ORIGINAL RESEARCH

Effect of Extreme Temperature on Naloxone Nasal Spray Dispensing Device Performance

Michael Estephan, MD;[1] Carly Loner, MD;[2] Nicole M. Acquisto, PharmD[2,3]

1. University of Rochester School of Medicine and Dentistry, Rochester, New York USA
2. Department of Emergency Medicine, University of Rochester, Rochester, New York USA
3. Department of Pharmacy, University of Rochester Medical Center, Rochester, New York USA

Correspondence:
Nicole M. Acquisto, PharmD
Departments of Pharmacy and Emergency Medicine
University of Rochester Medical Center
601 Elmwood Avenue, Box 638
Rochester, New York 14642 USA
E-mail: nicole_acquisto@urmc.rochester.edu

Conflicts of interest: none

Keywords: administration; intranasal; naloxone; nasal sprays; temperature

Abbreviations:
MDI: metered dose inhalers
RBF: round bottom flask
WHO: World Health Organization

Received: October 16, 2019
Accepted: December 08, 2019

doi:10.1017/S1049023X20000400

Abstract

Introduction: The opioid epidemic has led to the wide-spread distribution of naloxone to emergency personnel and to the general public. Recommended storage conditions based on prescribing information are between 15°C and 25°C (59°F and 77°F), with excursions permitted between 4°C and 40°C (39°F and 104°F). Actual storage likely varies widely with potential exposures to extreme temperatures outside of these ranges. These potentially prolonged extreme temperatures may alter the volume of naloxone dispensed from the nasal spray device, which could result in suboptimal efficacy.

Study Objective: The aim of this study was to assess the naloxone volume deployed following nasal spray device storage at extreme temperatures over an extended period of time.

Methods: Naloxone nasal spray devices were exposed to storage temperatures of -29°C (-20°F), 20°C (68°F), and 71°C (160°F) to simulate extreme temperatures and a control for 10 hours. First, the density was measured under each temperature condition. Following the density calculation part of the experiment, the mass of naloxone dispensed from each nasal spray device at each temperature was captured and used to calculate volume: calculated volume (microliter, µl) = spray mass (mg converted to g)/mean density (g/mL). Measurements and calculations are reported as means with standard deviation and standard error, and a one-way ANOVA was used to evaluate mean dispensed volume differences at different temperatures.

Results: There was no difference in the mean volume deployed at -29°C (-20°F), 20°C (68°F), and 71°C (160°F), and measurements were 101.44µl (SD = 9.56; SE = 5.52), 99.01µl (SD = 6.31; SE = 3.64), and 108.28µl (SD = 2.04; SE = 1.18), respectively; P value = .289, F-statistic value = 1.535.

Conclusion: The results of this study suggest that naloxone nasal spray devices will dispense the appropriate volume, even when stored at extreme temperatures outside of the manufacturer's recommended range.

Estephan M, Loner C, Acquisto NM. Effect of extreme temperature on naloxone nasal spray dispensing device performance. *Prehosp Disaster Med.* 2020;35(3):272–275.

Introduction

Opioid overdose is the leading cause of death amongst all instances of drug overdoses in the United States. From 1999 to 2017, the death toll from overdoses involving opioids has more than quintupled, and presently two out of every three deaths attributed to drug overdose involves an opioid.[1,2] In an attempt to curb this, naloxone use in the prehospital setting by both emergency personnel and laypersons has increased substantially in recent years, leading to an overall reduction in mortality following an opioid overdose.[3] The World Health Organization (WHO; Geneva, Switzerland) guideline, opioid overdose management in the community, recommends that "people likely to witness an opioid overdose have access to naloxone and be instructed in its administration."[4] Subsequent studies have shown that take-home naloxone programs reduce overdose mortality among both program participants and in the surrounding community with a low rate of adverse events.[5] In 2015, naloxone was added to the WHO Model List of Essential Medicines.[6]

