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Massive Sodium Nitrite Overdose: A Case for Prehospital Methylene Blue

Carlos A. Garcia-Galindo, DO[a], Lesley C. Pepin, MD[a,b,c], Travis D. Olives, MD[a,b,c], Jon B. Cole, MD[a,b,c], Holly M. Drone, PharmD[a,d], Gregg A. Jones, MD[a,b,d], Nicholas S. Simpson, MD[a,b,d], Ryan T. Fuchs[a,b,c], and Aaron E. Robinson, MD, MPH[a,b,d,*]

[a]Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, MN, USA
[b]Department of Emergency Medicine, University of Minnesota, Minneapolis, MN, USA
[c]Minnesota Poison Control System, Minneapolis, MN, USA
[d]Hennepin EMS, Hennepin Healthcare, Minneapolis, MN, USA

***Corresponding Author:** Aaron E. Robinson, MD, MPH, aaron.robinson.em.md@gmail.com

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ABSTRACT

Sodium nitrite overdose leads to profound methemoglobinemia and may quickly progress to death. It is an increasingly common method of suicide and is often fatal. Methylene blue is an effective but time-sensitive antidote that has the potential to save lives when administered early. In this case report, we describe a fatal sodium nitrite overdose and the subsequent creation of a prehospital protocol for our large urban Emergency Medical Services system.

Keywords: sodium nitrite overdose, methemoglobinemia, methylene blue, cardiac arrest, methemoglobin

INTRODUCTION

Sodium nitrite is a powerful oxidizing agent that can severely limit oxygen carrying capacity of red blood cells by inducing methemoglobinemia.(1,2) Even small ingestions can be rapidly lethal to humans as a consequence; a fatal dose of sodium nitrite may be as small as 700 mg.(3) Highly concentrated products are readily available through online retailers for industrial purposes, or for home projects such as meat curing. Likely related to sodium nitrite's accessibility and toxicity, intentional use of the compound for suicide attempts is on the rise both in the United States and internationally with mortality rates up to 33%.(2–6) A manuscript by McCann, et al outlined the rise of sodium nitrite exposure since 2017, with 84% of cases reporting serious complications including death.(3) Suicide via sodium nitrite has become the topic of multiple media articles.(7–9) Methylene blue is an effective antidote that can restore oxygen carrying capacity by reducing methemoglobin.(10,11) In massive nitrite overdoses, prompt administration of methylene blue is crucial as it can take 30 minutes to reach peak effect and may require redosing.(12) In this case report we discuss an intentional overdose of sodium nitrite in an adult woman that resulted in rapid clinical decline and cardiac arrest in the prehospital setting, illustrating the value of time-sensitive antidote availability in the prehospital setting.

SETTING

Hennepin EMS is a third-service, urban, advanced life support provider with an annual run volume of approximately 94,000 based at Hennepin Healthcare. It covers a primary service area of 266 square miles and an approximate population of 1.5 million people. The Minnesota Poison Control System is an accredited poison center that handles approximately 60,000 poisoning calls annually and is also housed at Hennepin Healthcare and provides poison control for the providers and residents in the states of Minnesota, North Dakota, and South Dakota.

