CASE REPORT

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A Fatal Drug Interaction Between Clozapine and Fluoxetine

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ABSTRACT: A case is presented of a fatal drug interaction caused by ingestion of clozapine (Clozaril™) and fluoxetine (Prozac™). Clozapine is a tricyclic dibenzodiazepine derivative used as an ''atypical antipsychotic'' in the treatment of severe paranoid schizophrenia. Fluoxetine is a selective serotonin reuptake inhibitor used for the treatment of major depression. Clinical studies have proven that concomitant administration of fluoxetine and clozapine produces increased plasma concentrations of clozapine and enhances clozapine's pharmacological effects due to suspected inhibition of clozapine metabolism by fluoxetine. Blood, gastric, and urine specimens were analyzed for fluoxetine by gas chromatography/mass spectrometry (GC/MS) and for clozapine by gas-liquid chromatography (GLC). Clozapine concentrations were: plasma, 4.9 μg/mL; gastric contents, 265 mg; and urine, 51.5 μg/mL. Fluoxetine concentrations were: blood, 0.7 μg/mL; gastric contents, 3.7 mg; and urine 1.6 μg/mL. Norfluoxetine concentrations were: blood, 0.6 μg/mL, and none detected in the gastric contents or urine. Analysis of the biological specimens for other drugs revealed the presence of ethanol (blood, 35 mg/dL; vitreous, 56 mg/dL; and urine 153 mg/dL) and caffeine (present in all specimens). The combination of these drugs produced lethal concentrations of clozapine and high therapeutic to toxic concentrations of fluoxetine. The deceased had pulmonary edema, visceral vascular congestion, paralytic ileus, gastroenteritis and eosinophilia. These conditions are associated with clozapine toxicity. The combined central nervous system, respiratory and cardiovascular depression of these drugs was sufficient to cause death. The death was determined to be a clozapine overdose due to a fatal drug interaction.

KEYWORDS: forensic science, forensic toxicology, clozapine, fluoxetine, drug interaction

Clozapine (Clozaril™), 8-chloro-11-(4-methyl-1-piperazinyl)-5-dibenzo[b,e][1,4]diazepine, is a tricyclic dibenzodiazepine derivative which is used as an ''atypical antipsychotic'' in the treatment of severe paranoid schizophrenia that is unresponsive to standard therapies. Clozapine interferes with the binding of dopamine at both D_1 and D_2 receptors but does not induce catalepsy nor inhibit apomorphine-induced stereotypy. Clozapine is classified as an ''atypical antipsychotic'' drug because its dopamine receptor binding and dopamine mediated behavioral effects differ from the typical antipsychotic drugs. Clozapine's preferential binding to limbic rather than to striatal dopamine receptors explains its relative lack of extrapyramidal side effects. Clozapine is also antagonistic to adrenergic, histaminergic, cholinergic and serotonergic receptors (1,2). Pharmacokinetic data for clozapine are given in Table 1.

Fluoxetine (Prozac™), (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-p-tolyl)oxy]propylamine hydrochloride, is a selective serotonin reuptake inhibitor, chemically unrelated to tricyclic, tetracyclic or other available antidepressant agents, used for the treatment of major depression (6,7). Fluoxetine is metabolized to an active metabolite, norfluoxetine and other inactive metabolites (8,9). Pharmacokinetic data for fluoxetine are given in Table 2.

Clozapine therapy has increased due to its effectiveness in treatment-resistant schizophrenic cases and a relatively low risk of extrapyramidal side effects (10). It has been combined with fluoxetine in the effective treatment of psychotic mood disorders (11,12). The clinical combination of these medications has resulted in the elevation of plasma clozapine concentrations and increased signs of clozapine toxicity (10–15). Elevated clozapine levels with concomitant administration of fluoxetine have been attributed to fluoxetine's affinity and selectivity for microsomal oxidases. Fluoxetine's inhibition of N-dealkylation and N-oxidation of clozapine via P_{450} isozyme 2D6 produces elevated plasma concentrations of the parent clozapine (10,11,15). Although the combinations of clozapine/phenytoin and clozapine/fluvoxamine have caused fatal drug interactions due to clozapine toxicity (16), this is the first reported case of a death by clozapine overdose due to a fatal drug interaction with fluoxetine.