With such wide-spread possession of naloxone by laypeople, law enforcement and fire personnel, and prehospital medical providers in the community, it can be inferred that conditions amongst which it is stored vary widely. Prescribing information for naloxone nasal spray states that the device should not be allowed to freeze and should be stored at room temperature between 15°C and 25°C (59°F and 77°F), with excursions permitted between 4°C and 40°C (39°F and 104°F).[7] Similarly, it is recommended that naloxone

injection used for intravenous, intramuscular, subcutaneous, or intranasal with a nasal atomizer is stored at controlled room temperature between 20°C and 25°C (68°F and 77°F).[8] However, there are several studies showing storage temperature fluctuations for medications in emergency response vehicles.[9-11] Specifically, ambulance medication storage is reported as low as -14°C (7°F) and greater than 40°C (104°F), depending on the season, and within air-medical helicopters to range between 13°C and 31°C (55°F and 89°F).[9,10] One study found that the temperature at which medications are stored in emergency response vehicles in five geographically diverse locations (Arizona, Florida, Kansas, New York, and Oregon USA) reached temperatures outside of United States Pharmacopeia (USP; Bethesda, Maryland USA) controlled temperature standards when observed over one year.[11]

Storage recommendations are often not considered by laypeople, and even law enforcement officials who receive specialized training in the administration of naloxone provide recommendations inconsistent with prescribing information. The Bureau of Justice Assistance National Training and Technical Assistance Center (Washington, DC USA; a national organization dedicated to providing training for state and local law enforcement agencies) recommends intranasal and intramuscular naloxone storage between 15°C and 30°C (59°F and 86°F), and states: "In most law enforcement settings, naloxone can be stored in the cab of the vehicle."[12] This recommendation is especially concerning since reports have shown that car dashboard surface temperatures can reach up to 69°C (156°F) after sitting in the sun for only an hour, and that automobile glove compartment chambers can reach temperatures exceeding 66°C (150°F).[13,14] The naloxone nasal spray device has become the preferred delivery system for the lay community, law enforcement, and fire personnel due to ease of use. Exposure to these extreme temperatures outside the recommended range may negatively impact delivery of naloxone through the device to the patient. Prior studies have shown that the dose of medication delivered by metered dose inhalers (MDIs) can be significantly altered by exposure to extreme temperatures, with one study finding a 70% dose reduction for a canister temperature of -13°C (9°F).[15,16] Although the mechanism of the naloxone nasal spray device is different from that used by MDIs, both devices store their drug in a reservoir that is likely to be affected by freezing and evaporation. In addition, both devices involve moving parts made out of different materials which can be subject to distortion in extreme temperature conditions.[17]

The naloxone nasal spray device consists of five major parts: a plastic outer shell, a plastic cylindrical inner tube, a glass vial containing the naloxone reservoir which resides inside the inner tube, a rubber cork that sits in the glass vial directly above the naloxone reservoir, and a hollow needle connected to the discharge opening located at the distal tip of the outer shell nozzle.[18] When the user applies an upward force to the bottom of the inner tube, the weak connections fixing the inner tube to the outer shell break. The minimum upward force required to break the connections between the inner tube and outer shell is also the minimum force required to dispense the full dose. Severing these connections permits the inner tube to freely slide upwards into the outer shell, allowing the cork to be pierced by the hollow needle. The cork-needle apparatus then acts like a piston by using the upward motion of the inner tube to generate pressure in the bottom of the glass vial containing the reservoir. This buildup of pressure violently forces the solution through the hollow needle and out of the discharge opening at the distal tip of the outer plastic shell's nozzle.

Extreme temperatures have the potential to disrupt this mechanism by either altering the properties of naloxone or the mechanics of the device itself. For example, exposure to temperatures below the recommended minimum of 15°C (59°F) could decrease the minimum force required for breaking the connections to below what is required to dispense the full dose, or could even cause the solution itself to freeze. Exposure to temperatures above the recommended maximum of 40°C (104°F) could warp and distort the plastic parts of the device, or could cause some solution to evaporate. The aim of this study was to determine the effect that temperature has on the volume of naloxone dispensed from the naloxone nasal spray device.

