AFRL-RH-WP-SR-2020-0005

Pharmaceutical Degradation in EMS Deployment and in Extreme Temperature Simulation

Madeline Foertsch, PharmD, BCCCP

24 Mar 2020

Air Force Research Laboratory
711th Human Performance Wing
C-STARS Cincinnati
2510 Fifth St.
Wright-Patterson AFB, OH 45433-7913

NOTICE AND SIGNATURE PAGE

AFRL-RH-WP-SR-2020-0005 HAS BEEN REVIEWED AND IS APPROVED FOR PUBLICATION IN ACCORDANCE WITH ASSIGNED DISTRIBUTION STATEMENT.

//SIGNED//	//SIGNED//
TAMERA G. BORCHARDT, Lt Col, NC	GUY R. MAJKOWSKI, Col, BSC
Branch Chief, Biomedical Impact of Flight	Division Chief, Warfighter Medical Optimization

This report is published in the interest of scientific and technical information exchange, and its publication does not constitute the Government's approval or disapproval of its ideas or findings.

The views and conclusions contained herein are those of the authors and should not be interpreted as necessarily representing the official policies or endorsements, either expressed or implied, of 711th HPW/RHMF or the U.S. Government

"This material is based on research sponsored by 711th HPW under agreement number FA8650-15-2-6605. The U.S. Government is authorized to reproduce and distribute reprints for Governmental purposes notwithstanding any copyright notation thereon."

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From – To)*
24 Mar 2020	Final Report	19 Apr 17 – 18 Jan 2020

4. TITLE AND SUBTITLE

Pharmaceutical Degradation in EMS Deployment and in Extreme Temperature Simulation

5a. CONTRACT NUMBER
FA8650-15-2-6605

5b. GRANT NUMBER
FA8650-17-2-6G27

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Nicole Harger, PharmD, BCCCP;
Dr. Victor Heh; PhD
Eric Mueller PharmD, FCCM, FCCP;
Chris Droege, PharmD, BCCCP, FCCM, FASHP
Dario Rodriquez, Jr., MSc, RRT, FAARC

5d. PROJECT NUMBER
17-090

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Cincinnati
Sponsored Research Services
51 Goodman Drive, Suite 530
Cincinnati, OH 45221-0222

8. PERFORMING ORGANIZATION REPORT NUMBER
AFRL-RH-WP-SR-2020-0005

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
USAF School of Aerospace Medicine
Air Force Expeditionary Medical Skills Institute/C-STARS Cincinnati
2510 Fifth St.
Wright-Patterson AFB, OH 45433-7913

10. SPONSORING/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Distribution A: Approved for public release; distribution is unlimited. Case Number: Case Number: 88ABW-2020-1413, 16 Apr 2020

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Background:
In active combat zones medications may not be stored in an environment where the temperature can be highly regulated. Medications may be exposed to extreme temperatures and the effect on stability could be profound in combat zones. In these areas, over a course of a year temperature can vary from 0ºC (32°F) to 40ºC (105°F) or even higher. There is no data on such large temperature fluctuations and how that may affect drug stability. This study will provide stability data in these extreme temperature ranges for the most commonly used analgesic by the military, ketamine. This study included three research objectives. 1) Evaluate the stability of ketamine in a simulated environment where large temperature fluctuations can be seen. This will be done by comparing the difference in measured and labeled medication concentrations after 1 to 6 months of exposure. 2) Evaluate the stability of ketamine on active EMS units in Cincinnati, OH during the summer months. This will be done by comparing the difference in measured and labeled medication concentrations after 1 to 6 months of exposure. **Results:** In this study, despite exposure to extreme temperatures, all ketamine samples reflected minimal degradation. Ketamine concentrations were maintained at ≥ 95% of the labeled concentration despite being exposed to extreme temperature environments. **Conclusion:** The ketamine samples in this study exhibited limited degradation when exposed to fluctuating extreme temperature environments. Although it is recommended to store ketamine at the temperatures specified by the manufacturer, this study does demonstrate that ketamine did not undergo significant degradation when exposed to high temperature environments. Further studies are required to validate these results.

