Delayed asystolic cardiac arrest after diltiazem overdose; resuscitation with high dose intravenous calcium

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Emerg Med J 2002;**19**:355–357

A 51 year old man took a mixed overdose including 1.8–3.6 g of diltiazem, paracetamol, aspirin, isosorbide nitrate, and alcohol. He initially presented to hospital after six hours with mild hypotension and was treated with activated charcoal and intravenous fluids. Eighteen hours after the overdose he had two generalised tonic-clonic seizures. The patient remained unresponsive with junctional bradycardia, unrecordable blood pressure, and then became asystolic. He was resuscitated with high dose (13.5 g) intravenous calcium and adrenaline (epinephrine). He required inotropic support and temporary pacing over the next 48 hours. This case suggests there is a role for aggressive high dose intravenous calcium therapy in severe diltiazem overdose, particularly with the onset of asystole. It should be considered early in cases of cardiac arrest after diltiazem overdose. The case also highlights the problems with delayed toxicity when whole bowel irrigation is not administered.

Calcium channel blocker (CCB) overdose is relatively uncommon, but has a higher mortality and morbidity compared with other drug overdoses.[1] Diltiazem overdose has been reported previously, mainly as case reports[2–8] and in a few case series.[1 9] In particular, overdose of its slow release formulations may lead to severe toxicity if appropriate decontamination is not started.[3] There remains considerable controversy about the treatment of severe CCB overdose, particularly with the use of intravenous calcium.[10–13]

Here is reported an overdose of slow release diltiazem causing delayed asystolic arrest, and successful resuscitation with rapidly administered, high dose calcium gluconate.

CASE REPORT

A 51 year old white man took a mixed overdose comprising diltiazem 1.8–3.6 g (slow release preparation), paracetamol, aspirin, isosorbide nitrate, and alcohol. He presented to hospital six hours after the overdose complaining of nausea, vomiting, weakness, and lethargy. He had a past history of ectatic coronary arteries and cardiomyopathy, asthma, bipolar mood disorder, and alcohol misuse.

Examination on presentation revealed: heart rate (HR) 80 bpm and blood pressure (BP) 90/40 mm Hg. He was orientated and cooperative. Cardiovascular, respiratory, and neurological examinations were normal. An electrocardiograph (ECG) showed sinus rhythm. He was treated with 50 g activated charcoal, 3 litres of intravenous crystalloid solution, and 1 g of calcium gluconate. BP improved to 100/50. Salicylate and paracetamol concentrations were not in the toxic range. Whole bowel irrigation was not undertaken. Over the next 12 hours he remained alert and well, with no significant decrease in BP or HR.

Eighteen hours after the overdose, he had two generalised tonic-clonic seizures and remained unresponsive with a junctional bradycardia, HR 43, BP unrecordable. He then became asystolic with no palpable pulses. He was intubated and ventilated while cardiopulmonary resuscitation was started. Over a period of 12 minutes he was given 10 g calcium gluconate as 1 g boluses and 9 mg of adrenaline (epinephrine). He responded with HR 54 (junctional bradycardia) and BP 137/80 mm Hg. Five minutes later, he had a second asystolic cardiac arrest and was given a further 2.5 g calcium gluconate and 1 mg adrenaline (total of 12.5g of calcium gluconate given over 28 minutes). An external pacemaker was attached, and an adrenaline infusion (6 mg/100 ml at 5 ml/h) and a calcium gluconate infusion of 1 g in 100 ml/h were started.

After one hour, calcium was stopped but high dose noradrenaline (norepinephrine) and dobutamine were required to maintain blood pressure, and a temporary pacing wire was necessary to maintain rhythm. There was no response in haemodynamic parameters to glucagon. Severe metabolic acidosis (pH 6.83 base excess 26) and acute renal failure were treated with a bicarbonate infusion and 24 hours of continuous veno-venous haemofiltration. Insulin was required for hyperglycaemic control.

Over 48 hours inotropes were weaned, the acidosis resolved, renal function improved, and pacing was stopped (table 1 presents serial blood parameters). The only other complication was pulmonary oedema. This was initially treated as aspiration pneumonia with antibiotics and oxygen therapy, but radiographical findings were more consistent with pulmonary oedema. The patient was discharged from intensive care on day 5 and discharged himself against medical advice eight days after presentation. On subsequent attendances to the emergency department, he had a normal neurological examination, normal chest radiograph, ECG, and creatinine.

