CHEST

High-Dose Insulin Euglycemic Therapy in the Treatment of a Massive Caffeine Overdose

Charles Hensher, MBBS; and John Vogel, MBBS

A 33-year-old woman experienced 90 min of in-hospital cardiac arrest following an intentional overdose of anhydrous caffeine powder. In the face of prolonged and apparently futile resuscitation attempts, high-dose insulin euglycemic therapy was initiated. A loading dose of 1 IU/kg/h of IV insulin resulted in a dramatic improvement in perfusion. This was augmented by a 72-h infusion reaching a maximal rate of 10 IU/kg/h. The patient recovered full neurologic function and survived to discharge. Although high-dose insulin is effective in beta-blocker, calcium channel blocker, and tricyclic antidepressant overdose, this is seemingly the first description of its successful use in caffeine toxicity. CHEST 2020; 157(5):e145-e149

KEY WORDS: caffeine; high-dose insulin euglycemic therapy; insulin; overdose; toxicity

Case Report

A 33-year-old woman was brought to the ED after consuming an unknown quantity of pure anhydrous caffeine powder. She was confused, ataxic, and hypotensive. An ECG revealed an irregular, narrow complex tachycardia. She experienced a tonic-clonic seizure, immediately followed by a prolonged series of cardiac arrests alternating between shockable rhythms and pulseless electrical activity. These were managed according to national guidelines, and a mechanical compression device was applied. A total of 14 mg of IV epinephrine, seven defibrillation attempts, and 300 mg of IV amiodarone were administered (Table 1). On advice from the National Poisons Information Service, calcium chloride, lipid emulsion, magnesium sulfate, and supplementary potassium chloride were also given, in addition to empirical naloxone and hydrocortisone.

Following 90 min of CPR, spontaneous circulation appeared to return. However, a bedside echocardiogram showed minimal cardiac contractility, and a central pulse was barely perceptible. Biochemically, arterial pH remained below the lowest recordable limit of 6.75, serum lactate level was 26 mM, and the clinical team discussed discontinuing resuscitation. As a last therapeutic attempt to improve cardiac output, high-dose insulin euglycemic therapy (HIET) was initiated. A loading dose of short-acting human insulin 1 IU/kg with 20 g of glucose was administered centrally, based on a treatment protocol for verapamil overdose (Table 2).[1] Immediately, there was a sudden rise in end-tidal CO_2 from 13.5 mm Hg to 33 mm Hg, noninvasive BP became recordable, and the patient exhibited spontaneous limb movements. This clinical improvement was mirrored by a simultaneous fall in serum lactate concentration from 26 mM to 19 mM, and pH rose above 6.75 (Fig 1A).

ABBREVIATION: HIET = high-dose insulin euglycemic therapy

AFFILIATIONS: From the Intensive Care Department, Ealing Hospital, London North West University Healthcare NHS Foundation Trust, Southall, United Kingdom.

This case was the subject of an oral presentation delivered by C. H. at the Association of Anaesthetists of Great Britain and Northern Ireland Annual Congress, September 11, 2019, Glasgow, United Kingdom.

CORRESPONDENCE TO: Charles Hensher, MBBS, BSc (Hons), Intensive Care Unit, Ealing Hospital, London North West University Healthcare NHS Foundation Trust, Southall, London, UB1 3HW United Kingdom; e-mail: chensher@doctors.org.uk

DOI: https://doi.org/10.1016/j.chest.2019.11.030

TABLE 1] Resuscitative Medications

Medication	Total IV Dose
Epinephrine 1:10,000	14 mg
Amiodarone	300 mg
Lipid emulsion (intralipid 20%)	500 mL
Calcium chloride 10%	10 mL
Hydrocortisone	200 mg
Magnesium sulfate	2 g
Naloxone	400 μg

In addition to standard resuscitation drugs that were administered according to national guidelines, others were given empirically or on the advice of the National Poisons Information Service.

Given this apparent response, an insulin infusion of 0.5 IU/kg/h was then commenced in addition to the dextrose with potassium chloride.

