

# Stability of Drugs Stored in Helicopters for Use by Emergency Medical Services: A Prospective Observational Study

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**Study objective:** Drugs stored in rescue helicopters may be subject to extreme environmental conditions. The aim of this study was to measure whether drugs stored under the real-life conditions of a Swiss helicopter emergency medical service (HEMS) would retain their potency over the course of 1 year.

**Methods:** A prospective, longitudinal study measuring the temperature exposure and concentration of drugs stored on 2 rescue helicopters in Switzerland over 1 year. The study drugs included epinephrine, norepinephrine, amiodarone, midazolam, fentanyl, naloxone, rocuronium, etomidate, and ketamine. Temperatures were measured inside the medication storage bags and the crew cabins at 10-minute intervals. Drug stability was measured on a monthly basis over the course of 12 months using high-performance liquid chromatography. The medications were considered stable at a minimum remaining drug concentration of 90% of the label claim.

**Results:** Temperatures ranged from  $-1.2^{\circ}\text{C}$  to  $38.1^{\circ}\text{C}$  ( $29.84^{\circ}\text{F}$  to  $100.58^{\circ}\text{F}$ ) inside the drug storage bags. Of all the temperature measurements inside the drug storage bags, 37% lay outside the recommended storage conditions. All drugs maintained a concentration above 90% of the label claim. The observation periods for rocuronium and etomidate were shortened to 7 months because of a supply shortage of reference samples.

**Conclusion:** Drugs stored under the real-life conditions of Swiss HEMS are subjected to temperatures outside the manufacturer's approved storage requirements. Despite this, all drugs stored under these conditions remained stable throughout our study. Real-life stability testing could be a way to extend drug exchange intervals. [Ann Emerg Med. 2022;■:1-7.]

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## INTRODUCTION

### Background

In the out-of-hospital setting, emergency drugs are sometimes exposed to extreme environmental conditions. How such exposure affects drug potency and reliability is largely unknown. Most drugs used by emergency medical services (EMS) require storage at room temperature, and some require refrigeration. As defined by the European Pharmacopoeia, this entails a temperature range between  $15^{\circ}\text{C}$  to  $25^{\circ}\text{C}$  ( $59^{\circ}\text{F}$  to  $77^{\circ}\text{F}$ ) and  $2^{\circ}\text{C}$  to  $8^{\circ}\text{C}$  ( $35.6^{\circ}\text{F}$  to  $46.4^{\circ}\text{F}$ ), respectively.<sup>1</sup> Studies have shown that storage conditions in EMS vehicles, including helicopters, often lie outside these requirements.<sup>2,3</sup>

A helicopter EMS (HEMS) study reported problems with drug usage at extreme temperatures, such as frozen ampoules.<sup>4</sup> At the other extreme, temperatures of up to

$50^{\circ}\text{C}$  ( $122^{\circ}\text{F}$ ) were measured inside ambulance storage bags even in zones with moderate climates.<sup>5</sup> In addition to the environmental exposure on scene, drugs stored in HEMS are subject to constant vibration, sudden changes in altitude, and accelerated temperature changes. Studies investigating drug stability during out-of-hospital storage have mostly been conducted in laboratory settings with constantly changing extremes in temperatures, sometimes reporting conflicting results.<sup>3</sup> The intensity of these laboratory conditions further limits the extrapolation of their observations to real-life scenarios.

### Importance

Stability studies under realistic storage conditions of out-of-hospital emergency medicine are scarce and often limited in scope.<sup>2,3</sup> Previous studies have established

**Editor's Capsule Summary***What is already known on this topic*

Air ambulances undergo wide and rapid temperature changes that can affect the concentration of stored medications.

*What question this study addressed*

Compared to medications stored under controlled conditions, what effect does storage on an air ambulance have on the content of 9 common emergency medications?

*What this study adds to our knowledge*

The concentrations of 9 emergency medications were not significantly affected by temperature variation, which ranged from 30 °F to 101 °F.

*How this is relevant to clinical practice*

Despite the temperature on an air ambulance, the studied medications maintain their potency.

temperature exposure as one of the most important factors in drug degradation.<sup>2,3,6,7</sup> Efforts to comply with the recommended storage conditions often require expensive technology or frequent replacement of drugs because of

presumed degradation. This adds significant economic, ethical, and procurement dimensions to the clinical question of out-of-hospital drug stability.

**Goals of This Investigation**

The primary objective of this study was to investigate whether drug storage in HEMS complies with mandatory temperature standards. The secondary objective was to investigate the stability of these drugs under real-life storage conditions.

