High-dose insulin euglycaemic therapy (HIET): How high is high enough and what are the risks?

A Dos Santos,[1] MB ChB, DA (SA), Dip PEC (SA); **S Feris,**[1] MB ChB, FCEM (SA); **Z Farina,**[1,2] MB ChB, FCA (SA)

[1] *Department of Anaesthesia and Critical Care, Greys Hospital, Pietermaritzburg, South Africa*
[2] *Department of Anaesthesia and Critical Care, University of KwaZulu-Natal, Pietermaritzburg, South Africa*

Corresponding author: *A Dos Santos (Alessandreds@gmail.com)*

Calcium-channel blockers (CCBs) are widely prescribed in South Africa and are frequently implicated in overdose-related morbidity and mortality. We report a case of amlodipine overdose in a teenager. Her management is notable for the exceptionally high dose of insulin used as part of high-dose insulin euglycaemic therapy (HIET), far exceeding standard protocol. Despite the aggressive dosing, no clinically significant hypoglycaemia or hypokalaemia occurred. The patient showed progressive improvement and was discharged from the intensive care unit on day 3, making a full recovery. This case demonstrates that insulin doses significantly exceeding conventional protocols may be safe and effective in resource-limited settings when supported by experienced staff and close monitoring. More research is needed to guide optimal HIET dosing and safe discontinuation protocols.

Keywords. calcium-channel blocker overdose; overdose, high-dose insulin euglycaemic therapy, hypoglycaemia, hypokalaemia, adverse events, critical care, toxicology, judicious fluid therapy.

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Contribution of study

This case demonstrates that concentrated insulin formulations, combined with appropriate monitoring and level of care, can safely deliver higher than usual insulin doses. The use of concentrated insulin significantly reduces its contribution to total fluid administration, providing a practical approach to fluid stewardship. The report highlights a clinical management gap: the absence of standardised protocols for discontinuing insulin and dextrose infusions after high-dose insulin euglycaemic therapy. This case provides data on successful weaning and cessation of HIE and dextrose therapy following unconventionally high insulin dosing. High insulin doses may warrant consideration in severe calcium channel blocker toxicity when conventional haemodynamic support is unavailable or deemed insufficient.

Prescription medication is significantly implicated in cases of deliberate self-harm in South Africa (SA), and is a common cause of morbidity and mortality.[1] In particular, antihypertensives such as calcium-channel blockers (CCBs) feature prominently on the essential drug list and are widely used.[2] Overdose of CCB medication is known to be life-threatening and requires prompt treatment to achieve a good outcome.[3]

The amount of insulin administered in this case was well above the maximum rate of 10 IU/kg/h as per an accepted guideline.[4] At its peak, the rate of insulin infusion reached 32 IU/kg/h. The decision to deviate from the protocol was multi-factorial: the severity of the patient's condition; delay in presentation; lack of routine access to vasopressors, e.g. noradrenaline; and availability of an ICU bed with access to close monitoring by experienced doctors and nurses. We were encouraged by literature outlining aggressive insulin administration strategies with good outcomes.[5,6]

A 2017 consensus of experts suggested noradrenaline being preferable to adrenaline in cases of dihydropyridine overdose (OD).[4] This is due to the predominant vasoplegia observed but may not necessarily hold true owing to loss of receptor selectivity in large overdoses. Our centre – and others in the area – does not routinely have access to noradrenaline, and is consequently reliant on available therapies. Adrenergic agents have routinely been used as first-line agents. However, HIET is increasingly being advocated for as first-line therapy.[7,8]

One retrospective case review series looked at 22 patients with cardiovascular toxicity secondary to CCB and/or beta-blocker (BB) OD.[9] They found no association comparing the amount of insulin administered with the rate of adverse events; specifically, clinically significant hypoglycaemia and hypokalaemia. The maximum rate of insulin administration is most often quoted as 10 IU/kg/h, and reports of higher rates are scant. When this has been the case it has been due to human error and remedied upon discovery.[12-14] One case report described a need for prolonged dextrose administration.[11]

Case

A 13-year-old girl with no known comorbidities was transferred to the ICU in shock almost 24 hours after consuming a significant amount of amlodipine. A peripheral adrenaline infusion had been started after non-response to a fluid bolus, and was infused at a rate of 0.34 µg/kg/min. At presentation, her vital signs were as follows: blood pressure 80/38 mmHg (mean arterial pressure 52 mmHg); heart rate 153 beats per minute, respiratory rate 21 breaths per minute, and oxygen saturation 96% on room air. An arterial blood gas (ABG) sample demonstrated a compensated metabolic acidosis, with a pH of 7.41, lactate of 11.7 mmol/L, pCO_2 of 3.3 kPa, standard bicarbonate of 15.9 mmol/L and base excess of –8.9 mmol/L.

