The Journal of Emergency Medicine, Vol. 64, No. 3, pp. 397–399, 2023

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2022.12.010

Selected Topics: Toxicology

Use of Naloxone in Angiotensin-Converting Enzyme Inhibitor Overdose: A Case Report

Alexandra D. Haluska, MD,* Austin Davis, BS,† Noor Tarabishy, MD,* and Margarita E. Pena, MD*,‡

*Department of Emergency Medicine, Ascension St. John Hospital, Detroit, Michigan, †St. George's University School of Medicine, True Blue, Grenada, West Indies, and ‡Wayne State University School of Medicine, Detroit, Michigan

Reprint Address: Alexandra Haluska, MD, 1325 W. 59th St Upper, Cleveland OH 44012

□ **Abstract—Background: Angiotensin-converting enzyme (ACE) inhibitor overdose is an uncommonly presenting toxicologic emergency. Management is primarily supportive care, but a small body of evidence exists to support naloxone for management of hypotension. Case Report: We present a case of accidental ACE inhibitor overdose. The patient took approximately 300 mg lisinopril over 48 h and presented for evaluation of syncope. He was hypotensive and unresponsive to fluids. We administered naloxone with immediate and sustained resolution in hypotension. The mechanism of action is briefly discussed. Why Should an Emergency Medicine Physician Be Aware of This?: Naloxone is a rapid, low-risk, low-cost, and effective intervention for hypotension due to ACE inhibitor toxicity. It is supported by basic science research and clinical experience.**

□ **Keywords—ACE inhibitor overdose; toxicology; hypotension; naloxone; Narcan; lisinopril overdose**

Introduction

Angiotensin-converting enzyme (ACE) inhibitor overdose is an uncommonly presenting toxicologic emergency. It is typically characterized by hypotension and acute renal failure, and rarely, by bradycardia and lethargy, requiring intubation (1,2). Classic management is supportive care with fluids and vasopressors, and airway management, if necessary (1,3). Severe cases may require hemodialysis (1).

ACE inhibitors potentiate the effect of endogenous opioids by inhibiting the enzyme enkephalinase, which degrades β-endorphin (4,5). This endogenous opioid, β-endorphin, directly inhibits angiotensin II in the central nervous system (5). Naloxone's effect in an opioid overdose is due to direct competition of binding at the mu receptor, but in the case of ACE inhibitor overdose, it is believed to return the effect of enkephalinase, leading to increased degradation of endogenous opioids, although the mechanism is not, as yet, well described (6,7). Literature dating back to the 1980s demonstrates the antihypotensive effect of naloxone on captopril overdose in animal and human models, with a few subsequent human case reports in support, yet this does not seem to be commonly accepted into the standard armamentarium of ACE inhibitor overdose management (2,4,6–9). Here, we describe a case of a lisinopril overdose with hypotension successfully managed with naloxone.

Case Report

A 49-year-old man with a past medical history of hypertension, insulin-dependent diabetes, and poor medication adherence presented to the Emergency Department (ED) at the urging of his family after a witnessed syncopal event at home. The patient reported a home prescription of lisinopril 30 mg and an insulin regimen for which the patient could not provide the dosing, and he

Received: 3 May 2022; Final submission received: 26 September 2022;
Accepted: 13 December 2022

Table 1. Timeline of Patient Course While in the Emergency Department.

Time	Vital Signs	Interventions
22:18	BP 77/53, P 97, RR 22	Patient placed in resuscitation area; 22:25 1-L bolus LR started; POC glucose 146
22:40	BP 75/57, P 89, RR 18	
23:15	BP 84/59, P 89, RR 17	00:08 second 1-L LR bolus started
00:14	BP 75/40, P 90, RR 24	00:51 Naloxone 0.4-mg i.v. push
00:52	BP 94/63, P 84, RR 19	
01:10	BP 95/55, P 85, RR 17	
02:00	BP 90/62, P 83, RR 17	
02:40	BP 91/62, P 79, RR 18	
03:51	BP 104/70, P 82, RR 18	
04:32	BP 112/61, P 74, RR 20	04:35 Patient transferred to floor

BP = blood pressure (mm Hg); P = pulse (beats/min); RR = respiratory rate (breaths/min; LR = lactated ringers; POC = point of care.

reported not taking any other medications. The electronic medical record showed prescriptions filled in the last 90 days for loratadine 10 mg, empagliflozin-linagliptin 10 mg/5 mg, Lantus Solostar (Sanofi US, Bridgewater, NJ) 30 units twice daily, ketotifen 0.025% ophthalmic drops, amoxicillin-clavulanate 875/125, hydrocortisone/neomycin/polymyxin B otic, lisinopril 30 mg, azithromycin 250 mg, and ofloxacin otic. Social history included occasional cannabis use, and he denied opioid use. Review of the Michigan Automated Prescription System showed no opioid prescriptions. He stated that 4 days prior to presentation he developed a headache, which he thought may be due to his blood pressure. He began taking additional doses of lisinopril up to every 4 h while awake for the subsequent 2 days. The total volume of the overdose was uncertain, estimated to be approximately 10 30-mg tablets over 48 h. He suffered four episodes of syncope over the last 48 h, related to postural changes, prompting his presentation to the ED.