The patient was transferred to the ICU, where invasive cardiac output monitoring was commenced. A specialist assay revealed a serum caffeine concentration of 300 mg/L; no other drugs were identified in toxicology samples. The rate of insulin administration was gradually uptitrated to a peak of 10 IU/kg/h as pH and serum lactate levels continued to improve (Fig 1B). A normal cardiac index was obtained with a cumulative fluid balance of +3 L (Fig 1C). Norepinephrine was commenced on day 2 to counteract the vasodilatory effect of insulin (Fig 2). The patient was subsequently weaned from the HIET, and it was fully discontinued 72 h after commencement.

Hypoglycemia and hypokalemia were prevented throughout admission, despite a total dose of 33,920 IU of IV insulin. Serum pH normalized completely within 24 h of discontinuing the infusion, and sinus rhythm returned on day 3. Apart from complete event amnesia, the patient achieved a full neurologic recovery and was cleared by the liaison psychiatry team prior to discharge.

TABLE 2] High-Dose Insulin Euglycemic Therapy Infusion Protocol

Bolus Dose	IV Infusion (Initial Rate)
1 IU/kg short-acting human insulin IV STAT + 20 g glucose IV STAT (100 mL dextrose 20%)	0.5 IU/kg/h short-acting human insulin IV (2 IU/mL in 0.9% NaCl) + 1 L dextrose 20% + 40 mmol potassium chloride (adjusted to glycemia/electrolyte measurement)

Insulin was administered according to a weight-based initial dose and subsequent continuous central IV infusion. The rate was titrated against serum pH and lactate concentration. Concurrent fluid administration was adjusted according to glycemia and electrolyte monitoring by regular arterial blood gases. Dextrose 50% with 40 mM of potassium chloride replaced the starting fluid within 1 h of commencing the infusion. The treatment protocol was based on that described by Nickson and Little.[1] STAT = statim.

Discussion

Caffeine (1,3,7-trimethylxanthine) is a naturally occurring alkaloid and psychostimulant used in many consumer products, formulated medications, and as a dietary supplement.[2] The US Food and Drug Administration advises that daily oral intake below 400 mg (6 mg/kg) is unlikely to cause adverse effects in healthy adults.[2,3] When toxicity does occur, symptoms may be: cardiovascular (arrhythmias, palpitations, and infarction), GI (diarrhea, abdominal pain, and vomiting), or neuropsychological (anxiety, headache, and seizures).[2] There is no precise threshold at which these symptoms appear, although severe toxicity is anticipated following oral ingestion of 15 to 30 mg/kg.[4] There are relatively few reported fatalities; however, a lethal dose is estimated to be 100 to 200 mg/kg[4] or that causing a serum concentration of 80 to 100 mg/L.[5] Although we were unable to confirm the dose taken, the current study patient remarkably survived a concentration threefold greater than this upper limit.

The physiological behavior of caffeine is complex and poorly understood at toxic doses. Its first-order kinetic profile (with a half-life of 3-7 h) becomes unreliable when metabolic pathways are saturated with excess substrate.[6] Widespread cellular hyperexcitation is driven by a range of molecular mechanisms, including antagonism of gamma-aminobutyric acid and adenosine receptors, phosphodiesterase inhibition, and direct catecholamine release via $beta_1$-adrenoceptors. The resultant cardiac and neurologic instability means that resistant ventricular fibrillation is a commonly cited cause of death and is frequently preceded by seizures.[7,8] Rhabdomyolysis[8] and hypokalemia[9] have also been reported.

