Case Report

Lethal Diltiazem Poisoning

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Abstract

A 60-year-old man presented to an emergency department 2 h after the ingestion of 8 g of diltiazem (about 40 slow-release capsules, 200 mg/each) in a suicide attempt. The subject was treated with a gastric lavage and activated charcoal; then, a temporary transvenous pacing was also inserted. Despite emergency pharmacological treatment, the subject died about 20 h after ingestion. Postmortem diltiazem and desacetyl-diltiazem concentrations, measured by gas chromatography–mass spectrometry, were as follows: 31.1 mg/mL diltiazem and 9.7 mg/mL desacetyl-diltiazem in blood; 33.1 mg/g diltiazem and 13.7 mg/g desacetyl-diltiazem in brain; 179.5 mg/g diltiazem and 47.5 mg/g desacetyl-diltiazem in lung; 41.8 mg/g diltiazem and 10.1 mg/g desacetyl-diltiazem in heart; 182.1 mg/g diltiazem and 47.3 mg/g desacetyl-diltiazem in liver; 49.2 mg/g diltiazem and 22.6 mg/g desacetyl-diltiazem in kidney; and 294.9 mg/mL diltiazem and 29.4 mg/mL desacetyl-diltiazem in bile. It is interesting to note that although several cases of acute diltiazem poisoning have been reported in literature, only a few were lethal. Diltiazem concentrations found in our case are notably higher than those reported in other studies, including those in which diltiazem ingestion resulted in the death of the patient. Notably, in many of these latter cases, the doses of diltiazem ingested were higher than those taken by our patient.

Introduction

Diltiazem is a calcium-channel blocker currently used in the treatment of angina pectoris, hypertension, and cardiac arrhythmias. Because of the frequent prescription of calcium-channel blocker in clinical practice, this class of drugs is often the cause of severe poisoning, both acute and chronic, due to overdose. Although in literature various cases of acute poisoning by diltiazem have been reported (1–9), those with a lethal outcome are relatively rare (10–16) and are sometimes due to concomitant assumption of alcohol or other drugs (12–14,17–19).

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Because of the generally favorable evolution, the case reports relative to diltiazem overdose are prevalently focused on the clinical and therapeutic management. Therefore, even in lethal cases there are few data available on tissue concentrations of the drug.

Here is reported the unusually high diltiazem and desacetyl-diltiazem concentrations detected in various tissues and biological fluids in a case of acute lethal poisoning.

Case History

A 60-year-old male, treated with nitrates, calcium-antagonists, and anticoagulants for a chronic cardiopathy, ingested about 40 capsules (200 mg/each) of slow-release diltiazem in a suicide attempt. On admission, 2 h after ingestion, the subject underwent a gastric lavage and was then hospitalized in the intensive coronary care unit where a transvenous temporary pacemaker was implanted. His clinical conditions were continuously monitored and therapy was started. At hospitalization, the subject was conscious, lucid, and able to provide the hospital staff with information about the type and quantity of the drug ingested. However, despite intensive hospital care, the patient's clinical condition progressively deteriorated, and death occurred about 20 h after diltiazem ingestion.

Experimental

Procedure

A blood sample, directely collected from the heart cavity, was preliminarly assayed for basic and neutral organic drugs using a toluene/isoamyl alcohol (100:1.5) extraction and gas chromatographic–mass spectrometric (GC–MS) analysis. The sample analyzed showed the presence of diltiazem and excluded the concomitant presence of other drugs or toxic substances. Ethyl alcohol was not found. All volatile substances were tested by headspace GC.