Case History

A 44-year-old white male was found dead, lying on his back at the edge of the Nolichuckey River in his yard approximately 150 to 200 ft from his residence. Medications found at the scene were Clozaril (clozapine), 7 of 35 prescribed 100 mg tablets, and Prozac (fluoxetine), 23 of 60 prescribed 20 mg tablets. The dates of the prescriptions and number of remaining tablets revealed that the deceased had been taking his medications as prescribed.

Materials and Methods

Specimen Collection

Blood (90 mL) was collected by cardiac puncture of the ventricles and stored in sterile plain Vacutainer™ tubes or Vacutainer

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TABLE 1—*Clozapine pharmacokinetics.**

Formulation	25 and 100 mg tablets
Dosage	12.5 mg initial increased @ 25 to 100 mg/week to 300 to 400 mg/day
Therapeutic concentrations	0.06–1.0 μg/mL
Peak plasma concentrations	0.14 μg/mL (0.07 to 0.34 μg/mL at 1.5 h after 100 mg orally
Maximum daily dose	900 mg/day
Duration of action	4–12 h
Bioavailability	55 ± 12% (oral)
Biotransformation	extensive first pass effect
Excretion	80% as metabolites (50% urine, 30% feces)
Plasma binding	95%
Volume of distribution	5 L/kg
Half life	4.5 to 7.5 h
Clearance	6.1 ± 1.6 mL/min/kg

* Based on Refs 1–5.

TABLE 2—*Fluoxetine pharmacokinetics.**

Formulation	20 mg capsul or 20 mg/5 mL liquid (oral)
Dosage	20 mg/day increased to 80 mg/day over several weeks
Therapeutic concentrations	0.03–0.05 μg/mL
Peak plasma concentrations	0.015 to 0.055 μg/mL within 6 to 8 h after 40 mg orally
Maximum daily dose	80 mg/day
Onset of action	1–4 weeks after initiation of therapy
Bioavailability	>60% (oral)
Biotransformation	hepatic metabolism to active metabolite norfluoxetine and numerous other metabolites
Excretion	80% excreted in the urine, 5% excreted biliary in feces
Plasma binding	94.5%
Volume of distribution	26 L/kg
Half life	1 to 3 days
Clearance	9.6 ± 6.9 mL/min/kg

* Based on Refs 6–9.

tubes containing potassium oxalate and sodium fluoride. Vitreous humor was collected from the posterior chambers of both eyes and stored in sterile Vacutainer tubes. Urine was collected by bladder puncture and stored in a plastic specimen container. Serum and plasma were separated by centrifugation at 2000 rpm for 10 min. Biological fluids were stored at 2 to 4°C until analysis. No tissue samples were collected from this autopsy.

Analytical Methods

Blood and urine specimens were screened for ethanol using the Abbott TDx-Radiative Energy Attenuation (REA) Ethanol assay. Ethanol quantitations were determined by gas-liquid chromatography (GLC) (17). The biological fluids were screened for the presence of numerous acidic, basic and neutral drugs and metabolites including narcotics and other analgesics, barbiturates and other sedative hypnotics, benzodiazepines, cannabinoids, cocaine, phencyclidine, phenothiazines, sympathomimetic amines and tricyclic antidepressants by a combination of thin-layer chromatography, gas-liquid chromatography, gas chromatography/mass spectrometry (GC/MS), enzyme immunoassays [enzyme multiplied immunoassay (EMIT) and fluorescence polarization immunoassay (FPIA)] and specific colorimetric procedures.

