American Journal of Emergency Medicine (2008) **26**, 566–573

The American Journal of Emergency Medicine

www.elsevier.com/locate/ajem

Original Contribution

Alteration in prehospital drug concentration after thermal exposure☆

Dustin L. Gammon CCEMT-P[a,b,*], Shujun Su PhD[b], Janet Jordan MD[a], Robert Patterson EMT-P[a], Phillip J. Finley MS[c], Cindy Lowe BS, CCRP[c], Roger Huckfeldt MD[c]

[a]*St. John's Emergency Medical Services, Springfield, MO 65804, USA*
[b]*Department of Chemistry, Missouri State University, Springfield, MO 65897, USA*
[c]*St. John's Trauma Services and Research Department, Springfield, MO 65804, USA*

Received 14 August 2007; revised 8 September 2007; accepted 9 September 2007

Abstract

Objective: The aim of the study was to determine the remaining concentration of 23 commonly carried emergency medical services medications used in the United States after they have experienced thermal extremes that have been documented in the prehospital environment for a period of 1 month.

Methods: Pharmaceuticals were thermally cycled (−6°C and 54°C) every 12 hours and then assayed by high-performance liquid chromatography.

Results: Eight (35%) of 23 prehospital pharmaceuticals revealed ending concentrations of less than 90% with strong correlation to thermal exposure time. These included lidocaine, diltiazem, dopamine, nitroglycerin, ipratropium, succinylcholine, haloperidol, and naloxone.

Conclusion: A decrease in concentration was found to be statistically significant in 8 (35%) of 23 commonly carried emergency medical services pharmaceuticals. These results provide new information and perspective regarding stability of emergency drugs in the prehospital environment by evaluating a broad range of pharmaceuticals as well as by using thermal exposure points that have been documented in the United States.

1. Introduction

Numerous studies have validated that emergency medical services (EMS) medication storage temperatures are not consistent with the United States Pharmacopeia storage recommendations [1-9]. The effect of these temperature deviations on drug concentration, however, has not been well studied. Because no widely published work is offered regarding specific environmental limits for prehospital pharmaceuticals, researchers are now trying to quantify true stability ranges or correlate actual conditions with stability and concentration.

This project was presented in poster form at the 21st annual Combined Clinical Conference on Emergency Care; Osage Beach, Missouri, August 8-10, 2007.

☆ Funding sources: This project was funded by St John's Emergency Medical Services and St John's Trauma Services. Additional cost coverage provided by the author; instrument utilization, supervision, and consultation, provided by Missouri State University.

* Corresponding author. St. John's Emergency Medical Services, Springfield, MO 65804, USA.

E-mail address: dustin.gammon@mercy.net (D.L. Gammon).

0735-6757/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.ajem.2007.09.004

To date, the majority of investigations have typically addressed in-hospital environments by evaluating very mild or extremely harsh deviations from storage recommendations, neither of which is applicable to the prehospital field. Although there are a limited number of various EMS-focused studies, many have used excessive temperature exposures (ie, 70°C), or, the analytical instrumentation procedures have been questioned regarding appropriateness for thermal stability testing. Specifically questioned are analyses by gas chromatography owing to required superheating of samples to vaporize the sample for assaying [10,11]. In addition, studies have repeatedly limited their investigational focus to a small subset of the more popular advanced cardiac life support used drugs and thus far have had inconsistent degradation results when taken in combination [12-15].

This study addresses the effect of thermal exposure on the concentration of a broad range of EMS medications commonly carried on ambulances in the United States. This study uses quantitative measuring by high-performance liquid chromatography, considered the "gold standard" in the pharmaceutical industry for stability and quantitative testing operations [16]. The primary objective of this study was to determine, quantitatively, the remaining concentration of commonly carried EMS medications used in the United States after they have experienced thermal extremes documented in the prehospital environment [8].

In this investigation, it is anticipated that the pharmaceuticals commonly carried by prehospital care providers will retain an amount greater than or equal to 90% of their initial concentration after 1 month exposure to thermal extremes which have been documented in the out-of-hospital environment.

2. Methods

2.1. Study design

This was an in vitro study design that used reversed-phase HPLC (RP-HPLC) with ultraviolet (UV) spectroscopy. Institutional review board exemption was obtained before the initiation of the study.