**MATERIAL AND METHODS****Study Design**

We conducted a prospective, longitudinal study measuring the drug concentration and temperature exposure of 9 emergency medications labeled for storage at room temperature or under refrigeration (Table). Drugs were stored on 2 different EMS helicopters during all missions over 1 year.

**Setting**

Swiss Air-Rescue (Rega) operates 12 helicopter bases, ranging from low-lying airfields in midland and urban areas to mountain bases at high elevations in the Swiss Alps.<sup>8</sup> The 2 helicopters involved in this study were an Airbus H145 on a midlands base and an AugustaWestland Da

**Table.** Study drugs.

Drug Name	Brand Name (Manufacturer)	Concentration	Manufacturer Required Storage Conditions
Epinephrine	Adrenalin Sintetica (Sintetica SA, Mendrisio, Switzerland)	1 mg/mL	Store at room temperature (15-25 °C) (59-77 °F). Protect from light.
Norepinephrine	Noradrenalin Sintetica (Sintetica SA, Mendrisio, Switzerland)	1 mg/mL	Store at room temperature (15-25 °C) (59-77 °F). Protect from light.
Amiodarone	Amiodaron Labatec (Labatec Pharma SA, Meyrin, Switzerland)	150 mg/3 mL	Store at room temperature (15-25 °C) (59-77 °F). Do not refrigerate. Protect from light.
Midazolam	Midazolam Sintetica (Sintetica SA, Mendrisio, Switzerland)	15 mg/3 mL	Store at room temperature (15-25 °C) (59-77 °F). Protect from light.
Fentanyl	Fentanyl Janssen (Piramal Critical Care Limited, London, Rüschnikon, Switzerland)	0.1 mg/2 mL	Store at room temperature (15-25 °C) (59-77 °F). Protect from light.
Naloxone	Naloxon (OrPha Swiss GmbH, Küsnacht, Switzerland)	0.4 mg/mL	Do not store above 30 °C (86 °F). Do not freeze. Protect from light.
Etomidate	Etomidat-Lipuro (B. Braun Medical AG, Sempach, Switzerland)	20 mg/10 mL	Store at room temperature (15-25 °C) (59-77 °F). Do not store above 25 °C. Do not freeze. Protect from light.
Ketamine	Ketamin Sintetica (Sintetica SA, Mendrisio, Switzerland)	100 mg/2 mL	Store at room temperature (15-25 °C) (59-77 °F). Protect from light.
Rocuronium	Rocuronium Fresenius (Fresenius Kabi AG, Kriens, Switzerland)	100 mg/10 mL	Refrigerate (2-8 °C) (35.6-46.4 °F). Can be stored for a maximum of 12 wk without refrigeration at a temperature of 8-30 °C. Do not refrigerate after the medication has been removed from refrigeration.

Vinci on a mountain base. The HEMS mission spectrum ranged from intensive care transport and primary EMS missions to technical alpine rescue operations.

The H145 helicopter was stationed in the city of St Gallen (elevation 656 m), an urban midlands base in a temperate, oceanic climate zone.<sup>9</sup> The Da Vinci helicopter was stationed on a mountain base at Europe's highest operating airport in Samedan (elevation 1,706 m). The mountainous areas of operation are classified as tundra with sometimes subarctic conditions.<sup>9</sup> At night, both aircrafts were stored in hangars. These were heated during wintertime but not cooled during summer.

### Storage

Drugs were placed in storage bags (PAX Ampoule Holder; X-CEN-TEK GmbH & Co. KG) that were equivalent to the regular backpacks on the helicopters. The bags were not insulated. The outer shell contained a foam padding and was impermeable to ultraviolet rays. All drugs were marked as study drugs. The bags were opened only for monthly retrieval of drug samples. All drugs had an expiration date beyond their testing period. Temperature was recorded by automatic temperature loggers (tempmate-S1; tempmate) at 10-minute intervals with an accuracy of  $\pm 0.2$  °C (0.67 °F). One set of temperature loggers was placed inside the drug storage bags, and another was placed inside the crew cabin on the aircraft. The bags were kept in their respective compartments and were not removed during missions or standby time at the base.

