Diltiazem Overdose Haemodynamic Response to Hyperinsulinaemia-Euglycaemia Therapy: A Case Report

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ABSTRACT
A 59-year-old woman was admitted to the intensive care unit after ingesting 5.76 g of an extended release preparation of diltiazem. The patient was hypotensive and bradycardic and was treated initially with intravenous fluids, adrenaline, noradrenaline, vasopressin and standard insulin doses to maintain the blood glucose levels between 6 - 10 mmol/L. As the patient remained inotrope dependent the insulin dose was increased to 25 U/hr with an infusion of 50% dextrose to maintain the blood glucose levels between 6 - 8 mmol/L. Within 30 minutes, the mean arterial pressure increased from 65 mmHg to 80 mmHg and within 60 minutes all vasoactive agents were discontinued. A right heart catheter inserted before the increased dose of insulin revealed that the predominant haemodynamic effect of the hyperinsulinaemia-euglycaemia therapy appeared to be an increase in the peripheral vascular resistance. (Critical Care and Resuscitation 2004; 6: 28-30)

Key words: Diltiazem poisoning, calcium-channel blocker, severe hypotension, bradycardia, insulin

Calcium-channel blockers act predominantly at the plasma membrane to block the slow current influx of Ca\(^{2+}\) during the plateau phase of the action potential.\(^1\) They are used for one or more of their cardiovascular effects of inhibition of conduction, chronotropism and refractoriness (particularly at the SA and AV nodes, to treat supraventricular tachycardias), negative inotropism (to treat hypertrophic subaortic stenosis) and vasodilation (to treat hypertension, angina and cerebral vasospasm).\(^1,2\)

Diltiazem is a benzothiazepine calcium channel blocker which has a similar action to verapamil, although its ability to directly reduce the rate of SA node discharge appears to be greater. It has a lower vascular/cardiac effect ratio compared with other calcium channel blockers (e.g. amlodipine and nifedipine), although its peripheral vasodilator effect is not insignificant.\(^3\) Overdosage of diltiazem is characterised by hypotension due to a combination of a negative inotropic and chronotropic effects, arrhythmias (e.g. heart block) and peripheral vasodilation.\(^4\)

We report a case of diltiazem overdosage managed initially by intravenous calcium, glucagon, adrenaline, noradrenaline, vasopressin and insulin therapy which rapidly responded to hyperinsulinaemia-euglycaemia therapy by increasing the patient’s peripheral vascular resistance.

CASE REPORT
A 59 year-old female was admitted to the intensive care unit following the ingestion of 24 x 240 mg diltiazem extended release capsules (5.76 g), 12 x 10 mg zolpidem tablets and 4 x 1 mg lorazepam tablets. She had a past history of hypertension, depression and...
five previous suicide attempts.

On examination she was drowsy but oriented. Her blood pressure was 60/35 mmHg and pulse rate was 40 beats per minute. During the next 30 minutes 2 g calcium chloride (13.6 mmol), 2 mg glucagon and 1.5 litre of 0.9% saline, were administered, resulting in her mean blood pressure increasing to 60 mmHg although her pulse remained at 40 beats per minute (Figure 1).

Plasma biochemistry revealed a sodium of 140 mmol/L, potassium 4.3 mmol/L, bicarbonate 18 mmol/L, glucose 9.0 mmol/L and a total calcium of 3.43 mmol/L. The arterial gas analysis revealed a $P_{O_2}$ of 92 mmHg, $P_{CO_2}$ 30 mmHg, pH 7.4, lactate 4 mmol/L and ionised calcium of 1.79 mmol/L.

She was admitted to the intensive care unit where a central venous catheter was inserted. She was given 50 g activated charcoal orally and adrenaline by intravenous infusion. Within 6 hours the adrenaline infusion rate had increased to 32 $\mu$g/min. A noradrenaline infusion was added and increased to 25 $\mu$g/min over the next 4 hours. Finally a vasopressin infusion at 2 U/hour was introduced. An intravenous infusion of actrapid varying between 5 - 8 U/hr was used to keep the plasma glucose level between 6 - 10 mmol/L.