2.2. Sample selection

Common EMS pharmaceuticals were defined as non-scheduled medications that are typically used by paramedics in the prehospital phase of patient care in which storage state is in aqueous solution for intravenous administration and not reconstituted before use. Each sample was obtained from the EMS stock of a regional hospital–based EMS. Emergency medical services stock is delivered directly from hospital pharmacy storage and complies with United States Pharmacopeia "controlled room temperature" or manufacturer storage recommendations at all times. Samples were in concentration and packaging as they are carried on-

Table 1 Pharmaceutical drug list

Drug name	Expiration	Total concentration (mg or U)	Total volume (mL)	Recommended storage (°C) [a]
Adenosine	1-Feb-08	6	2	20-25
Albuterol	1-May-09	2.5	3	15-25
Amiodarone	1-Aug-07	150	3	20-25
Atropine	1-Apr-09	1	10	15-30
Diltiazem	1-May-07	25	5	2-8
Dopamine	1-Jul-07	400	250	25
Epinephrine	1-Mar-08	1	10	15-30
Etomidate	1-Jul-07	40	20	15-30
Haloperidol	1-Jan-08	4	1	15-30
Heparin	1-Jul-07	10000	1	20-25
Hydralazine	1-Dec-07	20	1	15-30
Ipratropium	1-May-09	0.5	2.5	15-30
Labetalol	1-Apr-07	20	4	2-30
Lidocaine	1-Mar-08	100	5	15-30
Naloxone	1-Oct-07	40	10	20-25
Nitroglycerin	1-Sep-07	50	250	15-30
Oxytocin	1-Jul-07	100	10	15-30
Procainamide	1-May-07	1000	2	15-30
Succinylcholine	1-Apr-08	200	10	2-8
Terbutaline	1-Dec-07	1	1	20-25
Thiamine	1-Apr-08	200	2	15-30
Vasopressin	1-Dec-07	20	1	15-30
Ondansetron	1-Jul-09	4	2	15-30

∗Study period: 2/6/07 to 3/13/07.
[a] Labeled recommendation.

Table 2 Advanced cardiac life support: cardiac arrest category

Drug	Initial concentration (mg/mL)	% Initial concentration remaining					Pearson's *R*
		Day 7	Day 14	Day 21	Day 28		
Amiodarone	50.00 ± 0.1	94.80 ± 1.16	87.74 ± 1.08	91.84 ± 0.43	92.95 ± 1.38	(P = .282)	0.60
Atropine	0.100 ± 0.001	93.60 ± 0.91	96.03 ± 0.82	102.08 ± 0.64	97.25 ± 1.22	(P = .820)	0.14
Epinephrine	0.100 ± 0.001	91.93 ± 0.44	81.96 ± 0.45	87.75 ± 1.35	79.52 ± 0.70	(P = .053)	0.87
Lidocaine	20.00 ± 0.003	98.61 ± 0.45	92.47 ± 1.26	86.89 ± 0.42	86.24 ± 0.44	(P = .006)	0.96
Procainamide	500.00 ± 0.004	101.39 ± 0.45	98.58 ± 0.51	95.79 ± 0.64	98.29 ± 1.36	(P = .205)	0.68
Vasopressin (U)	20.00 ± 0.003	93.37 ± 1.33	98.31 ± 1.02	80.56 ± 0.73	92.49 ± 1.50	(P = .308)	0.57

Mean ± SD of triplicate injections; n = 15, α = .05.

ambulance. Each medication had an expiry date beyond the study completion date. Refer to Table 1 for a comprehensive list of investigational pharmaceuticals.

Excluded medications were any scheduled narcotics; those which required reconstitution before use; and the individual drugs: diphenhydramine, hydroxyzine, and furosemide, owing to incompatibility with analytical testing conditions.

2.3. Procedures

After acquisition, samples were taken to an instrument laboratory in the Department of Chemistry at Missouri State University. All samples were visually inspected for color, clarity, and viscosity; expiration, concentration, and storage recommendations were also documented (Table 1). Samples were wrapped in aluminum foil to protect from UV exposure and stored in locked cabinet at approximately room temperature. Storage temperature was monitored throughout the study with an electronic temperature recording device with memory for minimum and maximum storage temperatures. Medications that were stored in plastic packages that required irreversible opening were aseptically transferred to glass vials so that multiple aliquots could be sampled; otherwise, all samples were maintained in their original vials.

Medications were divided into convenience groups for thermal cycling and weekly sampling. A baseline concentration was obtained by RP-HPLC for each medication on the day that group's thermal exposure was initiated. Initial concentration was determined by taking the average chromatographic peak of interest area response for 3 serial column injections at ambient temperature and setting proportionality ratios to volume injection of labeled medication concentration. The group of medicines was then cycled at thermal points of −6°C and 54°C (2.12°F-129.20°F).