### Testing

During each of the 12 months of the study period, 1 prepacked plastic bag containing the study ampoules for the given month was removed from each of the 2 helicopters and transported, under room temperature conditions, to the laboratory. Drug ampoules used as reference were fresh ampoules, stored according to their specific storage conditions at the hospital pharmacy, and were delivered directly to the testing laboratory on a monthly basis. Before testing, the ampoules were checked visually for breakage or any changes in color or viscosity that was not described in the manufacturers' instructions. Stability testing was performed using a quantitative confirmatory analysis using high-performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS). A total of 3 analyses were performed for each analyte and time point. A total of 3 HPLC-MS/MS runs were performed for each study ampoule. All measurements were recorded as the percentage of the remaining drug concentration in relation to the reference samples. The reference samples were set as a drug concentration of 100% of the label claim. Study

drugs were considered stable at a minimum remaining drug concentration of 90% of the label claim.<sup>10</sup>

### Statistical Analysis

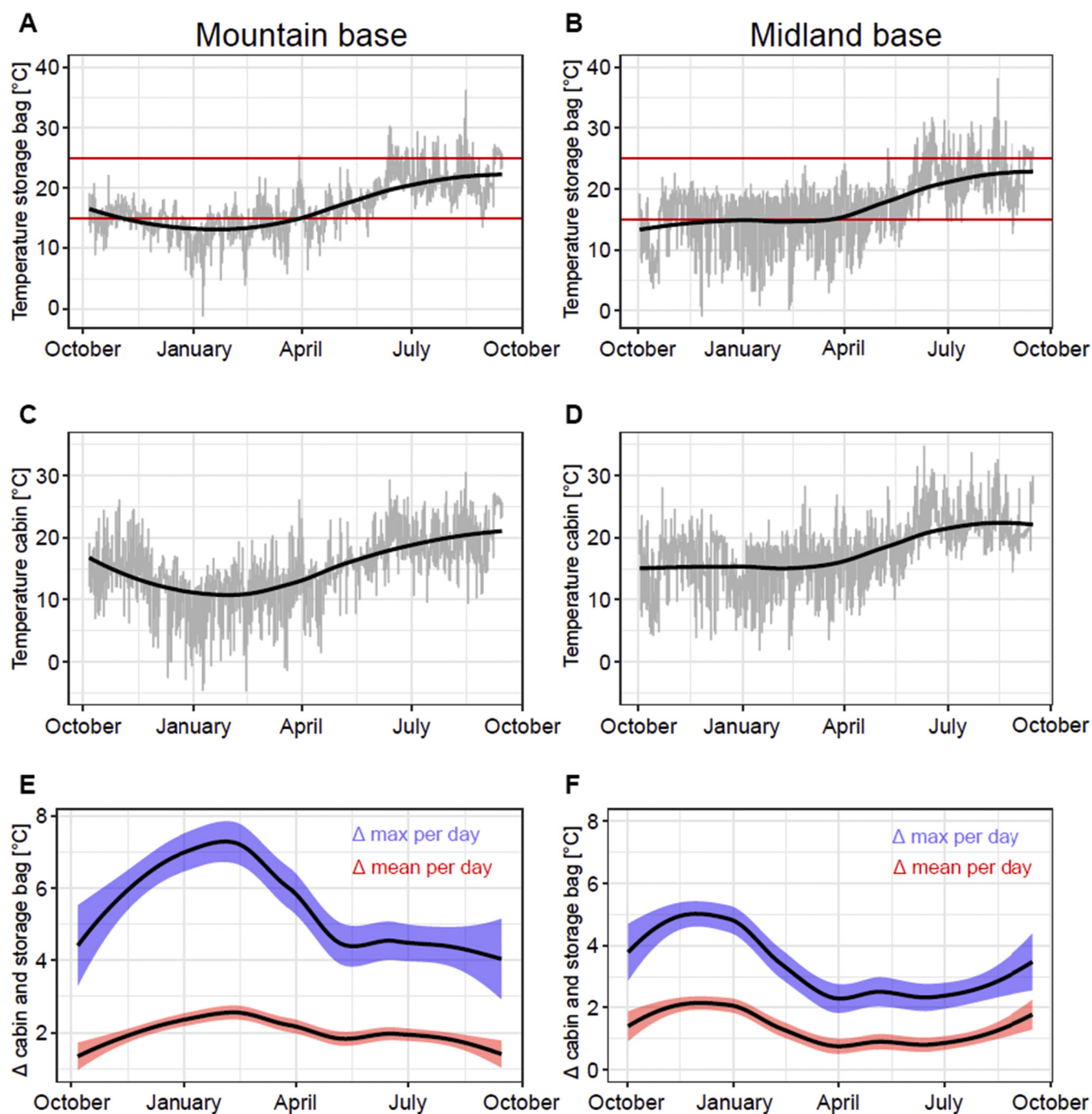
By taking the arithmetic mean of the 3 HPLC-MS measures per ampoule for each drug, including the reference drugs from each helicopter, a single estimate of a drug's performance for each month could be derived. All individual HPLC estimates of a single ampoule were within 25% of each other, with 2 exceptions: those samples that had to be discarded and the first 2 measurements for ketamine. This mean value was divided by the mean value of the respective reference sample, thus expressing a given drug's performance as a percentage relative to the reference. The reference samples were assigned a concentration of 100% of the label claim. For the temperature data, we assessed normality by visual inspection of the quantile plot. Data were analyzed with the software R, version 4.1.1 (R Foundation for Statistical Computing).<sup>11</sup>

