CASE REPORT

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Toxicological Findings in a Fatal Overdose of Verapamil

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ABSTRACT: Presented is a case where the death was attributed to the deliberate ingestion of an overdose of verapamil (V). Blood, urine, and gastric concentrations of the drug were determined by gas chromatography with nitrogen phosphorus detection (GC-NPD). Identification of norverapamil (NV) was made. A presumptive identification of *o*-demethylnorverapamil (DNV) was also made.

KEYWORDS: toxicology, suicide, verapamil, norverapamil, *o*-demethylnorverapamil

Verapamil (V) (Fig. 1) is a calcium channel antagonist often used to control supraventricular tachyarrhythmias and angina pectoris [*1*]. Its effects have been fully investigated and reported by Rosen et al. in 1975 [*2*]. Oral doses undergo extensive first pass metabolism [*3*] and peak plasma concentrations are generally less than 0.4 mg/L [*4*], even after chronic therapy of as much as 480 mg/day. Although there have been reports of accidental overdoses in children [*5*], and suicidal attempts in young adults [*6,7*], documented deaths attributable to verapamil ingestion are rare and patients have survived oral doses as large as 5.6 g [*8*].

Case Report

The decedent, a 22-year-old white male had a history of suicide attempts by drug ingestion. He was found dead on the couch at his family home and was last seen alive the previous evening. Also discovered at the scene were two suicide notes in the decedent's handwriting and an empty prescription bottle of verapamil. The prescription was in the name of the young man's father who had a chronic heart condition.

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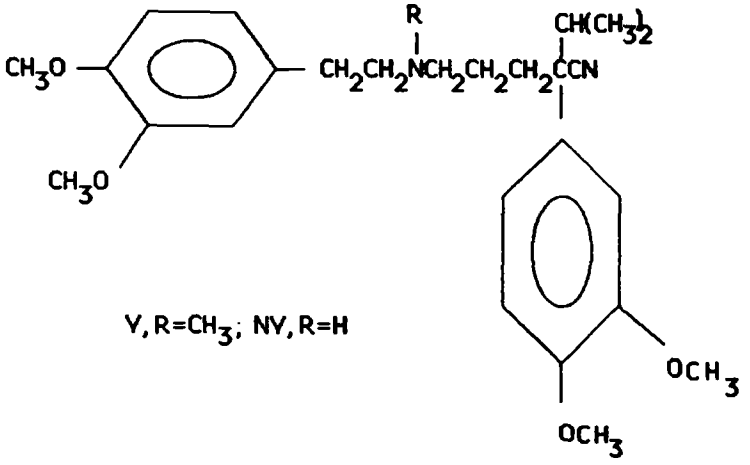

FIG. 1—*Structure of verapamil.*

At autopsy the body showed no signs of external injury. Internally, there was acute hemorrhagic gastritis and the stomach contained 200 mL of bloody fluid with small yellow granules; however, no intact tablets were present. The bladder contained only 5 mL of urine. There were no other significant findings.

Experimental Procedure

Instrumentation

A Hewlett-Packard 5730A gas chromatograph (GC) equipped with nitrogen phosphorus (NP) detectors was used for the presumptive identification of basic drugs in the blood and for the quantitation of V in the biological fluids.

Confirmation of V and metabolites was performed with a Hewlett-Packard 5970A gas chromatograph-mass spectrometer (GC-MS) utilizing electron impact (EI) ionization.

Screening-Quantitation

Initial screens for drugs of abuse by radioimmunoassay and commonly encountered acidic and neutral drugs by gas chromatography with flame ionization detection (GC FID) were negative. However, on analysis of the blood for basic drugs by GC-NPD, one major and two minor peaks eluting at relative retention times of 1.24, 1.31, and 1.41 respective to flurazepam were detected. Screening was performed on a 1.2-m by 2-mm inside diameter (ID) silanized glass column packed with 1.5% OV-17 on Gas Chrom Q 100–120 mesh. Following an initial hold for 2 min, the oven temperature was programmed from 130 to 280°C at 8°/min. The final temperature was maintained for 8 min. Quantitation of V was achieved using the same column at a temperature of 270°C.

