Received: 20 October 2022 | Accepted: 5 December 2022

DOI: 10.1111/bcp.15642

SHORT COMMUNICATION

High-dose insulin should NOT be used without vasopressors in calcium channel blocker toxicity

Saskia J. Rietjens[1] | Tessa E. van Riemsdijk[1] | Maaike A. Sikma[1,2] | Dylan W. de Lange[1,2]

[1]Dutch Poisons Information Center, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands

[2]Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands

Correspondence
Saskia J. Rietjens, Dutch Poisons Information Center, University Medical Center Utrecht, Utrecht University, PO Box 85500, Utrecht 3508 GA, Netherlands.
Email: s.rietjens@umcutrecht.nl

KEYWORDS: calcium channel blocker, high-dose insulin, intoxication, overdose, poisoning, vasopressors

1 | CALCIUM CHANNEL BLOCKER OVERDOSE: CLINICAL EFFECTS AND TREATMENT

Calcium channel blockers (CCBs) are widely prescribed for different cardiovascular disorders, e.g., hypertension, coronary artery disease and cardiac arrhythmias. The primary mechanism of action of CCBs is inhibiting calcium influx by antagonism of the L-type voltage-gated calcium channels in vascular smooth muscle cells and cardiomyocytes. In overdose, CCBs can cause serious complications, such as severe hypotension, bradycardia and a diversity of conduction disturbances. Within the group of cardiovascular drugs, CCBs are the leading class of drugs associated with the largest number of poisoning fatalities.[1] Treatment of CCB overdose should first be aimed at aggressive gastrointestinal decontamination, particularly in case of patients with large recent ingestions, and supportive care, i.e., the administration of intravenous fluids, and correction of metabolic acidosis and electrolytes.[2,3] Patients with severe CCB poisoning may need a well-tailored combination of interventions, e.g., the administration of calcium, high-dose insulin (HDI) and vasopressors.[4,5] In patients refractory to these treatments, intravenous lipid emulsion or extracorporeal life support should always be considered as last resort therapy.[4,5]

2 | PROPOSED MECHANISM OF ACTION OF HDI

HDI is nowadays recommended as a first-line therapy for severe CCB poisoning based upon methodologically very modest evidence.[5] There are many proposed mechanisms for the effects of HDI in CCB poisoning. It is thought that HDI supports cardiac metabolism during cardiogenic shock. When cardiomyocytes become 'stressed', their metabolism switches from free fatty acids to glucose. HDI enhances inotropic function by increasing myocardial glucose uptake. In addition, during overdose, CCBs may inhibit calcium channels outside the cardiovascular system. Blockage of calcium channels of pancreatic islet cells decreases insulin release resulting in hyperglycaemia.[6,7] In this context, HDI improves the metabolic dysfunction observed following CCB poisoning. Furthermore, HDI is thought to alter intracellular calcium handling, which also contributes to the inotropic effect.[8] In addition, HDI causes vasodilatory effects, likely by increasing endothelial nitric oxide synthase (eNOS) activity via activation of the phosphatidylinositol-3-kinase (PI3K) pathway. This results in increased production of endothelial nitric oxide (NO), enhancing microvascular perfusion. The HDI-induced decrease in vascular resistance (vasodilation) results in enhanced cardiac output.[8] In cell culture systems, supraphysiological doses of insulin are often required to increase

eNOS activity above basal levels,[9] which is consistent with the need for relatively high insulin dosing to elicit beneficial vascular effects during CCB overdose. In order for HDI to be of greatest benefit, it should ideally be initiated early in the course of the intoxication rather than as a rescue therapy in refractory cases.[8,10,11]

3 | CURRENT EVIDENCE FOR USING HDI IN CCB OVERDOSE: METHODOLOGICALLY FLAWED

A workgroup of experts involved in the care of poisoned patients developed evidence-based recommendations to guide the in-hospital management of CCB poisoning.[5] The workgroup recommends the use of HDI in symptomatic patients as a first-line therapy if evidence of myocardial dysfunction is present. The proposed dose regimen of HDI includes a bolus of 1 U/kg followed by an infusion of 1 U/kg/h with maintenance of euglycemia with a dextrose infusion as needed. For the therapy of patients in refractory shock or periarrest, the workgroup recommends as rescue treatment incremental doses of HDI (up to 10 U/kg/h) if evidence of myocardial dysfunction is present.