The diltiazem and desacetyl-diltiazem concentrations were

measured on viscera (brain, lung, heart, liver, and kidney) and biological fluids (blood and bile) collected during autopsy. The analysis was performed as following: 1 g of each tissue specimen and 1 mL of blood and bile were homogenized with 1 mL of distilled water and 1 mL of phosphate buffer at pH 7.5. Internal standard (50 mg promazine) was added to each sample. After extraction with 4 mL chlorobutane, the organic phases were collected and extracted with 2 mL of sulfuric acid 0.2N; after centrifugation, the aqueous phase was collected, alkalinized with phosphate buffer (pH 8.5) to pH 7.5, and extracted with 2 mL of ethyl acetate. Then the organic phase was dried under a nitrogen flow. N,O-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) + 1% trimethylchlorosilane (TMCS) (50 mL) was added to the dry extract, which was then sealed and heated at 70°C for 30 min. The samples were analyzed by GC–MS. The derivatization was necessary for the GC separation of diltiazem from its metabolite desacetyl-diltiazem.

Calibration curves were constructed by analyzing blank blood samples added to diltiazem (0, 10, 50, 100, 200, and 300 mg/mL), desacetyl-diltiazem (0, 5, 10, 25, and 50 mg/mL), and internal standard (promazine 50 mg/mL).

Apparatus

The GC–MS analysis was performed using a Hewlett-Packard model 5890 (series II) GC coupled to a 5989B mass selective detector. An HP Ultra-2 crosslinked fused-silica capillary column (12 m × 0.20-mm i.d.) with a 0.33-mm film thickness was linked to the mass selective detector through a direct capillary interface. The injector and interface temperatures were 280°C. The oven temperature was maintained at 70°C for 2 min, then programmed to 200°C at 50°C/min, to 260°C at 5°C/min, to 290°C at 10°C/min, and maintained at 290°C for 2 min. Source temperature was 230°C, and quadrupole temperature was 100°C. The carrier gas was helium with a flow rate of 1 mL/min.

Results and Discussion

The concentrations of diltiazem and desacetyl-diltiazem found in the viscera and biological liquids are shown in Table I.

On the basis of our findings, the cause of death was exclusively related to acute diltiazem poisoning. It was possible to exclude that other toxic substances played a role, even marginal, in causing the death.

Table I. Concentrations of Diltiazem and Desacetyl-diltiazem Found in Viscera and Biological Fluids

Sample	Diltiazem	Desacetyl-diltiazem
Blood (mg/mL)	31	9.7
Brain (mg/g)	33.1	13.7
Lung (mg/g)	179.5	47.5
Heart (mg/g)	41.8	10
Liver (mg/g)	182	47.3
Kidney (mg/g)	49.2	22.6
Bile (mg/mL)	294.9	29.4

The importance of this case rests on the concentrations observed both in the viscera and in the biological fluids. Generally, the therapeutic range of blood diltiazem concentrations is about 0.1 to 0.3 mg/mL (6,13). Higher diltiazem blood levels are closely related to symptomatologic patterns; in fact, an increase of drug concentration is associated with a concomitant worsening of clinical conditions. It has been reported that with blood levels up to 0.5 mg/mL first-degree heart block and sinus bradycardia may be observed in an asymptomatic patient; from 0.5 to 1 mg/mL, hypotension has been observed; and from 1 to 1.5 mg/mL, conduction abnormalities and hypotension have been observed. At levels above 1.5 mg/mL, cases require temporary pacemakers; at levels above 6.1 mg/mL, most patients die (13). Constant monitoring of hematic diltiazem levels would allow the verification of the quality and efficacy of the therapeutic protocols used; the persistence of high levels, despite the use of therapeutic protocols, could be predictive of lethality.

Table II illustrates the concentrations of diltiazem reported by other authors in fatalities caused solely by this drug, and Table III shows the concentrations of diltiazem and other drug(s) found in further reported fatalities. The diltiazem concentrations found in our case were clearly higher than those generally believed to be lethal, and were higher than those found in analogous cases of lethal overdose (10–16). The overall high levels of diltiazem and desacetyl-diltiazem found in all the samples examined (see Table I) could be ascribed to a substantially higher than normal absorption of this drug. In fact, in several cases in which ingestion of diltiazem at doses higher (1,4,21) than those (about 8 g) taken by the subject of this study, complete remission has been observed; in these cases, however, blood diltiazem concentrations were lower. The high levels of diltiazem were probably due to two factors: (1) inefficiency of gastric lavage that caused a high absorption of the drug and (2) low blood pressure from diltiazem caused slower metabolism and elimination of the drug.