Light-protected vials were placed into sealed plastic bags and then thermal exposure was achieved by placing sealed vials into circulating water bath for upper temperature range and standard refrigerator/freezer for lower temperature range, both with manual temperature controls and equipped with minimum and maximum recording capabilities by an electronic temperature recorder. Heat and cold exposure were equally divided in time every 24 hours at 12-hour consecutive exposure blocks with calculated mean kinetic temperatures of 33°C. Each drug was exposed to a total of 336 hours of heat and 336 hours of cold with 168 hours defining intrasampling time (84 hours cold/84 hours heat). Samples were then individually assayed each week, for 1 month. After each sample was analyzed, thermal exposure was again resumed.

2.4. High-performance liquid chromatographic conditions

Reversed-phase HPLC procedures were built upon previous published studies in which robust conditions, appropriate for a broad range of sample types, were developed [17-19]. The HPLC system[1] was equipped with a manual injection port and 20-μL sample injection loop. A C-18 octadecyl silane column[2] type with a variable-wavelength UV-light detector[3] was used for detection, all of which were connected to a data integrator.[4] The mobile phase components were all of HPLC quality and consisted of acetonitrile, 0.025% phosphoric acid, and buffer, mixed in a 25:10:5 ratio. Buffer was 9 mL concentrated phosphoric acid and 10 mL triethylamine in 900 mL water, adjusted to pH of 3.25 with dilute phosphoric acid. Mobile phase was filtered through 0.2-μm filter, degassed, and stored in an amber bottle. Flow rate was 1 mL/min.

With the exception of procainamide, each sample was injected onto the column, undiluted in 20-μL aliquots, and at ambient temperature. Procainamide was diluted 1:10 to prevent column overload and injected as a 20-μL aliquot. Concentrations were based on the average chromatographic peak area of triplicate injections. Results of replicate injections at each period were appropriate [16,19-21], having standard errors of less than 2%.

2.5. Statistical measures

Data obtained were input into Excel and statistical tests used were descriptive, simple linear regression, and Pearson's correlation. Statistical calculations were performed

[1] ProStar Model 210 (Varian, Inc, Palo Alto, Calif).
[2] Supelcosil LC-18-DB; 25 cm × 4.6 mm, 5*m*m (Sigma-Aldrich Corp, St. Louis, Mo).
[3] ProStar Model 340 (Varian).
[4] Star Chromatography Work Station v. 5.51 (Varian).

Table 3 Advanced cardiac life support: miscellaneous category

Drug	Initial concentration (mg/mL)	% Initial concentration remaining					Pearson's *R*
		Day 7	Day 14	Day 21	Day 28		
Adenosine	3.00 ± 0.001	100.60 ± 1.32	94.27 ± 0.69	98.82 ± 0.73	97.97 ± 1.40	(P = .538)	0.37
Diltiazem	5.00 ± 0.001	94.16 ± 1.18	91.88 ± 1.23	92.26 ± 0.72	83.19 ± 0.88	(P = .022)	0.92
Dopamine	1.600 ± 0.001	92.75 ± 0.42	88.85±0.68	90.49 ± 1.26	82.78 ± 0.74	(P = .023)	0.92
Heparin (U)	1000.0 ± 0.099	92.89 ± 0.59	84.02 ± 0.49	87.69 ± 1.38	86.06 ± 1.18	(P = .093)	0.81
Labetalol	5.00 ± 0.001	102.23 ± 0.76	100.81 ± 0.50	101.43 ± 0.76	98.29 ± 1.35	(P = .454)	0.44
Nitroglycerin	0.200 ± 0.001	90.61±0.98	84.68 ± 1.26	70.05 ± 1.10	58.65 ± 1.21	(P = .001)	0.99

Mean ± SD of triplicate injections; n = 15, α = .05.

using SPSS [22]. Statistical significance for regression analysis was based on α = .05, n = 15, and a clinically significant reduction in concentration was defined as a decrease of 10% or more of initial concentration [23]. Significant correlation between concentration and thermal exposure time was defined as a Pearson's correlation coefficient (R) of 0.75 or higher. For findings with statistical significance, confidence intervals of 95% are calculated for correlation using Fisher's z transformation.

3. Results

Twenty-three pharmaceuticals (Table 1) commonly used by paramedics in the United States were investigated in this study for the effect of thermal extremes on drug concentration after thermal exposures outside of the manufacturer's recommended storage conditions for 1 month. These thermal exposures have been validated by actual conditions experienced in the prehospital environment [8]. These drugs were exposed to cyclic temperatures of −6°C and 54°C (2.12°F-129.20°F) and assayed each week for concentration remaining.