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CASE REPORT

A 31 year-old woman called 9-1-1 after ingestion of a massive quantity (exact dose unknown) of sodium nitrite in a suicide attempt 5 to 10 minutes earlier. She noted that she ingested sodium nitrite, and this was the first piece of information noted in the call notes. Paramedics made initial contact with the patient within 11 minutes of the original 911 call. On paramedics' arrival, the patient answered questions and reported regretting the ingestion and a desire to live. Initial assessment by paramedics noted a Glasgow Comas Score (GCS) of 15, unsteady gait to the ambulance, rapid development of pallor and cyanosis, tachypnea, and diaphoresis. The patient had an oxygen saturation of 84% by pulse oximeter prompting initiation of 10 liters of supplemental oxygen via non-rebreather mask, which was ineffective in correcting hypoxemia, supporting a diagnosis of methemoglobinemia. The Minnesota Poison Control System was promptly notified of this case by prehospital providers; Poison Control recommended rapid transport to a facility with methylene blue. The total scene time was 23 minutes, the majority of which was patient contact and extrication. During transport, 36 minutes from time of ingestion, the patient became more cyanotic and obtunded, then displayed tonic-clonic activity. Paramedics administered 5 mg of midazolam intravenously with cessation of the activity. Oropharyngeal intubation and bag valve mask ventilation were both attempted but were difficult due to significant jaw clenching and massive emesis. The crew did not have rapid sequence intubation (neuromuscular blocker) capabilities per local protocol, but did have surgical airway capabilities.(13) During transport, a surgical airway attempt was in progress when the patient went into pulseless electrical activity (PEA) cardiac arrest. Chocolate brown-colored blood was noted during the surgical airway attempt. End tidal capnography was not applied due to task saturation with the treating provider combined with the proximity to the treating facility. Advanced Cardiac Life Support (ACLS) was immediately initiated. She arrived at the Emergency Department (ED) in asystole 3 minutes after loss of pulses. The total transport time to ED from the scene was 9 minutes.

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A prehospital paging notification made the ED team aware of an incoming unstable massive sodium nitrite ingestion case. This allowed the ED pharmacist to begin preparation of methylene blue preemptively. On arrival to the ED, it was noted that the surgical airway attempt was either mispositioned (false passage) or had become dislodged. The patient's clenched jaw had now relaxed due to cardiac arrest, so the patient's airway was initially managed with a supraglottic device and shortly after secured with orotracheal intubation. The providers elected to orotracheally intubate (versus reperforming the surgical airway) due to the patient's significantly challenging body habitus and the fact that the patient's jaw had relaxed due to cardiac arrest. The attending emergency medicine physician verified through the wound that the endotracheal tube had successfully passed into the trachea and not via a possible defect from the previous surgical airway attempt, along with waveform capnography. The surgical airway wound continued to bleed significantly so it was packed with multiple rolls of gauze with hemostasis. In addition to standard ACLS, the patient received 40 units of vasopressin and six 50 mEq doses of sodium bicarbonate intravenously to counter suspected vasoplegia and severe acidosis, respectively. A 2 mg/kg dose of methylene blue (170 mg) was administered as rapid push (due to cardiac arrest) intravenously 14 minutes after ED arrival. The dose of 170 mg was chosen based on our regional poison center guidelines for moribund patients with methemoglobinemia (2 mg/kg). Despite prenotification, administration was still delayed as the medication was stocked in the central hospital pharmacy and required additional bedside preparation.

Throughout the resuscitation, the patient exhibited findings consistent with severe methemoglobinemia including chocolate brown-colored blood from intravenous attempts and the surgical airway wound, profuse cyanosis throughout with mottled and cool extremities. Despite resuscitative efforts, the patient remained in asystole without cardiac activity on

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emergently placed transesophageal echocardiography and time of death was called 22 minutes from cardiac arrest. Laboratory results confirmed the patient had a methemoglobin level of 84.4%. Additional venous labs included a pH of 7.27, HCO3 of 20 mmol/L, and lactate of 20 mmol/L. These labs were collected during the concomitant administration of sodium bicarbonate by the ED team in the contralateral extremity, but prior to methylene blue administration. On postmortem follow up 168 hours after time of death, the postmortem methemoglobin was still markedly elevated at 45%.

DISCUSSION

We report a case of rapidly fatal acquired methemoglobinemia secondary to intentional ingestion of sodium nitrite. The patient decompensated from a hemodynamically stable state with normal mental status to cardiac arrest within 40 minutes of the estimated time of ingestion secondary to severe methemoglobinemia. The timeline of the patient's clinical course is outlined in Figure 1. Methylene blue does not reverse methemoglobinemia instantaneously. Prehospital access to this antidote prior to cardiac arrest may have improved the outcome in this case. Similar cases with slightly faster times to methylene blue administration have resulted in survival.(12,14,15) Neth, et al recently described a similar case report and how early notification and rapid recognition is key in survival.(1) Our goal is to take it a step further and place the antidote in the hands of prehospital clinicians.