The patient's parents were updated regarding the severity of the

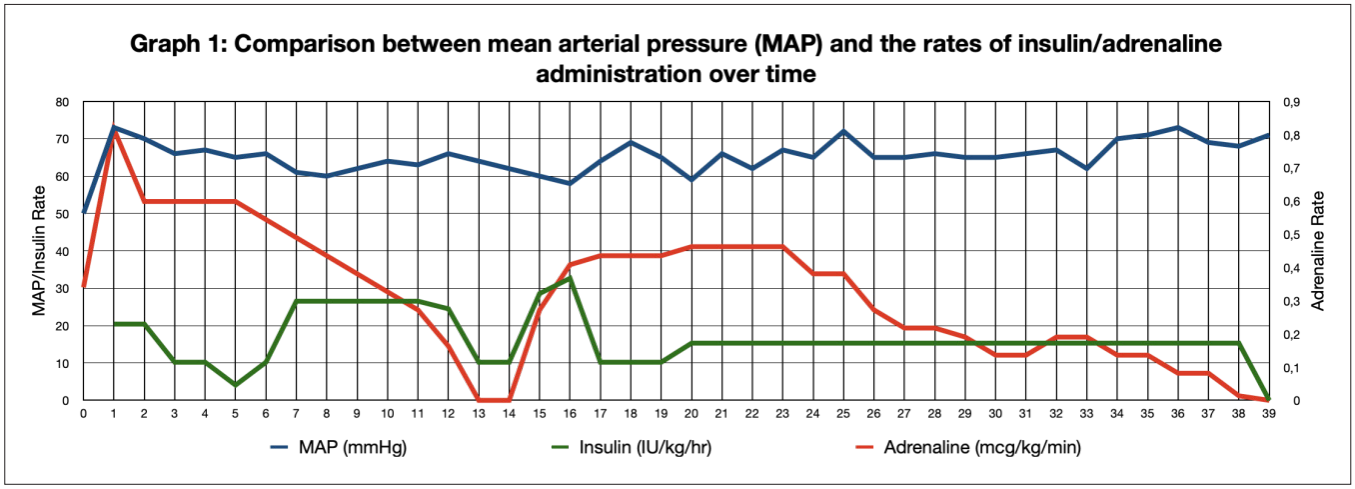

Fig. 1. Comparison between mean arterial pressure and the rates of insulin/adrenaline administration over time.

