Case Report

A Fatal Case of Amlodipine Poisoning

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Abstract

A fatal case attributed to amlodipine intoxication is presented. The deceased was a 15-year-old girl who allegedly ingested 14 10-mg Istin tablets. Amlodipine concentration in peripheral blood was determined (2.7 mg/L) and was compared with published therapeutic and toxic data for amlodipine and some other dihydropyridine calcium channel-blocking agents. Amlodipine concentrations in liver, blood, and stomach contents were also determined.

Introduction

Amlodipine is a dihydropyridine calcium channel blocking agent used as an antihypertensive. It is prescribed in the United Kingdom as Istin (Pfizer, Sandwich, U.K.) tablets containing 5 or 10 mg of amlodipine besylate. Other drugs included in this category are diltiazem, felodipine, isradipine, nicardipine, nimodipine, and nifedipine.

Amlodipine, unlike other dihydropyridine and nondihydropyridine calcium antagonists, has very low metabolic clearance, which allows relatively constant plasma concentrations to be maintained when administered once daily.

We have only been able to find one report in the literature relating to amlodipine overdosage. This involved a 63-year-old woman who ingested 70 mg amlodipine and an unknown quantity of oxazepam.

Our report describes a case in which an overdose of Istin (allegedly 14 10-mg tablets) was taken by a 15-year-old girl who subsequently died in the hospital approximately 6 h after taking the tablets. Postmortem blood and liver blood amlodipine concentrations were determined along with the total quantity of amlodipine present in the gastro-jejunal contents.

Case History

The deceased was a school girl who had been healthy and had appeared normal before the incident. In the evening, she went to her bedroom and about an hour later explained to her sister that she had taken an overdose of 10 Ponstan capsules (mefenamic acid) and 14 10-mg Istin tablets, which were prescribed for her mother. Approximately 1 h later (midnight), in the hospital, she quickly became hypotensive with a blood pressure of 70/40 mm Hg and a pulse rate of 130. She was then transferred to intensive care where she was 14/14 on the Glasgow coma scale. Her blood pressure remained low, and she was given intravenous fluids and 10 mL 10% calcium gluconate. At 3:40 a.m., her breathing became labored, and she was cyanosed. She had an extensor spasm, and her breathing stopped. The cardiac monitor showed an asystolic cardiac arrest. After cardiopulmonary resuscitation and administration of intravenous adrenaline, atropine, calcium chloride, and sodium bicarborate, electrical complexes returned and blood pressure reached 100/60 mm Hg with a pulse rate of 105. About 20 min later, however, she again deteriorated. Despite continuing attempts at resuscitation, there was no further response, and she was pronounced dead at 5:35 a.m.

Autopsy showed the girl was 5 ft. 6 in. in height and weighed 73.2 kg. Her heart was completely normal, but the lungs were heavy, congested, and edematous; the right lung weighed 950 g and the left lung 840 g. Microscopic examination showed intensely congested edematous lungs with foci of terminal aspiration. There was quite clearly no disease to cause her death.

Methods

Amlodipine analysis was performed using the general HPLC screening method used in this laboratory for the determination of a wide range of basic and acidic drugs (1). The hardware consisted of a Waters 996 photodiode array detector coupled to a Waters 717 autosampler and was controlled with Millennium software (Millipore, Watford, U.K.). The analytical column was an Inertsil 5ODS2 (15 cm × 4.6 mm) from GL Sciences, Inc. (Tokyo, Japan).

The eluent consisted of a binary mixture of acetonitrile and water, each containing 2.5 mL/L H_2SO_4 (2.5M). Gradient elution was performed from 30 to 50% acetonitrile within 20

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min, and the flow rate was set at 2 mL/min. The detector scanned the eluent from 220 to 450 mm, and the monitor wavelength was set at 240 nm.

Extracts of postmortem samples were prepared by liquid–liquid extraction. Blood (peripheral blood and liver blood) and diluted gastric contents (1 mL) were mixed with 20 µL internal standard solution (prazepam, 50 µg/mL), M Tris (1 mL), and *n*-butyl acetate (1 mL). After vortex mixing for approximately 1 min and centrifuging for 5 min, the upper organic layer was transferred to a disposable tube and evaporated to dryness in a centrifugal evaporator. The dry extract was dissolved in 35 µL methanol. After vortex mixing briefly, the extract was transferred to an autosampler vial, and an aliquot (20 µL) was injected on a high-performance liquid chromatograph (HPLC). Quantitation was carried out using a calibration curve (amlodipine/prazepam area ratio versus amlodipine concentration) prepared from a series of spiked blood samples (0–5 mg/L) using 240 nm as chromatographic wavelength.

Amlodipine eluted at a retention time of approximately 3.5 min with a symmetrical peak. The UV spectrum of this peak had a maximum wavelength of 240 nm.

Results and Discussion

Amlodipine was detected in peripheral blood, liver blood, and gastro-jejunal contents (Table I). A therapeutic concentration of mefenamic acid (2.0 mg/L) was detected in the blood. No alcohol was detected.

Because of its low metabolic clearance, constant plasma concentrations of amlodipine can be maintained by a single daily dose. Therapeutic dosage of the drug usually results in relatively low plasma concentrations. Faulkner et al. (2) found that peak plasma concentrations (12 volunteers) following a single 10-mg dose were 5.9 µg/L. Given once daily for 14 days, the peak concentration was 18.1 µg/L.

These concentrations were much lower than those achieved by therapeutic doses of other calcium channel-blocking hypertensives. For example, the effective nifedipine daily dosage is 30–120 mg. This gave rise to a mean serum concentration of 0.115 mg/L in 12 patients (3).

Diltiazem dosage is higher than that of nifedipine. Steady-state serum concentrations of 0.10–0.20 mg/L were found in 12 patients (4).

Table I. Concentration of Amlodipine in Postmortem Samples

Sample	Amlodipine
Blood (peripheral)	2.7 mg/L
Blood (liver)	15.4 mg/L
Gastro-jejunal contents	24.0 mg

Unlike amlodipine, the toxicity of both nifedipine and diltiazem has been well documented. Nifedipine was injected intravenously (60 mg) by two young adults who died within minutes. The mean postmortem blood concentrations were 0.16 mg/L (5). A 38-year-old female who ingested 900 mg diltiazem was successfully treated in the hospital and was found to have a peak plasma diltiazem concentration of 1.7 mg/L (6). Postmortem blood concentrations of diltiazem ranged from 6.7 to 33 mg/L in five cases (7).

The previously published case of amlodipine overdosage (8) involved a 63-year-old woman who ingested 70 mg amlodipine (half the quantity taken by the deceased in our case) and some oxazepam. The peak plasma amlodipine concentration was found to be 0.185 mg/L approximately 11 h after ingestion. Death occurred 26 h after ingestion.

Conclusion

An overdose of 140 mg amlodipine by a 15-year-old girl resulted in death 6 h after ingestion despite resuscitation measures and treatment with calcium, adrenaline, and atropine. The postmortem blood amlodipine concentration was found to be 2.7 mg/L.

The quantity of amlodipine found in the gastro-jejunal contents represents approximately two 10-mg tablets.

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