15. SUBJECT TERMS

Ketamine, Degradation, Extreme Temperatures

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			James B. Lehman
U	U	U	SAR	14	19b. TELEPHONE NUMBER *(include area Code* *513-558-7462*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

This page intentionally left blank.

TABLE OF CONTENTS

Section:

1.0 BACKGROUND:

Ketamine is a phencyclidine derivative that affects numerous receptors, but its primary mechanism of action is an N-Methyl-D-Aspartate (NDMA) receptor antagonist. Ketamine's unique properties make it an ideal agent for pain control in the prehospital setting (i.e. field medics, special operators, etc.); it has less respiratory depression when compared to opiates and provides adequate pain control in both opiate naïve and opiate tolerant patients.[1-4] Additionally, ketamine has shown in clinical trials to be at least as effective as morphine and the combination of ketamine and morphine provides superior pain relief when compared to morphine alone.[2,3] Ketamine has also been found to decrease opioid requirements.[4] The tactical combat casualty care (TCCC) guidelines include the use of ketamine as an alternative to morphine for moderate-severe pain in combat casualties and ketamine has become the most common analgesic administered in the prehospital combat setting.[5-7]

The ketamine package insert recommends that it be stored at controlled room temperature at all times. The definition of controlled room temperature according to the United States Pharmacopeia (USP) is a temperature range from 20 to 25º C (68º – 77º F) that results in a mean kinetic temperature (MKT) of no greater than 25 º C (77º F).[6] There can be excursions from 15º to 30º C (59º-86º F) and temperatures spikes up to 40º C (104º F) are permitted, as long as it does not occur for more than 24 hours.[10] Temperatures in the prehospital setting are unpredictable and frequently outside the USP definition for controlled room temperature.[7] Prior studies have indicated significant degradation with lorazepam when stored in the prehospital setting.[8, 9]

Ketamine hydrochloride 50 mg/mL diluted to 10 mg/mL with sterile water has been analyzed for stability at room temperature. Six samples were assayed via high-performance liquid chromatography on days 7, 14, 28, 56, 91, and 182. The percentage of initial concentration remaining at each interval was 99.5 ± 1.2, 99.2 ± 0.9, 98.8 ± 0.9, 99.5 ± 0.8, 98.0 ± 0.3, and 96.2 ± 0.9 respectively.[10] Another investigation completed by the same author evaluated the stability of ketamine mixed with morphine at various concentrations in normal saline at two different temperatures at days 7, 14, 28, 56, and 91. When ketamine 2 mg/mL was mixed with morphine 2 mg/mL and evaluated at 5º C (41 º F), the percentage of the initial ketamine concentration remaining was 100.5 ± 1.5, 99.9 ± 1.1, 98.9 ± 1.0, 99.7 ± 0.7, and 99.1 ± 1.3, respectively. Similarly, when ketamine 2 mg/mL was mixed with morphine 2 mg/mL and stored at 23º C, the percentage of the initial ketamine concentration remaining was 100.2 ± 1.4, 100.2 ± 0.8, 100.3 ± 1.7, 101.4 ± 1.7, and 99.7 ± 1.2, respectively.[11]

There is minimal information regarding the stability of ketamine in extreme temperatures available in the literature today. A study completed by Kupper, et al. found that ketamine may be stable when stored at both -15º C (5º F) and 40º C (104º F).[12] Unfortunately, it is unclear from the study description how long the ketamine was stored at these temperatures and the type of analysis that was performed to assess the stability. Due to the unfortunate paucity of data in this arena, this study aimed to: 1) Evaluate the stability of ketamine on an active Emergency Medical Service (EMS) unit in Cincinnati, Ohio during the summer months and 2) Evaluate the stability of ketamine in simulated environments where large temperature fluctuations can be seen.