Methods

Overview and Rationale

Naloxone HCl nasal spray devices (Narcan Nasal Spray; Adapt Pharma Inc.; Radnor, Pennsylvania USA) containing 4mg in 0.1mL of volume were used throughout the experiment (12 were used in total). Storage temperatures were -29°C (-20°F), 20°C (68°F), and 71°C (160°F) and were chosen to simulate the storage of naloxone within a vehicle during extreme temperatures in the winter and summer with a room temperature control. These temperatures were determined based on previously reported temperature extremes in emergency response and lay vehicles, and manufacturer recommendations for controls, as well as available freezer and incubator equipment.[7-11] Each device was allowed to acclimate to the surrounding temperature for exactly 10 hours. This timeframe was used to simulate the maximum amount of time that one would expect the temperature to stay relatively constant, on average, based on day/night temperature changes.

There were two necessary steps to answer the research question. Since density is a function of temperature, it was first necessary to measure the density (g/mL) of naloxone following acclimation at each temperature to then ensure accurate volume calculations in the second part of the experiment. Following the density experiment, the mass (mg) of naloxone dispensed from each nasal spray device was measured by spraying the contents into pre-weighed containers. Using the mean result of the previously calculated measured densities, the volume of naloxone dispensed at each temperature was then calculated: calculated volume (microliter, µl) = spray mass (mg converted to g)/mean density (g/mL).

Density Measurement

To measure density, a Microlit (Iselin, New Jersey USA) RBO Single-Channel Fixed Volume Micropipette, 200µl (20-200µl), and an analytical scale were both calibrated before use. During device equilibration, a rack containing three pipette wells was placed on the analytical scale and tared to zero. After 10 hours, the device was removed and a laser thermometer was used to measure the temperature of the outer plastic shell. The device was then disassembled to allow access to the naloxone solution by micropipette.

To disassemble the naloxone nasal spray device, a serrated knife was used to cut through the nozzle of the outer plastic shell exactly 1.5cm from the base of the shell in order to access the inner plastic tube which contains the glass vial naloxone reservoir. The plastic inner tube was removed from the outer shell, and then the glass vial removed from the plastic inner tube. The black rubber cork that sealed the glass reservoir was removed. The 100µl volume in the naloxone reservoir was drawn up with the micropipette.

Temperature Group	Measurement 1	Measurement 2	Measurement 3	Mean (SD)
Step 1: Density[a]				
Mass (mg)				
–29°C	19.4	19.8	20.5	19.90 (SD = 0.56)
20°C (control)	20.4	20.4	19.6	20.13 (SD = 0.46)
71°C	20.8	20.2	19.9	20.30 (SD = 0.46)
Density (g/mL)				
–29°C	0.97	0.99	1.025	0.995 (SD = 0.03)
20°C (control)	1.02	1.02	0.98	1.01 (SD = 0.02)
71°C	1.04	1.01	0.995	1.02 (SD = 0.02)
Step 2: Nasal Spray Deployment[b]				
Mass (mg)				
–29°C	90.0	105.5	107.3	100.93 (SD = 9.51)
20°C (control)	106.1	93.4	99.5	99.67 (SD = 6.35)
71°C	110.2	111.8	107.7	2.07 (SD = 2.07)
Calculated Volume Sprayed (µl)[c,d]				
–29°C	90.45	106.03	107.84	101.44 (SD = 9.56)
20°C (control)	105.40	92.78	98.84	99.01 (SD = 6.31)
71°C	108.57	110.15	106.11	108.28 (SD = 2.04)

Table 1. Naloxone Measurements and Calculations

[a] Separate naloxone nasal spray devices were used for each temperature and the 100µl naloxone volume removed was weighed three times (three devices total).

[b] Separate naloxone nasal spray devices were used for spray deployment for each measurement at each temperature (nine devices total).