Vitals on arrival were significant for hypotension 77/53 mm Hg, heart rate 97 beats/min, respiratory rate 22 breaths/min with room air oxygen saturation of 98%, and temperature 37.0°C. See Table 1 for ED timeline. Physical examination showed adequate peripheral perfusion with normal capillary refill, symmetric peripheral pulses, and Glasgow Coma Scale score of 15. The patient was in no acute distress at rest, but experienced dizziness with postural changes. The patient was initially evaluated in the resuscitation area and started on a 1-L crystalloid bolus. Initial battery of laboratory work showed acute renal failure, with creatinine 6.64 mg/dL and blood urea nitrogen 63 mg/dL, mild hyponatremia 132 mmol/L, mild hypokalemia 3.1 mmol/L, mild anion gap metabolic acidosis with bicarbonate 20 mmol/L, and anion gap of 16. Lactate at the time of presentation was 3.3 mmol/L. Initial troponin-I was 0.10 ng/mL, presumed secondary to renal insufficiency.

On multiple reevaluations throughout fluid resuscitation of a total of 2 L crystalloid, the patient remained hypotensive, with systolic blood pressure persistently 70–80 mm Hg. Poison control was consulted and they recommended continued supportive care with administration of vasopressors, if necessary. An on-shift literature review was performed, which produced three case studies of hypotension related to ACE inhibitor overdose successfully treated with naloxone. We administered 0.4 mg naloxone i.v. bolus, with the plan to start a continuous infusion if repeat doses were required, and to start norepinephrine infusion if unsuccessful. Blood pressure prior to administration was 75/40 mm Hg and one min post administration improved to 94/63 mm Hg. The resolution of hypotension was sustained without further intervention. The patient did not require any additional naloxone doses. The patient was admitted to a monitored bed and discharged the next day within 24 h of presentation. He received two additional liters of crystalloid at 100 mL/h for further management of his acute renal failure, which normalized prior to discharge. He did not have any further episodes of hypotension.

Discussion

Naloxone administration for ACE inhibitor overdose has supporting evidence of both biologic mechanism and in vivo efficacy in animal and healthy human models (6,7,9). This case report adds to at least four currently in the literature of clinical efficacy in humans (2,3,5,8). In our patient, naloxone seems to be responsible for resolution of hypotension in a delayed presentation of ACE inhibitor

overdose. The patient was opioid naïve, and mental status and respiratory rate on arrival do not suggest any nondisclosed opioid use. The presumed mechanism is related to return of enkephalinase function, which had been inhibited by the lisinopril, with return of function leading to increased degradation of endogenous opioids (6,7). This cheap and simple intervention seems to have saved the patient from an invasive central line, vasopressor infusion with the associated risks, and facilitated his admission to a monitored floor bed rather than an intensive care unit bed in short supply during the COVID-19 pandemic. Research suggests that naloxone is a very low-risk drug in patients not on chronic opioid therapy, with no significant side effects (3). One negative case report was identified on literature review, detailing a patient in extremis with profound hypotension and depressed level of consciousness without response to naloxone bolus or infusion, although no apparent harm of the infusion was reported (10). It seems to be a reasonable intervention in initial management of hypotension suspected to be secondary to ACE inhibitor overdose (1).

Why Should an Emergency Physician Be Aware of This?

Naloxone is a rapid, low-risk, low-cost, and effective intervention for hypotension due to ACE inhibitor toxicity. It is supported by basic science research and clinical experience.

References

1. Lucas C, Christie GA, Waring WS. Rapid onset of haemodynamic effects after angiotensin converting enzyme-inhibitor overdose: implications for initial patient triage. Emerg Med J 2006;23:854–7.
2. Robert M, De Bels D, Chaumont M, Honoré PM, Gottignies P. Angiotensin converting enzyme inhibitor intoxication: naloxone to the rescue? Naloxone for ACE inhibitor intoxication. Am J Emerg Med 2019;37:1217 e1–2.
3. Trivedi V, Glezerson BA, Chaudhuri D, Davidson M, Douflé G. Naloxone as an antidote for angiotensin converting enzyme inhibitor poisoning: a case report. Can J Anaesth 2020;67:1442–3.
4. Di Nicolantonio R, Hutchinson JS, Takata Y, Veroni M. Captopril potentiates the vasodepressor action of met-enkephalin in the anaesthetized rat. Br J Pharmacol 1983;80:405–8.
5. Varon J, Duncan SR. Naloxone reversal of hypotension due to captopril overdose. Ann Emerg Med 1991;20:1125–7.
6. Ajayi AA, Campbell BC, Rubin PC, Reid JL. Effect of naloxone on the actions of captopril. Clin Pharmacol Ther 1985;38:560–5.
7. Millar JA, Sturani A, Rubin PC, Lawrie C, Reid JL. Attenuation of the antihypertensive effect of Captopril by the opioid receptor antagonist naloxone. Clin Exp Pharmacol Physiol 1983;10:253–9.
8. Samanta S, Samanta S, Baronia AK, Pal A. Ramipril poisoning rescued by naloxone and terlipressin. Saudi J Anaesth 2014;8:311–12.
9. Summy-Long JY, Keil LC, Deen K, Rosella L, Severs WB. Endogenous opioid peptide inhibition of the central actions of angiotensin. J Pharmacol Exp Ther 1981;217:619–29.
10. Barr CS, Payne R, Newton RW. Profound prolonged hypotension following captopril overdose. Postrad Med J 1991;67:953–4.