2.0 RESEARCH DESIGN AND METHODS:

This pharmaco-stability trial was conducted at the University of Cincinnati Medical Center (UCMC) in conjunction with a local EMS agency. UCMC is an urban, academic Level 1 Trauma Center that treats more than 3,500 trauma patients each year. There is a long history of academic collaboration with EMS agencies, including participation in prehospital interventional trials. To achieve our Specific Aims, we performed two separate phases: a moderate heat phase and high heat phase.

Moderate heat phase:

The moderate heat phase portion of the study was conducted for a period of six months during the summer (May-October 2019) in Cincinnati, Ohio where the average summer temperature is 54-86 º F. Two instrumented study boxes each containing 12 vials of ketamine 50mg/mL (10mL vials) were placed in an EMS vehicle. The instrumented study boxes each contained a digital thermistor that recorded temperatures to a micro-SD card for later analysis; measurements were captured every minute. The boxes were tamper-evident and allowed for security of controlled substances that met Drug Enforcement Agency (DEA) requirements. The boxes have been successfully used in prior and current prehospital trials involving controlled substances. Two ketamine vials were removed from each box at 30, 60, 90, 120, and 180 (+/- 2) days to evaluate the ketamine sample for drug degradation.

High Heat Phase:

To gain information regarding the stability of ketamine in extreme heat environments, ketamine was exposed to various extreme temperatures via simulated environments for a total six months. The environments were simulated utilizing Cincinnati Sub-Zero (CSZ) microclimate test chambers. The chambers can be set to a static temperature or to cycle through temperatures ranging from -86º F (-30º C) to +375º F (+190º C). The chambers monitored and recorded temperature every 60 seconds. The chambers were locked and located in the investigational drug pharmacy, which met the DEA requirements for secure controlled substance storage.

Ninety-six ketamine 50 mg/mL (10mL vials) were placed in four controlled temperature chambers. Chamber 1 was set to a static temperature of 120º F (49ºC). Chamber 2 was set to fluctuate temperatures from 86º F (30 º C) to 120º F (49º C) over the course of 24 hours, programmed to mimic the daily temperature fluctuations of the Middle East, specially Kuwait. Chamber 3 was set to a wider 24 hour temperature variation of 40º F (4º C) to 120º F (49º C). Chamber 4 was set to a static temperature of 70º F (21º C); this is representative of the manufacturer recommended storage temperature. Twenty-four ketamine vials were placed in each chamber and four vials were removed from each chamber on days 30, 60, 90, 120, and 180 (+/- 2 days) to sample the medication for drug degradation.

Drug Stability Testing

The ketamine samples were sent to an outside laboratory (Dynalabs) for analysis, which is a Food and Drug Administration (FDA) and DEA accredited laboratory that performs quality control testing. All of the ketamine samples were mailed directly to the laboratory and a certificate of concentration analysis was reported for each sample.

Mean Kinetic Temperature (MKT) Determination

MKT was calculated for each sample of ketamine. MKT was utilized for comparison between the samples instead of a simple average of the exposed temperatures, as MKT takes into account accelerated rate of thermal degradation of the substance at higher temperatures.[13,14]

The instrumented study boxes contained a digital thermistor that recorded temperature every 60 seconds onto secure digital (SD) card. The chambers also recorded temperature every 60 seconds; the temperature data was recorded and transferred to a laptop computer using software provided by CSZ. The chambers have the capability to record and store temperature data, so temperature data was also extracted from each of the chambers to a zip drive as backup in the case of a software malfunction. All of the temperature data files were exported to a commercially available MKT calculator (iStabilityMKT).

Outcomes

The primary outcome for this study was to describe the ketamine concentrations at each time point in which the ketamine samples were removed from the study environments.

Statistical Approach

This was an exploratory analysis and descriptive statistics were used to describe the concentration changes at each time point. Given the exploratory nature of this research and the lack of available literature in the area, the components for a formal power analysis do not exist. Statistical analysis was performed using SPSS (version 25).