A recent abstract by Olives, et al reviewed the ability of Twin Cities, MN hospitals to treat methemoglobinemia. All hospitals in the Minneapolis - St. Paul metro area carry methylene blue except for one smaller Level III Trauma Center in Burnsville, MN, a suburb of Minneapolis. However, only two of these hospitals carry methylene blue in their ED, possibly risking a delay in therapy.(16)

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This case triggered a review of sodium nitrite overdoses in our primary service area. Medical Direction at Hennepin EMS is heavily involved with EMS operations both in the field and the ED, and we are frequently collaborating with various specialties to improve patient care. In this case, we involved our toxicology colleagues to come up with a solution. We reviewed both our EMS / hospital internal data and more national data. Once it was decided to move forward with methylene blue, it took approximately 3 months from this case to deployment, a relatively rapid system change in EMS operations. This is partly due to the fact Hennepin EMS has an Emergency Medicine Pharmacist specifically dedicated to EMS. This EMS pharmacist is a novel role, but we have noted many benefits beyond rapid medication changes/deployment. These additional benefits are beyond the scope of this manuscript.(17)

The effectiveness of methylene blue in the treatment of methemoglobinemia is dependent on intact systemic circulation as well as multiple successful reduction-oxidation reactions. Though methylene blue itself is an oxidizing agent, when in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) and the enzyme NADPH methemoglobin reductase, methylene blue is rapidly reduced to leukomethylene blue. Leukomethylene blue subsequently reduces methemoglobin to hemoglobin. Methylene blue readily accepts and donates electrons allowing it to act as both an oxidizing and reducing agent. Leukomethylene blue in turn can donate an electron to the oxidized form of iron (ferric or Fe3+) in methemoglobin, restoring hemoglobin (ferrous iron or Fe2+)(18). Within minutes methylene blue begins to correct methemoglobinemia, with peak effect reached in approximately 30 minutes.(19) Pulse oximetry readings will be inaccurate in the setting of methemoglobinemia, as occurred in this case. This occurs because most pulse oximeters are not calibrated properly to read methemoglobin, resulting in an inaccurate pulse oximetry reading that typically remains between 84 - 86% regardless of supplemental oxygen. Pulse oximetry becomes additionally unreliable in the moments immediately after methylene blue administration; pulse oximetry will typically read falsely very low in the minutes immediately after methylene blue administration

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due to the absorption wavelength of methylene blue. In both circumstances blood gas measurements are typically needed to determine an accurate oxygen saturation.(20)

It is incredibly rare to survive cardiac arrest secondary to profound methemoglobinemia.(14) Thus, prompt and often necessarily empiric administration of methylene blue in patients who are critically ill with history and clinical findings to support a diagnosis of methemoglobinemia is vital.(12,14,21,22) Though methemoglobin levels greater than 70% are commonly associated with death, survival is reported with methemoglobin levels as high as 92% if methylene blue is promptly administered.(21) In our case, a narrow window where methylene blue could have been lifesaving was limited primarily to the prehospital setting.

Though not a surgical airway focused manuscript, the authors feel that discussion of the surgical airway attempt is paramount given its rarity but necessity in the prehospital setting.(13) Prehospital medical direction reviewed this case extensively with the providers. Medical Direction agrees with the indication to perform a surgical airway in this case in the absence of paralyzing agents. Challenges for this attempt include extreme body habitus with a thick, short, and round neck. Prehospital clinicians should pull over during critical and rare but necessary procedures to maximize success, and end tidal capnography should be utilized immediately. Had the jaw not been completely relaxed on arrival to the ED, the EM Physicians had planned on re-attempting the surgical airway via the wound. Of note, there were no major vessels damaged on the post-mortem examination. The surgical airway wound was extremely bloody, and it demonstrated to us just how much these can bleed. It truly is a procedure of “feel.”

