

Medication Storage in the EMS Environment: Understanding the Science and Meeting the Standards



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It's the middle of winter, and you've been dispatched to a possible heart attack at a local assisted-living facility. As you and your partner drive toward the location, the ambulance heater barely keeps the cab warm, and you're both shivering when you arrive on scene. As you walk into the building's lobby, you're shocked to see two things: Someone is actually doing CPR, and the victim appears to be relatively young—maybe 35 or 40 years old. A quick look reveals ventricular fibrillation, and you administer three defibrillations without response. Your partner intubates the patient, you start an IV and administer epinephrine, and—with assistance from a second unit—you continue through the entire ACLS algorithm, transporting the patient to the nearest emergency department. Unfortunately, the patient never regains a pulse.

It's the middle of summer, and you've been dispatched to a possible asthma attack at a nearby playground. As you and your partner drive toward the park, the ambulance's air conditioner can barely cool the cab, and you're both sweating profusely before you even arrive on scene. Once there, you find a 15-year-old girl in severe respiratory distress. You apply oxygen and begin to administer breathing treatments, but she doesn't get better. En route to the hospital, you start an IV and continue the nebulizers, but there's still no response. At the emergency department, she is placed on continuous nebulizer therapy and begins to improve. She is eventually admitted to the hospital, but she does not require intubation and is discharged the next day.



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Neither of these scenarios is particularly uncommon. Sometimes, prehospital interventions simply don't work and, although that's always disappointing, usually nobody thinks there's anything more to it. But is there?

Medication Storage Standards

In the United States, standards for medicines are set by the United States Pharmacopeial Convention Inc. (USP), a nongovernment entity that establishes standards intended to ensure the quality of medicines and other healthcare technologies.¹ The role of USP and its National Formulary (USP-NF) is recognized in federal law under the Federal Food, Drug and Cosmetic Act.^{2,3} Among other things, the USP-NF prescribes the packaging, storage and distribution of medications.

Most of the medications commonly used by EMS are intended for storage at controlled room temperature. The USP has the following very specific and technical definition for controlled room temperature:

A temperature maintained thermostatically that encompasses the usual and customary working environment of 20°–25°C (68°–77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15°–30°C (59°–86°F) that are experienced in pharmacies, hospitals and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to 40°C are permitted, as long as they do not exceed 24 hours. Spikes above 40° may be permitted if the manufacturer so instructs. Articles may be labeled for storage at controlled room temperature or at up to 25°C, or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variations. (See also Stability under Pharmaceutical Dosage Forms <1151>.)⁴

Table I lists some common EMS medications and the temperature-related storage directions on the package label (the package label may also address light and humidity, among other things). Clearly, the official definition for storage conditions is much more complex than what appears on a medication package. When a medication package says "store between 59°–86°F," that really means "store at controlled room temperature." When a medication package says, "store at 25°C," that also means "store at controlled



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room temperature. □ Further, medications are supposed to be stored in a manner that □s compliant with the entire definition of controlled room temperature, so simply measuring the range of temperatures at which medications are stored, or the maximum temperature, or even the average temperature doesn □t actually address whether medications are appropriately stored.

Understanding that the requirements for medication storage are both complicated and clinically important raises some significant questions:

1. Are medications that are kept on ambulances stored in compliance with the standard for □controlled room temperature □?
2. If medications are not stored at □controlled room temperature, □ does that affect their potency?
3. If medication potency is affected by improper storage, is it enough to decrease the clinical effectiveness of the medication?

Research Review: Ground EMS

People questioned the temperatures to which EMS medications are exposed as early as 1985, when researchers in Salt Lake City placed a disc-recording thermometer inside a Plano drug box and compared the temperatures recorded inside the drug box with the outside temperature.⁵ On the day of the experiment, the outside temperature peaked at 34.4°C (94°F), but the temperature in the drug box reached more than 40.6°C (105°F). The experiment was repeated several times throughout the summer, with temperatures inside the drug box climbing as high as 60°C (140°F).

Building on the experience in Salt Lake City, researchers in Arizona conducted an experiment in which temperatures inside four Plano drug boxes were recorded during four weeks of summer.⁶ The drug boxes were stocked with 23 common EMS medications and placed in a white metal storage shed, which □was chosen for drug storage because it was easily secured and approximated the internal temperatures of a paramedic vehicle parked in the sun. □ Temperatures inside the storage shed ranged from 24° □43°C (75.2° □109.4°F), and the temperatures inside the drug boxes ranged from 26° □38°C (78.8° □100.4°F). When the medications were analyzed, only two □epinephrine and isoproterenol □showed significant changes. There was no chemical breakdown of the epinephrine, but there were signs of alterations in the buffer compound in which the drug is dissolved. The isoproterenol actually degraded: 4% after just one week and 11% after four weeks.