The successful treatment of caffeine overdose and its sequelae using lipid emulsion,[10] hemoperfusion or dialysis,[11] vasoactive drugs,[12,13] beta-blockers,[9] and other antidysrhythmic agents[13] has been reported. To our knowledge, however, this application is the first of HIET in this context, and the apparent physiological response was dramatic. After 90 min of otherwise unsuccessful resuscitation, the sudden increase in end-tidal CO_2, improved neurologic status, newly recordable

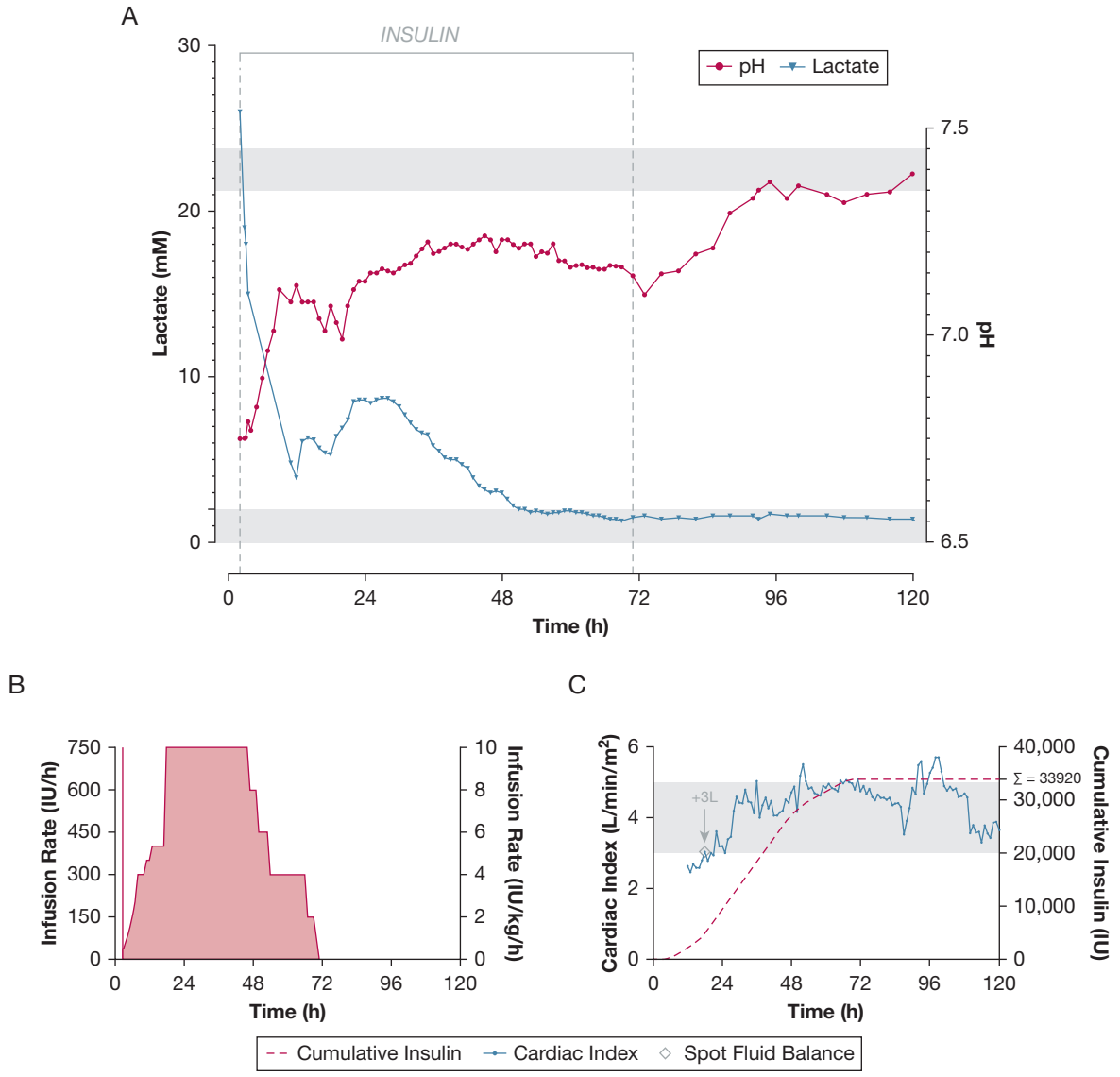

Figure *1 – A, The effect of insulin on serum pH and lactate concentration. High-dose insulin euglycemic therapy provoked correction and ultimate normalization of a severely increased serum lactate concentration. Serum pH only resolved completely following discontinuation of the insulin infusion, possibly due to hyperchloremia from administration of excess sodium chloride as a vehicle for dilute insulin. B, Insulin infusion rate. A bolus of insulin was followed by an infusion that was started at a rate of 0.5 IU/kg/h and peaked at 10 IU/kg/h. This was achieved by titration every 30 min against serum pH, lactate, and derived cardiac output measurements. It was fully discontinued 72 h after commencement. C, Cardiac index vs cumulative insulin dose. A total of 33,920 IU of insulin was given, which correlated with an increase in cardiac output. Cardiac index was first measured in the normal range with a fluid balance of +3 L (gray diamond). Shaded areas highlight normal reference ranges, where appropriate.*

BP, and metabolic correction were remarkable. Insulin is a vasodilator and potent inotrope at high doses, and it may be given safely to make use of these properties if its predictable hypoglycemic and hypokalemic effects are anticipated. So-called "glucose-insulin-potassium" infusions have improved serum lactate levels and cardiac indices in other critical low-output states (eg, septic shock, resistant heart failure) without adverse effects.[14,15] Unlike HIET, however, these regimens typically incorporate much lower insulin doses of up to 1 IU/kg/h.[14] In contrast to catecholamines, insulin forces the myocardium to metabolize glucose in preference to less efficient free fatty-acid chains, while also enhancing intracellular calcium signaling and lactate clearance.[15-18] The global effect of vasodilation, microvascular recruitment, and enhanced glucose metabolism improves myocardial perfusion and provides nonadrenergic inotropy to increase cardiac output.[16] HIET, rather than glucose-insulin-potassium, was used in this case due to its reported success in the treatment of the cardiac depression associated with beta-blocker, calcium channel blocker, and tricyclic antidepressant

