

Clinical Toxicology

Fatal diltiazem overdose: report of four cases and review of the literature

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Summary: Four fatal cases of diltiazem overdose are described and compared with previously published cases. Clinical sequelae include all grades of heart block, hypotension and ultimately death. Management includes gastric lavage and oral administration of activated charcoal at presentation. Further symptomatic treatment with inotropic agents and temporary cardiac pacing may be required. If these measures are successful, recovery occurs within 36 hours in uncomplicated cases. Toxicological data have been reviewed but currently drug levels can only offer a retrospective analysis of the severity of overdoses.

As the use and risk of abuse of diltiazem increases, these reports serve to highlight the possible hazards and to alert physicians to what must be regarded as a dangerous and potentially lethal drug in overdosage.

Introduction

Since its launch in the UK in June 1985, diltiazem has been increasingly prescribed in the treatment of angina. Case reports of overdosage are increasing in number, but to date, only one confirmed death has been published.¹ This article describes four further fatal cases and reviews the medical and toxicological data from the medical literature. As the use and risk of abuse of diltiazem increases, these reports serve to highlight the possible hazards and to alert physicians to what must now be regarded as a dangerous and potentially lethal drug in overdosage.

Case 1

A 21 year old asthmatic male and known alcohol abuser was admitted acutely having taken an overdose of 25 diltiazem 60 mg tablets and 10 propranolol 80 mg tablets. This was a suicidal gesture and involved the taking of the prescribed medication of both his parents. On admission his heart rate was 10 per minute with an unrecordable blood pressure, his pupils were fixed and dilated and he was semiconscious. He was treated with intravenous (i.v.) atropine, i.v. glucagon, i.v. calcium

and oxygen with little effect. He was then given an i.v. bolus of adrenaline, further calcium gluconate and glucagon, followed by an adrenaline infusion. At this point his pulse picked up to 30–40/minute and his blood pressure to 70 mmHg systolic. Following this he was given isoprenaline, plasma expanders and had a temporary pacing wire inserted. He was admitted to intensive care where further inotropic support with dobutamine, dopamine and phenylephrine was administered. Unfortunately despite these measures he deteriorated and expired in asystole 7 hours post-admission.

His autopsy confirmed acute heart failure, and samples of blood and tissues were sent to the County Analyst's laboratory for further examination. This revealed blood levels of diltiazem 1,500 µg/l, of propranolol 200 µg/l and of alcohol of 143 mg/dl.

Case 2

A 68 year old man was found dead in bed. Postmortem examination revealed 5,400 mg of diltiazem in the stomach with a blood level of 2,500 µg/l. His stomach also contained 1,700 mg of paracetamol, the blood level was only in the high therapeutic range and 84 mg of trifluoperazine representing 8 times the normal dose. The blood alcohol level was 83 mg/dl.

Case 3

A woman known to be suffering from depression was found dead in bed with a suicide note. Post-mortem examination revealed 3,300 mg of diltiazem in the stomach with a blood level of 4,000 µg/l. Traces of codeine were detected in the urine but insignificant levels were present in the blood and low levels of fluoxetine were also present. Alcohol was not detected in the blood.

Case 4

A 58 year old man was known to have ischaemic heart disease and suffering recurrent chest pain. He had recently acquired a prescription for more anti-anginal medication but was later found dead in bed. Referral to the Coroner and postmortem examination revealed stomach contents of 650 mg of diltiazem, with a corresponding blood level of 8,000 µg/l. The blood alcohol level was 109 mg/l.

Discussion

The true epidemiology of diltiazem overdose is not known but a telephone survey of all the poison centres in the UK revealed that they had been contacted only infrequently about this drug. Only one centre, the National Poisons Information Service (London), kept a database specifically for diltiazem overdose between 1983 and 1988. This revealed 24 cases of diltiazem alone or in combination with other medication (usually cardiac drugs). Five of these were children under 12 years and probably represented accidental ingestion. Final outcomes were not recorded. A survey of the French poison centres² between 1979 and 1988 revealed 134 cases, 51 accidental poisonings in children and 83 overdoses in adults. None was fatal.