### RESULTS

During the 12-month study period, the H145 helicopter based in the midlands recorded 2,970 takeoffs with a total flight time of 29,143 minutes. The Da Vinci helicopter stationed on the mountain base recorded 2,482 takeoffs with a total flight time of 20,310 minutes.

Overall, the recorded temperatures inside the storage bags ranged from 38.1 °C to  $-1.2$  °C (100.4 °F to 29.84 °F) (Figure 1A and B). Temperatures inside the cabin ranged from 34.7 °C to  $-4.7$  °C (94.46 °F to 23.54 °F) (Figure 1C and D). The mean temperature inside the storage bags was 17.1 °C (SD  $\pm 4.6$  °C) (62.78 °F (SD  $\pm 40.28$  °F)). Of all the temperature measurements, 37.0% lay outside of room temperature (30.9% below 15 °C (59 °F), 6.1% above 25 °C (77 °F)). The mean temperature difference between the inside of the storage bag and the crew cabin was 1.7 °C (30.06 °F) (95% confidence interval 1.69 °C to 1.72 °C (35.04 °F to 35.09 °F) on both helicopters. The maximum temperature difference between the storage bag and the crew cabin was 18.2 °C (64.76 °F) on the H145 helicopter and 16.5 °C (62.24 °F) on the Da Vinci helicopter (Figure 1E and F).

For stability testing, 216 drug measurements were analyzed (12 sampling points for 9 different drugs measured on 2 helicopters). Twenty-eight samples were not evaluated because the monthly reference was missing. Four samples had to be declared void because of a preanalytical issue in preparation of the samples for HPLC testing. Of the remaining 184 samples, all retained a drug concentration above 90% of the label claim throughout the observation period (Figure 2A to I).

