CASE REPORT

Gary W. Kunsman,[1,2] Ph.D.; Cynthia M. Kunsman,[2] N.D.; Carolyn L. Presses,[1] B.S.; Jan C. Garavaglia,[1] M.D.; and Norma J. Farley,[1] M.D.

A Mixed-Drug Intoxication Involving Venlafaxine and Verapamil*

REFERENCE: Kunsman GW, Kunsman CM, Presses CL, Garavaglia JC, Farley NJ. A mixed-drug intoxication involving venlafaxine and verapamil. J Forensic Sci 2000;45(4):926–928.

ABSTRACT: This case report describes the suicide of a 52-year-old woman whose cause of death was attributed to a mixed-drug intoxication involving venlafaxine and verapamil. Venlafaxine is prescribed for the treatment of depression and should be used with caution in patients with cardiovascular disease. Verapamil is a calcium channel blocker primarily used for treatment of cardiovascular disorders. The following drug concentrations were determined in postmortem fluids: verapamil—3.5 mg/L (femoral blood), 9.4 mg/L (subclavian blood), and 1.0 mg/L (vitreous fluid); norverapamil—1.0 mg/L (femoral blood), 2.1 mg/L (subclavian blood), and 0.20 mg/L (vitreous fluid); verapamil and norverapamil could not be detected in bile or urine due to the high levels of erythromycin present; venlafaxine—6.2 mg/L (femoral blood), 8.6 mg/L (subclavian blood), 5.3 mg/L (vitreous fluid), 54.0 mg/L (bile), and 72.3 mg/L (urine); and O-desmethylvenlafaxine—5.4 mg/L (femoral blood), 8.3 mg/L (subclavian blood), positive (vitreous fluid), 29.2 mg/L (bile), and 9.5 mg/L (urine). The cause of death was determined to be a mixed-drug intoxication resulting from an overdose of verapamil and venlafaxine. The manner of death was determined to be suicide.

KEYWORDS: forensic science, verapamil, venlafaxine, drug overdose, mixed-drug intoxication

Venlafaxine, (1-[2-(dimethylamino)-1-(4-methoxy-phenyl) ethyl)] cyclohexanol hydrochloride), is marketed by Wyeth-Ayerst Laboratories as Effexor® and is prescribed for the treatment of depression. Venlafaxine is a phenethylamine derivative and is chemically unrelated to tricyclic, tetracyclic, selective serotonin reuptake inhibitors, or other antidepressants. It is metabolized extensively in the liver by demethylation via the cytochrome P450 isozyme 2D6 (CYP2D6) to an active metabolite, O-desmethylvenlafaxine (ODV), and a number of inactive metabolites such as mono-N-desmethylvenlafaxine and di-N-desmethylvenlafaxine. Venlafaxine is also a weak inhibitor of both CYP2D6 and CYP3A4. The mechanism of action of venlafaxine and its active metabolite is believed to be due to the potentiation of neurotransmitter activity in the central nervous system (CNS). These compounds are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. The initial recommended dose of venlafaxine is 75 mg/day administered in two to three divided doses. The dose may be increased, if necessary, in increments of 75 mg/day at intervals of four or more days to a total dose of 225 mg/day. Steady-state plasma concentrations of both venlafaxine and ODV were reached in three days with chronic dosing. Subjects on a chronic dosing schedule receiving 150 mg venlafaxine/day had plasma venlafaxine concentrations of 70 ng/mL and ODV concentrations of 254 ng/mL. Venlafaxine has an apparently high therapeutic index, but overdose may result in hypertension, cardiac arrhythmias, seizures, and coma. Adverse side effects from venlafaxine administration include nausea, vomiting, dizziness, nervousness, anxiety, tremor, and blurred vision (1–4).