Although HDI is currently proposed as a first-line treatment for severe CCB poisoning, the clinical evidence is limited, as it is largely based upon animal studies and low-quality observational studies, which are prone to confounding and bias.[12] In the consensus recommendation article by St-Onge et al.,[5] the level of evidence of HDI therapy in CCB poisoning was classified as 'Grade D: very low level of evidence', i.e., 'our estimate of the effect is just a guess, and it is very likely that the true effect is substantially different from our estimate of the effect'. Especially case reports have a high risk of publication bias, i.e., positive effects of HDI in CCB overdose are more likely to be published than negative findings.

In the consensus recommendation article by St-Onge et al.,[5] it was stated that prioritization of first-line interventions in symptomatic patients (i.e., IV calcium, HDI, vasopressors) was not possible as comparative studies were rare, and often multiple treatments were concurrently applied in patients with severe CCB overdose, making it hard to identify the true effect of a specific intervention. Therefore, the workgroup emphasized that first-line treatments for symptomatic patients should be 'prioritized based on the desired effect tailored to the individual patient's clinical condition'. Furthermore, patients often have ingested concomitant toxicants, and analytical confirmation is frequently lacking, which further complicates the interpretation of observational studies in this field.

4 | SIDE EFFECTS AND DISADVANTAGES OF USING HDI

Although HDI is proposed as a first-line treatment in CCB poisoning, it may have several disadvantages, especially considering the increasing insulin doses which are now being used. Page et al. showed that despite the apparent beneficial effects of HDI in the treatment of toxin-induced cardiac toxicity, it caused significant disruption of glucose and electrolyte homeostasis.[13] Hypoglycaemia was common and in nine of the 22 patients, hypoglycaemia was severe (<2.5 mmol/L). Hypoglycaemia occurred just as frequently during HDI therapy as after HDI was ceased. Hypokalaemia was also common, although this was often mild. Rebound hyperkalaemia after cessation of HDI occurred in a small proportion of patients. Hypomagnesaemia and hypophosphataemia were also common. There was no relationship between insulin dosing and the severity of hypoglycaemia, hypokalaemia, hypomagnesaemia or hypophosphataemia.[13] Cole et al.[14] also showed that hypoglycaemia and hypokalaemia were common adverse effects of HDI treatment, highlighting the need for close monitoring of glucose and electrolytes. Hypoglycaemia occurred less frequently when more concentrated maintenance dextrose infusions were used. Also, the use of concentrated dextrose infusions may help to reduce the risk of volume overload.[14] Schult et al.[15] showed that volume overload occurred in approximately 60% of patients with β-blocker or CCB overdose who were treated with HDI, based on documentation of pulmonary oedema, peripheral oedema or hyponatraemia.

After HDI is ceased, hypoglycaemia is common and glucose supplementation is often required for a prolonged time. A possible explanation for this finding could be that large doses of glucose administered during HDI to maintain euglycaemia stimulate endogenous insulin secretion resulting in hypoglycaemia when HDI is ceased and glucose weaning is attempted.[13] On the other hand, persistently elevated exogenous insulin could also explain the occurrence of hypoglycaemia after HDI is ceased.[16] A higher insulin infusion rate and total insulin dose were associated with a longer duration of glucose administration after ceasing HDI. This suggests that higher insulin dosing is associated with a more pronounced disruption of insulin/glucose homeostasis.[13] Discontinuation of HDI and dextrose infusions requires careful monitoring. In addition, too early insulin withdrawal could result in recurrent hypotension in patients with CCB overdose, requiring restarting or again increasing the dose of insulin.[17–19]

Another disadvantage of using HDI is that physicians may be unfamiliar with HDI and the implementation of this cumbersome therapy.[14] In contrast, physicians are much more familiar with the use of vasopressors in the treatment of shock. Furthermore, HDI does take more preparation time than the use of vasopressors and the onset of HDI-induced effects is rather slow (approximately 15 to 45 min).[2,8]

5 | HDI: ONE SIZE FITS ALL?