Prehospital access to antidotes is not a novel concept. Currently, antidotes available to EMS in the U.S. include naloxone for opioids, atropine and pralidoxime for organophosphates, sodium bicarbonate for sodium channel blocking agents and hydroxocobalamin for cyanide. Hennepin

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EMS maintains access to all of those antidotes. Frequency of use of these medications differ and the protocols in place to support prehospital personnel may range from standing protocols to involvement of medical direction for guidance. However, all these antidotes share the common thread of being time-sensitive. Despite best efforts in this case, the patient did not receive the antidote for over an hour from time of ingestion. Multiple aspects of the primary service area must be considered, including EMS transport times, dispatch processes, "jump car" availability, and hospital capability. We feel the addition of methylene blue to our prehospital antidotes has the potential to have a significant impact on these patients. Based on our timeline, even if methylene blue was administered immediately prior to scene departure (time = 34 minutes), it would have been 30 minutes faster than had the patient received it in an ED (time = 64 minutes in our case). Finally, in practice, methylene blue does not require unique storage conditions and is straightforward to dose and deliver to patients with few contraindications, such as glucose-6-phosphate dehydrogenase deficiency.

Hennepin EMS developed a novel methylene blue protocol in response to this case. While methylene blue is relatively expensive compared to other medications that the service carries, this is a medication that has the potential to make a significant difference in prehospital care and typically is less expensive than some other antidotes, such as hydroxocobalamin. To combat the higher cost, Hennepin EMS has developed a system of storing the methylene blue in a supervisor's vehicle. With our dispatch protocols and primary service area, with timely dispatch of the supervisor vehicle, they should be able to arrive on scene within minutes of the primary crew. There is always at least one supervisor on duty at all times with a vehicle to cover a 266 square mile primary service area, with a maximum response time of about 22 minutes in the most remote areas. At times, a second supervisor or EMS physician will also be in the field with the same antidotes. The entire service had already been trained on recognition of methemoglobinemia, however, the only definitive treatment available was rapid transport. All

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supervisors (approximately 20 paramedics) were trained on the indications, preparation, and administration of methylene blue via protocol update education. Training was short, roughly 30 minutes. After review of our most recent sodium nitrite overdoses resulting in 911 calls, all mention “sodium nitrite” in the pre-arrival information that the dispatcher collects. We suspect this is from the background research required of someone with the intent to fatally overdose on a substance, and the common internet fallacy that sodium nitrite ingestion is a rapid, painless method of completing suicide. In our protocol, we added other potential names for sodium nitrite, including “sodium nitrate,” “curing salt,” and “pink salt.” Sodium nitrate is not identical to sodium nitrite, but may be mistakenly used interchangeably, and it is also an oxidizing agent. If this type of overdose is suspected, the dispatcher will automatically dispatch the EMS Supervisor to the scene. If there are findings on scene or with the patient that indicate sodium nitrite ingestion, methylene blue will be given per protocol at 100 mg, which equals 1-2 mg/kg for most adult-sized patients. If the supervisor is not yet on scene and the crew is ready to depart, crews will not delay transport for the EMS supervisor. An en route rendezvous may be considered depending on circumstances, though most of our transport times do not exceed 20 minutes. Precautions such as pregnancy and contraindications such as G6PD deficiency are included but can be discussed with Medical Control or the Poison Control System. Additional guidance to administer doses of methylene blue over 5 minutes, as well as anticipatory guidance of expected unreliable SpO2 monitoring after administration and possible paradoxical methemoglobin formation if rapidly injected, have also been deployed. If the patient is already in cardiac arrest, the protocol instructs to administer methylene blue as a rapid bolus. Administering additional doses of methylene blue may then be considered once to the receiving ED.(18) Of note, our ED at Hennepin County Medical Center will also start stocking methylene blue in the Stabilization Room Omnicell (instead of inpatient pharmacy) due to this case as well. Paramedics already maintain expertise in the administration of time-sensitive antidotes and thus

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emergency medical services should consider adding methylene blue to their armamentarium of antidotal therapies.