Two reports of overdose in which the patients survived the ingestion of 2.75 g and 2.5 g of venlafaxine resulted in peak plasma concentrations of 6.24 and 2.35 mg/L venlafaxine and 3.37 and 1.3 mg/L ODV, respectively. No other drugs were involved in either of these ingestions (2,4). A report of a mixed-drug intoxication in which the individual survived following the ingestion of 4.5 g of venlafaxine resulted in a peak plasma concentration of 6.1 mg/L venlafaxine and 1.8 mg/L ODV. That individual was reported to have ingested diphenhydramine and thiothixene along with venlafaxine in a suicidal gesture (5). Several accounts of fatalities attributed to venlafaxine overdose report postmortem peripheral blood concentrations ranging from 16 to 78 mg/L venlafaxine and a single case reported an ODV concentration of 7.1 mg/L. Accounts of mixed-drug overdose deaths involving venlafaxine report postmortem peripheral blood concentrations ranging from 0.82 to 46 mg/L venlafaxine and 0.30 to 7.1 mg/L ODV (6–11).

Verapamil, a benzenoacetonitrile calcium channel blocker, is a synthetic papaverine derivative introduced as an antianginal agent in 1962. It has subsequently been identified as beneficial for the treatment of arrhythmias and essential hypertension, and is also indicated for the treatment of these conditions. Verapamil is extensively metabolized by the cytochrome P450 isozyme 3A4 (CYP3A4) to a single active metabolite, norverapamil, and at least two inactive metabolites, desalkyl- and bis-desalkylverapamil.

The mechanism of action of verapamil and its active metabolite is the result of the inhibition of transmembrane calcium flux in ex-

[1] Bexar County Medical Examiner's Office and Forensic Toxicology Laboratory, San Antonio, TX 78229.

[2] For Tox Consulting, 7028 Bandera Rd., San Antonio, TX 78238.

* Presented in part at the 1999 annual meeting, American Academy of Forensic Science.

Received 8 June 1999; and in revised form 22 Oct. 1999; accepted 25 Oct. 1999.

citable tissues. The contractile action of cardiac and vascular smooth muscle is dependent upon the movement of extracellular calcium into these cells through calcium ion channels. The resultant pharmacological effect of this inhibition of calcium ions across the cellular membranes is depression of cardiac and smooth muscle contractility, impulse formation (automaticity), and conduction velocity. The recommended initial dose of verapamil for angina is 80 to 120 mg three times/day. The dosage range for the treatment of arrhythmias is 240 to 320 mg/day in three or four divided doses (atrial fibrillation) and 240 to 480 mg/day in three or four divided doses (paroxysmal supraventricular tachyarrhythmia). The initial dose of verapamil in the treatment of essential hypertension is 80 mg three times/day. Peak blood concentrations of verapamil and norverapamil in patients receiving chronic therapy with 480 mg verapamil/day averaged 0.355 and 0.207 mg/L, respectively, 1 h after a 160-mg dose. Side effects of verapamil use include nausea, weakness, dizziness, bradycardia, hypotension, and atrioventricular block. Blood concentrations in 19 deaths due to acute verapamil overdose ranged from 0.9 to 85 mg/L with an average concentration of 11 mg/L (2,4,12).

Case History

A 52-year-old white female was found unresponsive in her residence by the schoolchildren for whom she acted as an after-school babysitter. Three suicide notes and an empty pill bottle were found at the scene. The prescription bottle was for Effexor® (venlafaxine), 37.5 mg with a total count of 60 tablets, issued to a woman not the decedent. The decedent's only known prescription, found elsewhere in the house, was for erythromycin. The decedent had a previous history of suicide threats and suicide attempts. Her previous attempts were by means of carbon monoxide and cutting her wrists. There were no signs of forced entry into the house and no apparent trauma noted to the body.