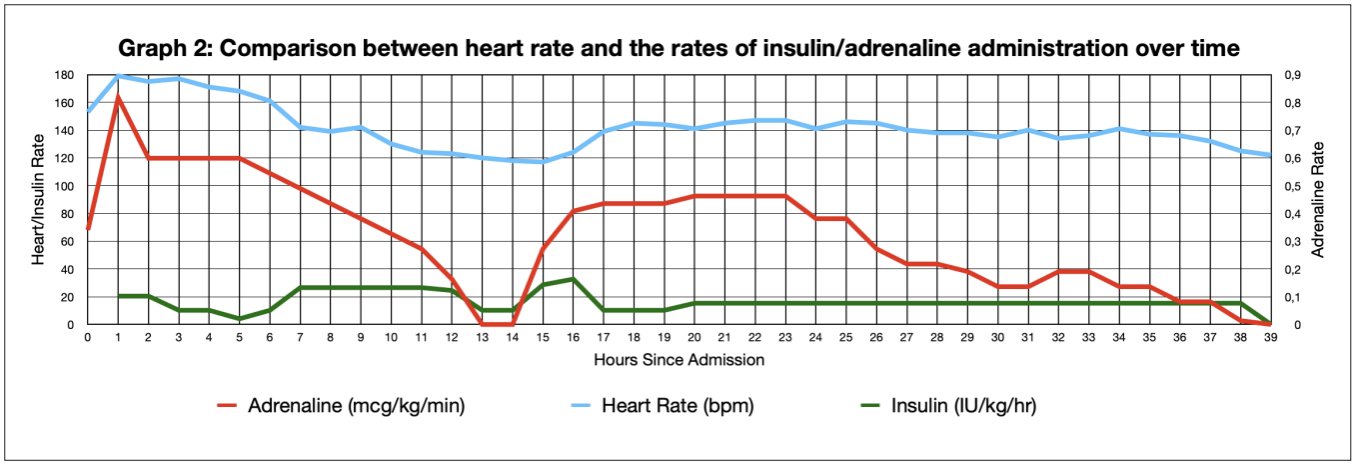

Fig. 2. Comparison between heart rate and the rates of insulin/adrenaline administration over time.

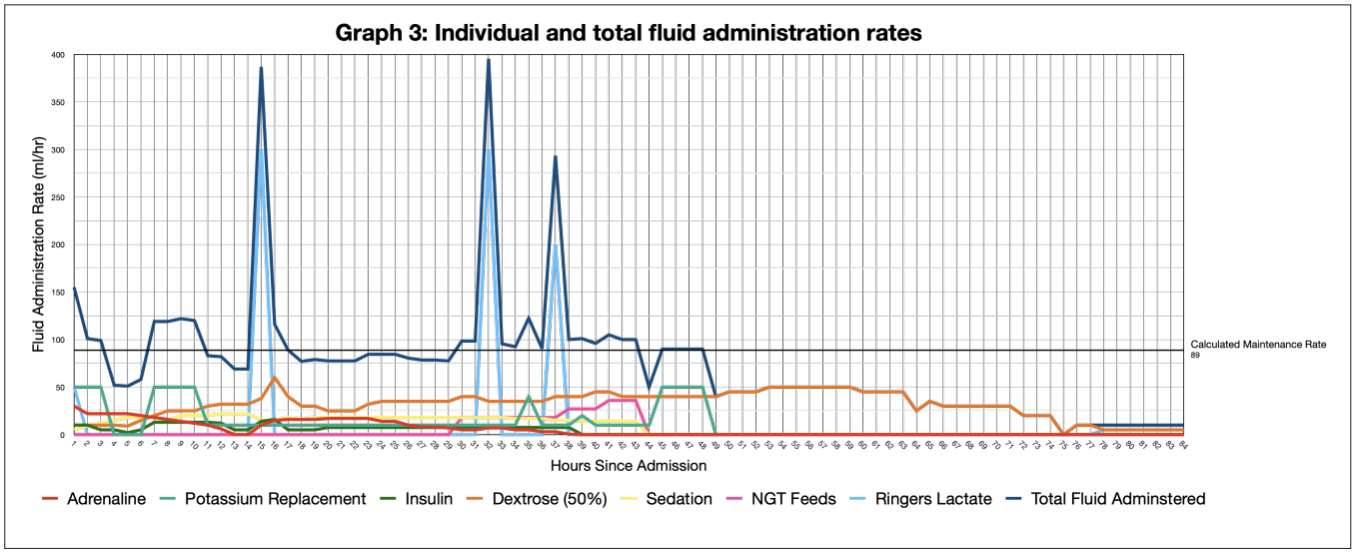

Fig. 3. Individual and total fluid administration rates.

situation and together it was decided that an aggressive approach to management would be in her best interests. Central and arterial catheters were inserted, followed by titration of the adrenaline infusion targeting a mean arterial pressure (MAP) >65 mmHg. Intubation was uneventful and was followed by commencement of central infusions of 50% dextrose, potassium phosphate (20 mmol potassium/10 mL) and insulin. Undiluted insulin (100 IU/mL) was used instead of a conventional 10 IU/mL dilution. The initial insulin infusion rate was set to 5 IU/kg/hour, and titrated upwards in accordance with potassium and glucose measurements. Potassium concentration was measured hourly until it was >3.5 mmol/L; thereafter, it was measured at the discretion of the attending clinician, who was also obliged to perform an ABG prior to the morning ward round. Glucose was measured every 20 minutes for the first hour, half-hourly for the next 4 hours and hourly thereafter. Standard glucose

monitoring in the unit occurs 4-hourly and hypoglycaemia is defined as glucose less than 4 mmol/L.