Outcomes were categorized into 4 divisions based on remaining concentration and the strength of correlation. For those with ending concentrations of less than 90%, 2 categories based on strong or weak correlation to thermal exposure time; and, secondly, those retaining concentrations greater than 90%, 2 categories, also based on strong or weak correlation.

Ten (43%) of the 23 evaluated pharmaceuticals degraded to less than 90% while correlating well to thermal exposure time, and 1 (4%) showing weak correlation. Eleven (48%) maintained greater than 90% of initial concentration and were weakly correlated to thermal exposure time, and 1 (4%) maintained greater than 90% of initial concentration and was strongly correlated to thermal exposure time. Regression analysis revealed statistical significance for 8 (35%) of the 23 evaluated pharmaceuticals, all of which noted a greater than 10% reduction in concentration and a strong correlation to thermal exposure time. These included (with 95% confidence interval of correlation) lidocaine (0.88-0.99), diltiazem (0.77-0.97), dopamine (0.77-0.99), nitroglycerin (0.96-0.99), ipratropium (0.85-0.98), succinylcholine (0.91-0.99), haloperidol (0.80-0.97), and naloxone (0.91-0.99). Individualized results are grouped based on common use and presented in Tables 2-5 and graphically in Figs. 1A to 4B.

4. Discussion

To our knowledge, this study is the first investigation covering a broad range of EMS pharmaceuticals exposed to thermal extremes experienced in the contiguous United States and assayed by RP-HPLC. This study provides additional insight into the issue of EMS medications' exposure to thermal environments outside of the recommended storage conditions and confirms that such exposures can result in the decrease in concentration of select EMS pharmaceuticals.

Table 4 General: airway category

Drug	Initial concentration (mg/mL)	% Initial concentration remaining					Pearson's *R*
		Day 7	Day 14	Day 21	Day 28		
Albuterol	0.833 ± 0.001	89.14 ± 0.41	89.77 ± 1.18	91.74 ± 1.16	89.30 ± 1.27	(P = .238)	0.64
Etomidate	2.00 ± 0.001	95.41 ± 0.66	101.41 ± 0.45	102.32 ± 1.10	96.94 ± 0.43	(P = .946)	0.04
Ipratropium	0.200 ± 0.001	101.75 ± 0.49	93.53 ± 1.23	89.89 ± 1.04	84.58 ± 1.34	(P = .013)	0.95
Succinylcholine	20.00 ± 0.002	97.98 ± 0.48	82.60 ± 0.67	57.28 ± 0.99	44.25 ± 1.32	(P = .006)	0.97
Terbutaline	1.000 ± 0.001	98.77 ± 1.02	105.22 ± 1.17	98.71 ± 0.55	98.64 ± 0.20	(P = .802)	0.15

Mean ± SD of triplicate injections; n = 15, α = 0.05.

Table 5 General: miscellaneous category

Drug	Initial concentration (mg/mL)	% Initial concentration remaining					Pearson's *R*
		Day 7	Day 14	Day 21	Day 28		
Haloperidol	5.00 ± 0.001	99.02 ± 0.19	93.19 ± 1.02	93.73 ± 1.35	84.93 ± 0.32	(P = .020)	0.93
Hydralazine	20.00 ± 0.002	96.44 ± 0.90	102.53 ± 0.50	104.54 ± 1.22	99.75 ± 1.27	(P = .514)	0.39
Naloxone	4.00 ± 0.001	100.13 ± 0.67	95.21 ± 1.22	92.78 ± 1.13	89.62 ± 1.33	(P = .005)	0.97
Oxytocin (U)	10.00 ± 0.001	93.02 ± 0.76	94.09 ± 0.51	88.88 ± 0.64	93.39 ± 1.37	(P = .198)	0.68
Thiamine	100.00 ± 0.016	99.19 ± 0.66	102.07 ± 0.49	101.35 ± 0.88	101.28 ± 1.35	(P = .241)	0.64
Ondansetron	2.00 ± 0.001	98.13 ± 0.98	97.50 ± 1.03	97.99 ± 0.73	92.90 ± 0.53	(P = .062)	0.85

Mean ± SD of triplicate injections; n = 15, α = .05.

This study finds that the influence of exposure temperature on the concentration of EMS pharmaceuticals varies. Based on these results, of greatest concern are those in the first group having fairly narrow dosing ranges. Two (lidocaine and diltiazem) are used primarily in emergent cardiac situations, 1 (haloperidol) for behavioral emergencies, and 1 (succinylcholine) to achieve paralysis for emergent airway control. Others in this group (dopamine, nitroglycerin, and ipratropium), although important, are typically administered based on patient response rather than a narrow dosage range.

Both succinylcholine and diltiazem were anticipated to show a decrease in their concentrations during the study period owing to their recommended storage conditions. It has been suggested that without refrigeration, these medicines experience accelerated decreases in concentrations, but may

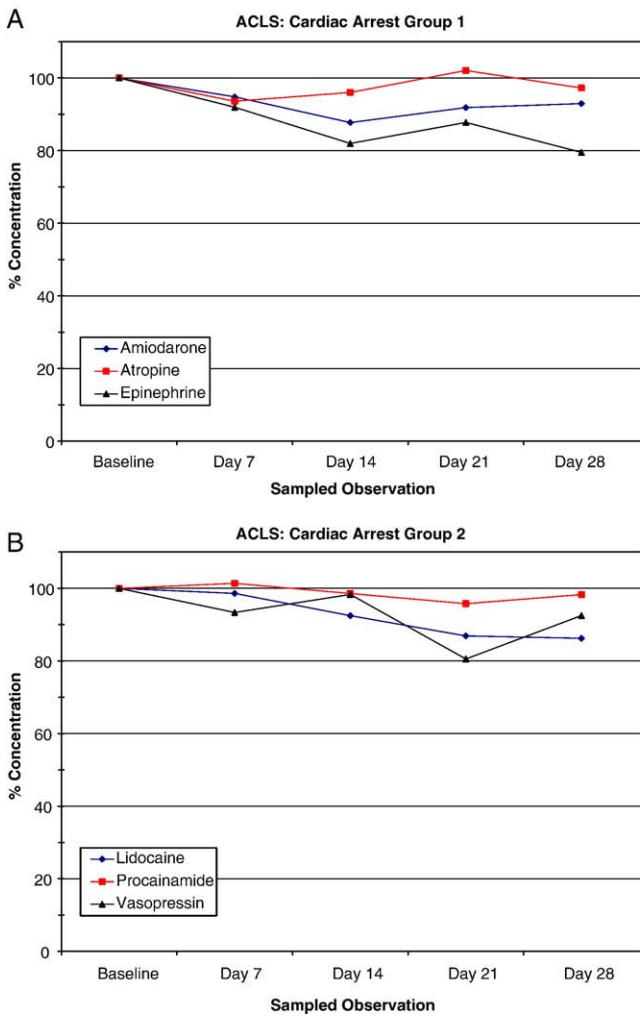

Fig. 1 Advanced cardiac life support. A, Cardiac arrest group 1. B, Cardiac arrest group 2.

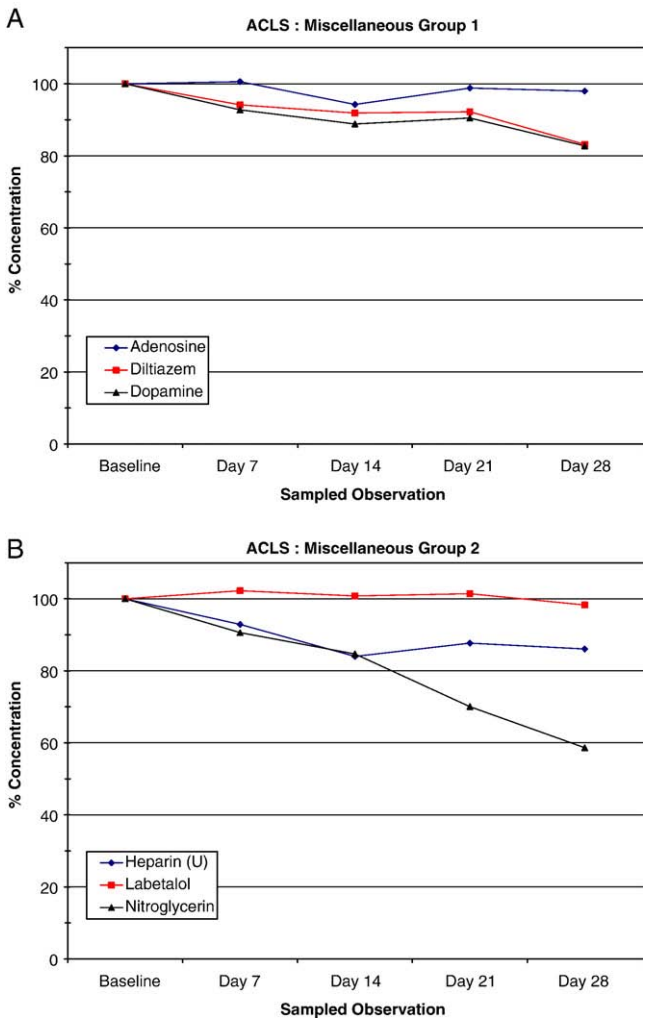

Fig. 2 Advanced cardiac life support. A, Miscellaneous group 1. B, Miscellaneous group 2.

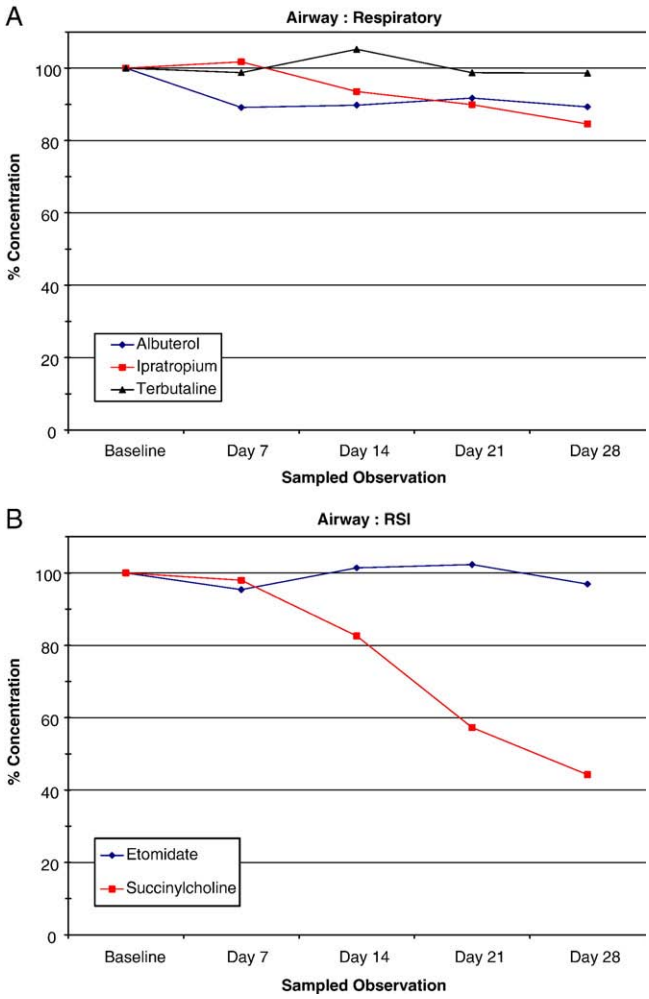

Fig. 3 Airway. A, Respiratory. B, Rapid sequence intubation (RSI).

be used for 1 month if stored at room temperature [24,25]. Although this storage procedure may be appropriate for controlled room temperature, the data suggest that accelerated degradation does occur and is more noticeable when further excursions from labeled recommendations occur. Therefore, this recommended time interval may not be appropriate for the prehospital environment.

Although published results are limited, findings in this study are similar to those that show a more appreciable reduction in some drug concentrations and very little with others, regardless of analytical methodology. This is in agreement with current consensus in that longer and more extreme thermal exposures outside of recommended storage conditions increase the probability that a more severe deviation from labeled conditions may result. In addition, these results may further validate previous studies whose results are derived from gas chromatography analysis.

For purposes of this study, the exposure regimen was derived from taking high/low averages with the inclusion of approximately 2 SDs from a multi-site study conducted by Brown et al [8]. Admittedly, the thermal exposure range is wide, but possible if medications were to be refrigerated during out-of-service times and then placed unprotected on-ambulance during in-service times.

Although it is beyond the purpose and scope of this study, it would still be very interesting to postulate the causes that could account for these observations. These may be specific chemical structure stability of individual drugs and corresponding thermal conditions that exceed bond dissociation energies leading to structural modification; interactions between active compound and any preservatives caused by altering energy input into the solution; or sorption effects of the actual storage container in which the drug is packaged, at elevated temperatures.

