Novel treatment (new drug/intervention; established drug/procedure in new situation)

Massive calcium channel blocker overdose: intravenous insulin and glucose as a therapy

Gareth Rosser, Simon William Dubrey

Department of Cardiology, Hillingdon Hospital, Uxbridge, Middlesex, UK

Correspondence to Dr Simon William Dubrey, simon.dubrey@thh.nhs.uk

Summary

We describe a case of massive overdosage with cardiac medications that proved resistant to conventional support, including fluid replacement, inotropes, mechanical ventilation, cardiac pacing and haemofiltration. The use of a high-dose insulin and glucose infusion proved to be beneficial in the acute management although the patient has been left with significant impairment of cardiac function.

BACKGROUND

Overdose, both accidental and deliberate, of cardiac medicines is commonly occurring. Together, calcium channel blockers (CCBs) and β -blockers account for around 40% of these cases and, in the USA, account for around 65% of cardiovascular medicine-related deaths.¹

The case described here proved refractory to full conventional cardiovascular support, including inotropes, intravenous calcium, haemofiltration, mechanical ventilation and cardiac pacing, and required the addition of high-dose insulin therapy with glucose and potassium supplementation.

CASE PRESENTATION

A 43-year-old woman presented to a district general hospital following a deliberate polypharmacy overdose. In total, she had ingested 3360 mg of diltiazem, 1800 mg of gabapentin, 560 mg citalopram, 115 mg of diazepam and 1800 mg of irbesartan. The medical history included hypertension and chest pain. Coronary angiography was normal 4 years prior to presentation. Prior to this overdose, the patient was working and in good health.

At presentation she was conscious, profoundly hypotensive (systolic 70 mm Hg), bradycardic at 20 beats/min and in complete heart block which was resistant to atropine. Recurrent episodes of pulmonary oedema, compounded by profound hypoxia, required large doses of diuretics. The blood pressure was persistently low.

The patient was treated on intensive care for 30 days and was discharged home after full psychiatric assessment after a further 2 weeks. Ten weeks later, the patient had stable chronic kidney impairment and continued left ventricular impairment, the latter not clinically manifest for many weeks.

INVESTIGATIONS

Echocardiograms performed on days 3 and 12 of the admission showed normal cardiac dimensions and left ventricular ejection fraction (73%). However, the most recent (approximately 3 weeks after presentation) showed the left ventricular function to have deteriorated from normal to severely impaired (ejection fraction 30%).

TREATMENT

Temporary cardiac pacing was commenced and the patient was intubated and ventilated because of a drop in conscious level. Owing to profound hypotension, inotropic support was started using noradrenaline (0.01–1.40 $\mu\text{g/kg/min}$), adrenaline (0.02–0.20 $\mu\text{g/kg/min}$) and vasopressin (0.02 IU/min). Calcium supplementation was also provided using intravenous calcium chloride. The patient was now in a paced rhythm at 80 beats/min with a blood pressure of 79/30 mm Hg.

Discussion with a Poisons unit recommended treatment with high-dose insulin and glucose infusion for reversal of this CCB overdose. Dosage was suggested to start at 2 units/kg/h and to titrate against arterial blood pressure, in 2 unit increments, to a maximum infusion rate of 10 units/kg/h.

In this case, an infusion rate of 1.25 units/kg/h was used (equivalent to 2458 units/day), with 50% dextrose to maintain euglycaemia. However, higher rates of up to 350 units/h (~4.5 units/kg/h) were also initially tried over a period of 8 h. The insulin and glucose infusion was provided for 72 h, following which the haemodynamic status improved (BP 128/78 mm Hg), but renal function deteriorated and increasing anuria required haemofiltration. On day 8, a levosimendan infusion was commenced and infused at between 0.15 and 0.2 $\mu\text{g/kg/h}$ for 24 h. The cardiovascular system stabilised although persistent hypoxia necessitated consideration of extracorporeal membrane oxygenation therapy. Complete heart block recurred after the insulin infusion was stopped, which required re-establishment of temporary cardiac pacing for a further 48 h.

Frequent haemofiltration was required and subsequently over the following week, although renal function remained impaired, with a creatinine of 200 $\mu\text{mol/l}$. ACE inhibitors were started and the patient was discharged (after 30 days in an intensive care unit (ITU)) with a stable cardiac and renal status to a psychiatric unit for ongoing assessment.