DISCUSSION

This case illustrates the potentially life threatening effects of slow release diltiazem overdose and the problems with delayed toxicity if decontamination is incomplete or not undertaken. The clinical effects in the patient described were consistent with CCB overdose. The spectrum of CCB toxicity includes hypotension (combination of vasodilatation and negative inotropic effects), bradycardia, conduction abnormalities (sinus node depression and AV conduction block), pulmonary oedema, metabolic effects (hyperglycaemia and metabolic acidosis), and neurological symptoms (lethargy, coma, seizures).[1–7 9 14] The pharmacokinetics and mechanism of toxicity have been reviewed previously.[5 14]

Whole bowel irrigation is being used increasingly in poisoning with slow release formulations.[15] Similar to most treatment modalities in clinical toxicology, the evidence for the use of whole bowel irrigation in slow release CCB overdose is based on case reports alone. There is a reported case of two

Abbreviations: CCB, calcium channel blocker; BP, blood pressure; HR, heart rate

Table 1 Serial biochemical parameters including corrected serum calcium concentrations; 13.5 g calcium gluconate given 18 hours after the overdose

Time after overdose (h)	7	13	19 ½	28	58	86	112
Creatinine (μmol/l) (Range: 50–120 μmol/l)	112	252	174	201	405	351	268
Corrected serum calcium (mmol/l) (range: 2.20–2.60 mmol/l)	2.23	2.51	3.36	2.45	–	2.16	2.28
pH (7.35–7.45)	7.45	–	6.83	7.40	7.42	7.37	–
Base excess	–6.7	–	–26	–1.7	3.3	3.3	–
Blood glucose (glucometer)	6.5	–	18.1	11.1	7.8	9.6	–

patients who took similar doses of slow release verapamil, where one patient had whole bowel irrigation and developed only minimal toxicity, while the other patient, who did not receive whole bowel irrigation, developed severe toxicity.[16] Although whole bowel irrigation has not been proved effective in controlled trials of slow release CCB overdoses, the seriousness of this poisoning and the effectiveness of whole bowel irrigation in previous case reports,[16] make it an important consideration for decontamination, until clinical trials are undertaken.

The patient had two generalised tonic-clonic seizures minutes before the asystolic arrest. Seizures have been reported uncommonly with calcium channel overdoses.[17] Quezado *et al* also reported a generalised seizure before asystole in a verapamil overdose.[17] It may be hypothesised that the seizures precipitated asystole by causing acidosis and increasing the amount of ionised drug available for channel blockade.

There is disagreement about the use of intravenous calcium in CCB overdose.[10–13] Recently published Toxicologic-Oriented Advanced Cardiac Life Support guidelines recommend the use of 1 g–3 g of intravenous calcium as a slow intravenous bolus, only after shock is refractory to other treatments.[12] However, there is some evidence that intravenous calcium is a useful first line therapy.[16 18] There is one report of an asystolic arrest after diltiazem overdose responding to 2 g of calcium gluconate alone.[6]

In situations of severe haemodynamic compromise, such as asystole, larger doses may be beneficial.[13 16] In the case reported here, much larger doses were administered rapidly, and then repeated after a second episode of asystole, with good response. High dose intravenous calcium, that is, greater than 3 g, has been reported in a number of cases of CCB overdose,[13 16 18] but not previously in diltiazem overdose.[5]

In contrast, in cases of CCB poisoning reporting failure of intravenous calcium, the dose was 1 g–3 g.[3 4 8] Failure of high dose intravenous calcium seems to occur less commonly,[19] suggesting that a higher dose may be more appropriate in severe poisoning. Proponents of high dose calcium suggest that in cases of failure, the overdose is often refractory to all treatment.[1] No serious side effects have been reported despite transient high serum calcium (up to 4.8 mmol/l).[13 16 18] Multicentre clinical trials will be required to test the hypothesis that high dose intravenous calcium is beneficial in CCB poisoning because it is an uncommon poisoning.

Although the severe delayed toxicity in this case most probably resulted from inadequate decontamination, his pre-existing cardiac disease may have exacerbated it. However, good outcomes with severe CCB toxicity have been reported in patients with a history of coronary artery disease,[6 8] and poor outcomes have been reported in otherwise healthy persons.[16 20] It is unclear if continuing the calcium infusion postcardiac arrest would have reduced the amount and time inotropes were required. Previous case reports have suggested that continuing a calcium infusion is beneficial,[7 16 18] but a controlled trial would be required to test this hypothesis.

This case suggests there is a role for aggressive intravenous calcium therapy in severe diltiazem (and other CCB) overdose, particularly with the onset of asystole. It should be considered early in cases of cardiac arrest after CCB overdose. The case also highlights the problems with delayed toxicity when whole bowel irrigation is not administered.

