples were run with their matching matrices as well. To each tube, 1 mL of the respective matrix (porcine blood, porcine liver, or DI water) was added. Each tube was diluted to 5 mL with DI water and vortex mixed for 10 s. Fifty microliters of cyclizine working solution (0.5 mg/L) was added to each tube (except blanks), and the tubes were vortex mixed again for 10 s. Fresh concentrated ammonium hydroxide (1 mL) was then added to each tube, and tubes were vortex mixed again for 10 s. Tubes then had 6 mL of 1-chlorobutane added and were capped and extracted by rotation for 30 min. When finished, tubes were centrifuged at 3200 rpm for 5 min. Any emulsions still present after centrifugation was eliminated by the addition of sodium sulfate in necessary quantities. All tubes were centrifuged for another 5 min at 3200 rpm and then the top organic solvent (1-chlorobutane) phase was extracted by pipette into a clean glass tube. Extracted organic layers were put into screwcap tubes and 3.5 mL of 1 N HCl was added to each tube. Tubes were capped and extracted by rotation for 30 min. Following extraction by rotation and centrifugation at 3200 rpm for 5 min, the organic 1-chlorobutane layer was aspirated to waste. A 1-mL aliquot of concentrated ammonium hydroxide was added to the remaining acid layer of each tube, and the tubes were vortex mixed for 10 s. Then 3 mL of 1-chlorobutane was added to each tube, and tubes were capped and extracted by rotation for 30 min. The tubes were then centrifuged for 15 min at 3200 rpm, and the top organic layer was extracted carefully to clean culture tubes. The culture tube solvent was evaporated to dryness under nitrogen at room temperature. Dry extracts were reconstituted with 100 µL of ethyl acetate and vortex mixed for 10 s. Extracts were then transferred to autosampler vials fitted with glass volume inserts.

Calibrators were back calculated to original known concentrations and were within 20% of target value. Calibration curves were constructed from a minimum of four non-zero points. The calibration curve used a linear regression fit ($r^2 \geq 0.99$). Both positive control samples were back calculated to known value of 0.5 mg/L. All specimen tubes were diluted, so concentration would be expected to fall within the range of the calibration curve. Accuracy and precision of the method have been established with more than 50 analyses of both fluoxetine and nor-
fluoxetine over 2 years. The accuracy and precision of the method for fluoxetine have been established with 58 analyses and were 96% with a coefficient of variation of 12%, respectively, at a concentration of 0.50 mg/L. The accuracy and precision of the method for norfluoxetine have been established with 52 analyses and were 93% with a coefficient of variation of 15%, respectively, at a concentration of 0.50 mg/L.

Results

Our analyses revealed central blood concentrations of 33 mg/L fluoxetine and 12 mg/L norfluoxetine and liver concentrations of 1400 mg/kg fluoxetine and 460 mg/kg norfluoxetine. Vitreous fluoxetine and norfluoxetine were 5.2 and 2.2 mg/L, respectively. Only 2 mg fluoxetine was detected in the gastric contents. Basic and acid/neutral drug screening did not reveal any additional compounds in excess of trace amounts and no ethanol was detected. The cause of death was attributed to fluoxetine intoxication. The manner of death was classified as suicide based on the excessive fluoxetine concentrations in the setting of a history of depression and previous suicidal ideations.

Discussion

Fluoxetine and norfluoxetine are subject to postmortem redistribution and have reported heart/femoral concentration ratios ranging from 1.2 to 5.4 and 1.3 to 6.6, respectively (5). Our measured central blood fluoxetine concentrations greatly exceed the previously reported fluoxetine and norfluoxetine concentrations of 22 and 6.8 mg/L, respectively. Tissue recovery technicians failed to collect peripheral blood specimens, as per protocol, prior to removal of bones, tendons, and blood vessels from the extremities. Therefore, we could not calculate a heart/femoral blood concentration ratio.

Other authors have described elevated peripheral postmortem blood fluoxetine and norfluoxetine concentrations following the ingestion of fluoxetine alone (7,8). Compton et al. (8) report a 37-year-old male with a peripheral blood concentration of 4.5 mg/L following the ingestion of 12 g of fluoxetine. Given the relatively broad range of reported heart/femoral concentration ratios and the relatively small sample sizes from which these values are derived, attempting to accurately extrapolate peripheral blood concentrations for comparative analysis with those reported by other authors would be difficult.

With respect to liver fluoxetine and norfluoxetine concentrations, only scant data are available. The liver concentrations we measured greatly exceed the few previously reported concentrations. Given the degree of metabolism that fluoxetine undergoes, combined with the large volumes of distribution of fluoxetine and norfluoxetine (range 20–42 L/kg) (9), it is not surprising that the liver would concentrate these substances following a massive ingestion.

Although there are few published reports of vitreous fluoxetine concentrations, a recent manuscript cites the distribution coefficient for fluoxetine as 0.10 ± 0.03 for vitreous humor at therapeutic concentrations (9). The data of this case report substantiate the distribution profile with a ratio of 0.15 for vitreous to central blood concentrations.

When fatal overdoses associated with fluoxetine have been reported, SSRIs in general are relatively safe in the overdose setting (10). Only after extremely large ingestions would life-threatening symptoms such as seizures, coma, or cardiotoxicity be expected (11). Given the lack of detailed information regarding the circumstances surrounding the decedent’s exposure, the described clinical symptoms, markedly elevated blood and liver fluoxetine concentrations, lack of other detected drugs, and non-specific autopsy findings, it would appear that the patient’s death was a direct result of fluoxetine poisoning.

Conclusions

Even without co-ingestants or significant co-morbidities, fluoxetine can be associated with fatal poisonings in the overdose setting. Utilizing a sensitive and specific analytical procedure, we report the highest recorded central blood and liver fluoxetine and norfluoxetine concentrations.

References


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