There are three classes of CCBs: dihydropyridines (e.g., nifedipine and amlodipine), phenylalkylamines (verapamil) and benzothiazepines (diltiazem). They differ in their relative selectivity towards cardiac *vs.* vascular calcium channels.[20] At therapeutic doses, dihydropyridines predominantly affect vascular smooth muscle cells and show little effect on the myocardium, and are mainly used to treat hypertension. In contrast, non-dihydropyridines (verapamil and diltiazem) are relatively selective for the myocardium and are used to treat cardiac arrhythmias or angina. In general, overdose of non-dihydropyridines

can cause serious hypotension, bradycardia and a diversity of conduction disturbances, including complete atrioventricular blockage.[2,21] In contrast, dihydropyridine poisoning generally causes more prominent hypotension accompanied by reflex tachycardia.[2,21] However, in severe CCB poisoning, the selectivity for cardiac *vs*. peripheral vascular effects can be profoundly decreased, making the cardiovascular effects less predictable.[2]

Review articles and consensus recommendations with respect to the management of CCB overdose basically recommend the same therapeutic strategy for all types of CCBs and do not focus on individual CCBs, as it is assumed that selectivity is lost at very high CCB doses.[5,22] However, it is conceivable that the effectiveness and potential side effects of specific therapeutic interventions vary across the different CCB classes involved or even within one class of CCBs. In other words, can the same therapeutic strategy be recommended for all types of CCBs or should the treatment advice be more tailored to the specific CCB involved? For example, HDI causes vasodilation, through enhancing eNOS activity. Amlodipine (in contrast to other dihydropyridines) also shows vasodilatory actions via increasing the release of NO in the peripheral vasculature.[2,23,24] At least theoretically, HDI could cause synergistic vasodilation when used in patients with amlodipine overdose. Therefore, despite increasing cardiac output through positive inotropy and vasodilation, it might also cause low systemic pressures and regional hypoperfusion.

In addition, it is also imaginable that HDI could be less optimal or even detrimental in specific patients. For example, HDI was ineffective in a patient with hypertrophic cardiomyopathy who had overdosed on diltiazem, metoprolol and amiodarone.[25] In this case report it has been suggested that the inotropic effect of HDI induced outflow tract obstruction in a patient with hypertrophic cardiomyopathy. Obviously, HDI may aggravate haemodynamics in patients with pre-existing obstructive cardiomyopathy.[25] Additionally, patients with pre-existing cardiomyopathy with diminished left ventricular ejection fraction may receive little benefit from HDI, and the clinical course may even worsen in such patients due to the vasodilatory effects of HDI.[14,25] Moreover, there are some theoretical concerns about the safety of HDI in children due to their lower glycogen stores and potentially greater risk of hypoglycaemia.[26] It seems, therefore, inappropriate to use a 'one size fits all' solution when treating CCB overdose, considering the different type of CCBs that are currently on the market and the fact that not all patients will respond in the same way to HDI. The patient most likely to benefit from HDI is one with a heart that has a baseline normal ejection fraction that now has drug-induced cardiogenic shock.[14]

6 | VALUE OF VASOPRESSORS IN CCB OVERDOSE

In general, the selection of vasopressors should be guided by the type of shock. It is recommended to use norepinephrine to increase blood pressure in vasoplegic shock (or if myocardial function has not yet been assessed). The use of epinephrine is also recommended to increase contractility and heart rate.[5] In the presence of myocardial dysfunction, dobutamine can also be used.[5] High infusion rates of vasopressors and inotropes may be required.[5,27]

One of the main targets for the treatment of CCB overdose is to maintain adequate tissue perfusion and oxygenation. In a porcine model of poison-induced cardiogenic shock, the pigs that were treated with a combination of HDI and norepinephrine had the best cerebral tissue oxygenation and longer survival time.[28] Although the pathophysiological mechanism for this better cerebral oxygenation needs to be elucidated, we can hypothesize that HDI causes some cerebral vasodilation which prevents cerebral ischaemia and the norepinephrine provides additional driving pressure (i.e., higher mean arterial pressure) for an adequate brain perfusion.[28]

