Impact of Ambient Temperature on 5 Emergency Drugs Aboard an Emergency Medical Car Over a 1-Year Period

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Study objective: Drugs in emergency medical service (EMS) cars are often exposed to temperature variations that could affect the stability of these drugs. We aimed to study the influence of real-life temperature exposure on the stability of 5 drugs onboard an EMS vehicle.

Methods: Concentrations of active principles of 5 emergency drugs (amiodarone, rocuronium, fentanyl, succinylcholine, and epinephrine) aboard an EMS vehicle were analyzed every 3 months up to 1 year. The samples were compared to the same drugs stored for 1 year either at room temperature or in a refrigerator in the pharmacy. Succinylcholine was additionally analyzed once a week for 4 weeks after being taken out of the refrigerator. The dosage of the active principle was measured using high-pressure liquid chromatography coupled with ultraviolet detection.

Results: After the 12-month period, all drugs from the EMS car, except succinylcholine, presented concentrations still above 90% of the concentrations measured at the start of the project. Concentrations ranged from 96.3% to 103%. For succinylcholine at 12 months, the remaining concentration was 89%. Temperatures in the EMS car ranged from 13.9 °C to 33.9 °C (median, 22.8 °C [interquartile range, 20.5 °C to 25.8 °C]).

Conclusion: In real-life conditions, amiodarone, rocuronium, fentanyl, succinylcholine, and epinephrine onboard an EMS vehicle did not suffer pharmacologically relevant degradation from temperature variations. All concentrations measured remained in the specification intervals given by the manufacturers. [Ann Emerg Med. 2022;80:358-363.]

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INTRODUCTION

Drugs in emergency medical service (EMS) vehicles are exposed to temperature changes that are difficult to control except by storing the drugs in refrigerators or temperature-controlled boxes. However, storing emergency drugs in such cooling devices is not a very practical solution as emergency situations often do not allow, because of time loss, them to be retrieved from locations other than the ready-to-use emergency bags. For this reason, drugs are generally stored inside the emergency bags and are, thus, exposed to ambient temperature.

The expiration date of drugs provided by the manufacturers are based on standard temperature storage conditions, generally within a temperature range from 15 °C to 25 °C for ambient temperature and 2 °C to 8 °C for drugs stored in the refrigerator. Manufacturers conduct temperature stability tests in controlled environments.[1] In EMS vehicles, these tight ranges often cannot be achieved, and the question arises if drugs exposed to real-life temperature variations decompose and become unfit for use.

Although the medication storage conditions in the out-of-hospital setting are not fully compliant with storage recommendations defined by manufacturers, only limited stability data on medications stored in EMS vehicles, outside a controlled temperature environment, are available. Most previous studies either controlled the "abnormal" temperatures by putting the drugs in temperature-controlled areas[2,3] or did not monitor the temperature in the EMS car but extrapolated the ambient temperature from general meteorology data,[4] thus introducing a certain degree of imprecision of the actual temperature inside the drug bag. We did not find any study monitoring the temperature continuously and close to the drugs with active pharmaceutical ingredient concentration determination for 1 year.

Editor's Capsule Summary

What is already known on this topic

Storage temperature variability can alter the quality of medications.

What question this study addressed

Compared to medications stored under controlled conditions, what effect does storage in an emergency medical service vehicle have on the content of 5 common medications?

What this study adds to our knowledge

The concentrations of amiodarone, rocuronium, fentanyl, succinylcholine, and epinephrine were not significantly affected by temperature variation, although the temperatures experienced were not extreme.

How this is relevant to clinical practice

Clinicians can be confident that these medications stored under varying temperature conditions in emergency medical service vehicles will be effective.

With this study, we aimed to analyze the stability of 5 emergency drugs stored aboard an EMS vehicle with close temperature monitoring and compare them with control samples stored according to manufacturer specifications. The primary endpoint was the analysis of the effect of temperature variations on the concentration of the active pharmaceutical ingredients in finished products stored in real-life conditions in an EMS vehicle over 12 months.

METHODS

Selection of Drugs

This study was designed to quantify the active pharmaceutical ingredients in 5 selected emergency drugs contained in ampoules or vials aboard 1 EMS vehicle of the National Fire and Rescue Corps of Luxembourg. The drugs included in the study are summarized in Table 1.

We selected those 5 drugs because of their relevance in emergency medicine and because of limited shelf life at room temperature, indicated by the manufacturer for some of the drugs (rocuronium, succinylcholine, and epinephrine), thus presumably being at greater risk of deterioration if exposed to uncontrolled ambient temperature over a longer period of time.