3.0. RESULTS:

Moderate Heat Phase:

Twenty-four ketamine vials were placed in an EMS vehicle in Cincinnati, Ohio from May 2019 through November 2019. Four vials were taken every 30 days (± 2 days), except on month four (approximately day 120); due to extenuating circumstances, there was about a seven day delay in removing the vials from the EMS vehicle to be sent for concentration analysis. The MKT measured from the ketamine EMS vehicle samples varied, ranging from 73.6° F to 80.7° F (see Table 1). No clinically significant ketamine degradation occurred during the six month course of the study (Figure 1 and Table 2). Pairwise comparison analysis indicated months four and six had a significant degradation compared to month one (Table 3). This significant change in concentration was also seen when months four and six were compared to the room temperature chamber (Table 4). Month four did have one sample in which the concentration was significantly lower than the other samples at 42.00 mg/mL; this concentration was re-evaluated and verified by the laboratory.

High Heat Phase:

Twenty-four ketamine vials were placed in each the chambers starting in February 2019. Four vials were taken out of each chamber every 30 days (±2 days) and sent for concentration analysis. The MKT stayed constant for each chamber over the six month course of the study (Chamber 1 MKT: 120° F, Chamber 2 MKT: 107.3° F, Chamber 3 MKT: 96.5° F, Chamber 4 MKT: 70° F). No clinically significant ketamine degradation occurred during the course of the study in any of the chamber environments (Figure 1 and Table 2). Pairwise comparisons were performed to identify if significant degradation occurred over the course of the study. No clinically significant degradation occurred when month one was compared to the other months

(Table 3). In addition, no significant degradation was found when all the chamber environments were compared to the chamber with the manufacturer recommended storage temperature (MKT 70º F) (Table 4).

4.0. DISCUSSION:

In this study, despite exposure to extreme temperatures, all ketamine samples reflected minimal degradation. Ketamine concentrations were maintained at ≥ 95% of the labeled concentration despite being exposed to extreme temperature environments. As mentioned above, there was one sample that was taken from the EMS vehicle on month four where the concentration was 42mg/mL (84% of labeled concentration) when analyzed. It is unclear why this particular sample had such a low concentration, as the other three samples removed from the vehicle at the same time were all found to have concentrations > 48 mg/mL. This outlier likely caused the significant concentration change seen in when month four was compared to month one and Chamber four (MKT 70º F). All the other ketamine samples taken from the EMS vehicle had concentrations > 47 mg/mL when analyzed.

This study does have some notable limitations. Primarily, the sample size was small and a power analysis was not feasible a priori. Additionally, the initial plan was to have ketamine samples taken from different manufacturer lot numbers, due to the potential for slight variations in concentrations between lots. As a result of the national shortage of ketamine that occurred in 2017-2018, only one lot number of ketamine was able to be procured for study purposes. All ketamine vials were removed on day 30 +/- 2 days except as noted above on month four of the EMS vehicle removal; this removal was delayed seven days. Unfortunately, a study participant was deployed for national disaster aid and was unable to retrieve the ketamine sample on the pre-specified date. It should be noted that the extended time in the EMS unit was accounted for in the MKT calculation. Finally, the ketamine was not in a controlled temperature environment when being shipped to the laboratory for analysis.

5.0. CONCLUSIONS:

The ketamine samples in this study exhibited limited degradation when exposed to fluctuating extreme temperature environments. Although it is recommended to store ketamine at the temperatures specified by the manufacturer, this study does demonstrate that ketamine did not undergo significant degradation when exposed to high temperature environments. Further studies are required to validate these results.