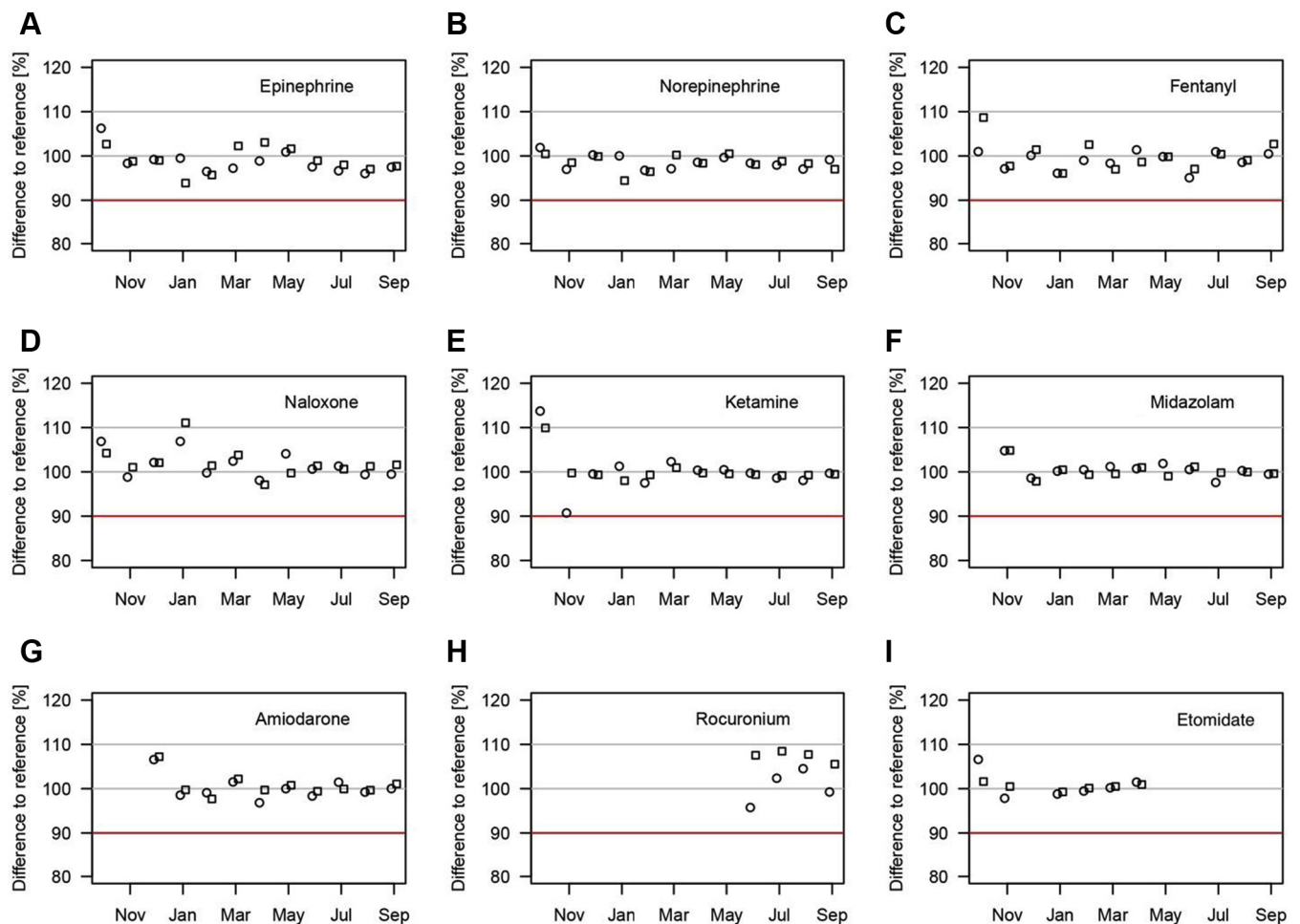


**Figure 1.** Temperature exposure. Left: Helicopter based in the mountains (Da Vinci). Right: Helicopter based in the midlands (H145). *A and B*, Temperatures in degree Celsius measured over the 12-month observation period inside the drug storage bag; red lines indicate manufacturer storage range for the majority of drugs. *C and D*, Temperature recorded inside the crew cabin. *A to D*, the black line represents smoothed regressions, and gray shows the variation in temperature (time-series). *E and F*, The graphs show the daily absolute maximum (blue) and daily mean (red) temperature difference between the drug storage bag and crew cabin with 95% confidence intervals. *max*, maximum.

## LIMITATIONS

Our study has several limitations. First, we could not reproduce the environmental conditions that drugs would be exposed to when being removed from the aircraft to

treat a patient on scene. Second, limitations in the length of the observation period applied to rocuronium and etomidate because of a coronavirus disease 2019 (COVID-19) pandemic-related supply shortage of reference samples,



**Figure 2.** Study drug performance. Performance of each drug throughout the observation year. A to I, Each panel shows the performance of a single drug, sampled from either helicopter (circles: mountain base; squares: midlands base), relative to the reference samples (y-axis; as percentage difference of the mean of the helicopter samples compared to the mean of the reference samples). Gray lines indicate 100% performance (same values for helicopter samples and reference samples), and red lines mark the 90% threshold. A total of 12 monthly sampling points were available (x-axis; October 2020 to September 2021; points are slightly offset in x-direction to improve visibility). The observation periods for rocuronium and etomidate were shortened by a COVID-19 pandemic-related supply shortage of reference samples. Missing values indicate that no reference sample was measured. Because of a preanalytical issue in preparing the samples for high-performance liquid chromatography testing, the first measurements of midazolam and the first 2 measurements of amiodarone were declared void.

shortening the observation period for etomidate to 7 months. Reference samples for rocuronium were available again for the last 4 months of the study and remained stable, suggesting that despite missing data points at the beginning of the study, rocuronium remained stable throughout the observation period. Third, because of a preanalytical issue in preparing the samples of midazolam and amiodarone for HPLC-MS testing, the values measured in the first 2 months of the study had to be declared void. Fourth, pharmaceutical stability testing involves 5 areas of drug stability. We measured the concentration of the active pharmaceutical ingredient as a surrogate parameter of chemical stability and inspected the

ampoules for physical changes but did not perform microbiologic, therapeutic, or toxicologic analysis.