CONCLUSION

Sodium nitrite ingestions are often rapidly fatal, increasing in prevalence, and have a very specific and highly effective antidote. EMS services may consider adding methylene blue to their protocols to reduce mortality in this critically ill population.

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REFERENCES

1. Neth MR, Love JS, Horowitz BZ, Shertz MD, Sahni R, Daya MR. Fatal Sodium Nitrite Poisoning: Key Considerations for Prehospital Providers. Prehosp Emerg Care. 2021;25:844–850. Cited: in: : PMID: 33074043.

2. Padovano M, Aromatario M, D'Errico S, Concato M, Manetti F, David MC, Scopetti M, Frati P, Fineschi V. Sodium Nitrite Intoxication and Death: Summarizing Evidence to Facilitate Diagnosis. Int J Environ Res Public Health [Internet]. 2022;19. doi: 10.3390/ijerph192113996. Cited: in: : PMID: 36360874.

3. McCann SD, Tweet MS, Wahl MS. Rising incidence and high mortality in intentional sodium nitrite exposures reported to US poison centers. Clin Toxicol. 2021;12:1–6. Cited: in: : PMID: 33787434.

4. Hickey TBM, MacNeil JA, Hansmeyer C, Pickup MJ. Fatal methemoglobinemia: A case series highlighting a new trend in intentional sodium nitrite or sodium nitrate ingestion as a method of suicide. Forensic Sci Int. 2021;326:110907. Cited: in: : PMID: 34298207.

5. Wettstein ZS, Yarid NA, Shah S. Fatal methaemoglobinemia due to intentional sodium nitrite ingestion. BMJ Case Rep [Internet]. 2022;15. doi: 10.1136/bcr-2022-252954. Cited: in: : PMID: 36524260.

6. Saleh D, Lucyk S, McGillis E. Methemoglobinemia caused by sodium nitrite overdose. CMAJ. 2022;194:E1066–E1067. Cited: in: : PMID: 35940618.

7. U.K. police say 88 people who bought lethal substance from Canadian websites have died. CBC News [Internet]. 2023 Aug 26 [cited 2024 Mar 26]; Available from: https://www.cbc.ca/news/world/britain-law-nitrite-probe-1.6947359.

8. Crawford A, Smith T. Poison seller tied to suicide forum tracked down by BBC. BBC [Internet]. 2024 Mar 1 [cited 2024 Mar 26]; Available from: https://www.bbc.com/news/uk-68347415.

9. Al-Arshani S. Former Canadian chef Kenneth Law accused of selling suicide kits faces 14 counts of murder. USA Today [Internet]. 2023 Dec 13 [cited 2024 Mar 26]; Available from: https://www.usatoday.com/story/news/world/2023/12/13/suicide-kits-chef-charged-murder-kenneth-law-canada/71905908007/.

10. Sikka P, Bindra VK, Kapoor S, Jain V, Saxena KK. Blue cures blue but be cautious. J Pharm Bioallied Sci. 2011;3:543–545. Cited: in: : PMID: 22219589.

11. McDonagh EM, Bautista JM, Youngster I, Altman RB, Klein TE. PharmGKB summary: methylene blue pathway. Pharmacogenet Genomics. 2013;23:498–508. Cited: in: : PMID: 23913015.

12. Mudan A, Repplinger D, Lebin J, Lewis J, Vohra R, Smollin C. Severe Methemoglobinemia and Death From Intentional Sodium Nitrite Ingestions. J Emerg Med. 2020;59:e85–e88. Cited: in: : PMID: 32713620.

13. Reardon RF, Robinson AE, Kornas R, Ho JD, Anzalone B, Carlson J, Levy M, Driver B.

Accepted Manuscript

Information Classification: General

Prehospital Surgical Airway Management: An NAEMSP Position Statement and Resource Document. Prehosp Emerg Care. 2022;26:96–101.

