

A Case of Fatal Felodipine Overdose

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Learning Points

1. Consideration of gastric lavage and whole bowel irrigation within hours of ingestion (in the absence of contraindications)
2. Early identification and management in an area of high dependency
3. Mainstay of management comprises high dose calcium therapy, high dose insulin-dextrose infusion and inotropic support

Abstract

A 54 year gentleman was admitted to hospital within four hours of taking an overdose of modified release felodipine tablets, with a total dose of approximately 250mg. The initial management comprised fluid resuscitation, calcium chloride and glucagon. He remained hypotensive and was commenced on hyperinsulinaemia-euglycaemic therapy. Hypotension persisted with the development of progressive metabolic acidosis despite increasing inotropic support, haemofiltration and high dose insulin-dextrose infusions. The patient died 60 hours post overdose. The case highlights the profound, refractory circulatory collapse and lethal consequences of significant calcium channel blocker overdose and also reviews potential management strategies to attempt to reverse these changes. Despite the lack of evidence of whole bowel irrigation in overdose per se, its role in the removal of modified release compounds has not been studied. We would strongly urge emergency departments to consider this therapeutic modality, especially in overdoses involving delayed release preparations of calcium channel blockers, which are extremely toxic in overdose and are associated with very high mortality.

Case History

The patient presented to the accident and emergency department of our hospital approximately 4h after admitting to ingesting about 50 tablets of 5mg modified release felodipine, a long acting calcium channel blocker (CCB) and 2 cans of strong lager, in a deliberate, but unplanned suicide attempt. He had not left a suicide note and despite his initial intent, expressed regret at his action. He had been discovered by his wife in a confused, drowsy state complaining of dizziness and paraesthesiae in his fingers and toes. On arrival in the department he was also complaining of nausea and had vomited once. The past medical history was remarkable for manic depression, hypertension, asthma and

epilepsy. There were previous attempts at deliberate self harm and the patient had attended the accident and emergency department on several occasions in the previous month expressing suicidal ideation, but did not wait to be seen by a doctor. Prescribed medications included Felodipine 10mg once daily, fluoxetine 20mg mane, bendroflumethiazide 2.5mg once daily, carbamazepine 1g twice daily, lamotrogine 100mg twice daily and asthma inhalers. He was poorly compliant with medication.

On presentation, he was drowsy but readily roused with a Glasgow coma scale of 15/15. He was hypotensive with a blood pressure of 88/56mmHg and a heart rate of 88 beats per minute. Cardiovascular, respiratory, abdominal and neurological examinations were otherwise normal. The electrocardiograph showed a junctional tachycardia (Figure 1) and a plain chest radiograph was normal. Arterial blood gases revealed an alkalosis (pH 7.5, pCO₂ 3.37 kPa, pO₂ 21.4 kPa, base excess -1.9mmol l⁻¹) and a raised lactate (3.31mmol l⁻¹). At presentation haematological and biochemical indices, including serum creatinine and calcium concentrations were normal. Paracetamol, salicylate and carbamazepine levels were undetectable. Plasma glucose concentration was 8.2mmol l⁻¹.

Initial management comprised intravenous fluid resuscitation with 2l of 0.9% sodium chloride solution and 11 gelofusin, intravenous metoclopramide 10mg, 2 vials of 10ml of 10% calcium chloride solution and intravenous glucagon 1mg. There was no significant change in blood pressure (90/60mmHg). Activated charcoal was considered, but not given in view of the 4hour delay between presentation and drug ingestion. A urinary catheter was inserted. Over the next 4hours urine output remained <8ml hour⁻¹ despite an additional 3l of intravenous crystalloid. Arterial blood gas sampling revealed a compensated metabolic acidosis (pH 7.39, base excess -12.5mmol l⁻¹ and bicarbonate 10.5mmol l⁻¹). A further 2 boluses

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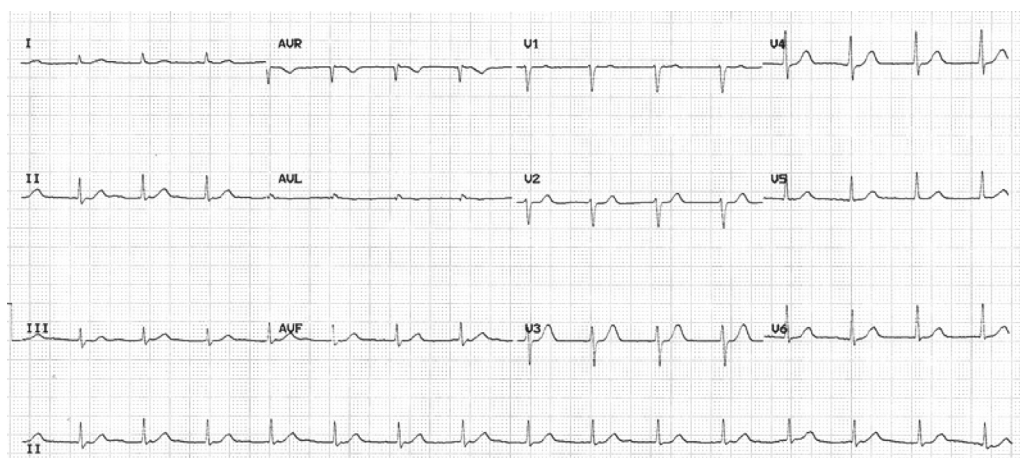