Another potential benefit of the combination of HDI with vasopressors is that this will limit the fluid transfusions necessary to compensate the vasodilation. While there is no clear-cut definition of fluid overload, recent research suggests increased mortality in critically ill patients that have increased fluid resuscitation *vs*. those with a more limited fluid resuscitation strategy.[29]

7 | CONCLUSIONS

We conclude that HDI is a very promising treatment for patients with a suppressed myocardium induced by CCBs. However, HDI should not be used injudiciously for every CCB overdose. HDI combined with ubiquitously available vasopressors might be a smarter start for treating CCB overdosed patients leading to better brain perfusion, less fluid overload and minimal peripheral vasodilation. To improve evidence to support the existing treatments, we need comparative studies to identify the optimal treatment for each specific class of CCB in various patient groups.

COMPETING INTERESTS

There is no conflict of interest to declare.

CONTRIBUTORS

All authors made substantial contributions to the literature search and the discussion of the available literature. S.J.R. drafted the manuscript, and all authors contributed substantially to its revision. All authors gave final approval of the version to be published.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ORCID

Saskia J. Rietjens https://orcid.org/0000-0002-0338-1350
Tessa E. van Riemsdijk https://orcid.org/0000-0002-8296-3112
Maaike A. Sikma https://orcid.org/0000-0003-3872-5771
Dylan W. de Lange https://orcid.org/0000-0002-0191-7270