Postmortem Examination

The body was that of a well-developed, white female with an appearance consistent with the age of 52 years. The external examination revealed horizontal, well-healed scars on both wrists; three scars on the right wrist and a single scar on the left wrist. Two tattoos were also noted, one on the shoulder and what appeared to be initials on the right hand. There were no needle tracks apparent. The heart weighed 470 g and sectioning of the coronary vessels revealed severe calcific atherosclerosis. Sectioning of the heart also revealed evidence of a recent myocardial infarction; no evidence of previous infarction was noted. The lungs had a combined weight of 1800 g and exhibited marked congestion and edema within all lobes. The liver and kidneys also exhibited mild congestion of the parenchyma. A diffuse reddening of the stomach mucosa with numerous hemorrhagic petechiae was noted, but no food material or tablet fragments were identified within the stomach or small intestine.

Materials and Methods

Materials

All solvents were Fisher pesticide grade and chemicals were Baker reagent grade. Verapamil was purchased from Aldrich Chemical Co., norverapamil was purchased from Alltech/Applied Science, venlafaxine was a gift from Wyeth-Ayerst Laboratories, and O-desmethylvenlafaxine was a gift from the Office of the Chief Medical Examiner, State of Maryland. TDx® reagent packs (phenytoin and barbiturates), calibrators, and controls were purchased from Abbott Laboratories. The TDx® was operated in accordance with the manufacturer specifications.

Analysis

Samples of femoral blood, subclavian blood, vitreous fluid, bile, and urine were submitted for routine toxicological analysis. Specimens were screened for the presence of ethanol, methanol, isopropanol, and acetone by gas chromatography (GC) (femoral blood and vitreous fluid), phenytoin and phenobarbital by TDx® fluorescence polarization immunoassay (FPIA) (urine), and alkaline drugs by GC (femoral blood). Verapamil, venlafaxine, and their metabolites were the only drugs identified on the initial toxicology screens.

Results and Discussion

Verapamil, venlafaxine, and their respective metabolites were identified using a modified Foerster alkaline drug screen procedure (13). The initial alkaline drug screen was performed using a femoral blood sample. Femoral blood extracts were analyzed using a Hewlett-Packard 6890 GC equipped with an HP-1 (Hewlett-Packard) capillary column and a flame ionization detector (FID). Confirmation was performed on a Hewlett-Packard 5972 gas chromatograph/mass selective detector (GC/MSD) operated in the full-scan electron impact mode.

Verapamil, norverapamil, venlafaxine, and O-desmethylvenlafaxine were well separated using the HP-1 capillary column. Mono-N-desmethylvenlafaxine and N-desalkylverapamil, minor metabolites with little pharmacologic activity, co-eluted using this column under the alkaline drug screen operating conditions. Additional specimens were subsequently analyzed using the alkaline drug procedure and the concentrations determined are detailed in Table 1. Concentrations were calculated using linear regression analysis based on 3-point calibration curves generated by plotting

TABLE 1—*Venlafaxine and verapamil concentrations.*

	Drug Concentration (mg/L)			
Specimen	Verapamil	Norverapamil	Venlafaxine	O-Desmethylvenlafaxine
Femoral blood	3.5	1.0	6.2	5.4
Subclavian blood	9.4	2.1	8.6	8.3
Vitreous fluid	1.0	0.20	5.3	Positive (qns†)
Bile	ND*	ND*	54.0	29.2
Urine	ND*	ND*	72.3	9.5

* Verapamil and norverapamil could not be detected due to the presence of high concentrations of erythromycin.
† O-desmethylvenlafaxine was identified in the vitreous humor, but the quantity was insufficient for quantitation.

the ratio of the GC peak area for the analytes of interest to the area of the internal standard, methapyrilene. Calibrators were prepared by spiking negative control bovine blood with methanolic drug standards.