Finally, an insidious side effect associated with the therapeutic use of calcium-channel blockers should be considered.

Table II. Concentrations of Diltiazem Reported by Other Authors in Two Fatal Cases of Solely Diltiazem Overdose*

Reference	Sample	Diltiazem (mg/mL or mg/g)
Kaliciak et al. (1992)	Blood	6.7
	Liver	79
	Urine	5.4
	Vitreous humor	5.5
Della Casa et al. (1998)	Blood	12
	Liver	2.6
	Brain	6.2
	Bile	18.3
	Urine	2.6
	Gastric	8.9

* Desacetyl-diltiazem was not assayed.

Table III. Concentrations of Diltiazem and Other Drug(s) Found in Viscera and Biological Fluids in Reported Fatalities*

Reference	Sample	Diltiazem (μg/mL or μg/g)	Other Drug(s)
Holzbecher et al. (1988)	Blood:	11.0	Ethanol, 0.16 (g/100 mL)
	Urine:	11.0	Ethanol, 0.29 (g/100 mL)
	Vitreous humor:	3.5	
	Bile:	180	
	Gastric:	600 (mg total)	
Wiese et al. (1988)	Blood:	15.0	Ethanol, 0.117 (g/100 mL)
	Urine:	60.0	Ethanol, 0.148 (g/100 mL)
	Liver:	41.0	
	Gastric:	120 (mg total)	
Garriot et al. (1991)	Blood:	9.52	Diazepam, 0.63 (μg/mL) Nordiazepam, 0.02 (μg/mL)
Kaliciak et al. (1992)	Blood:	1.8	Ethanol, 0.12 (g/100 mL)
Kaliciak et al. (1992)	Blood:	1.8	Ethanol, 0.08 (g/100 mL) Acetaminophen, 290 (μg/mL) Salicylates, 300 (μg/mL) Metoprolol, 33 (μg/mL) Metoclopramide, 1.0 (μg/mL)
Kalin et al. (1994)	Blood:	6.9	Ethanol, 0.182 (g/100 mL) Propanolol, trace
	Urine:	4.7	Ethanol, 0.251 (g/100 mL)
Engelhart et al. (1997)	Blood:	5.9	Pentoxifylline, 6.3 (μg/mL)
	Urine:	11.7	Pentoxifylline, 0.8 (μg/mL)
	Gastric (200 mL):	2.8	Pentoxifylline, 0.2 (μg/mL)
	Bile:	4.0	Pentoxifylline, 2.2 (μg/mL)
	Liver:	Present	Pentoxifylline, Present
	Spleen:	Present	Pentoxifylline, Present
	Kidney:	Present	Pentoxifylline, Present

* In the case reported by Engelhart et al. (19), desacetyl-diltiazem was detected but not quantitated.

Various studies have shown that cardiopathic patients often develop mood disorders, especially depression (22–24); depressive states have also been observed in subjects under calcium-channel blockers treatment (e.g., diltiazem, verapamil, and nifedipine [25–28]). Suicide is often consequent to a depressive state. It has indeed been suggested that depression related to cardiovascular diseases and to calcium-channel blocker treatment may increase the risk of suicide (28). More specifically, the suicide risk in users of calcium-channel blockers has been estimated to be about fivefold compared with the risk in non-users treated with other anti-hypertensive agents (28).

Because many suicide attempts have been reported in subjects treated with calcium-channel blockers (1,2,4,7,14,17,20), toxicological evaluation should be recommended in all cases of cardiac death, especially in those related to cardiopathic patients treated with these drugs.

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Manuscript received May 29, 2001;
revision received November 12, 2001.