Study Design and Setting

All ampoules or vials of each drug belonged to the same production batch, and their indicated expiration dates were beyond the end of the study period. The study was conducted over 12 months (July 2020 to June 2021) in Luxembourg, a moderate continental climate zone with average monthly air temperatures from 1 °C to 21.2 °C and an average humidity of 70.2% (range of 59.6% to 93.5%).[5] The 5 drugs were split into 7 batches (controls 1 and 2 and batches 0 to IV). Each batch contained 3 unopened original vials of each drug for every time point of analysis and storage location. No multiple punctures of 1

Table 1. Drugs analyzed based on manufacturer specifications and storage recommendations*.

Commercial Name/Conditioning	Manufacturer	Active Pharmaceutical Ingredient	Active Pharmaceutical Ingredient Concentration	Active Pharmaceutical Ingredient Specification (%)	Storage Recommendations	Manufacturer-Allowed Temperature Excursion
Lysthenon (ampoule)	Takeda Austria GmbH, Linz, Austria	Succinylcholine dihydrate	110 mg/5 mL	90-107.5	2 °C-8 °C	1 week below 25 °C
Cordarone (ampoule)	Delpharm Dijon, Quétigny, France	Amiodarone	150 mg/3 mL	95-105	<25 °C, protected from light	-
Esmeron (vial)	MSD Belgium, Brussels, Belgium	Rocuronium bromide	50 mg/5 mL	92-105	2 °C-8 °C	12 weeks at 8 °C-30 °C
Fentanyl-Janssen (ampoule)	Janssen Pharmaceutica, Beerse, Belgium	Fentanyl	0.5 mg/10 mL	90-110	15 °C-30 °C, protected from light	-
Suprarenin (ampoule)	Delpharm Dijon, Quétigny, France	Epinephrine	1 mg/1 mL	90-115	2 °C-8 °C, protected from light	6 months at max 25 °C

max, maximum.

*Manufacturer-allowed temperature excursion: advanced storage conditions as indicated by the manufacturer in the drug labeling.

Figure 1. *A,* Emergency medical service car (Di Millo E, 2020, the National Fire and Rescue Corps of Luxembourg). *B,* Bag containing ampoules or vials (medication storage bag) and the temperature loggers. *C* and *D,* Location of the bag inside the emergency medical service car.

vial or multidose vials were used, but measurements were done at each time point on 3 dedicated vials for each drug. The control 1 batch was stored on a shelf in the pharmacy at ambient temperature (20 °C±5 °C), whereas the control 2 batch was stored at 5 °C±3 °C in the refrigerator of the central pharmacy of the National Fire and Rescue Corps of Luxembourg. The ampoules or vials of batches I to IV were placed in a medication storage bag and stored inside an active EMS vehicle (Figure 1). No specific measures regarding temperature management were taken for the drugs placed in the car. The EMS vehicle was used for normal service 365 days a year between 6 AM and 10 PM, running some 1,900 emergencies per year. When not on the field during interventions, it was stationed in the garage of a fire station. The commercially available medication storage bag (PAX Ampullarium L; X-CEN-TEK GmbH & Co. KG) used corresponded to the standard model used by the out-of-hospital emergency services in Luxembourg and was sealed to prevent erroneous removal of the drugs intended for the study. To follow the evolution of the temperature at the different storage points, we used 4 temperature loggers (Testo 174T; Testo SE & Co. KGaA) recording at 30-minute intervals. Two loggers, for redundancy, were placed inside the medication storage bag in the EMS car (batches I to IV), 1 logger was placed in the control 1 batch on the pharmacy shelf, and 1 logger was placed in the pharmacy refrigerator near the control 2 batch. Control and download of the temperature data were done on a monthly basis.

Assays of batch 0 were done at the start of the project on ampoules/vials directly received from the manufacturer to determine baseline drug concentration (day 0). Batches I to IV were analyzed every 3 months, starting with batch I at 3 months, batch II at 6 months, batch III at 9 months, and batch IV at 12 months. The control 1 and control 2 batches were analyzed after the 12-month study period. For succinylcholine, additional analyses were performed after a time period of 1, 2, 3, and 4 weeks after retrieval from the refrigerator because the manufacturer indicated stability for only 7 days at ambient temperature.[6]

Table 2. Mean concentrations from 3 ampoules or vials of drugs measured at different time intervals and storage locations*.

	Baseline		Drugs Stored in EMS Car								Drugs at 20 °C		Drugs at 5 °C	
	Month 0 Batch 0		Month 3 Batch I		Month 6 Batch II		Month 9 Batch III		Month 12 Batch IV		Month 12 Control 1		Month 12 Control 2	
Specification (%)	mg/vial	% TC	mg/vial	% TC	mg/vial	% TC	mg/vial	% TC	mg/vial	% TC	mg/vial	%TC	mg/vial	% TC
Succinylcholine	90-107.5	108.8	98.9	104.8	95.3	105.5	95.9	101.3	92.1	97.9	89.0	101.1	91.9	105.7	96.1
Amiodarone	95-105	147.9	98.6	148.7	99.2	148.3	98.9	152.3	101.5	144.4	96.3	144.7	96.5	145.6	97.1
Rocuronium bromide	92-105	51.8	103.4	51.7	103.0	50.3	100.6	50.6	101.2	50.9	101.7	51.3	103	51.5	103
Fentanyl	90-110	0.497	99.4	0.492	98.5	0.492	98.4	0.502	100.4	0.490	98.0	0.49	98.1	0.49	98.2
Epinephrine	90-115	1.07	107.4	1.05	104.6	1.04	104.3	1.03	102.9	1.03	103.0	1.05	105	1.08	108

EMS, emergency medical service; *TC*, theoretical concentration; *% TC*, percentage of the active principle measured compared with the theoretical concentration.
*All standard deviations for % TC were less than 1.0%.

Analysis

Assays were carried out using high-pressure liquid chromatography coupled with an ultraviolet detector (1290 Infinity II HPLC System; Agilent Technologies, Inc). All analyses were performed according to confidential methods obtained from the drug manufacturers. All analyses were done in triplicate; the results indicated in Table 2 are the mean values of the 3 assays.

Statistics

Continuous variables are expressed either as medians and interquartile ranges (IQRs) or means with SDs. The results of the active pharmaceutical ingredient concentrations of the 3 ampoules or vials at each time point are expressed as mean (Table 2).

RESULTS

Temperature fluctuations were most pronounced in the EMS medication storage bag (Figure 2). The temperatures ranged from 13.9 °C to 33.9 °C, and the median temperature was 22.9 °C (IQR, 20.6 to 25.9). Similar temperatures were measured by the 2 loggers inside the medication storage bag. The median temperatures for the drugs stored on the shelf and the refrigerator were 18.5 °C (IQR, 16.8 to 21.6) and 4.9 °C (IQR, 4.8 to 5.0), respectively.

Assay results are summarized in Table 2. The concentrations of the active pharmaceutical ingredients in the EMS car showed high stability during the study period despite notable temperature variations. Overall degradation, defined as the percentage of the theoretical concentration measured at baseline minus the percentage of the theoretical concentration at 12 months, was 9.9% for succinylcholine, 2.3% for amiodarone, 1.7% for rocuronium, 1.4% for fentanyl, and 4.4% for epinephrine when compared with the baseline assay (Table 2). Except for succinylcholine stored for 12 months in the EMS vehicle, all active pharmaceutical ingredient concentrations remained more than 90% of the labeled potency, which is considered the minimum acceptable potency for clinical efficacy.[7] Succinylcholine concentrations remained stable during the first 4 weeks at ambient temperature in the EMS car, with the percentages of active pharmaceutical ingredients compared with the baseline concentration ranging from 96.3% to 98.1%.

As expected, degradation was slower when the samples were stored in controlled conditions (controls 1 and 2). For all drugs except succinylcholine, the degradation rate after 12 months was lower than 2.1% at room temperature and less than 1.5% at 5 °C when compared with the baseline assay. For succinylcholine, the degradation rate was −7.0% at room temperature and −2.8% at 5 °C.

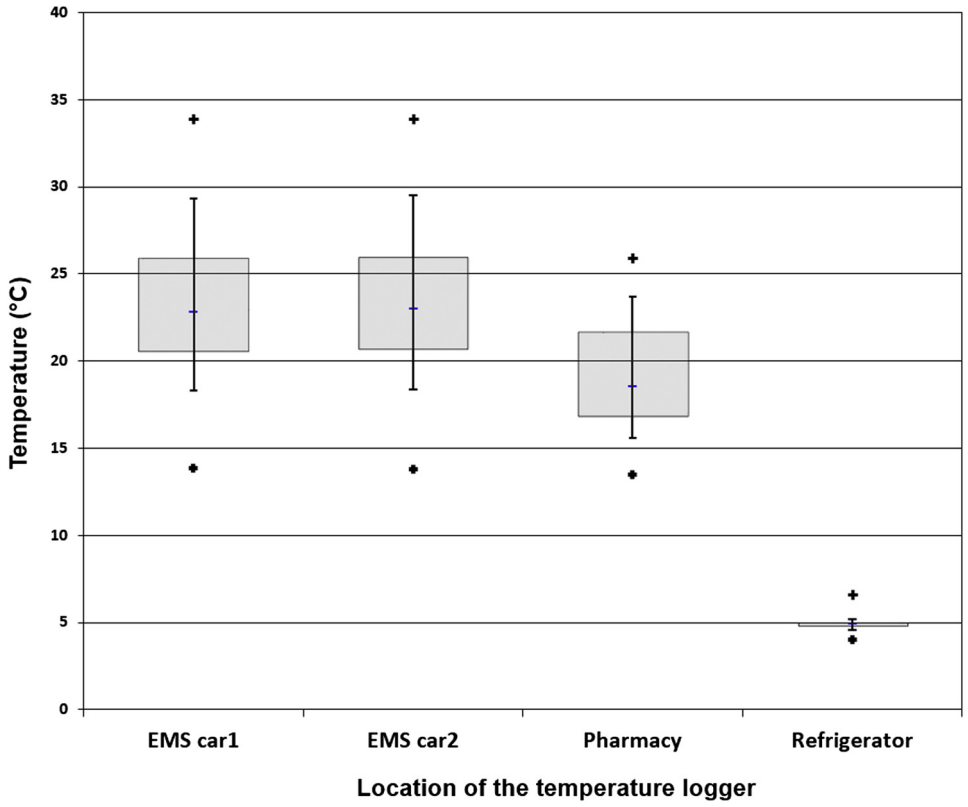

Figure 2. Representation of the median temperatures (°C) over the 1-year period (June 2020 to June 2021) according to the location of the temperature logger. "EMS car1" and "EMS car2" correspond to the 2 loggers included in the medication storage bag inside the emergency medical service car, and "pharmacy" and "refrigerator" correspond to the logger on the shelf and inside the refrigerator, respectively, at the central pharmacy. The horizontal lines within the boxes represent the median values, whereas the boxes represent the interquartile ranges. The vertical bars indicate the 5th to 95th percentile, and the crosses represent the absolute minimum and maximum values (outliers). *EMS,* emergency medical service.

DISCUSSION

We demonstrated that the active pharmaceutical ingredient concentrations of 5 selected emergency drugs remained stable over a 1-year period when exposed to real-life temperature changes onboard an EMS vehicle. Even drugs considered by the manufacturers as unstable outside controlled conditions, like rocuronium, succinylcholine, and epinephrine, maintained their concentrations inside the manufacturers' specifications limits (Table 2), with one exception (succinylcholine after 12 months), above the 90% limit generally admitted as pharmacologically relevant.

Manufacturers instruct users to use unopened ampoules of succinylcholine stored outside the refrigerator within 7 days. Our findings differ from those of De Winter et al[4] and Merlin et al,[8] who showed a steady decrease of succinylcholine concentrations over time, as we observed small changes only after 9 to 12 months. These differences might be explained by a different drug manufacturer or the use of different excipients. Interestingly, De Winter et al[4] also described the degradation of succinylcholine at room temperature but not when placed (unrefrigerated) in an EMS helicopter.[9] Our findings still contrast with the manufacturer's indications of a very short expiration date at room temperature.

In our study, the concentrations of fentanyl remained stable, whereas other studies on laboratory-controlled extreme heat and cold exposure found a significant decrease in the active principle already after 3 weeks.[4]

Generally, our results are in line with previous studies mainly done on epinephrine, showing no or a very low decrease in the active principle.[10] Epinephrine may be more robust than the current storage recommendations suggested by the manufacturer, especially given the fact that other commercially available forms of epinephrine need no refrigerator storage at all and are stored at room temperature.

The median temperatures measured in the EMS car remained within the recommended temperature ranges. The aim of this study was not to expose drugs to extreme temperature variations but rather to test the effect of real-life temperature fluctuations. Still, the measured fluctuations and changes may have influenced drug stability. The limited

fluctuations of the temperatures measured inside the medication storage bag might be due to the insulating effect of the type of medication storage bag itself. The use of another bag or direct exposition to sunlight might have resulted in higher temperature fluctuations and, thus, a more significant effect on drug stability.

In our study, we analyzed drugs from specific manufacturers. These results may not apply to other commercially available drugs with different concentrations, excipients, diluents, and packaging. The study was conducted in a moderate continental climate area without major temperature fluctuations. The results may, therefore, not be applicable in other climates of extreme heat or cold. Another limiting factor is that we used only a small sample of drugs from 1 single batch stored aboard 1 EMS car. As we did not specifically investigate degradation products, we did not take into account the effect of active degradation products. Given the stability of the drugs, it is unlikely that large amounts of degradation products were present.

Although we showed that the stability of these 5 drugs is maintained despite the temperature changes, we recommend adhering to the manufacturer expiration date. Our results potentially offer additional safety to use drugs exposed to temperature fluctuations onboard EMS vehicles, but, still, the limitations to our study prevent generalizability. There is still insufficient information on the effect of temperature variations on medications seen in the out-of-hospital environment, and the clinical implications of noncompliant storage remain unclear.

As a result of our analyses, we found that concentrations of active principles of amiodarone, rocuronium, fentanyl, succinylcholine, and epinephrine contained in ampoules or vials stored in EMS cars and exposed to real-life temperature variations in a moderate continental climate zone do not present pharmacologically relevant reduction over a 1-year period.

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