Clozapine is extracted from alkalinized specimens with butyl chloride, back extracted into hydrochloric acid and finally partitioned into chloroform which is evaporated to dryness under nitrogen (18). Residue is reconstituted in methanol and chromatographed on a Perkin Elmer 8500 gas chromatograph with 0.75 mm × 30 m SPB-1 capillary column (Supelco Inc., Bellefonte, PA) with an FID detector and a Hewlett Packard 3390A integrating recorder. Chromatographic conditions were: injector and detector 300°C; helium carrier at 10 mL/min; column 230°C for 0.5 min then 10°C/min to 280°C then held for 10.5 min; and hydrogen and air set for maximum sensitivity. Clozapine elutes in 13.21 min (relative retention time of 2.1727 to the internal standard trihexyphenidyl). Concentrations are determined by interpolation of peak area ratios.

Fluoxetine and norfluoxetine are extracted from alkalinized specimens with butyl chloride, back extracted into hydrochloric acid and finally partitioned into chloroform which is evaporated to dryness under nitrogen (18). Residue is reconstituted in methanol and chromatographed via a Hewlett Packard Automatic Liquid Sampler (HP61512A/HP18593A/HP18596B) on a Hewlett Packard 5890 Series II gas chromatograph with a Hewlett Packard 5972 Mass Selective Detector using a 0.25 mm × 30 m HP-5MS capillary with a 5% PH ME Siloxane film of 0.25 μm. Chromatographic conditions were: injector 250°C; transfer line 270°C; helium carrier at 1.0 mL/min; column 150°C for 0.5 min then 10°C/min to 270°C then held for 2.5 min. Mass spec detector conditions were set using Standard Spectra Autotune. Target ions (with a dwell of 100 ms per ion) are 309.3 for fluoxetine (retention time 7.25 min), 295.3 for norfluoxetine (retention time 6.99 min) and 314.3 for clomipramine (internal standard, retention time 12.34 min). Concentrations are determined by linear curve fitting of peak areas.

Results

Analytical results are given in Table 3. Alcohol analyses revealed a blood ethanol concentration of 35 mg/dL (0.035% w/v), a vitreous ethanol concentration of 56 mg/dL (0.056% w/v) and a urine ethanol concentration of 153 mg/dL (0.153% w/v). Drug screens of the biological fluids and gastric contents revealed the presence of caffeine and clozapine and metabolites in all specimens. Initial thin layer drug screens on the specimins did not reveal fluoxetine or norfluoxetine due masking by the large concentrations of clozapine and its metabolites and the relative small concentrations of fluoxetine and norfluoxetine. Clozapine concentrations

TABLE 3—*Analytical results.*

Specimen	Concentration
Ethanol	
Blood	35 mg/dL (0.035% w/v)
Vitreous	56 mg/dL (0.056% w/v)
Urine	153 mg/dL (0.153% w/v)
Clozapine	
Plasma	4.9 μg/mL
Gastric	117.8 μg/mL (total 265 mg)
Urine	51.5 μg/mL
Fluoxetine	
Blood	0.7 μg/mL
Gastric	16.5 μg/mL (total 3.7 mg)
Urine	1.6 μg/mL
Norfluxetine	
Blood	0.6 μg/mL
Gastric	none detected
Urine	none detected

were determined to be 4.9 μg/mL in the plasma, 51.5 μg/mL in the urine and 117.8 μg/mL (total of 265 mg) in the gastric contents. Fluoxetine concentrations were determined to be 0.7 μg/mL in the blood, 1.6 μg/mL in the urine and 16.5 μg/mL (total of 3.7 mg) in the gastric contents. Norfluoxetine concentrations were determined to be 0.6 μg/mL in the blood and none was detected in the gastric contents or urine.

Pathological Findings

Complete autopsy revealed visceral vascular congestion with acute passive congestion of the liver and spleen. The deceased had pulmonary edema, paralytic ileus of the sigmoid colonic segment, esophagitis, gastroenteritis and chronic obstructive pulmonary disease with emphysema, fibrosis and mild anthracosis. Foci of scant subarachnoid, epicardial and myocardial haemorrhagia were noted. Minor cutaneous contusions and abrasions were observed. Immunological and histopathological analysis revealed combined toxic and viral hepatitis (hepatitis C positive) with hepatic cirrhosis. Microscopic evaluation of histological sections of the bowel revealed eosinophilia of the ileocecal valve region.

Discussion and Conclusions

The disproportionalities in ethanol concentrations between the blood, vitreous and urine specimens (vitreous/blood = 1.16 and urine/blood = 4.37) indicate that the deceased had consumed a significant amount of ethanol prior to his death [between 27.5 and 85.3 g (0.97 and 3.01 oz) of ethanol (two to six 340 g (12 oz) 4% beers) in this 100 kg (220 lb) individual], and that he was in a post ethanol absorption phase with approximately 4.1 h to metabolize the ethanol he consumed prior to his death. The low blood ethanol concentration at his time of death would have produced minimal dispositional alterations, but not have produced significant central nervous system impairment of vital physiological functions.

The blood fluoxetine concentration of 0.7 μg/mL would be considered a high therapeutic concentration (therapeutic: 0.03 to 0.5 μg/mL; toxic: not reported; and lethal: 1.3 to 6.8 μg/mL) (9). The blood norfluoxetine concentration of 0.6 μg/mL would be considered a high therapeutic concentration (therapeutic: 0.18 to 0.466 μg/mL; toxic: not reported; lethal: 0.9 to 5.0 μg/mL) (9). The amount of fluoxetine in the gastric contents (3.7 mg) and the lack of significant elevated concentrations of norfluoxetine in the blood and urine would indicate that the deceased had been taking the medication as prescribed (two 20 mg capsuls in the morning) and had not taken a large overdose amount prior to his death. Acute overdoses of up to 1500 mg of fluoxetine have produced relatively benign toxicities including lethargy, tachycardia and hypertension (19). Ingestion of 1 to 2 g of fluoxetine has been reported in adult fluoxetine fatalities (9). The possibility of postmortem redistribution of fluoxetine and norfluoxetine could not be determined since multiple site collection of blood was not performed.

The blood clozapine concentration of 4.9 μg/mL is high and would be considered in a lethal concentration range (therapeutic: 0.06 to 1.0 μg/mL; toxic: not reported; lethal: 1.6 to 7.1 μg/mL) (5). The amount of clozapine in the gastric contents (265 mg) would indicate that the deceased had also been taking the clozapine as prescribed (a 100 mg tablet twice a day and three 100 mg tablets at bedtime) and had not taken a large overdose amount prior to his death. While chronic clozapine therapy can produce adverse reactions of tardive dyskinesia and hematological disorders, acute overdose can produce hypotension, seizure, cardiac arrhythmias, respiratory depression, coma and death. Fatal overdoses have been involved with ingestions of up to 2000 mg of clozapine (5).

Clozapine has been combined with numerous other medications (including valproic acid, phenytoin, carbamazepine, fluoxetine, fluvoxamine, paroxetine and sertraline) to treat various neurological disease states (15). Combination of clozapine with other medications which also undergo significant cytochrome P_{450} biotransformations has resulted in elevated clozapine serum concentrations and increased incidences of clozapine toxicity (11,15). The combination of clozapine with this type of medication warrants careful clinical monitoring of the patient's blood clozapine concentration and dosage adjustments as needed. Search of the literature for toxic or fatal drug interactions from concomitant administration of clozapine or fluoxetine and ethanol revealed no reported cases to date. While the presence of ethanol in the biological fluids of the deceased indicate that he had consumed and was influenced by ethanol prior to his death, it is apparent that he lived a significant number of hours after ingestion of the alcohol and prior to his death. The combinations of clozapine/phenytoin and clozapine/fluvoxamine have produced elevated serum concentrations of clozapine which were fatal (16). The pathological findings of pulmonary edema, visceral vascular congestion, paralytic ileus, gastroenteritis and eosinophilia in this case are consistent with clozapine toxicity as well as the lethal concentration of clozapine found in the deceased. The accounting of the deceased's prescribed medications and the amounts of fluoxetine and clozapine found in the gastric contents of the deceased would indicate that this was not an acute massive overdose of either drug but an overdose that was the result of a fatal drug interaction of these two medications. The combined central nervous system, respiratory and cardiovascular depression of these drugs was sufficient to cause the death of this individual. The death was determined to be a clozapine overdose due to a fatal drug interaction.

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