In 1999, researchers from the Denver, CO, area published a research abstract □but not a complete paper □about epinephrine stored on EMS vehicles there.⁷ The recorded temperatures ranged from -7.6° □38.6°C (18.3° □101.5°F) in urban settings and from 0.4° □40.2°C (32.7° □104.4°F) in rural settings, with mean kinetic temperatures of 23.6°C (74.5°F) and 20.8°C (69.4°F), respectively. By comparison, medications stored at the EMS office experienced temperatures that met the USP definition of □controlled room temperature. □ After six months on the ambulances, chemical degradation was evaluated using high-pressure liquid chromatography (HPLC). Physiologic activity was determined in a laboratory by injecting the epinephrine into heart tissues and observing the response. When compared with the epinephrine stored in the office, there

was significant degradation in both chemical structure and physiologic activity of the epinephrine stored on the EMS vehicles.

Researchers in New Jersey measured medication storage temperatures on ambulances during 12 weeks of summer and four weeks of winter.⁸ The on-ambulance temperatures were recorded inside the drug box, and the ambulances were parked in either a climate-controlled garage, in a garage with fans only, under a carport or in a parking lot. During summer, all of the ambulance drug boxes experienced mean kinetic temperatures above the controlled room temperature threshold of 25°C (77°F), ranging from 25.6°–28.9°C (78.1°–84°F). All of the drug boxes also recorded maximum temperatures above 30°C (86°F), and three of the drug boxes reached temperatures greater than 40°C (104°F). The highest recorded temperature was 58.3°C (136.9°F). During the winter months, all of the monitors recorded temperatures well below 15°C (59°F), with minimum temperatures ranging from -14.0°–8.9°C (6.8°–48°F).

A study of temperatures inside the medication storage compartments on fire department response vehicles in El Centro, CA, found that housing the vehicle inside a climate-controlled garage provided some protection from ambient temperature extremes, but active cooling of the medication storage compartment was required to significantly lower the temperatures to which medications were exposed.⁹ Still, even with active cooling of the medication storage compartment, temperatures often approached and sometimes exceeded 32.2°C (90°F).

Researchers from Los Angeles County, CA, recorded on-ambulance temperatures for 45 days at 14 different sites, then used HPLC to test epinephrine, atropine and lidocaine that had been stored on those ambulances.¹⁰ The highest temperature recorded was 52°C (125.6°F); seven sites recorded temperatures above 40°C (104°F) and 10 of the sites had mean kinetic temperatures above 25°C (77°F). Despite these high temperatures, there was no degradation in the tested samples of epinephrine, atropine or lidocaine.

Finally, in 2000 and 2001, USP and the American Ambulance Association collaborated on a multicenter, year-long observational study of EMS medication storage temperatures using the detailed USP definition of controlled room temperature.¹¹ Temperature recorders were placed on EMS vehicles in Arizona, Florida, Kansas, Oregon and New York. Ambulances in all five locations experienced medication storage temperatures outside of the USP's definition of "controlled room temperature." Four of the five cities experienced excessive heat, and all five cities experienced excessive cold.

Research Review: Air EMS

Two studies have measured medication storage temperatures in the air-medical setting. The first reported temperatures were recorded inside medication bags kept on two different helicopters in Delaware.¹² Average temperatures ranged from as low as 13.2°C (55.8°F) in winter to as high as 31.2°C (88.2°F) in summer. Roughly half of the winter temperature measurements were below 15°C (59°F) and about 40% of the summer temperature measurements were above 30°C (86°F). The second aeromedical study reported temperatures inside the drug box kept on one air-medical helicopter in northern New Jersey.¹³ The helicopter was usually stationed on a rooftop heliport, but it was moved into a hangar during bad weather. Temperatures were recorded for nine weeks during summer and three weeks during winter. More than a third (37%) of the summertime temperature measurements exceeded 25°C (77°F) and 6% exceeded 30°C (86°F); 83% of the wintertime temperature measurements were below 15°C (59°F). The mean kinetic temperature was 25.1°C (77.2°F) during summer and 12.7°C (54.9°F) during winter.

Research Review: Laboratory Studies

Three laboratory studies have been designed to simulate exposure to out-of-hospital environments and then test for changes in medication potency. The first study was conducted in 1993, when researchers exposed four EMS medications—atropine, lidocaine, epinephrine and naloxone—to temperatures ranging from -20° to 70°C (-4° to 158°F).¹⁴ When compared with control samples, none of the tested medications showed significant changes in their chemical makeup.