Figure 1. ECG showing a junctional tachycardia on admission.

of 10mls 10% calcium chloride were administered and an insulin-dextrose infusion was commenced. A bolus dose of insulin (Actrapid) 2 units/kg was followed by 0.5 units/kg per hour. A central venous catheter was inserted and intravenous fluids continued at 500 ml per hour. The patient was transferred to the intensive care unit and inotropic support commenced initially with adrenaline. The patient's blood pressure began to fall precipitously and he was subsequently intubated as an emergency before additional pressor agents (noradrenaline and vasopressin) were commenced. The hypotension persisted and the acidosis worsened (pH 7.05, bicarbonate 5.7 mmol l^{-1} , Lactate 13.7 mmol l^{-1} , base excess $-27.7 \text{ mmol l}^{-1}$. The plasma glucose was 6.9 mmol l^{-1}). Haemofiltration was commenced and a pulmonary capillary wedge catheter inserted.

On the second day of admission, the patient's condition deteriorated further. Despite increasing inotropic support, the refractory hypotension worsened with the development of progressive renal failure. Although ventilated, the patient developed ARDS and the plasma glucose also remained persistently high despite intensive insulin therapy (0.5 units/

kg/hour). The patient continued to deteriorate with no improvement in circulatory response and progressive, profound acidosis despite maximal therapy. After consultation with immediate family, the decision was made to withdraw treatment. The patient died 60 hours post overdose.

Discussion

Calcium channel blockers are widely used in the treatment of hypertension and prophylaxis of angina. Chemically they are subdivided into dihydropyridines (nifedipine, amlodipine, felodipine), phenylalkylamines (verapamil) and benzothiazepines (diltiazem). In recent years modified release preparations which permit once daily administration have been developed. All calcium channel blockers act on the slow L-type calcium channels, in particular, these are found in the myocardium, conducting system of the heart and vascular smooth muscle.¹ By blocking the transport of calcium ions across membranes in the myocardium and vascular smooth muscle, these drugs cause significant circulatory collapse. This is characterised by vasodilatation, hypotension, reduced myocardial contractility, and

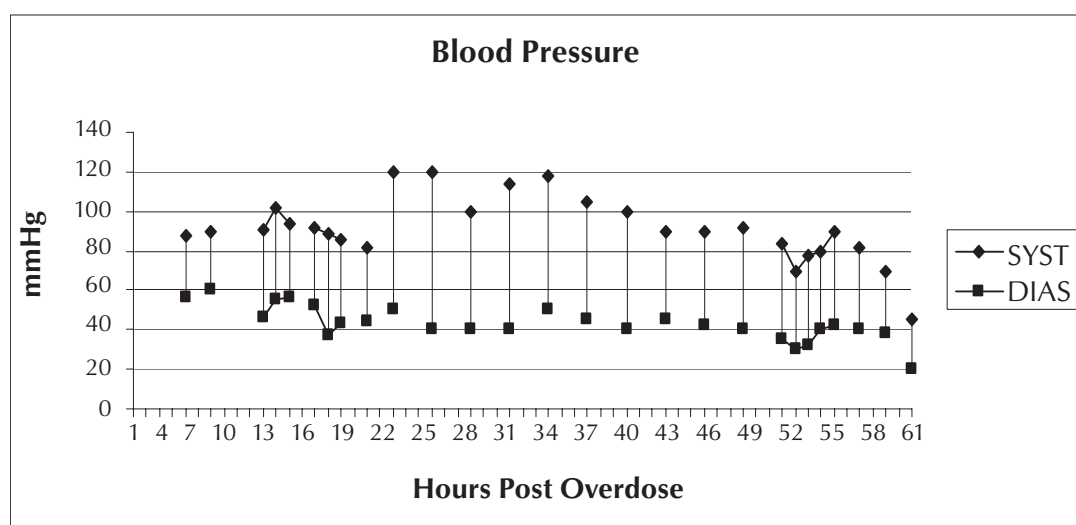


Figure 2. Systolic and diastolic blood pressures during admission. Inotropic support was commenced 19 hours post overdose.

