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5-Year Retrospective Review of Diltiazem Associated Deaths

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Research Article

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ABSTRACT

Diltiazem is a calcium channel blocker that is prescribed for the treatment of hypertension, angina pectoris, dysrhythmia and migraines. It is also a common adulterant of illicit drugs, such as cocaine. Acute diltiazem toxicity is infrequently associated with death. We report a retrospective review of all diltiazem related deaths over a 5 year period in Ontario. Our method included review of the history, post-mortem and toxicology reports to gather information about psychosocial issues, access to a prescription of diltiazem, major autopsy findings, manner of death, blood concentrations of diltiazem and its metabolite. From 2010 to 2014 there were 18 diltiazem related deaths, in which 10 deaths were attributed solely to diltiazem. The highest concentration of diltiazem was 18 mg/L in the post-mortem peripheral blood. Lower levels were observed in 2 cases (1.5 and 0.32 mg/L) in which the admission blood was tested up to 1 week after having been drawn. In 12 cases, a prescription to the deceased was documented. The most common cause of death was attributed to drug toxicity. This was largely due to the common presence of the detection of citalopram. No illicit drugs were detected. There was a female predominance (11:7=f:m) and deaths commonly involved an older age group (median: 65 years). The major autopsy findings in nearly all cases (16 cases) demonstrated structural heart disease, including cardiomegaly, ventricular hypertrophy and severe atherosclerotic plaques in the coronary arteries. This underlying structural heart disease suggests an indication for the diltiazem prescription. Additional findings at autopsy included the presence of pill matter within the stomach contents in half of the cases. The most common manner of death was suicide (10 cases). The high frequency of suicide was supported with the high incidence of depression/suicidal ideation in this series. This is the largest reported case series to review diltiazem-associated deaths. This case series indicates that an advanced forensic toxicologic overview is needed as part of a comprehensive medicolegal death investigation. Otherwise both the cause and manner of death may be misattributed to a natural heart disease, which is often seen in this older age group.

INTRODUCTION

Diltiazem is a calcium channel blocker that acts to inhibit calcium influx into cells via “slow channel” membrane pore thereby inhibiting excitation-contraction coupling [1]. Its affinity for conductive and vascular tissues makes diltiazem the prescription of choice for the treatment of hypertension, angina pectoris and dysrhythmia. It is also a common adulterant of illicit drugs, such as cocaine.

Diltiazem is metabolized by the liver via acetylation, N and O-demethylation and conjugation [1]. Metabolization follows first order kinetics [1]. Its main active metabolite is desacetylditiazem, which is a coronary artery vasodilator and has 40% activity of

its parent compound [1]. The previously recorded half-lives of diltiazem have been between 4.0-10.2 h [1]. In addition, rigorous conditions for the transport and treatment of the blood samples have been recommended to achieve accurate determination, including immediate centrifugation after collection or keeping the sample on ice for 1 h to prevent significant degradation and to ensure accurate measurements [2]. Alternatively, the sample should be immediately frozen at -80 °C and stored for up to 5 weeks, or frozen at -20 °C and stored for up to 3 weeks [2]. Although acute diltiazem toxicity has been known to be infrequently associated with death, diltiazem overdose is being seen more often.

METHOD

We report a retrospective review of all diltiazem related deaths over a 5 year period (2010-2014) in Ontario. Our method included review of the history, post-mortem and toxicology reports to gather information about psychosocial issues, access to a prescription of diltiazem, major autopsy findings, manner of death, blood concentrations of diltiazem and its metabolite in admission samples, post-mortem heart and peripheral blood. Blood samples are routinely refrigerated in plastic tubes with NaF (sodium fluoride) and diltiazem levels were detected using the LC-MS detection method.

Table 1. Summary of results of 18 cases of diltiazem related deaths.

Epidemiology			
	Sex	Male	7
		Female	11
	Age		41-100
Cause Of Death			
	Diltiazem only		10
	Mixed drug toxicity including diltiazem		8
Post mortem findings			
	Structural heart disease		16
	Cardiomegaly with left ventricular hypertrophy		14
	Severe coronary artery atherosclerosis		6
	Moderate coronary artery atherosclerosis		4
	Mild coronary artery atherosclerosis		2
	Pacemaker present		3
	Presence of pill matter within the stomach		9
Manner of death			
	Suicide		10
	Accident		5
	Undetermined		3

RESULTS

From 2010 to 2014, there were 18 diltiazem related deaths **(Table 1)**, in which 10 deaths were attributed solely to diltiazem. The highest concentration of diltiazem was 18 mg/L in the post-mortem peripheral blood. Lower levels were observed in 2 cases (1.5 and 0.32 mg/L) in which the admission blood was tested up to 1 week after having been drawn. In 12 cases, a prescription to the deceased was documented. The most common causes of death were drug toxicity in which another prescription drug was detected, with citalopram being the most frequently detected medication. No illicit drugs were detected.

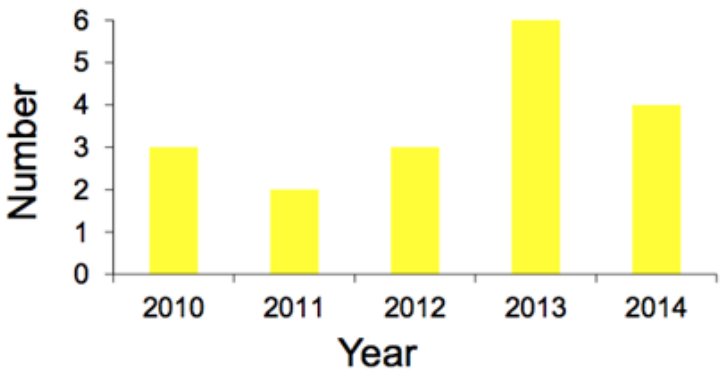

Figure 1. Increase in the number of Diltiazem associated deaths.