14. Fuchs RT, McHale EK, Zarzar RA, Cole JB. A woman with pallor, cyanosis, and bounding peripheral pulses immediately after overdose. J Am Coll Emerg Physicians Open. 2022;3:e12669. Cited: in: : PMID: 35387321.

15. McCann SD, Kennedy JM, Tweet MS, Bryant SM. Sodium Nitrite Ingestion: an Emerging Trend in Suicide Attempts Shared via Online Communities. J. Emerg. Med. 2021. p. 409–412.

16. Olives T., Goldstein J., Forgette M., Young P., Cole J. Are hospitals ready for the sodium nitrite surge? Availability of methemoglobin testing and methylene blue stocking in a 3-state region.". Clin Toxicol. 2022;60:1–162.

17. Negatu J. The unmet need for pharmacist-provided patient care within EMS [Internet]. American Pharmacists Association. 2019 [cited 2024 Mar 26]. Available from: https://www.pharmacist.com/Publications/Transitions/the-unmet-need-for-pharmacist-provided-patient-care-within-ems.

18. Ginimuge PR, Jyothi SD. Methylene blue: revisited. J Anaesthesiol Clin Pharmacol. 2010;26:517–520. Cited: in: : PMID: 21547182.

19. Hartmann AF, Perley AM, Barnett HL. A STUDY OF SOME OF THE PHYSIOLOGICAL EFFECTS OF SULFANILAMIDE. II. METHEMOGLOBIN FORMATION AND ITS CONTROL. J Clin Invest. 1938;17:699–710. Cited: in: : PMID: 16694616.

20. Kirlangitis JJ, Middaugh RE, Zablocki A, Rodriquez F. False indication of arterial oxygen desaturation and methemoglobinemia following injection of methylene blue in urological surgery. Mil Med. 1990;155:260–262. Cited: in: : PMID: 2122301.

21. Katabami K, Hayakawa M, Gando S. Severe Methemoglobinemia due to Sodium Nitrite Poisoning. Case Rep Emerg Med. 2016;2016:9013816. Cited: in: : PMID: 27563472.

22. Dela Cruz M, Glick J, Merker SH, Vearrier D. Survival after severe methemoglobinemia secondary to sodium nitrate ingestion. Toxicology Communications. 2018;2:21–23.

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Figure 1

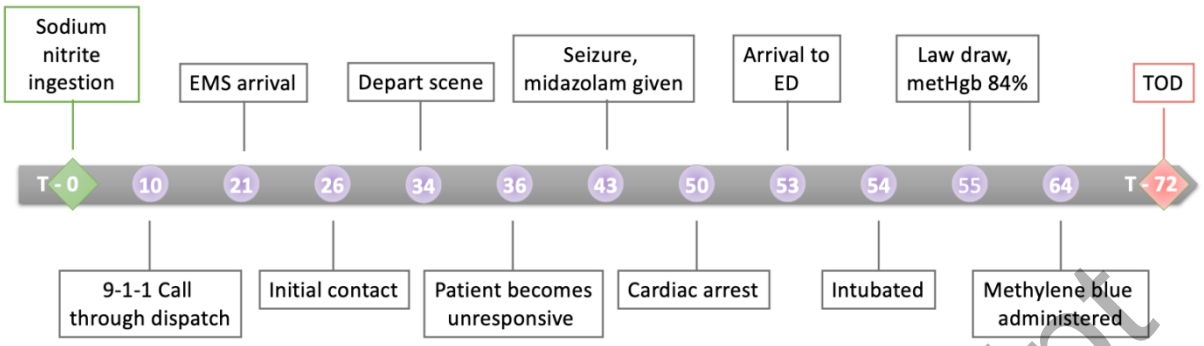


Figure 1: Timeline of the patient's prehospital course from ingestion of sodium nitrite to time of death in minutes.

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