OUTCOME AND FOLLOW-UP

Ten weeks after discharge from hospital, the patient has stable chronic kidney impairment and left ventricular impairment. The latter not clinically manifest for several weeks.

DISCUSSION

Overdose, both accidental and deliberate, of cardiac medicines is commonly occurring. Together, CCBs and β -blockers account for approximately 40% and about 65% of the deaths from such medications.¹ Treatment of β -blocker overdose is perhaps best understood with toxicity being pharmacologically reversed with intramuscular or intravenous glucagon.

The treatment of CCB overdose is less well appreciated, with several approaches in current use and common to both drug classes. Supportive treatments, including volume replacement, inotropic catecholamines, phosphodiesterase inhibitors, temporary pacing and intra-aortic balloon counter-pulsation, help maintain blood pressure and pulse rate.^{1–3} Some case reports indicate that supratherapeutic doses of calcium show promise through repeat boluses of calcium gluconate/chloride.^{4–5} Intralipid infusions are also used in treating CCB overdose,⁶ after initial descriptions of success in reversing toxicity from local anaesthetic agents. Their mechanism is one of sequestration of drug and effectively removing it from the serum.⁶

High-dose insulin with glucose and potassium supplementation has now emerged as a potent treatment for both severe CCBs and or β -blocker toxicity.⁷ A clear understanding of this mechanism is not evident, although a direct inotropic effect of insulin on the heart, an improvement in glucose uptake and metabolism by cardiac myocytes and improved microvascular perfusion are likely to be contributory.⁸ Whatever the mechanism, several case reports and animal studies have now demonstrated the superiority of an intravenous insulin and glucose regime, compared to calcium, glucagon or catecholamines.⁹ The calcium sensitiser, and cardiac inotrope, levosimendan has also been advocated for serious CCB overdoses,¹⁰ and was briefly tried in our patient.

The deterioration of cardiac function after 30 days in the ITU remains unexplained. The monitoring of the left ventricular function is scheduled over the coming months, with expectations of improvement.

Learning points

- Calcium channel blocker (CCB) overdose is potentially lethal through the combined effects on cardiac and vascular tissues.
- High-dose insulin and glucose infusion has proved an effective treatment for both CCB and beta blocker toxicity.
- Additional therapies in current use to treat CCB overdose include intralipid infusions to sequester the CCB and the calcium sensitiser levosimendan.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. *Toxicol Rev* 2004;**23**: 223–38.
2. Quezada Z, Lippmann M, Wertheimer J. Severe cardiac, respiratory, and metabolic complications of massive verapamil overdose. *Crit Care Med* 1991;**19**:436–8.
3. Orr GM, Bodansky HJ, Dymond DS, *et al*. Fatal verapamil overdose. *Lancet* 1982;**2**:1218–19.
4. Kenny J. Treating overdose with calcium channel blockers. *BMJ* 1994;**308**:992–3.
5. Buckley NA, Whyte IM, Dawson AH. Overdose with calcium channel blockers. *BMJ* 1994;**308**:1639–9.
6. French D, Armerian P, Ruan W, *et al*. Serum verapamil concentrations before and after Intralipid therapy during treatment of an overdose. *Clin Toxicol (Phila)* 2011;**49**:340–4.
7. Engebretsen KM, Kaczmarek KM, Morgan J, *et al*. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. *Clin Toxicol (Phila)* 2011;**49**:277–83.
8. Farah AE, Alousi AA. The actions of insulin on cardiac contractility. *Life Sci* 1981;**29**:975–1000.
9. Shepherd G, Klein-Schwartz W. High-dose insulin therapy for calcium channel blocker overdose. *Ann Pharmacother* 2005;**39**:923–30.
10. Varpula T, Rapola J, Sallisalmi M, *et al*. Treatment of serious calcium channel blocker overdose with levosimendan, a calcium sensitizer. *Anaesth Analges* 2009;**108**:790–2.

This pdf has been created automatically from the final edited text and images.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit

<http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Rosser G, Dubrey SW. Massive calcium channel blocker overdose: intravenous insulin and glucose as a therapy. *BMJ Case Reports* 2012;10.1136/bcr.03.2012.6114, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow