CASE REPORT

Management of a mixed overdose of calcium channel blockers, β -blockers and statins

Reena Thakrar,¹ Rob Shulman,² Geoff Bellingan,^{1,3} Mervyn Singer³

¹Department of Critical Care, University College London Hospital Foundation Trust, London, UK

²Pharmacy Department, University College London Hospital Foundation Trust, London, UK

³Bloomsbury Institute of Intensive Care Medicine, University College London, London, UK

Correspondence to

Reena Thakrar,
reena_thakrar13@hotmail.com

Accepted 23 May 2014

SUMMARY

We describe a case of extreme mixed overdose of calcium channel blockers, β -blockers and statins. The patient was successfully treated with aggressive resuscitation including cardiac pacing and multiorgan support, glucagon and high-dose insulin for toxicity related to calcium channel blockade and β -blockade, and ubiquinone for treating severe presumed statin-induced rhabdomyolysis and muscle weakness.

BACKGROUND

Overdoses with cardiovascular-active drugs are associated with significant morbidity and mortality.¹ Overdose with β -blockers or calcium channel blockers (CCBs) often have a similar presentation, with hypotension and bradycardia predominating,² and there is considerable overlap in treatment. Statin overdose/poisoning is not as well understood, with no consensus on the mechanisms underlying muscle myopathy and rhabdomyolysis. Its presentation is also often delayed.³

CASE PRESENTATION

A 32-year-old male prisoner was brought to the emergency department following a deliberate mixed overdose of his cell mate's medication. In total, he ingested 200 mg bisoprolol, 5040 mg modified release diltiazem and 280 mg simvastatin. He had a medical history of self-harm, suicidal attempts and depression for which mirtazapine had been prescribed, though he had been non-compliant prior to admission.

On presentation he was hypothermic (34.1°C), profoundly hypotensive (systolic blood pressure (BP) 28 mm Hg) and in complete heart block with a heart rate of 28 bpm. The attending paramedics had intubated him at the scene during cardiopulmonary resuscitation for an asystolic arrest. Return of spontaneous circulation was achieved but, on arrival in hospital, his Glasgow Coma Scale score was 3.

INVESTIGATIONS

Admission blood gas showed a mixed metabolic-respiratory acidosis with severe hypoxaemia (pH 7.17, PaCO₂ 8.36 kPa, PaO₂ 1.48 kPa, lactate 6.1 mmol/L, base deficit 5.5 mEq/L). Blood tests revealed glucose 24 mmol/L, urea 5.8 mmol/L and creatinine 169 μ mol/L. He was hypokalaemic (K⁺ 2.7 mmol/L) and creatine kinase (CK) was 51 IU/L.

TREATMENT

The patient was mechanically ventilated on arrival. Despite fluid resuscitation with 3 L colloid, he had

persisting bradycardia and hypotension (heart rate 40 bpm, BP 70/35 mm Hg) so he underwent transvenous cardiac pacing. Over the next 8 h he required high-dose vasopressor support including variable combinations of epinephrine (up to 1.4 μ g/kg/min), norepinephrine (up to 1.4 μ g/kg/min), vasopressin (up to 0.03 IU/min) and dobutamine (up to 10 μ g/kg/h). Following advice from the National Poisons Unit, he was also started on an infusion of glucagon (50–150 μ g/kg/h). This treatment regimen produced a paced rhythm of 80 bpm and blood pressure 85/50 mm Hg. Cardiac output (CO) rose to 13.2 L/min, signifying profound vasodilation.

Eight hours into his admission, he also received 30 mL of 10% calcium gluconate followed by a further three boluses over 6 h, and 20% fat emulsion (1.5 mL/kg), followed by a further 700 mL over 8 h. He was given a bolus of methylene blue (2 mg/kg) intravenously, after which his BP rose to 95/47 mm Hg. However, his lactate and base deficit rose, peaking at 17.9 and 17.2 mmol/L, respectively. In view of this severe acidosis, a 50 mL bolus of 8.4% sodium bicarbonate was given followed by an infusion running at 100 mL/h. In view of a rapid rise in creatinine (to 221 μ mol/L) and oliguria, he was started on continuous venovenous haemodiafiltration. He was also started on an insulin infusion running at 0.25 units/kg/h with supplemental glucose and potassium titrated to maintain normoglycaemia and normokalemia. After 24 h, the epinephrine, norepinephrine and glucagon were weaned, and the lactate (2.4 mmol/L) and base excess (4.4 mmol/L) had improved significantly. The glucose–insulin–potassium (GIK) infusion was discontinued after 28 h at which time his BP was 124/62 mm Hg, heart rate was paced at 80 bpm and CO was 5.7 L/min.

He made good progress, with cardiac pacing discontinued on day 3, and weaning from mechanical ventilation by day 12. There was a full neurological recovery. However, he remained oligoanuric, requiring on-going continuous renal replacement therapy, and CK continued to rise, reaching 103 000 IU/L by day 16 (figure 1). In conjunction, he developed progressive arm and leg weakness with a Medical Research Council score for muscle strength of 1–2 (a score of 5 being normal). A presumed diagnosis of statin-induced myopathy was made and he was started on oral ubiquinone 100 mg twice daily for 9 days. Unfortunately, the blood sample taken for ubiquinone levels was unsuitable for analysis. However, there was prompt improvement in his rhabdomyolysis over the next 1–2 days and, over the next week, progressive improvement in his muscle strength.

CrossMark

To cite: Thakrar R, Shulman R, Bellingan G, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-204732

Figure 1 Creatine kinase rise (CVVHDF, continuous venovenous haemodiafiltration; ICU, intensive care unit).

OUTCOME AND FOLLOW-UP

The patient was transferred 24 days after admission to a neighbouring hospital with a facility for ongoing dialysis. At this hospital he was dialysed once. Owing to improving renal function he was discharged back to prison 2 days later.

DISCUSSION

β -Adrenoreceptors are members of the G protein-coupled receptor family with three known subtypes.⁴ β_1 Receptors regulate myocardial tissue and the rate of contraction, β_2 receptors regulate smooth muscle tone and influence vascular and bronchiolar relaxation, while β_3 receptors mainly affect lipolysis. Stimulation of the β_1 receptor results in transduction of intracellular signalling pathways leading to a rise in intracellular cyclic AMP (cAMP) with consequent increases in intracellular calcium, actin-myosin cross-bridge formation and cardiomyocyte contraction. While β -blockers have relative selectivity for different β -subreceptors, in an overdose situation the receptor selectivity may be lost, leading to effects not normally seen at therapeutic doses.⁵

CCBs prevent opening of voltage-gated calcium channels in myocardial cells, smooth muscle cells and β -islet cells of the pancreas, resulting in reduced calcium entry into these cells.⁶ Dihydropyridine CCBs, such as amlodipine and nifedipine, act predominantly on peripheral vascular muscles, reducing afterload and therefore systemic blood pressure. Verapamil and diltiazem are less selective and cause negative inotropic and chronotropic effects on cardiac muscle in addition to peripheral vascular activity. CCB overdose is associated with hypotension and conduction disturbances, including sinus bradycardia and varying degrees of atrioventricular block.⁶

Initial treatment of CCB and β -blocker overdose includes airway protection and mechanical ventilation for obtunded patients, and aggressive resuscitation to restore an adequate circulation. Decontamination with orogastric lavage, activated charcoal or whole bowel irrigation are also recommended based on the clinical situation.⁷ Lavage and charcoal should be used when presentation occurs within an hour of ingestion. Whole bowel irrigation is appropriate for overdose of modified release preparations. Glucagon is recognised as a first-line therapy for severe hypotension, heart failure and cardiogenic shock resulting from either β -blocker and/or CCB overdose.⁷ It activates adenylate cyclase in cardiac tissue through stimulation of a G protein on the β -receptor, which increases intracellular cAMP. It is thus particularly useful in cases that involve concomitant β -blocker poisoning.⁸ An intravenous bolus of 5–10 mg should

be administered over 1–2 min to adults, followed by an infusion started at 50–150 μ g/kg/h and titrated to clinical response. The duration of treatment with glucagon and other supportive therapies depends not only on the clinical response but also the likely duration of effect of the CCB and β -blocker ingested, that is, five times the plasma half-life ($T_{1/2}$). Bisoprolol has a $T_{1/2}$ of 10–12 h while the once daily diltiazem preparation has a $T_{1/2}$ of 6–8 h. Our patient was given glucagon, but due to the high infusion rate required (5 mg/h) it was difficult to maintain an adequate supply. Case reports do cite success with glucagon used in conjunction with other agents.^{5–9} However, only a few report success when used as a sole agent, while several reports cite glucagon failure.^{5–10–13} This variable response is thought to be due to a combination of patient-specific factors, the timing of therapy and differences in the type of β -blockers ingested.⁹ Our patient received 325 vials of glucagon, exhausting all local supplies, at a cost of £3744.

High-dose insulin with supplemental glucose and potassium (GIK) is being increasingly used to support the circulation following β -blocker and/or CCB overdose. Indeed, animal studies demonstrate increased survival when compared with glucagon and other therapies.¹⁴ Proposed mechanisms underlying its beneficial effects are attributed to the promotion of carbohydrate metabolism and direct inotropic effects¹⁵ as compared with glucagon, which enhances fatty acid metabolism resulting in ketosis.¹⁶ GIK can increase blood pressure,¹⁷ however, its actions on heart rate and CO are thought to be the major factors responsible for improved survival.^{15–18} The effect is not seen for several hours so other measures will be needed to maintain the circulation in the interim. In our patient, this included fluid replacement, pacemaker insertion, β -agonists and α -adrenergic agonists, and calcium gluconate.¹⁹ Other vasoconstrictor options include vasopressin that activates G protein-coupled V1 receptors on vascular smooth muscle, and the guanylate cyclase inhibitor and nitric oxide scavenger, methylene blue. The rationale underlying methylene blue is that CCBs cause vasodilation through reduced influx of calcium ions into smooth muscle and by increasing endothelial nitric oxide that binds to guanylate triphosphate creating a cascade that ultimately results in vasodilation.²⁰ Intralipid infusions can also be considered in refractory cases of persistent cardiovascular collapse or asystole. The suggested antidotal mechanism is through sequestration of lipophilic toxins, decreasing their distribution into tissues.²¹ Although Toxbase advises that 1 unit/kg/h insulin would maximally saturate receptors and achieve the desired effect on contractility and blood pressure,⁷ increasing benefit is reported at higher rates, even as high as 22 unit/kg/h have been reported.¹⁵ Our patient was started on insulin at a rate of 0.25 units/kg/h, which followed our Unit guidelines for the use of high-dose GIK. As his blood pressure, heart rate and CO progressively improved, further dose increases were not required.

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, inhibit the conversion of HMG-CoA to mevalonic acid, the second step in cholesterol biosynthesis.^{22–23} A serious side effect associated with statin use is rhabdomyolysis. This results from the breakdown of skeletal muscle leading to release of myoglobin and renal tubular obstruction, presenting as acute kidney failure. It is associated with muscle pain and/or weakness and a substantial rise in CK levels.

Mechanisms by which statins cause skeletal muscle damage are complex and there is no clear consensus of opinion. Impaired synthesis of cholesterol may modify the behaviour of the myocyte membrane.²⁴ However, in vitro models have not demonstrated myotoxicity,²⁵ and inherited disorders of

cholesterol synthesis are not associated with myopathy.²⁶ Another proposed mechanism is the depletion of isoprenoids, lipid products of the HMG-CoA reductase pathway, which prevents myofibre apoptosis.^{27–28} There may also be impaired synthesis of other compounds in the mevalonate pathway, in particular ubiquinone (coenzyme Q10, CoQ10). Ubiquinone is an integral cofactor in the mitochondrial respiratory chain and is also a potent antioxidant that helps to maintain cell integrity. Deficiency leads to mitochondrial dysfunction in muscles leading to myopathy.^{29–32} Several studies have demonstrated a relationship between statin use and reduced blood CoQ10 levels, however evidence of the same relationship in muscle levels of CoQ10 is less consistent; in one report CoQ10 levels were only reduced at high therapeutic doses of specific statins, such as simvastatin and atorvastatin.³³

CoQ10 administration can increase blood CoQ10 levels in patients treated with statins,^{34–37} and may also reduce symptoms of statin-induced myopathy in patients treated with massive statin doses.^{38–40} In our patient the start of CoQ10 corresponded with a fall in CK levels from 113 228 to 269 IU/L over 9 days. Ubiquinone is a safe, cheap and readily available agent for consideration in this scenario where the patient failed to respond to conventional treatment.

More established treatments for statin-induced rhabdomyolysis include volume replacement with the aim of diluting myoglobin within the renal tubules⁴¹ and urinary alkalinisation with sodium bicarbonate to stabilise oxidised myoglobin that causes renal injury.⁴² Haemodiafiltration may also be useful in effectively removing myoglobin from the circulation in more severe cases where acute kidney failure develops or substantial hyperkalaemia is present. Combination of haemodiafiltration with alkalinisation is more effective than urinary alkalinisation alone.⁴³

Learning points

- ▶ Owing to its short half-life, high doses of glucagon may be required, and this may exhaust local stocks.
- ▶ High-dose glucose–insulin–potassium infusion will also improve cardiac performance though the effect is not immediate.
- ▶ Ubiquinone may be an effective treatment of statin-induced myopathy and rhabdomyolysis.

Contributors RT wrote the manuscript. MS, RS and GB critically reviewed the draft. All authors read and approved the final manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Shepherd G. Treatment of poisoning caused by beta-adrenergic and calcium-channel blockers. *Am J Health Syst Pharm* 2006;63:1828–35.
- 2 Reith DM, Dawson AH, Epid D, et al. Relative toxicity of beta-blockers in overdose. *J Toxicol Clin Toxicol* 1996;34:273–8.
- 3 Greve T. [Case of severe rhabdomyolysis after protracted overdose of simvastatin]. *Ugeskr Laeger* 2008;170:2981.
- 4 Buscher R, Herrmann V, Insel PA. Human adrenoreceptor polymorphisms: evolving recognition of clinical importance. *Trends Pharmacol Sci* 1999;20:94–9.
- 5 Kerns W, Kline J, Ford MD. Beta-blocker and calcium channel blocker toxicity. *Emerg Med Clin North Am* 1994;12:365–90.
- 6 Salhanick S, Shannon M. Management of calcium channel antagonist overdose. *Drug Saf* 2003;26:65–79.
- 7 National Poisons Information Service. Bisoprolol fumarate. Toxbase. April 2010. <http://www.toxbase.org/Poisons-Index-A-Z/B-Products/Bisoprolol-Fumarate> (accessed Dec 2013).
- 8 Young AC, Velez LI, Kleinschmidt KC. Intravenous fat emulsion therapy for intentional sustained-release verapamil overdose. *Resuscitation* 2009;80:591–3.
- 9 Bailey B. Glucagon in beta-blocker and calcium channel blocker overdoses: a systemic review. *J Tox Clin Toxicol* 2003;41:595–602.
- 10 Toet AE, Werner J, Vleeming W, et al. Experimental study of the detrimental effect of dopamine/glucagon combination in d,l-propranolol intoxication. *Hum Exp Toxicol* 1996;15:411–21.
- 11 Ramoska EA, Spiller HA, Winter M, et al. A one-year evaluation of calcium channel blocker overdoses: toxicity and treatment. *Ann Emerg Med* 1993;22:196–200.
- 12 Yuan TH, Kerns WP, Tomaszewski CA, et al. Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. *J Toxicol Clin Toxicol* 1999;37:463–7.
- 13 Erickson FC, Ling LJ, Grande GA, et al. Diltiazem overdose: case report and review. *J Emerg Med* 1991;9:357–66.
- 14 Kline JA, Leonova E, Raymond RM. Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized canine. *Crit Care Med* 1995;23:1251–63.
- 15 Engerbresten KM, Kaczmarek KM, Morgan J, et al. High-dose insulin therapy in beta-blocker and calcium channel blocker poisoning. *Clin Toxicol* 2011;49:277–83.
- 16 Kline JA, Raymond RM, Leonova ED, et al. Insulin improves heart function and metabolism during non-ischemic cardiogenic shock in awake canines. *Cardiovasc Res* 1997;34:289–98.
- 17 Liang C, Doherty JU, Faillace R, et al. Insulin infusion in conscious dogs. Effects on systemic and coronary hemodynamics, regional blood flows, and plasma catecholamines. *J Clin Invest* 1982;69:1321–36.
- 18 Kerns W, Schroeder D, Williams C, et al. Insulin improves survival in a canine model of acute beta-blocker toxicity. *Ann Emerg Med* 1997;29:748–57.