Erythromycin, a macrolide antibiotic, was detected by GC and confirmed by GC/MSD during the alkaline analysis of the bile and urine samples. The amount of erythromycin in these samples was so great that it was not possible to detect the presence of verapamil or norverapamil. Multiple peaks with mass spectra consistent with erythromycin were detected in the bile and urine with retention times ranging from approximately 6.5 min throughout the remainder of the chromatographic run; 12.5 min total run time. There was no significant amount of erythromycin detected in the blood samples or in the vitreous fluid sample, therefore, no interference with the quantitation of verapamil or norverapamil was suspected. Although erythromycin is a CYP3A4 substrate and inhibitor and its use is associated with prolongation of the QT interval, its presence in this case was not considered to be relevant due to its low concentration in the blood (12).

Conclusion

Based on the autopsy and toxicological findings the medical examiner determined the cause of death to be a mixed-drug intoxication. The intoxication resulted from the decedent taking an overdose of verapamil and venlafaxine. The intent of the decedent to take an overdose of her medications was apparent from the suicide notes found at the scene. Significant postmortem findings were the elevated blood levels of these two drugs and their active metabolites and acute passive congestion of the lungs, kidneys, and liver. The decedent also had severe coronary atherosclerosis, a recent myocardial infarction of the posterior left ventricle, and pulmonary edema. This death may be primarily attributable to the cardiotoxicity associated with a verapamil overdose because there is only a minimal metabolic interaction between verapamil and venlafaxine. Although verapamil is a substrate for the CYP3A4 isozyme, it is not contraindicated with CYP3A4 inhibitors such as erythromycin and venlafaxine, a weak CYP3A4 inhibitor. The elevated venlafaxine concentration, however, must be considered as a contributory factor in this mixed-drug fatality, because this drug is supposed to be used with caution in patients with coronary heart disease and elevated blood pressure; this warning is included in the drug literature. The manner of death in this case was determined to be suicide.

References

1. Wyeth-Ayerst Laboratories, Philadelphia, PA: Effexor® package insert, 29 December 1993.
2. Olin BR, editor-in-chief. St. Louis, MO: Drug facts and comparisons®, 1996.
3. Goldberger BA. Venlafaxine, analyte of the month. AACC TDM/Tox Jan. 1995;16(1).
4. Baselt RC, Cravey RH. Disposition of toxic drugs and chemicals in man. 4th ed. Foster City, CA: Chemical Toxicology Institute, 1995.
5. Fantaskey A, Burkhart KK. A case report of venlafaxine toxicity. Clin Toxicol 1995;33(4):359.
6. Parsons AT, Anthony RM, Meeker JE. Two cases of venlafaxine poisoning. J Anal Toxicol 1996;20:266–7.
7. Jaffe PD, Batziris HP, van der Hoeven P, DeSilva D, McIntyre IM. A study involving venlafaxine overdoses: comparison of fatal and therapeutic concentrations in postmortem specimens. J Forensic Sci 1999;44(1):193–219.
8. Levine B, Jenkins AJ, Queen M, Jufer R, Smialek JE. Distribution of venlafaxine in three postmortem cases. J Anal Toxicol 1996;20:502–50.
9. Budd RD, Anderson DT. Postmortem tissue distribution of venlafaxine: six case studies (abstract). 1996 Society of Forensic Toxicologists Annual Meeting.
10. Wu Chen NB, Donoghue ER, An TL, Choi E, Jones NL, Mittel KA, et al. Venlafaxine-related deaths—postmortem tissue distribution (abstract). 1996 American Academy of Forensic Sciences Annual Meeting.
11. Banham NDG. Fatal venlafaxine overdose. Med J Aust 1998;169:445–6.
12. Michalets EL. Reviews of therapeutics, update: clinically significant cytochrome P-450 drug interactions. Pharmacotherap 1998;18(1):84–112.
13. Foerster EH, Hackett D, Garriott JC. A rapid comprehensive screening procedure for basic drugs in blood or tissue by gas chromatography. J Anal Toxicol 1972;2:50.

Additional information and reprint requests:
Gary W. Kunsman, Ph.D.
Chief Toxicologist
Bexar County Medical Examiner's Office
7337 Louis Pasteur
San Antonio, TX 78229-4565