Up-titration of insulin to 26.5 IU/kg/h coincided with cessation of adrenaline administration at 13 hours after admission. This prompted the lowering of the insulin infusion to 10.2 IU/kg/h in accordance with maximum dosing as per the HIET protocol in the unit (10 IU/kg/h). However, the adrenaline infusion was soon recommenced 2 hours later at 0.27 μg/kg/min and the insulin infusion rate was increased to 28.6 IU/kg/h. This time corresponded to 05h00 – during the course of the morning, the in-coming team favoured down-titration of insulin and up-titration of adrenaline.

The average total fluid administration rate during insulin administration period was 111.4 mL/h. The percentage contribution of each infusion was as follows: insulin (7.4%), 50% dextrose water (26.8%), potassium phosphate (15.6%), adrenaline (10.8%), ketofol (15.4%), nasogastric tube feed (4%) and Ringer's lactate (20.1%). The cumulative fluid balance for this time period equated to 35 mL, while urine output averaged 1.9 mL/kg/h. Hypoglycaemia was never recorded, nor did arrhythmogenic levels of hypokalemia ever occur. The lowest glucose and potassium values measured were 5.1 mmol/L and 2.5 mmol/L, respectively.

The patient's condition steadily improved. Adrenaline and insulin were slowly weaned and stopped at 38 and 39 hours after admission, respectively. She was extubated 48 hours postintubation and placed on high-flow nasal-cannula oxygen. Respiratory support was sequentially de-escalated in accordance with respiratory effort and oxygen requirements. The patient was discharged to a medical ward 84 hours post admission, where she continued treatment for a hospital-acquired pneumonia. The medical team discontinued the dextrose infusion 5 hours later at 07h00 when day-staff arrived. No hypoglycaemic events were recorded, and the patient was discharged the next day to the psychiatric ward for further management.

Discussion

Supraphysiological insulin levels carry risks related to glucose and potassium derangements. The aforementioned case review series found no association between the amount of insulin administered and the rate of adverse events but did report a global need for supplemental dextrose after cessation of HIE therapy.[9] The duration of a dextrose infusion increased when higher rates and total amount of insulin were given. This is reflected in the comparison between their median time for glucose administration and that seen in our patient (18 and 50 hours, respectively) and supports their suggestion that higher insulin doses may be associated with greater disruption in insulin/glucose homeostasis.

Corcoran *et al.*[13] reported a case of persistent hyperinsulinaemia in a patient who had received HIE therapy. A dextrose infusion continued for almost 10 days post cessation of insulin, lending credence to fears of prolonging length-of-stay. The authors did however mention significant limitations to their study, stating that persistent hyperinsulinaemia and strict glucose targets of >4.4 mmol/L encouraged continuation of dextrose administration. The patient received 10 IU/kg/h of insulin for 37 hours, which was significantly less than the patient in our case report, who received an average of 16.7 IU/kg/h over 38 hours.

Reports of insulin administration rates greater than 10 IU/kg/h are scant, and when this occurred it has often been due to human error. One such report detailed an inadvertent insulin rate of 16.7 IU/kg/h without adverse effects.[10] Another described an unintentional insulin infusion of 22 IU/kg/h, albeit for only 2 hours, with the patient having made a full recovery with no adverse events.[11] Place *et al.*[12] reported an accidental 10 IU/kg bolus of insulin in a patient with verapamil OD which led to rapid improvement in haemodynamics, with no adverse events.

Judicious fluid management is a cornerstone of critical care, and the use of concentrated solutions has long been used as a strategy to limit iatrogenic fluid overload. Had a conventional 10 IU/ml insulin solution and equivalent total dosage of insulin been administered, the average rate of fluid infusion would have increased from 106.9 mL/h to 176.7 mL/h. This reflects a 76% increase in total amount of fluid given, far exceeding the calculated maintenance rate for her weight (87 mL/h).

Echocardiography was not performed in the management of this case. This is a limitation in that assessment of ejection fraction could have provided information on response to initiation and titration of vasoactive infusions. The down-titration and cessation of adrenaline at 13 hours coincided with lowering of the heart rate, which rose once more after adrenaline was reinitiated. This may be an advantage of insulin over adrenaline in that drug-induced sympathomimetic effects may be reduced without compromising MAP targets.