This study does have limitations. Because of limited funding, preexposure baseline concentrations were used for comparisons rather than separate control. In the absence of a controlled comparison, this study assumed that adequate compliance by manufacturers with Food and Drug Administration regulations would ensure 100% concentration during the study period. Although, without a true control comparison, estimates of mean reversion presence, if one

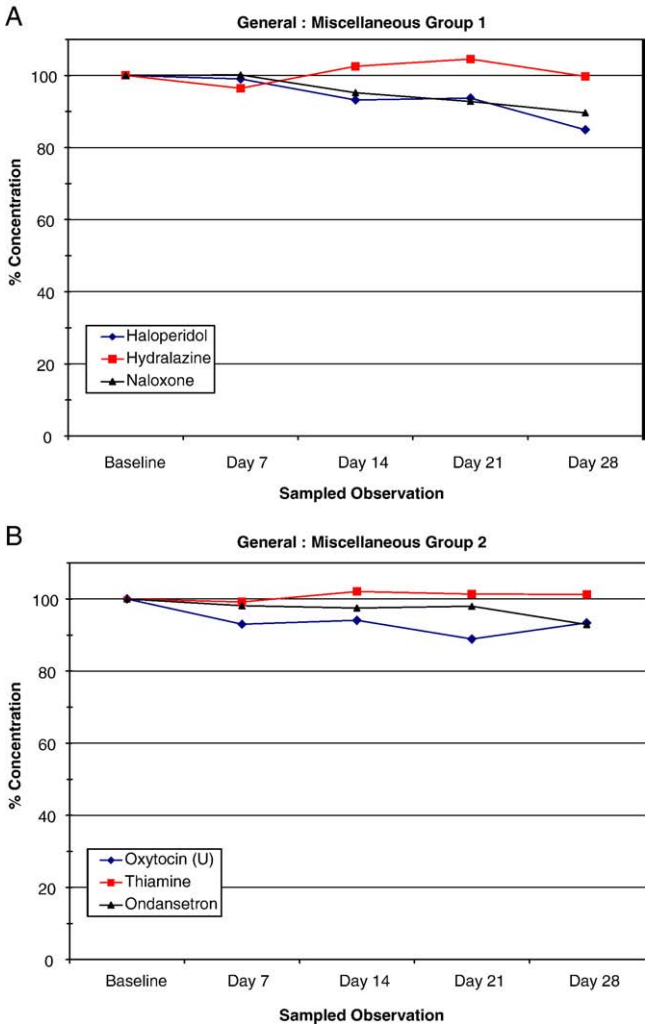

Fig. 4 General. A, Miscellaneous group 1. B, Miscellaneous group 2.

were to exist, could not be evaluated. In addition, as such a large group of medicines were evaluated, the individual number of sample observations was constrained to 5 sample periods in triplicate. This limited sampling restricts the formation of highly accurate regression equations for point estimates. It is possible that a more frequent sampling period or conditions that are more representative of service-specific field conditions could provide alternate degradation findings; therefore, our results need confirmation from additional data observations. The biological activity of the exposed medicines was not included in the study; therefore, direct clinical implications of the resultant concentration potency cannot be established. And, finally, although a broad range of EMS pharmaceuticals were evaluated, the extremely important subset of scheduled drugs for sedation and pain management was not investigated.

It was noted that an apparent cycling pattern of select drugs existed. As standard errors around each observation show adequate precision of injection repeatability, it would be a low probability that incorrect injection size or sample loss during instrumentation is the reason for this observation. Two postulates for accounting for this observation are proposed: first, as injection temperature was not fully controlled at each sample period, the possibility of the solution lacking homogeneity throughout the vial could exist; and, secondly, because multiple sampling was taken from the same vial throughout the study, there exists the possibility of relative changes in active compound to solvent ratio due to passive evaporation/condensation through the vial stopper puncture sites from intervial pressure changes during the thermal cycling process.

As a last interesting observation from a possible clinical standpoint is the noted stability of amiodarone and vasopressin vs that of lidocaine and epinephrine. Although not implying any current associations, interest is piqued based on recent studies which show possible improvement in prehospital cardiac arrest by the use of the former drug combination [26-28]. Hypotheses surrounding potency explanations versus pharmacological action for this observation could prove fruitful for future research.

5. Conclusion

Over the period of 1 month, a decrease in concentration was found to be statistically significant and well correlated in 8 (35%) of 23 commonly carried EMS pharmaceuticals when exposed to cycled thermal extremes that have been documented as actual temperature points on ambulances across the United States. Until the stability of all on-ambulance pharmaceuticals are well understood and the legal implications from their off-label use are known, it is advisable for EMS professionals, administrators, and medical directors to attempt to mitigate temperature excursions of the on-ambulance drug storage compartment.