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depressed sinoatrial and atrioventricular conduction.^{1,2} The toxic effects of excessive L-type calcium channel blockade include pulmonary oedema, profound metabolic effects (hyperglycaemia due to impaired pancreatic β -islet cell insulin secretion and metabolic acidosis due to poor peripheral tissue perfusion), neurological dysfunction (lethargy, coma, seizures) and gastrointestinal smooth muscle relaxation which may predispose to severe constipation, ileus, colonic pseudo-obstruction and even perforation.³

Current understanding of the clinical course and clinical response to various therapeutic strategies in managing CCB overdose is derived from isolated case reports and small case series. We believe this is one of the first published cases of fatal modified release felodipine overdose. CCB toxicity is predictably characterised by circulatory collapse. This is usually secondary to profound peripheral vasodilatation, although impaired cardiac output resulting from negative inotropism and/or chronotropism. Our patient was also taking bendroflumethiazide, which may have exaggerated the haemodynamic response to felodipine. In view of his age and established hypertension, the resulting hypotension was also likely to have provoked more profound ischaemic consequences. The presentation of our patient was typical of patients presenting with significant overdose of dihydropyridine CCBs.

Harris recently published the most comprehensive case report detailing the optimal management of modified release dihydropyridine CCB overdose.⁴ The patient was managed in a tertiary referral centre and was aggressively instituted on high dose intravenous calcium and high dose insulin-dextrose therapy (the so called euglycaemic-hyperinsulinaemia regime). The patient was intubated early and bowel decontamination rapidly commenced via nasogastric tube. The patient survived a total dose ingestion of about 1000 mg. A case analysis of 13 patients with CCB overdose treated with euglycaemic-hyperinsulinaemia therapy has been reported previously.⁵ In the majority of cases this was associated with a positive outcome, although of course this assertion is prone to obvious reporting and publication bias. Despite limited data to support the use of euglycaemic-hyperinsulinaemia therapy after calcium channel blocker poisoning, this is currently advocated by TOXBASE as a means of correcting haemodynamic effects. The rationale for euglycaemic-hyperinsulinaemia therapy is based on replacement of depleted endogenous insulin following CCB mediated reduction in pancreatic β -islet cell activity. In this setting hyperinsulinaemia is also speculated to optimise cardiac myocyte metabolism by promoting cardiac carbohydrate utilisation.⁵ High dose insulin is also thought to be weakly inotropic.⁵

Toxin removal is a desirable therapeutic goal in the management of any significant overdose. Unfortunately, CCBs are highly protein bound and consequently techniques such as dialysis, are ineffective. Bowel decontamination remains a contentious issue in the poisoned patient. However, the rationale for bowel decontamination is

especially pertinent in patients ingesting delayed release CCB. Delayed gastrointestinal absorption occurs with all modified release preparations, but CCBs also antagonise gastrointestinal smooth muscle causing a marked reduction in gastrointestinal motility and transit time, potentially causing even greater delay in drug absorption and providing an even longer time window for therapeutic purgatives to be potentially effective. However, if the high volume of fluid administered as part of whole bowel irrigation is to be contemplated safely in patients who have ingested drugs with the potential to precipitously impair consciousness, it is mandatory to manage such patients in a high dependency area. In this setting early or prophylactic airway protection with endotracheal intubation should be considered in the event of reduced conscious level.

Although there is no clear evidence in the setting of felodipine overdose, current UK guidelines recommend using activated charcoal for patients presenting within 1 hour of ingestion, in the absence of any contraindications. Paralytic ileus is a recognised complication of calcium channel blocker overdose and clinicians should be vigilant to exclude this possibility before contemplating either gut decontamination or activated charcoal.

The patient discussed in this report had a documented history of mental illness and had previously expressed suicidal ideation. Prescribing CCBs, which are frequently catastrophic in overdose, in patients at high risk of suicide should perhaps also be tempered with caution. One study has even suggested that CCB themselves may increase the risk of suicide.⁶

Conclusion

The use of modified release calcium channel blockers is increasing and overdose may become a more common presentation. Acute physicians should be mindful of the potential for massive circulatory collapse with delayed onset, especially with modified release preparations. Early recognition of potentially toxic doses and early aggressive management is essential. Clinicians should perhaps prescribe calcium channel blockers with caution to patients at high risk of deliberate self harm. In this instance a dose of 250 mg (2.9 mg/kg of body weight) in an adult male was fatal.

In the absence of controlled trial data, there is a potential argument for renewing interest in whole bowel irrigation in the unique setting of modified release CCB overdose. In addition to the slow gastrointestinal absorption of CCB conferred by the delayed release mechanism, the potential of CCB to impair gastrointestinal smooth muscle and reduce gut transit time is likely to even further delay and prolong absorption. It could also be argued that "extended" or even late use of bowel irrigation should be considered in this setting because the half-life of felodipine is 11 hours and consequently toxic levels are likely to persist for at least 24 hrs following significant overdose.³ Additional focused research assessing the role of whole bowel irrigation following overdose of delayed release preparations is merited.

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