After 12 hours, despite the substantial vasoactive therapy, the blood pressure remained at 93/49 mmHg (MAP 64 mmHg) although the pulse rate had increased to 84 beats per minute. A right heart catheter was inserted and revealed a cardiac index (CI) of 4.17 L/min/m$^2$, pulmonary artery occlusion pressure (PAOP) of 20 mmHg, left ventricular stroke work index (LVSWI) of 30.4 g.m/m$^2$/beat and systemic vascular resistance index (SVRI) 1016 dyne.sec/cm$^5$/m$^2$.

After 15 hours the actrapid was increased from 5 U/hr to 0.5 U/kg/hr (25 U/hr) and 50% dextrose was infused to keep the hourly plasma glucose levels varying between 6 - 8 mmol/L. Within 30 minutes the mean arterial blood pressure had increased to 80 mmHg and after a further 30 minutes the adrenaline, noradrenaline and vasopressin infusions were discontinued. The haemodynamic parameters at this stage revealed a blood pressure of 107/58 mmHg (MAP 74 mmHg), pulse rate of 77 beats per minute, CI of 2.79 L/min/m$^2$, PAOP of 14 mmHg, LVSWI of 29.1 g.m/m$^2$/beat and SVRI 1750 dyne.sec/cm$^5$/m$^2$.

The insulin infusion was continued at 25 U/hr for a further 6 hours then reduced to 10 U/hr for 2 hours and thereafter the 50% dextrose was discontinued and the insulin varied between 0 - 4 U/hr to keep the plasma glucose level varying between 6 - 8 mmol/L.

DISCUSSION

Overdosage of a calcium channel blocker (e.g. verapamil, diltiazem, nifedipine or amlodipine) may be associated with hypotension, bradycardia, hyperglycaemia and lactic acidosis. Treatment includes gastric lavage and oral charcoal as well as haemodynamic...
support. Hypotension and bradycardia may respond to intravenous fluids and calcium chloride, although adrenaline, noradrenaline, dopamine, isoprenaline, glucagon, cardiac pacing, intra-aortic balloon pump and even extracorporeal membrane oxygenation may be required.

Normally, myocyte and vascular smooth muscle cells oxidise free fatty acids for energy, but during a state of shock the cells primarily metabolise glucose for energy. However, during calcium channel blockade, secretion of insulin by pancreatic beta cells is inhibited, causing hypoinsulinaemia and a reduction in cellular entry of glucose. Glucose, insulin and potassium infusions have been used to treat experimental myocardial depression associated with verapamil poisoning, and in clinical reports of severe calcium channel blocker poisoning (e.g. verapamil, amlodipine and diltiazem), hyperinsulinaemia-euglycaemia therapy (e.g. a continuous infusion of insulin 0.5 U/kg/hr or 35 U/70kg/hr and glucose) has been used successfully to manage patients.

While a negative inotropic effect and bradycardia are often believed to be the major cause of the haemodynamic compromise in calcium channel blocker toxicity, the haemodynamic features that have been reported in diltiazem overdose are low systemic vascular resistance in the presence of a good cardiac output.

Diltiazem poisoning in our patient was associated with severe hypotension and sinus bradycardia, which required large doses of vasoactive agents to maintain a mean arterial pressure greater than 60 mmHg. The insulin dose required to manage the plasma glucose level between 6 - 10 mmol/L did not negate the requirement for inotropic agents. However, within 30 minutes of increasing the insulin infusion to 25 U/hr and infusing 50% dextrose to maintain the plasma glucose level between 6 - 8 mmol/L the mean arterial blood pressure increased to 80 mmHg. The vasoactive agents were discontinued 30 minutes later. A right heart catheter revealed that the major haemodynamic effect of the hyperinsulinaemia-euglycaemia therapy was an increase in the peripheral resistance as the LVSVI and CI did not change significantly.

Received 5 February 04  Accepted 20 February 04

REFERENCES