Acknowledgments

The authors greatly appreciate the assistance of Drs Stearman and Biagioni from the Department of Chemistry at Missouri State University as well as Mrs Kathryn Patterson from St John's Trauma Services.

References

[1] Palmer RG, Zimmerman J, Brown PC, et al. Altered states: the influence of temperature on prehospital drugs. J Emerg Med Serv 1985;10(12):29-31.
[2] Valenzuela TD, Criss EA, Hammergren WM, et al. Thermal stability of prehospital medications. Ann Emerg Med 1989;18:173-6.
[3] Cairns CB, Cain BS, Honigman B, et al. Prehospital storage degrades the physiological effects of epinephrine in human myocardium. Ann Emerg Med 1999;34:S15 [abstract].
[4] Allegra JR, Brennan J, Lanier V, et al. Storage temperatures of out-of-hospital medications. Acad Emerg Med 1999;6:1098-103.
[5] Madden JF, O'Connor RE, Evans J. The range of medication storage temperatures in aeromedical emergency medical services. Prehosp Emerg Care 1999;3:27-30.
[6] Dubois WC. Drug storage temperatures in rescue vehicles. J Emerg Med 2000;18:345-8.
[7] Szucs P, Allergra JR, Fields LA, et al. Storage temperatures of medications on an air medical helicopter. Air Med J 2000;19:19-21.
[8] Brown LH, Bailey LC, Medwick T, et al. Medication storage on US ambulances: a prospective multi-center observational study. Pharm Forum 2003;29:540-7.
[9] US Pharmacopeia. National Formulary (USP-25/NF-20). Rockville (Md): United States Pharmacopeial Convention; 2000.
[10] Joyce JR, Bal TS. The decomposition of benzodiazepines during analysis by capillary gas chromatography/mass spectrometry. Biol Mass Spectrom 1984;11(6):284-9.
[11] Cairns TS, Siegmund EG, Stamp JJ, Skelly JP. Liquid chromatography/mass spectrometry of dexamethasone and betamethasone. Biomed Mass Spectrom 1983;10(3):203-8.
[12] Church WH, Hu SS, Henry AJ. Thermal degradation of injectable epinephrine. Am J Emerg Med 1994;12:306-9.
[13] Johansen RB, Schafer NC, Brown PI. Effect of extreme temperatures on drugs for prehospital ACLS. Am J Emerg Med 1993;11: 450-2.
[14] Grant TA, Carrol RG, Church WH, et al. Environmental temperature variations cause degradation in epinephrine concentration and biologic activity. Am J Emerg Med 1994;12:319-22.
[15] Gottwald MD, Akers LC, Liu PK, et al. Prehospital stability of diazepam and lorazepam. Am J Emerg Med 1999;17:333-7.
[16] Barron M. Stability testing operations. Pharm Technol 2003;27(n): 14-21.
[17] Koves EM. Use of high-performance liquid chromatography–diode array detection in forensic toxicology. J Chromatogr A 1995;692: 103-19.
[18] Ascah T, Liu F. Improving resolving power for active analytes by using an HPLC phase with unique selectivity. The Reporter 1995; 14(2):2-7.
[19] Sigma-Aldrich Co. GC and HPLC Phases and Packings for US Pharmacopoeia Methods. SUPELCO Bulletin; 1999. p. 879A.
[20] Klick S, Muijselaar P, Waterval J. Stress testing of drug substances and drug products. Pharm Technol 2005;29(2):48-66.
[21] Lucas T. A stability program for the distribution of drug products. Pharm Technol 2004;28(7):68-73.
[22] SPSS for Windows, Rel. 13.0. Chicago: SPSS Inc; 2004.

[23] Trissel LA. Avoiding common flaws in stability and compatibility studies of injectable drugs. Am J Hosp Pharm 1983;40:1159-60 [Editorial].
[24] Boehm JJ, Dutton DM, Poust RI. Shelf life of unrefrigerated succinylcholine chloride injection. Am J Hosp Pharm 1984;41(2): 300-2.
[25] Product Information: Cardizem(R), diltiazem. Kansas City, (Mo): Aventis Pharmaceuticals, Inc.; 2000.
[26] Dorian P, Cass D, Schwartz B, et al. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. N Engl J Med 2002;346:884-90.
[27] Wenzel V, Krismer AC, Arntz HR, et al. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med 2004;350:105-13.
[28] Wyer PC, Phillips P, Zhezhen J, et al. Vasopressin or epinephrine for out-of-hospital cardiac arrest. Ann Emerg Med 2006;48:86-97.