## DISCUSSION

The concentration of drugs stored on EMS helicopters did not decrease below 90% of the label claim over the course of 1 year although manufacturer-prescribed storage requirements were substantially violated in the HEMS environment.

The clinical impact of these findings varies greatly for the range of drugs investigated.

Epinephrine is an integral part of international resuscitation guidelines. It remained stable in both real-life

EMS and laboratory settings, only showing significant degradation when being subjected to prolonged episodes of excessive heat.<sup>3</sup> The stability of norepinephrine has been studied for in-hospital use only.<sup>3</sup> It remained stable throughout our study. Midazolam was found to be unstable in a laboratory setting when subjected to extremes in temperature.<sup>12</sup> An EMS study and our HEMS study described midazolam as stable in a real-life setting, thus highlighting the problem of extrapolating laboratory results to clinical practice.<sup>13</sup> Ketamine has been proven to remain stable in adverse storage conditions during shorter trials.<sup>2,14</sup> Our study confirmed this, extending the observation period to 12 months.

One laboratory study found fentanyl to be unstable under temperature extremes over 1 month.<sup>12</sup> Our study found that it remained stable for 12 months under real-life conditions. Naloxone has generated renewed interest because of its out-of-hospital stability during the opioid epidemic in North America; it has been proven to remain stable under strenuous storage conditions.<sup>15</sup> Our data confirm these findings and extend the observation period to 1 year. Rocuronium is labeled for refrigeration but is allowed to be stored at room temperature with a shelf life of 12 weeks. Our data documented its stability for 1 year without refrigeration and with exposure to temperatures of up to 38.1 °C (100.58 °F).

Our observations showed prolonged episodes of exposure to cold and freezing temperatures. Emulsions like etomidate and propofol have been found to be damaged irreversibly by freezing because of the formation of conglomerates in the lipophilic phase.<sup>10</sup> A study on propofol showed that conglomerates big enough to cause pulmonary embolism remained in the emulsion after complete rewarming.<sup>16</sup> This is important because mountainous HEMS missions often require patient sedation in temperatures below freezing.<sup>17</sup> A microscopic evaluation of etomidate ampoules that had been subjected to temperatures of −0.8 °C (30.56 °F) during our study revealed no conglomerates; however, the ampoules may not have been fully frozen, thus requiring future research. The drug concentration remained above 90% of the label claim. Amiodarone is prone to crystallization and should not be refrigerated or frozen. Its concentration remained stable throughout our study; however, the ampoules were subjected to temperatures below 8 °C (46.4 °F) for prolonged periods of time, limiting their immediate use in a patient because of possible crystallization. This could be especially important in HEMS, wilderness medicine, or avalanche rescue settings, where prolonged resuscitative efforts in inclement weather may be required.

The range of temperature exposure experienced in the out-of-hospital setting is currently not represented in the

guidelines for pharmaceutical stability testing.<sup>18</sup> Therefore, it is not included in shelf-life considerations. Because of this lack of data and out of an abundance of caution, many EMS and HEMS providers exchange drugs well before their expiration date. Based on our data of continued drug potency, this may not be economically and ethically sustainable.

While conducting this study, we—like many health care professionals worldwide—experienced COVID-19-related drug supply shortages. The dilemma on how to guarantee continuous patient care while facing supply shortages has been researched in the past. A study on epinephrine showed continued stability for years beyond its labeled expiration date when stored under controlled storage conditions.<sup>19</sup> Real-life stability testing has also been employed by the US Department of Defense to extend the shelf life of drugs in its emergency stockpile.<sup>20</sup>

These studies and our data suggest that extending medication exchange guidelines on the basis of real-life drug stability data has the potential to ensure continued drug availability during times of supply shortages. Future research on drug stability should define safe temperature ranges for drug storage so that easier monitoring methods, such as temperature logging, can be employed reliably.

In conclusion, emergency drugs remained stable in a Swiss HEMS setting even though their prescribed storage requirements could not be met. Discarding drugs on the basis of perceived degradation should be revisited to prevent unnecessary waste. Real-life drug stability testing could be a way to answer calls for sustainability and to safeguard drug availability during supply shortages.

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**Author contributions:** UP, RA, and JM conceived the study and designed the trial. JM and SS conducted the study and collected data. SS performed the laboratory analyses. DJ and AJ provided statistical advice on study design. UP, JM, JK, VW, WEH, AJ, and DJ analyzed the data. JM drafted the article, and all authors contributed substantially to its revision. UP takes responsibility for the paper as a whole.

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