[c] Calculated volume (microliter, µl) = spray mass (mg converted to g)/mean density (g/mL).

[d] ANOVA P value = .289; F-statistic value = 1.535.

Adequate prewetting of the micropipette tip was done by drawing up the naloxone volume and dispensing it back to the glass vial reservoir three times. After prewetting of the tip, the full volume of the naloxone reservoir was pipetted into one of the wells on the tared scale. The volume from the naloxone reservoir was weighed three times in the three separate wells following transfer and re-taring to ensure precise measurements. The measured mass of these three measurements were averaged to create a mean density for naloxone at that respective temperature. This process was repeated with one naloxone nasal spray device per each study temperature.

Measurement of the Volume Dispensed from Nasal Spray Devices

To measure the volume dispensed by spray from the naloxone nasal spray device, a round bottom flask (RBF) and calibrated analytical scale were used. During device equilibration, an RBF was placed on the scale in a horizontal orientation and the scale was tared to zero. After 10 hours, the device was removed and immediately the entire nozzle of the naloxone nasal spray device was inserted into the mouth of the RBF and the spray deployed. The experiment was performed in this fashion to achieve a spray angle that is the same as what would be used clinically (by simulating a person laying down and spraying horizontally into their nostril). Immediately after spraying, the naloxone nozzle was removed from the RBF and the displayed weight was recorded. These steps were repeated with three separate naloxone devices at each of the three temperature environments to yield a total of nine measurements. The volume dispensed for the three temperatures was calculated as measured mass/mean calculated density for that given temperature.

Data Analysis

Measurements and calculations are reported descriptively with actual value or calculation and mean, standard deviation (SD), and standard error (SE). A one-way ANOVA was used to determine if any of the mean dispensed volumes differ significantly from each other at different temperatures.

Results

All measurements and calculations are reported in Table 1. The mean volume deployed at -29°C, 20°C, and 71°C was 101.44µl (SD = 9.56; SE = 5.52), 99.01µl (SD = 6.31; SE = 3.64), and 108.28µl (SD = 2.04; SE = 1.18), respectively. No significant difference between volume dispensed was evident between the three different temperature groups; P value = .289, F-statistic value = 1.535. Of note, the temperature of the outer plastic shell of the intranasal device changed only slightly after being in its respective temperature environment for 10 hours. Measurements with the laser thermometer remained within 2°F-3°F of room temperature (68°F). There were also no device malfunctions.

Discussion

There was no significant difference between volume dispensed by the naloxone nasal spray device at each of the three temperatures. This is likely due to the high heat capacity of the plastic shell of the intranasal device. It was found that the temperature of the shell changed only slightly after sitting in its respective environment, and this could possibly help protect the drug reservoir from absorbing or losing too much heat from the ambient surrounding air temperature via convection. This could prevent naloxone from evaporating or freezing at these temperatures and prevent significant changes in dispensed volume of the intranasal device.

Limitations

A limitation of this study is that the micropipettes used for volume measurement do have an intrinsic accuracy error and precision

https://doi.org/10.1017/S1049023X20000400 Published online by Cambridge University Press

error. Naloxone nasal spray devices contain 0.1mL (100µl). At this volume, the micropipette used in this study has an accuracy error of 0.8% (0.8µl) and a precision error of 0.15% (0.15µl). This potential error is likely negligible due to the findings and would not be clinically significant. Another limitation is that the simulated temperature environments created in this study may differ from actual storage conditions that occur in the community and in emergency response vehicles. Also, naloxone is exposed to fluctuating temperatures in the real-world environment, which has been proposed to effect medication stability in other studies and could affect the volume dispensed, but was not assessed in this investigation.[19] Never-the-less, the results of this study suggest that naloxone nasal spray devices will dispense the appropriate volume, even when stored at extreme temperatures outside of the manufacturer's recommended range. This has important public health implications as it supports variable naloxone nasal spray storage conditions that are seen with wide-spread distribution of these devices in the community and other prehospital settings.