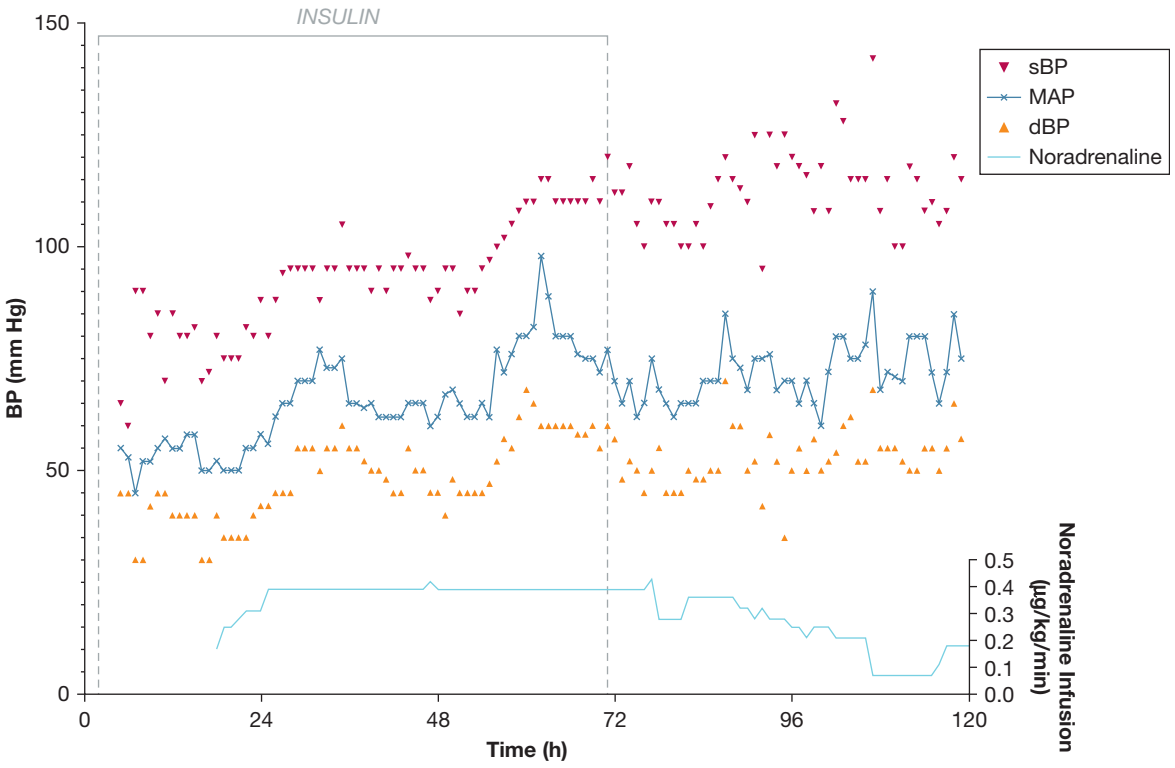

Figure 2 – *The effect of insulin and norepinephrine on BP. BP increased during administration of high-dose insulin euglycemic therapy. Norepinephrine was added latterly to support MAP by counteracting insulin's vasodilatory effect. dBP = diastolic BP; MAP = mean arterial pressure; sBP = systolic BP.*

overdoses.[19] Early use of high-dose insulin may be particularly beneficial compared with vasopressors in these cases of "toxin-induced" cardiogenic shock; insulin optimizes myocardial metabolism and promotes contractility rather than harmfully increasing afterload and cardiac work.[16,19,20] Interestingly, HIET has also been successful in cases of funnel-web spider envenomation, in which cardiogenic shock occurred following massive autonomic hyperstimulation and catecholamine release, a clinical picture similar to that of caffeine toxicity.[21] Being mindful that exogenous catecholamines also carry risks of immunologic, metabolic, and ischemic effects,[17,22] we used norepinephrine to counteract insulin's vasodilatory effect secondarily.

Although HIET does not perform as a direct antidote to caffeine, it is apparent that cardiac output, neurologic status, and acid-base imbalance improved substantially during its safe administration and most notably during resuscitation. It remains possible that the effects we observed were coincident with unrelated spontaneous recovery, endogenous caffeine clearance, delayed effect of other resuscitative medications, effective fluid administration, or a combination thereof. We regard this scenario as highly unlikely, however, due to the significant clinical and biochemical response (contemporaneous with administration of the insulin bolus), a serum caffeine level several times the lethal concentration, and because the patient had remained moribund after such prolonged resuscitation. Once spontaneous circulation returned, a normal cardiac output was also achieved with a modest positive fluid balance.

Notwithstanding the novel application of this treatment and some undescribed setbacks during admission, this patient's survival to discharge is remarkable. We believe this outcome was facilitated by HIET as a means of cardiovascular support in an unusual case of toxin-related myocardial dysfunction. We consider its efficacy to have derived from nonadrenergic metabolic and inotropic properties, which led to convincing clinical and biochemical evidence of improved perfusion. In particular, significant benefit was likely derived from its early use to optimize myocardial metabolism and contractility. In common with other descriptions of cardiotoxic drug overdoses, we suspect that increased afterload with early pressor use could have been disastrous for an already compromised myocardium.

Given both the limited therapeutic evidence available for treatment of caffeine toxicity and some concern regarding the appropriateness of catecholamines in similar clinical circumstances, we suggest this could provide an avenue for further therapeutic research.

Acknowledgments

Financial/nonfinancial disclosures: None declared.

Other contributions: The authors thank Bremner Hay, RNRO, Robert Taylor-Smith, MBBS, Priyada Pandya, MB BCh, Stuart Rosen, MD, and Harmandeep Singh, MD, as well as the ED and ICU staff at Ealing Hospital, for their relevant contributions. The authors are especially grateful to the patient for consent to publish details of her case; written consent was obtained prior to publication.