The therapeutic range of blood diltiazem concentrations is 100–200 µg/l. Further cases from the literature illustrate the effects at higher levels: up to 500 µg/l³ (1 case) the patient had first-degree heart block and a sinus bradycardia but was asymptomatic. From 500–1,000 µg/l⁴ (1 case), the patient developed hypotension alone which reversed with plasma expanders, dopamine and metaraminol (a pressor agent). From 1,000 to 1,500 µg/l^{5,6} (2 cases) both developed conduction abnormalities and hypotension: one case developed bifascicular block but only required inotropic support,⁶ the other case taken in conjunction with a beta blocker needed temporary pacing.⁵ At levels greater than 1,500 µg/l^{7–9} (3 cases), all cases required temporary pacemakers. At levels over 6,100 µg/l, all cases died (2 cases¹⁰ including case 4 reported above). It is important to point out that measurements of blood concentrations of diltiazem are not widely available and hence the levels quoted here can only presently be used retrospectively for determining the severity of an individual case.

The details of blood diltiazem levels in cases of overdose are listed in Table I. A blood diltiazem concentration of 6,090 µg/l⁹ was the maximum level at which survival took place; this represents a concentration of 30–60 times the therapeutic range. This patient, a 50 year old male, took the overdose in conjunction with alcohol and was admitted moribund and hypotensive with a bradycardia. He quickly required temporary pacing and inotropic support but subsequently survived. Death occurred at levels exceeding 6,100 µg/l but it is possible that rescue at higher drug levels will be reported in the future. Conversely, the lowest value for a fatality (case 1) occurred at 1,500 µg/l in a young man but involved the combination of diltiazem with a beta-blocker. Beta-blockers potentiate the conduction-retarding and negative inotropic properties of diltiazem even in therapeutic doses.¹⁰ It is logical to assume that in overdose beta-blockers can decrease the mortality

Table I A comparison of diltiazem concentrations in fatal and non-fatal case reports

Reference	Diltiazem concentration (µg/l)	Survivors		Fatalities	
		Time of drug assay from admission (hours)	Reference	Diltiazem concentration at autopsy (µg/l)	
Jakubowski <i>et al.</i> ³	563	8	Case 1	1,500	
Jaeger <i>et al.</i> ²	936	n/a	Case 2	2,500	
Anthony <i>et al.</i> ⁵	1,090	6	Case 3	4,000	
Buffet <i>et al.</i> ⁶	1,670	n/a	Case 4	8,000	
Malcolm <i>et al.</i> ⁷	1,180	8	Weise <i>et al.</i> ¹	15,000	
Snover <i>et al.</i> ⁸	4,000	n/a			
Ferner <i>et al.</i> ⁹	6,090	4			

threshold and precipitate death at much lower levels. Other circumstances such as extreme age, severe coronary disease, other co-existing medical problems, or multiple overdose with other drugs may also decrease the mortality threshold.

Diltiazem undergoes linear, first-order elimination with a half-life of 7.5 hours^{3-5,7,9} (the mean of 5 cases) in overdose. Treatment is essentially supportive and at presentation gastric lavage and the oral administration of activated charcoal may be of value.⁵ This is because diltiazem affects the smooth muscle of the gut and delays intestinal transit and absorption.⁹ Otherwise side effects such as hypotension and complete heart block should be treated with inotropes and cardiac pacing.

In cases involving beta-blocking drugs, severe

ischaemic heart disease and the elderly, a high index of awareness is necessary as temporary pacing may be required much earlier in the patient's management.

If therapeutic measures are successful then the patient usually recovers within 36 hours^{4,7-9} (mean of four cases), allowing the discontinuation of pacing or inotropic infusions.

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