Results and Discussion

A number of high performance liquid chromatographic (HPLC) [*9*], GC-MS [*10*], and GC [*9,11*] methods have been described to determine V in biological samples. Quantitations were performed by the method of Loi et al. [*11*]. This is a modification of the methods de-

scribed by Nelson et al. [*12*] and McAllister [*13*], which employs an internal standard and an alkaline extraction of the sample with heptane. No further treatment of the heptane fraction was needed before evaporation, reconstitution, and injection onto the GC column. The quantitation of V was linear from 0.05 to 1.0 mg/L. After appropriate dilutions, the blood was found to contain 9.3 mg/L, the urine 1.4 mg/L, and the gastric contents 180 mg total of verapamil. Deaths caused by ingestion of verapamil, as stated are rare. Table 1 shows results from two reported cases. Case 1 was a 40-year-old female who committed suicide [*9*]. Liver, kidney, blood, and gastric samples were analyzed. Data collected from a second documented death [*8*] as well as the present case are also summarized in the table. The blood concentration in this case was higher than that reported in Case 1 and greater than twice that found in Case 2. Neither previous case had urine for analysis.

The metabolism of V in man after oral doses has been described by Eichelbaum et al. [*3*]. He noted that V undergoes extensive first pass metabolism and only 3 to 4% of the parent drug is recovered in urine, which may partially explain the relatively low urine concentration found in this case. Additionally, death was rapid as evidenced by the gastric concentration of V, so complete absorption and metabolism of the drug did not occur.

The major metabolite of V, norverapamil (NV), (Fig. 1), has been identified in urine [*3*] and plasma [*9*] after acute doses. In the case reported here, NV was identified by GC-MS in the decedent's blood, however, the limited volume prohibited identification of NV in the urine. Although reference material was not available for quantitation of NV, the intensity of the NV peak from blood on GC and GC-MS was approximately 10 to 25% of the V peak. This might be used as an approximation of the NV concentration. Present also in the blood

TABLE 1—*Postmortem tissue concentrations of verapamil.*

	Urine, mg/L	Liver, mg/kg	Kidney, mg/kg	Blood, mg/L	Gastric, mg Total
Case 1	...	165	28	8.8	590 [*9*]
Case 2	...	13	10	4.0	... [*8*]
Present case	1.4	...	...	9.3	180

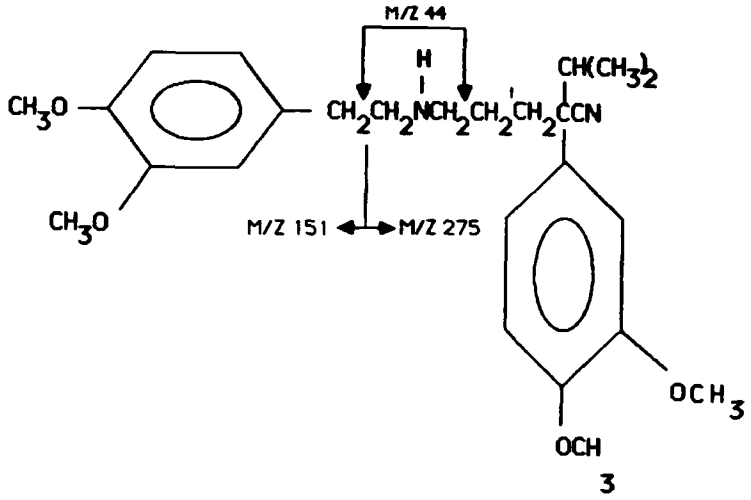

FIG. 2—*Structure of DNV and fragmentation.*

at an even lower concentration (approximately 1% of the V response) was a peak whose EI mass spectrum was consistent with that described by Eichelbaum [*3*] as *o*-demethylnorverapamil. The molecular weight of DNV (Fig. 2) is 426 AMU. Fragmentation should be favored between the alpha and beta carbons near the amino nitrogen and between the benzylic carbon especially C7-C8 (Fig. 2). Ions consistent with those expected m/z (44, 275, and 151 AMU) were present in the spectrum generated. The sum of the two most intense ions (275 + 151) result in the molecular weight. However, because of the trace quantity present, only the major ions were observed which precluded a positive identification. The detection of DNV is an unexpected finding since it is theorized that it would be rapidly conjugated and not found as the free compound in blood [*3*].

Conclusion

Presented has been one of the few documented cases of death as a result of verapamil ingestion. The blood concentration of V detected was consistent with those found in previous verapamil poisonings. Also detected, were NV and possibly DNV, both of which are pharmacologically active and could contribute to the toxicity of the parent drug.

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