- 19 Shepard G, Klein-Schwartz W. High dose insulin therapy for calcium channel blocker overdose. *Ann Pharmacother* 2005;39:923–30.
- 20 Berkles R, Taugert D, Bartels H, et al. Amlodipine increases endothelial nitric oxide by dual mechanism. *Pharmacology* 2004;70:39–45.
- 21 Kenny J. Treating overdose with calcium channel blockers. *BMJ* 1994;308:992–3.
- 22 Grundy S. HMG-CoA reductase inhibitors for treatment of hypercholesterolemia. *N Engl J Med* 1998;339:24–33.
- 23 Goldstein JL, Brown MS. Regulation of the mevalonate pathway. *Nature* 1990;343:425–30.
- 24 Bruckert E, Haymen G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovasc Drugs Ther* 2005;19:403–14.
- 25 Flint OP, Masters BA, Gregg RE, et al. Inhibition of cholesterol synthesis by squalene synthase inhibitors does not induce myotoxicity in vitro. *Toxicol Appl Pharmacol* 1997;145:91–8.
- 26 Gaist D, Rodriguez LA, Huerta C, et al. Lipid-lowering drugs and the risk of myopathy: a population based follow-up study. *Epidemiology* 2001;12:565–9.
- 27 Dirks AJ, Jones KM. Statin-induced apoptosis and skeletal myopathy. *Am J Physiol Cell Physiol* 2006;291:1208–12.
- 28 Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681–90.
- 29 Peltier AC, Russell JW. Advances in understanding drug-induced neuropathies. *Drug Saf* 2006;29:23–30.
- 30 Paiva H, Thelen KM, Van Coster R, et al. High-dose statins and skeletal muscle metabolism in humans: a randomised, controlled trial. *Clin Pharmacol Ther* 2005;78:60–8.
- 31 Caso G, Kelly P, McNurlan MA, et al. Effect of co-enzyme Q10 on myopathic symptoms in patients treated with statins. *Am J Cardiol* 2007;99:1049–412.
- 32 Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy: a systemic review. *J Am Coll Cardiol* 2007;49:2231–7.
- 33 Paiva H, Thelen KM, Van Coster R, et al. High-dose statins and skeletal muscle metabolism in humans: a randomized, controlled trial. *Clin Pharmacol Ther* 2005;78:60–8.
- 34 Folkers K, Langsjoen P, Willis R, et al. Lovastatin decreases coenzyme Q levels in humans. *Proc Natl Acad Sci USA* 1990;87:8931–4.
- 35 Miyake Y, Shouzu A, Nishikawa M, et al. Effect of treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on serum coenzyme Q10 in diabetic patients. *Arzneimittelforschung* 1999;49:324–9.
- 36 Bargossi AM, Grossi G, Fiorella PL, et al. Exogenous CoQ10 supplementation prevents plasma ubiquinone reduction induced by HMG-CoA reductase inhibitors. *Mol Aspects Med* 1994;(15 Suppl):s187–93.
- 37 Silver MA, Langsjoen PH, Szabo S, et al. Effect of atorvastatin on left ventricular diastolic function and ability of coenzyme Q10 to reverse that dysfunction. *Am J Cardiol* 2004;94:1306–10.
- 38 Love JN, Howell JM, Litovitz TL, et al. Acute beta-blocker overdose: factors associated with the development of cardiovascular morbidity. *J Toxicol Clin Toxicol* 2000;38:275–81.

- 39 Kim WS, Kim MM, Choi HJ, *et al.* Phase II study of high dose lovastatin in patients with advanced gastric adenocarcinoma. *Invest New Drugs* 2001;19:81–3.
- 40 Caso G, Kelly P, McNurlan MA, *et al.* Effect of co-enzyme Q10 on myopathic symptoms in patients treated with statins. *Am J Cardiol* 2007;99:1409–12.
- 41 Schreiber DH, Anderson TR. Statin-induced rhabdomyolysis. *J Emerg Med* 2006;31:177–80.
- 42 Ramrakha P, Moore K. *Oxford handbook of acute medicine*. 2nd Edn. New York: Oxford University Press, 2004:392–3.
- 43 Peltonen S, Ahlstrom A, Kylavainio V, *et al.* The effect of combining intermittent hemodiafiltration with forced alkaline diuresis on plasma myoglobin in rhabdomyolysis. *Acta Anaesthesiol Scand* 2007;51:553–8.

Copyright 2014 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.

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