References

1. Nickson CP, Little M. Early use of high-dose insulin euglycaemic therapy for verapamil toxicity. *Med J Australia*. 2009;191(6):350-352.
2. Willson C. The clinical toxicology of caffeine: a review and case study. *Toxicol Rep*. 2018;5:1140-1152.
3. Nawrot P, Jordan S, Eastwood J, Rotstein J, Hugenholtz A, Feeley M. Effects of caffeine on human health. *Food Addit Contam*. 2003;20(1):1-30.
4. Higdon JV, Frei B. Coffee and health: a review of recent human research. *Crit Rev Food Sci Nutr*. 2006;46(2):101-123.
5. Cappelletti S, Piacentino D, Fineschi V, Frati P, Cipolloni L, Aromatario M. Caffeine-related deaths: manner of deaths and categories at risk. *Nutrients*. 2018;10(5).
6. Jones AW. Review of caffeine-related fatalities along with postmortem blood concentrations in 51 poisoning deaths. *J Analytical Toxicol*. 2017;41(3):167-172.
7. Rudolph T, Knudsen K. A case of fatal caffeine poisoning. *Acta Anaesthesiol Scand*. 2010;54(4):521-523.
8. Campana C, Griffin PL, Simon EL. Caffeine overdose resulting in severe rhabdomyolysis and acute renal failure. *Am J Emerg Med*. 2014;32(1):111.e113-e114.
9. Li SF, Edwards L, Nguyen V. Treatment of caffeine toxicity with metoprolol. *Am J Emerg Med*. 2019;37(3):562.e565-562.e510.
10. Muraro L, Longo L, Geraldini F, Bortot A, Paoli A, Boscolo A. Intralipid in acute caffeine intoxication: a case report. *J Anesthesia*. 2016;30(5):895-899.
11. Ishigaki S, Fukasawa H, Kinoshita-Katahashi N, Yasuda H, Kumagai H, Furuya R. Caffeine intoxication successfully treated by hemoperfusion and hemodialysis. *Intern Med*. 2014;53(23):2745-2747.
12. Holstege CP, Hunter Y, Baer AB, Savory J, Bruns DE, Boyd JC. Massive caffeine overdose requiring vasopressin infusion and hemodialysis. *J Toxicol Clin Toxicol*. 2003;41(7):1003-1007.
13. Kapur R, Smith MD. Treatment of cardiovascular collapse from caffeine overdose with lidocaine, phenylephrine, and hemodialysis. *Am J Emerg Med*. 2009;27(2):253.e253-e256.
14. Slob EMA, Shulman R, Singer M. Experience using high-dose glucose-insulin-potassium (GIK) in critically ill patients. *J Crit Care*. 2017;41:72-77.
15. Hamdulay SS, Al-Khafaji A, Montgomery H. Glucose-insulin and potassium infusions in septic shock. *Chest*. 2006;129(3):800-804.
16. Holger JS, Engebretsen KM, Marini JJ. High dose insulin in toxic cardiogenic shock. *Clin Toxicol (Phil)*. 2009;47(4):303-307.
17. Levy B, Bollaert PE, Charpentier C, et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. *Intensive Care Med*. 1997;23(3):282-287.
18. Licker M, Diaper J, Sologashvili T, Ellenberger C. Glucose-insulin-potassium improves left ventricular performances after aortic valve replacement: a secondary analysis of a randomized controlled trial. *BMC Anesthesiol*. 2019;19(1):175.
19. Holger JS, Stellpflug SJ, Cole JB, Harris CR, Engebretsen KM. High-dose insulin: a consecutive case series in toxin-induced cardiogenic shock. *Clin Toxicol (Phila)*. 2011;49(7):653-658.
20. Skoog CA, Engebretsen KM. Are vasopressors useful in toxin-induced cardiogenic shock? *Clin Toxicol (Phila)*. 2017;55(4):285-304.
21. Isbister GK, Sellors KV, Beckmann U, Chiew AL, Downes MA, Berling I. Catecholamine-induced cardiomyopathy resulting from life-threatening funnel-web spider envenoming. *Med J Australia*. 2015;203(7):302-304.
22. Andreis DT, Singer M. Catecholamines for inflammatory shock: a Jekyll-and-Hyde conundrum. *Intensive Care Med*. 2016;42(9):1387-1397.