Epidemiology

There was a female predominance (11:7 = F: M) and deaths commonly involved an older age group (median: 65 years). Overall, there is an increase in number of diltiazem-associated deaths from 2010-2014 **(Figure 1)**.

Cause of Death

Out of the 18 diltiazem-associated deaths, 10 cases were attributed solely to diltiazem, with the highest level of 18 mg/L in post-mortem peripheral blood **(Table 2)**. The remaining cases involved drug toxicity, with citalopram being the most common prescription drug.

Post-mortem Findings

The major autopsy findings in nearly all cases (16 cases) demonstrated structural heart disease. Specifically, there were 14 cases with cardiomegaly with left ventricular hypertrophy, 6 severe coronary artery atherosclerosis and 3 pacemakers. Additional findings at autopsy included the presence of pill matter within the stomach contents in half of the cases.

Toxicological Findings

Table 2. Summary of levels in post mortem peripheral blood.

Substances	Average*	Range*
Diltiazem	6.7 mg/L	1.2 to 18 mg/L
Desacetyldiltiazem	2.38 mg/L	1.2 to 5.5 mg/L

*Admission blood excluded because analysis was delayed by a minimum of 1 week

Manner of Death

The most common manner of death was suicide (10 cases) followed by accident (5 cases) and undetermined (3 cases). The high frequency of suicide is in keeping with the high incidence (13 cases) of depression/suicidal ideation in this series.

DISCUSSION

The typical decedent is a depressed middle-aged female with access to diltiazem and underlying cardiovascular disease and diltiazem is commonly co-ingested with another prescription drug. However, the increase in number of diltiazem associated deaths from 2010-2014 could be attributed by the higher sensitivity involved in the search of the toxicological cause of death in recent years.

Mechanism of Death

The major autopsy finding of structural heart disease in nearly all cases suggests an indication for the diltiazem prescription. Diltiazem as a calcium channel blocker has both negative chronotropic and dromotropic effects on the sinoatrial and atrioventricular nodes, negative inotropic effects and vasodilative effects on vascular smooth muscle, which reduces systemic vascular resistance [1]. Overall, it leads to heart block, bradycardia and hypotension when used inappropriately.

Luomanma ki et al. [3] reported a case of diltiazem overdose with the ingestion of 240 mg slow release diltiazem, resulting in severe treatment-resistant hypotension and first-degree atrioventricular block. Another case study of a diltiazem overdose totalling 9000 mg was described by Connelly et al. [4] in which the patient experienced bradycardia, hypotension, and complete heart block with junctional escape rhythm and inferiolateral ST depression [4]. Interestingly, no illicit drugs were detected, despite the use of diltiazem as a cutting agent encountered in illicit drugs seized in the UK with a postulated effect of reducing cardiac risks associated with excessive cocaine use [5]. Although it was suggested that the toxicity of cutting agents is low when compared to the active component, this case series demonstrates that the adverse effect of diltiazem can be fatal on its own [5].

Fatal Dose

The usual therapeutic dose of diltiazem is between 0.05-0.2 mg/L, while the highest survivable level with aggressive cardiovascular support at 4.5 mg/L [1]. This shows an overlap between survivable and lethal concentrations, and likely suggests that toxicity is not linearly dependent on the dose ingested or plasma level. Post-mortem distribution plays a role when determining a “fatal” diltiazem level. Diltiazem tends to accumulate in the lungs and become rapidly redistributed into pulmonary venous blood and then into the left cardiac chambers at 16-hour interval post-mortem [6]. Therefore collecting plasma in the femoral vessels only may underestimate the true diltiazem levels. Furthermore, other studies consistently suggest the use of tubes containing NaF (sodium fluoride) or potassium oxalate (5:1, w/w) with Teflon-lined caps to store blood samples [7]. NaF (sodium fluoride) has a clear stabilizing effect on the diltiazem level in post-mortem blood, and the combination of freezing at -20°C and the addition of NaF had the least degradation [7].

Manner of Death

The majority of the decedents had both depression and prescription access. Limited clinical history prevented capturing this possible relationship.

In light of the suicidal nature of previous case reports, diltiazem has been reported to be associated with depression by a series of 8 case reports as part of the WHO collaborative programme for international drug monitoring for suspected adverse effects [8]. Their report suggested latency of onset of depressive symptoms including early morning rising, low mood and severe fatigue ranging from a day to months, with symptoms subsiding upon stopping diltiazem and a positive re-challenge in 2 cases [8]. It also suggested a dose-dependent effect, with most dosages at 180 mg daily or more [8]. However, patients with cardiovascular disease often develop mood disorders, especially depression [9]. Therefore, it is difficult to postulate whether diltiazem preceded depression, or vice versa. Nonetheless, depression related to diltiazem may increase the risk of suicide, and toxicological evaluation should be performed in all cases of cardiac death.

The other manners of death in this case series include accidental and undetermined. It reinforces the importance of assessing all aspects of each case, including review of the history, post-mortem and toxicology reports prior to arriving at a conclusion.

CONCLUSION

In summary, this is the largest series of diltiazem-associated deaths. The majority of cases exhibited a chronic, potential cause of death, of cardiovascular origin. Attributing death to an anatomical cause, in the absence of toxicological analysis would have misclassified both the cause and manner of death. While relatively rare, the incidence of diltiazem overdose is increasing.

In conclusion, we emphasize the importance of detecting and quantifying prescription medication levels in toxicology testing, as prescription medication overdose is often overlooked in some jurisdictions. Both detect and quantify prescription medications should be mandated in a post-mortem examination.

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