Conclusion

Naloxone nasal spray devices seem to dispense the appropriate volume when stored at extreme temperatures outside of the manufacturer's recommended range for 10 hours.

References

1. Centers for Disease Control and Prevention. Wide-ranging Online Data for Epidemiologic Research (WONDER). https://wonder.cdc.gov/WelcomeT.html. Accessed October 5, 2019.
2. Hedegaard H, Miniño AM, Warner M. Drug overdose deaths in the United States, 1999–2017. National Center for Health Statistics Data Brief, no 329. https://www.cdc.gov/nchs/data/databriefs/db329-h.pdf. Published 2018. Accessed October 5, 2019.
3. Rzasa Lynn R, Galinkin JL. Naloxone dosage for opioid reversal: current evidence and clinical implications. *Ther Adv Drug Saf.* 2017;9(1):63–88.
4. World Health Organization. Community Management of Opioid Overdose. https://apps.who.int/iris/bitstream/handle/10665/137462/9789241548816_eng.pdf;jsessionid=AA5FFCB846B0C38400980F94BD4068CC?sequence=1. Published 2014. Accessed October 5, 2019.
5. McDonald R, Strang J. Are take-home naloxone programs effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction.* 2016;111(7):1177–1187.
6. World Health Organization. Model List of Essential Medicines, 21st List. https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1. Published 2019. Accessed October 5, 2019.
7. Adapt Pharma, Inc.; Radnor, Pennsylvania USA. Naloxone nasal spray 4mg/0.1mL. Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208411lbl.pdf. Published 2015. Accessed October 5, 2019.
8. Mylan Institutional LLC; Rockford, Illinois USA. Naloxone injection 0.4 mg/1mL. Prescribing Information. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=f0932877-1f3b-4d5e-82d2-dd6c53db4730&type=display. Published 2018. Accessed October 5, 2019.
9. Allegra JR, Brennan J, Lanier V, Lavery R, MacKenzie B. Storage temperatures of out-of-hospital medications. *Acad Emerg Med.* 1999;6(11):1098–1103.
10. Szucs P, Allegra JR, Fields LA, et al. Storage temperatures of medications on an air medical helicopter. *Air Med J.* 2000;19(1):19–21.
11. Brown LH, Bailey LC, Medwick T, Okeke CC, Krumperman K, Tran CD. Medication storage temperatures on US ambulances: a prospective multicenter observational study. *Pharmoperial Forum.* 2003;29(2):540–544.
12. Bureau of Justice Assistance National Training and Technical Assistance Center. Law Enforcement-Naloxone Toolkit 2019. https://bjatta.bja.ojp.gov/naloxone/how-should-naloxone-be-stored. Accessed October 5, 2019.
13. Vanos JK, Middel A, Poletti MN, Selover NJ. Evaluating the impact of solar radiation on pediatric heat balance within enclosed, hot vehicles. *Temperature (Austin).* 2018;5(3):276–292.
14. Seymour R. The glove compartment is an oven, not a medicine cabinet. *JAMA.* 1987;258(13):1734.
15. Morin CMD, Ivey JW, Titosky JTF, et al. Performance of pressurized metered-dose inhalers at extreme temperature conditions. *J Pharm Sci.* 2014;103(11):3553–3559.
16. Wilson AF, Mukai DS, Ahdout JJ. Effect of canister temperature on performance of metered-dose inhalers. *Am Rev Respir Dis.* 1991;143(5 Pt 1):1034–1037.
17. McKeen LW. *The Effect of Temperature and Other Factors on Plastics and Elastomers.* 3rd ed. Norwich, New York USA: William Andrew; 2014.
18. Aptar Radolfzell GmbH. Apparatus for controllably discharging flowable media. United States; Patent US5813570A, 1998.
19. Loner C, Estephan M, Davis H, Cushman JT, Acquisto NM. Effect of fluctuating extreme temperatures on tranexamic acid. *Prehosp Disaster Med.* 2019;34(3):340–342.