REFERENCES

1. Gummin DD, Mowry JB, Beuhler MC, et al. 2020 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 38th annual report. *Clin Toxicol (Phila)*. 2021; 59(12):1282-1501. doi:10.1080/15563650.2021.1989785
2. Nelson LS, Howland MA, Lewin NA, et al. *Goldfrank's toxicologic emergencies*. 11th ed. New York, NY: McGraw-Hill Education; 2019.
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. Cardiovascular drug toxicity. *Crit Care Clin*. 2021;37(3): 563-576. doi:10.1016/j.ccc.2021.03.006
5. 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. doi:10.1097/CCM.0000000000002087
6. Kerns W. Management of beta-adrenergic blocker and calcium channel antagonist toxicity. *Emerg Med Clin N Am*. 2007;25(2):309-331. doi:10.1016/j.emc.2007.02.001
7. Ohta M, Nelson J, Nelson D, Meglasson MD, Erecińska M. Effect of Ca++ channel blockers on energy level and stimulated insulin secretion in isolated rat islets of Langerhans. *J Pharmacol Exp Ther*. 1993; 264(1):35-40.
8. Engebretsen KM, Kaczmarek KM, Morgan J, Holger JS. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. *Clin Toxicol (Phila)*. 2011;49(4):277-283. doi:10.3109/15563650.2011.582471
9. Clerk LH, Vincent MA, Lindner JR, Clark MG, Rattigan S, Barrett EJ. The vasodilatory actions of insulin on resistance and terminal arterioles and their impact on muscle glucose uptake. *Diabetes Metab Res Rev*. 2004;20(1):3-12. doi:10.1002/dmrr.414
10. Graudins A, Lee HM, Druda D. Calcium channel and beta-blocker antagonist antidotes and adjunct therapies. *Br J Clin Pharmacol*. 2016; 81(3):453-461. doi:10.1111/bcp.12763
11. Greene SL, Gawarammana I, Wood DM, Jones AL, Dargan PI. Relative safety of hyperinsulinaemia/euglycaemia therapy in the management of calcium channel blocker overdose: a prospective observational study. *Intensive Care Med*. 2007;33(11):2019-2024. doi:10.1007/s00134-007-0768-y
12. St Onge M, Dubé P, Gosselin S, et al. Treatment for calcium channel blocker poisoning: a systematic review. *Clin Toxicol (Phila)*. 2014; 52(9):926-944. doi:10.3109/15563650.2014.965827
13. Page CB, Ryan NM, Isbister GK. The safety of high-dose insulin euglycaemia therapy in toxin-induced cardiac toxicity. *Clin Toxicol (Phila)*. 2018;56(6):389-396. doi:10.1080/15563650.2017.1391391
14. Cole JB, Arens AM, Laes JR, et al. High dose insulin for beta-blocker and calcium channel-blocker poisoning. *Am J Emerg Med*. 2018; 36(10):1817-1824. doi:10.1016/j.ajem.2018.02.004
15. Schult RF, Nacca N, Grannell TL, Jorgensen RM, Acquisto NM. Evaluation of high-dose insulin/euglycemia therapy for suspected β-blocker or calcium channel blocker overdose following guideline implementation. *Am J Health-Syst Pharm*. 2022;79(7):547-555. doi:10.1093/ajhp/zxab439
16. 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. doi:10.1007/s13181-020-00796-2
17. Koliastasis L, Lampadakis I, Milkas A, et al. Refractory shock from amlodipine overdose overcomed with hyperinsulinemia. *Cardiovasc Toxicol*. 2022;22(1):63-66. doi:10.1007/s12012-021-09699-2
18. Woodward C, Pourmand A, Mazer-Amirshahi M. High dose insulin therapy, an evidence based approach to beta blocker/calcium channel blocker toxicity. *Daru*. 2014;22(1):36. doi:10.1186/2008-2231-22-36
19. Yuan TH, Kerns WP, Tomaszewski CA, et al. Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. *Clin Toxicol (Phila)*. 1999;37(4):463-474. doi:10.1081/CLT-100102437
20. Ferrari R. Major differences among the three classes of calcium antagonists. *Eur Heart J*. 1997;18(Suppl A):A56-A70. doi:10.1093/eurheartj/18.suppl_A.56
21. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. *Toxicol Rev*. 2004;23(4):223-238. doi:10.2165/00139709-200423040-00003
22. Schoffstall JM, Spivey WH, Gambone LM, Shaw RP, Sit SP. Effects of calcium channel blocker overdose-induced toxicity in the conscious dog. *Ann Emerg Med*. 1991;20(10):1104-1108. doi:10.1016/S0196-0644(05)81384-8
23. Boley SP, Mackenzie RB, LeRoy JM, et al. Development and feasibility of a porcine model of amlodipine toxicity. *J Med Toxicol*. 2020;16(1): 61-66. doi:10.1007/s13181-019-00721-2
24. Zhang X, Hintze TH. Amlodipine releases nitric oxide from canine coronary microvessels: an unexpected mechanism of action of a calcium channel-blocking agent. *Circulation*. 1998;97(6):576-580. doi:10.1161/01.CIR.97.6.576
25. Stellpflug SJ, Fritzlar SJ, Cole JB, Engebretsen KM, Holger JS. Cardiotoxic overdose treated with intravenous fat emulsion and high-dose insulin in the setting of hypertrophic cardiomyopathy. *J Med Toxicol*. 2011;7(2):151-153. doi:10.1007/s13181-010-0133-3
26. Otter J, Tresenriter M, Cantrell L, et al. High dose insulin-euglycemia therapy in pediatric calcium channel blocker overdose. *Clin Toxicol (Phila)*. 2019;57(10):1026.
27. Levine M, Curry SC, Padilla-Jones A, Ruha AM. Critical care management of verapamil and diltiazem overdose with a focus on vasopressors: a 25-year experience at a single center. *Ann Emerg Med*. 2013; 62(3):252-258. doi:10.1016/j.annemergmed.2013.03.018
28. Katzung KG, Leroy JM, Boley SP, Stellpflug SJ, Holger JS, Engebretsen KM. A randomized controlled study comparing high-dose insulin to vasopressors or combination therapy in a porcine model of refractory propranolol-induced cardiogenic shock. *Clin Toxicol (Phila)*. 2019;57(11):1073-1079. doi:10.1080/15563650.2019.1580372
29. Messmer AS, Zingg C, Muller M, et al. Fluid overload and mortality in adult critical care patients—a systematic review and meta-analysis of observational studies. *Crit Care Med*. 2020;48(12):1862-1870. doi:10.1097/CCM.0000000000004617

How to cite this article: Rietjens SJ, van Riemsdijk TE, Sikma MA, de Lange DW. High-dose insulin should NOT be used without vasopressors in calcium channel blocker toxicity. *Br J Clin Pharmacol*. 2023;89(4):1275-1278. doi:10.1111/bcp.15642