Table 1: MKT* Emergency Response Vehicle

Month Ketamine Removed	MKT (F)
1	73.6
2	76.4
3	79.8
4	80.3
5	80.7
6	79.1
*MKT: Mean kinetic temperature	

Table 2: Ketamine Concentration in all Environments

	Concentration (mg/mL), Mean (95% CI)				
Month Ketamine Removed	**Chamber 1 MKT: 120°F**	**Chamber 2 MKT: 107.3°F**	**Chamber 3 MKT: 96.5°F**	**Chamber 4 MKT: 70°F**	**EMS Vehicle**
1	49.35 (48.52-50.18)	49.95 (49.12-50.78)	50.18 (49.34-51.01)	50.28 (49.44-51.12)	49.63 (48.79-50.46)
2	49.58 (48.74-50.41)	49.00 (49.07-50.73)	50.05 (49.22-50.88)	49.23 (48.39-50.06)	49.58 (48.74-50.41)
3	49.875 (49.04-50.71)	49.88 (49.04-50.71)	49.15 (48.32-49.98)	49.85 (49.02-50.68)	50.58 (49.74-51.41)
4	49.53 (48.70-50.36)	49.78 (48.94-50.61)	49.93 (49.09-50.76)	49.58 (48.74-50.41)	47.30 (46.47-48.13)
5	48.38 (47.545-49.21)	49.68 (48.84-50.51)	49.38 (48.54-50.21)	49.35 (48.52-50.18)	50.05 (49.22-50.88)
6	49.70 (48.87-50.53)	49.60 (48.77-50.43)	49.58 (48.74-50.41)	48.50 (48.67-50.33)	48.05 (47.22-48.88)

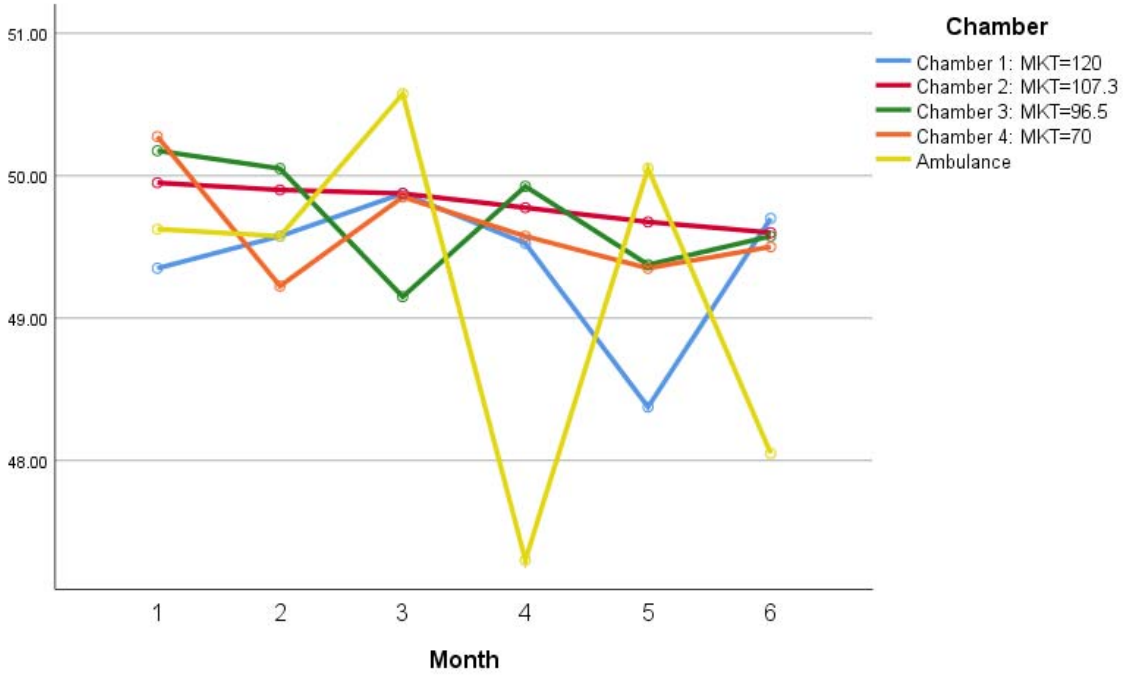
Table 3: Pairwise Comparison Month 1 compared to Subsequent Months

Environment	Month	Comparator Month	Mean concentration (mg/mL) difference (95% CI)	P value
Chamber 1 (MKT 120 °F)	1	2	-0.225 (-1.404-0.954)	0.705
		3	-0.525 (-1.704-0.654)	0.379
		4	-0.175 (-1.354-1.004)	0.769
		5	0.975 (-0.204-2.154)	0.104
		6	-0.350 (-1.529-0.829)	0.557
Chamber 2 (MKT 107.3 °F)	1	2	0.050 (-1.129-1.229)	0.933
		3	0.075 (-1.104-1.254)	0.900
		4	0.175 (-1.004-1.354)	0.769
		5	0.275 (-0.904-1.454)	0.644
		6	0.350 (-0.829-1.529)	0.557
Chamber 3 (MKT 96.5 °F)	1	2	0.125 (-1.054-1.304)	0.834
		3	1.025 (-0.154-2.204)	0.087
		4	0.250 (-0.929-1.429)	0.674
		5	0.800 (-0.379-1.979)	0.181
		6	0.600 (-0.579-1.779)	0.315
Chamber 4 (MKT 70 °F)	1	2	1.050 (-0.129-2.229)	0.080
		3	0.425 (-0.754-1.604)	0.476
		4	0.700 (-0.479-1.879)	0.241
		5	0925 (-0.254-2.104)	0.122
		6	0.775 (-0.404-1.954)	0.195
EMS Vehicle	1	2	0.050 (-1.129-1.229)	0.933
		3	-0.950 (-2.129-0.229)	0.113
		4	2.325 (1.149-3.504)	<0.001
		5	-0.425 (-1.604-0.754)	0.476
		6	1.575 (0.396-2.754)	0.009

Table 4: Pairwise Comparison Room Temperature (Chamber 4 MKT 70°F) compared to other Environments

Month	Environment	Comparator Environment	Mean concentration (mg/mL) difference (95% CI)	P value
1	Chamber 4 MKT 70°F	Chamber 1 (MKT 120 °F)	0.925 (-0.254-2.104)	0.122
		Chamber 2 (MKT 107.3 °F)	0.325 (-0.854-1.504)	0.585
		Chamber 3 (MKT 96.5 °F)	0.100 (-1.079-1.279)	0.867
		EMS Vehicle	0.650 (-0.529-1.829)	0.276
2	Chamber 4 MKT 70°F	Chamber 1 (MKT 120 °F)	-0.350 (-1.529-0.829)	0.557
		Chamber 2 (MKT 107.3 °F)	-0.675 (-1.854-0.504)	0.258
		Chamber 3 (MKT 96.5 °F)	-0.825 (-2.004-0.354)	0.168
		EMS Vehicle	-0.350 (-1.529-1.179)	0.557
3	Chamber 4 MKT 70°F	Chamber 1 (MKT 120 °F)	-0.025 (-1.204-1.154)	0.966
		Chamber 2 (MKT 107.3 °F)	-0.025(-1.204-1.154)	0.966
		Chamber 3 (MKT 96.5 °F)	0.700 (-0.479-1.879)	0.241
		EMS Vehicle	-0.725 (-1.904-0.454)	0.225
4	Chamber 4 MKT 70°F	Chamber 1 (MKT 120 °F)	0.050 (-1.129-1.229)	0.933
		Chamber 2 (MKT 107.3 °F)	-0.200 (-1.379-0.979)	0.737
		Chamber 3 (MKT 96.5 °F)	-0.350 (-1.529-0.829)	0.557
		EMS Vehicle	2.275 (1.096-3.454)	<0.001
5	Chamber 4 MKT 70°F	Chamber 1 (MKT 120 °F)	0.975 (-0.204-2.154)	0.104
		Chamber 2 (MKT 107.3 °F)	-0.325 (-1.504-0.854)	0.585
		Chamber 3 (MKT 96.5 °F)	-0.025 (-1.204-1.154)	0.966
		EMS Vehicle	-0.700 (-1.879-0.479)	0.241
6	Chamber 4 MKT 70°F	Chamber 1 (MKT 120 °F)	-0.200 (-1.379-0.979)	0.737
		Chamber 2 (MKT 107.3 °F)	-0.100 (-1.279-1.079)	0.867
		Chamber 3 (MKT 96.5 °F)	-0.075 (-1.254-1.104)	0.900
		EMS Vehicle	1.450 (0.271-2.629)	0.016