The following year, researchers from North Carolina—who had previously shown that cycles of heating cause different degradation patterns¹⁵—exposed both 1:1,000 and 1:10,000 concentrations of epinephrine to cycles of either heat or cold.¹⁶ Heated samples were warmed to 70°C (158°F) and then allowed to return to room temperature; cooled samples were placed in a freezer until they reached 5°C (41°F) and then removed and allowed to return to room temperature. The cycles were repeated for 12 weeks. Chemical degradation was determined using HPLC, and the biological activity of degraded samples was assessed by administering the medication to rats. While the potency of 1:1,000 epinephrine did not diminish, the 1:10,000 epinephrine that was exposed to cyclical heating underwent significant degradation, losing 64% of its potency after the 12-week experiment.

Finally, a laboratory experiment reported in 1999 compared degradation in diazepam and lorazepam samples exposed to three different storage schemes: refrigerated at 4° to 8°C (39.2° to 46.4°F), on an ambulance, and in an oven at 37°C (98.6°F).¹⁷ After 210 days, the concentration of refrigerated diazepam dropped 7%, diazepam stored on the ambulance had a 15% reduction in concentration, and diazepam stored at 37°C (98.6°F) had a 25% loss of concentration. Lorazepam stored in a refrigerator had a 0% drop in concentration, stored on the ambulance a 10% loss of concentration, and stored at 37°C (98.6°F) a 75% reduction in concentration.

Summarizing the Research

The ground EMS studies clearly show that on-ambulance medication storage is not consistent with the USP definition of “controlled room temperature.” This finding is consistent across all of the studies, independent of any system-specific characteristics. The same is probably true for the air-medical environment, although, so far, only two systems have been studied. Whether or not exposure to these temperatures causes significant degradation to medications remains unclear. One of the ground EMS studies found significant degradation in epinephrine, but that study has never been reported in full. The study from Arizona found degradation in isoproterenol, but not in any other EMS medication. The study from Los Angeles County found no degradation in epinephrine, atropine or lidocaine.

The laboratory studies don’t add much clarity. While one study found no degradation in atropine, lidocaine, epinephrine or naloxone, another did find significant degradation in 1:10,000 epinephrine exposed to cyclical heating. Both of these studies, however, used temperature exposures (i.e., 70°C /158°F) far outside of those recorded in any of the on-ambulance studies. Both diazepam and lorazepam stored on ambulances were shown to degrade—15% and 10%, respectively—after 210 days, but even the refrigerated diazepam degraded some.

So, are medications that are kept on ambulances stored in compliance with the standard for “controlled room temperature”? No. If medications are not stored at “controlled room temperature,” does that affect their

potency? Maybe some drugs, especially 1:10,000 epinephrine, isoproterenol, diazepam and lorazepam. Many medications, though, have never been tested. If medication potency is affected by improper storage, is it enough to decrease the clinical effectiveness of the medication? That, we simply don't know.

The Regulatory Response

As a result of the research and concerns raised in the medical and pharmaceutical communities, USP has published a new general information chapter in the USP-NF entitled "Emergency Medical Services Vehicles and Ambulances—Storage of Preparations." The chapter calls on EMS agencies to have an effective plan for the storage and handling of pharmaceuticals, and identifies some practices that should be considered, which are summarized in Table II. Because the chapter is classified as general information, USP does not view compliance with the chapter, or any of these specific practices, as mandatory. Instead, the chapter is intended to guide EMS agencies in their efforts to ensure the stability of the medications they stock, and the identified practices are the kinds of activities that will help achieve that goal.

Some states have also acted to address the issue of EMS medication storage. As a result of the 1985 study in Salt Lake City, the Utah Department of Health amended the state's EMS regulations to include a requirement that "medications shall be stored as per the manufacturer's recommendation."⁵ Since 1998, New Jersey has required temperature monitoring on all EMS vehicles, and that any place where EMS medications are stored "be sufficiently climate-controlled so that the medications and solutions are kept within the temperature range recommended by the manufacturer."¹⁸

What To Do?

Armed with this information, what should EMS agencies do? As with almost all problem-solving, the first step is to recognize—or accept—that there is a problem. The cumulative research leaves little doubt that EMS medication storage almost everywhere is not compliant with the USP standards. While it remains unclear whether the noncompliance corrupts the medications or impacts patient care, until that issue is resolved scientifically it is simply prudent to do everything possible to comply with the standards.

Every EMS system should develop a plan for addressing medication storage built around an understanding of the storage problems within that specific EMS system. Monitoring and recording on-ambulance temperatures, and then evaluating those temperatures using the official USP definition of controlled room temperature, should be the first step. A number of companies market temperature monitoring devices, and many of them will provide the necessary data analysis as well. Once a system knows quantitatively what it is up against, it will be easier to develop a meaningful plan. Some places will have to deal primarily with heat and occasionally with cold; some places will have to deal primarily with cold and occasionally with heat; some places will have to deal with both year-round. There will be no one-size-fits-all plan.