Conclusion

The optimum rate of insulin administration is unknown. High insulin doses are seemingly well-tolerated and may confer additional benefits, such as improved tissue perfusion and decreased reliance on adrenaline. Prolonged risk of hypoglycaemia may be overstated but remains a concern. No protocol-driven methods to guide the cessation of insulin or dextrose infusions in the setting of HIE therapy exist, leaving clinicians to exercise their own discretion. This may contribute to morbidity, such as longer ICU stays, unnecessary use of resources, or premature discharge from a higher-resourced unit. Further research is therefore required to elucidate approaches to this scenario. The use of concentrated insulin, vigilant monitoring and judicious fluid therapy may improve the safety of higher than usual doses of insulin as a third-line strategy to manage shock from CCB OD.

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1. Veale DJ, Wium CA, Müller GJ. Toxicovigilance. I: A survey of acute poisonings in South Africa based on Tygerberg Poison Information Centre data. S Afr Med J 2013;103(5):293-297. https://doi.org/10.7196/SAMJ.6647
2. Seedat YK, Rayner BL, Veriava Y; Hypertension Guideline Working Group. South African hypertension practice guideline 2014. Cardiovasc J Afr 2014;25(6):288-294. https://doi.org/10.5830/CVJA-2014-062. Erratum in: Cardiovasc J Afr. 2015;26(2):90.
3. Rietjens SJ, de Lange DW, Donker DW, Meulenbelt J. Practical recommendations for calcium channel antagonist poisoning. Neth J Med 2016;74(2):60-67.
4. St-Onge M, Anseeuw K, Cantrell FL, et al. Experts consensus recommendations for the management of calcium channel blocker poisoning in adults. Crit Care Med 2017;45(3):e306-e315. https://doi.org/10.1097/CCM.0000000000002087
5. Woodward C, Pourmand A, Mazer-Amirshahi M. High dose insulin therapy, an evidence-based approach to beta blocker/calcium channel blocker toxicity. J Pharmaceutical Sci 2014;22(1):36. https://doi.org/10.1186/2008-2231-22-36
6. Nickson CP, Little M. Early use of high-dose insulin euglycaemic therapy for verapamil toxicity. Med J Aust 2009;191(6):350-352. https://doi.org/10.5694/j.1326-5377.2009.tb02822.x
7. Cole JB, Arens AM, Laes JR, Klein LR, Bangh SA, Olives TD. High-dose insulin for beta-blocker and calcium channel-blocker poisoning. Am J Emerg Med 2018;36(10):1817-1824. https://doi.org/10.1016/j.ajem.2018.02.004

8. Seegobin K, Maharaj S, Deosaran A, Reddy P. Severe beta blocker and calcium channel blocker overdose: Role of high dose insulin. Am J Emerg Med 2018;36(4):736.e5-e6. https://doi.org/10.1016/j.ajem.2018.01.038
9. Page CB, Ryan NM, Isbister GK. The safety of high-dose insulin euglycaemia therapy in toxin-induced cardiac toxicity. Clin Toxicol 2017;56(6):389-396. https://doi.org/10.1080/15563650.2017.1391391
10. Engebretsen KM, Holger JS, Harris CR. Therapeutic misadventure of high dose insulin without adverse effects. Clin Toxicol 2008;46(7):604.
11. Stellpflug SJ, Harris CR, Engebretsen KM, Cole JB, Holger JS. Intentional overdose with cardiac arrest treated with intravenous fat emulsion and high-dose insulin. Clin Toxicol 2010;48(3):227-229. https://doi.org/10.3109/15563650903555294
12. Place R, Carlson A, Leikin J, Hanashiro P. Hyperinsulin therapy in the treatment of verapamil overdose. J Toxicol Clin Toxicol 2000;38:576-577.
13. Corcoran JN, Jacoby KJ, Olives TD, Bangh SA, Cole JB. Persistent hyperinsulinemia following high-dose insulin therapy: A case report. J Med Toxicol 2020;16(4):465-469. https://doi.org/10.1007/s13181-020-00796-2

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