Figure 1: Ketamine Concentration in all Environments



6.0 REFERENCES

[1]. Green SM, et al. Flinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation: 2011 Update. Annals of Emergency Medicine. 2011;57(5):449-61.
[2]. Tran KP, Nguyen Q, Truong XN, et al. A Comparison of Ketamine and Morphine Analgesia in Prehospital Trauma Care: A Cluster Randomized Clinical Trial in Rural Quang Tri Province, Vietnam. Prehospital Emergency Care. 2014;18:257–264.
[3]. Jennings PA, Cameron P, Bernard S, et al: Morphine and ketamine is superior to morphine alone for out-of-hospital trauma analgesia: a randomized controlled trial. Ann Emerg Med 2012; 59(6): 497-503.
[4]. Galinski M, Dolveck F, Combes X, et al. Management of Severe Acute Pain in Emergency Settings: Ketamine Reduces Morphine Consumption. Am J of Emergency Medicine. 2007; 25:385–390.
[5]. Butler FK, Kotwal RS, Buckenmaier CC, et al. A Triple-Option Analgesia Plan for Tactile Combat Casualty Care: TCCC Guideline Change 13-04. J Spec Oper Med. 2014;14:13-25.
[6]. General notices and requirements. USP 33–NF 28 Reissue; R1-12.
[7]. Brown LH, Krumperman K, and Fullagar CJ. Out-of-Hospital Medication Storage Temperatures: A review of the Literature and Directions for the Future. Prehospital Emergency Care. 2004;8(2):200-6.
[8]. McMullan JT, Pinnawin A, Jones E, et al. The 60-Day Temperature-Dependent Degradation of Midazolam and Lorazepam in the Prehospital Environment. Prehospital Emergency Care. 2013;17:1-7.
[9]. McMullan JT, Jones E, Barnhart B, et al. Degradation of Benzodiazepam after 120 Days of EMS Deployment. Prehospital Emergency Care. 2014;18(3):368-74.
15. Donnelly RF. Stability of diluted ketamine packaged in glass vials. Can J Hosp Pharm. 2013 May;66(3):198.
16. Donnelly RF. Physical compatibility and chemical stability of ketamine-morphine mixtures in polypropylene syringes. Can J Hosp Pharm. 2009 Jan;62(1):28-33.
17. Kupper TE, Schraut B, Rieke B, et al. Drugs and drug administration in extreme environments. J Travel Med. 2006 Jan-Feb;13(1):35-47.
[10]. Donnelly RF. Stability of diluted ketamine packaged in glass vials. Can J Hosp Pharm. 2013 May;66(3):198.
[11]. Donnelly RF. Physical compatibility and chemical stability of ketamine-morphine mixtures in polypropylene syringes. Can J Hosp Pharm. 2009 Jan;62(1):28-33.
[12]. Kupper TE, Schraut B, Rieke B, et al. Drugs and drug administration in extreme environments. J Travel Med. 2006 Jan-Feb;13(1):35-47.
[13]. Socarras S and Magari RT. Journal of Pharmaceutical and Biomedical Analysis. 2009;49:221-6.
[14]. Kommanaboyina B and Rhodes CT. Effects of Temperature Excursions on Mean Kinetic Temperature and Shelf Life. 1999;25(12):1301-6.