The practices recommended by USP can form the backbone of any EMS medication storage plan, but they'll have to be tailored to each system. Parking in climate-controlled garages or taking the drug bag into the station house when not on a call is simple enough, but only if the EMS system operates out of station houses and has garages. Developing stock rotation strategies might be tricky in busy systems with dynamic scheduling and vehicle posting—and it's not yet clear exactly how frequently medications should be rotated. Commercially available time-temperature indicators are reasonably inexpensive and could be applied to either

individual medication packages or to the outside of a sealed drug bag or medication cabinet, but someone would have to be responsible for applying and monitoring the indicators.

It is also important to regularly reevaluate whatever plan a system implements. To date, no studies have been specifically designed and implemented to test the effectiveness of any of the devices or schemes intended to maintain on-ambulance medications at controlled room temperature. Whatever strategies are used, they should be subjected to ongoing evaluation to be sure they're achieving the desired results.

Don't Do It Alone

Medical directors should be involved in the evaluation and planning of EMS medication storage strategies. Physicians have insights into medication stability that EMS administrators and field providers may not have. Perhaps more important, medical directors will also have access to resources that EMS agencies may not: specifically, hospital pharmacists. Whoever is responsible for guaranteeing that the pharmacy at the base hospital is compliant with USP standards could certainly be helpful to EMS systems trying to meet the same standards. In rural or remote areas without a local hospital, or for basic life support systems that don't have an identified medical director, any local pharmacist can likely be helpful too.

Summary

In most systems, current EMS medication storage practices are not consistent with USP standards. Exposure to excessive heat and excessive cold are both common. Although the clinical implications of noncompliant storage remain unclear, it's in the best interest of patients to do everything possible to meet the standards. To help in this effort, USP has generated EMS-specific guidance for medication storage. Most of the strategies for achieving compliance with USP standards are relatively simple and inexpensive. All EMS systems should develop a plan for medication storage that strives to achieve compliance with the USP standards, and reevaluate that plan on a regular basis.

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Table I: Common EMS Medications and Their Recommended Storage Temperatures
Medication – Recommended Storage Temperature

Adenosine – 15°-30°C (59°-86°F). Do not refrigerate.
 Albuterol sulfate – 2°-25°C (36°-77°F)
 Amiodarone – Controlled room temperature 25°C (77°F)
 Atropine – 15°-30°C (59°-86°F)
 Calcium chloride – 15°-30°C (59°-86°F)
 Diazepam – At or below 25°C (77°F)
 Diltiazem – 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)
 Diphenhydramine 15°-30°C (59°-86°F). Protect from freezing.
 Dopamine – Controlled room temperature 15°-30°C (59°-86°F)
 Epinephrine 1:1,000 15°-30°C (59°-86°F)
 Epinephrine 1:10,000 15°-30°C (59°-86°F)
 Furosemide – 15°-30°C (59°-86°F)
 Glucagon* Controlled room temperature 20°-25°C (68°-77°F)
 Ipratropium bromide 2°-25°C (36°-77°F)
 Lidocaine 2% – 25°C (77°F)
 Magnesium sulfate 15°-30°C (59°-86°F). Protect from freezing.
 Midazolam – 15°-30°C (59°-86°F)
 Morphine sulfate Controlled room temperature 15°-30°C (59°-86°F)
 Do not freeze.
 Naloxone – Controlled room temperature 15°-30°C (59°-86°F)
 Sodium bicarbonate 15°-30°C (59°-86°F)

*Glucagon before reconstitution.

Table II: Summary of Recommended Practices from the USP-NF Chapter

Emergency Medical Services Vehicles and Ambulances Storage of Preparations

Monitor and verify temperature profiles to compare with established limits, especially on hot summer and cold winter days.

On-board cabinets must be insulated, and should use active heating and cooling if necessitated by the local climate.

Consider using insulated portable carrying cases and, when they are not in use, keep them inside or in a climate-controlled cabinet to maintain controlled room temperature.

Consider using portable cases exclusively, instead of on-board cabinets, to facilitate rotation. Time-temperature indicators can be used to monitor temperature exposures of the portable case's entire contents.

Consider using time-temperature indicators to monitor individual medication packages, especially for environmentally sensitive and thermally sensitive preparations.

All medications should be protected from excessive heat (40°C+). Some medications may need to be stored in a cold and/or dry place, and environmentally sensitive medications should not be stored on EMS vehicles unless the storage cabinet is temperature-controlled or individual time-temperature indicators are attached to each medication package.

Consider stock rotation on a schedule based on local climate, perhaps every three days or so. The stock should be rotated into a climate-controlled environment. Stock rotation may be especially necessary for environmentally sensitive preparations.

Consider temperature exposures when parking ambulances. Park in heated and air-conditioned garages if possible. When parking outside, attempt to park in the shade.

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