ACKNOWLEDGEMENTS

Thanks to Dr Patricia McGettigan and Ms Corrine Balit for reading the manuscript. Thank you to Associate Professors Ian Whyte and Andrew Dawson for their comments on the manuscript.

Contributors

Geoffrey Isbister attended the patient in the emergency department, wrote and revised all manuscripts and will be guarantor for the paper. Ian Whyte and Andrew Dawson discussed the idea and focus of the case report with the author, but did not read the manuscript. Patricia McGettigan and Corrine Balit read and commented on the manuscript.

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Accepted for publication 31 January 2002

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An unusual case of paralytic ileus after jellyfish envenomation

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Emerg Med J 2002;**19**:357–358

A 31 year old tourist presented with paralytic ileus after jellyfish sting. This unusual presentation after jellyfish envenomation is reported and the literature reviewed for jellyfish envenomation syndromes.

Jellyfish venom contains a mixture of toxic and antigenic polypeptides, which are species specific. The manifestations of jellyfish envenomation in humans have been noted to include allergic reactions, cardiac syndromes presenting with cardiac arrest and heart failure, and neurological syndromes. Although a wide variety of neurological manifestations have been reported, no reports of paralytic ileus from jelly fish envenomations have been reported.

A case report of a 31 year old man stung by a jellyfish and who subsequently presented with paralytic ileus is discussed.

CASE REPORT

A 31 year old man was on a beach in Medan, Sumatra, when he came across a large jelly-like mass floating in the water. He picked it up and handled it for a minute or two before feeling a sharp pain on his left forearm. He immediately dropped the unknown creature and noticed a linear urticarial lesion on the left forearm (fig 1). This corresponded with a jellyfish sting reaction. Within half an hour he developed generalised malaise, weakness, lethargy, and joint pains followed by a sensation of abdominal bloatedness. He was treated at a local hospital but decided to seek further treatment in Singapore. The patient presented at the Department of Emergency Medicine at Singapore General Hospital 24 hours after envenomation. He complained of persistence of his original symptoms and was beginning to develop abdominal distension, vomiting, and had no urge to move his bowels since the incident. Examination revealed a lethargic looking patient with linear urticarial lesions on his left forearm. Vital signs were stable and neurological examination was essentially normal. Pupils were 4 mm, equal and reactive bilaterally. Abdominal distension was noted with absent bowel sounds. No abdominal tenderness was elicited and per rectal examination revealed soft brown stools. A clinical diagnosis of paralytic ileus (adynamic intestinal obstruction) was made. Abdominal radiographs showed distended small and large bowel loops with multiple fluids levels confirming the clinical suspicion. Full blood count, serum electrolytes, amylase, cardiac enzymes, liver function tests, and coagulation profile were all normal except for mildly increased total white with polysmorphonuclear leucocytosis of 81.6%. Electrocardiogram showed normal sinus rhythm with rate of 75 beats/minute. A surgical consultation was made and patient was treated conservatively with intravenous infusion and suction. The patient was admitted and treatment continued for four days before symptoms resolved and patient was able to move his bowels again. He was discharged on the fourth day and returned for review a week later when he was noted to be well and discharged without any further follow up.

Figure 1 Linear urticarial lesion on the forearm typical of jellyfish sting.

DISCUSSION

Jellyfish belong to the phylum called cnidarians or coelenterates. The unique feature of these organisms is the presence of millions of nematocysts (or stinging cells) on their tentacles, which surround the venom glands. These act as the plunger of the hypodermic syringe discharging the contents of the venom gland when activated either by contact or pressure. The organism has no control over the discharge of the nematocyst and hence, envenomation can occur when people brush against the tentacles even of dead jellyfish.

There are several species of jellyfish that have been known to produce envenomations in humans. These include the *Chironex fleckeri* (box jellyfish or sea wasp), *Carukia barnesi*, and *Physalia physalis* (Portuguese man of war). The Chironex is a large jellyfish, which has 50 to 60 tentacles each five to six feet long. Fatalities have been reported with envenomation with this species. This species tends to be found around the coastal waters of Australia and because of its lethal stings the emergency ambulance services carry the antivenom and have protocols for administering it in the prehospital setting. The Portuguese man of war jellyfish is found in tropical waters and floats on the water surface. It tends to cause severe local urticarial lesions and joint pain on being stung. *Carukia barnesi* is found off the coastal waters of Northern Australia. Its bell