NAVAL MEDICAL RESEARCH UNIT SAN ANTONIO

Simulating the Effects of Austere Hot and Humid Conditions on Anesthetics and Antibiotics used in Military Dentistry and Oral Surgery

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DECLARATION OF INTEREST

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government. This research was supported by Naval Medical Research Command-Naval Advanced Medical Development (NMRC-NAMD), Work Unit Number G1812. I am a military service member or federal/contracted employee of the United States government. This work was prepared as part of my official duties. Title 17 U.S.C. 105 provides that `copyright protection under this title is not available for any work of the United States Government.' Title 17 U.S.C. 101 defines a U.S. Government work as work prepared by a military service member or employee of the U.S. Government as part of that person's official duties.

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ABBREVIATIONS

ADAL	Authorized Dental Allowance List
AECTP	Allied environmental conditions and test publications
AMAL	Authorized Medical Allowance List
ANOVA	Analysis of variance
AR	Army regulation
ESI	Electrospray ionization
IS	Internal standard
LC-MS	Liquid chromatography-mass spectrometry
MIL-HDBK	Military Handbook
MIL-STD-801G	Military Standard 810G
MRM	Multiple reaction monitoring
NAMRU-San Antonio	Naval Medical Research Unit San Antonio
NATO	North Atlantic Treaty Organization
STANAG	Standardization agreements

EXECUTIVE SUMMARY

Background: Dental restorations and oral-facial surgeries rely heavily on pharmaceuticals for successful treatment. Local pain management is essential in dental restorations and general anesthesia is the cornerstone of more invasive oral-facial surgeries. For recovery, a similarly important focus is infection prevention with the use of antibiotics. Some pharmaceuticals are known to be susceptible to degradation above room temperature, while the temperature-related drug degradation profiles of others are unknown. The U.S. military operates in a variety of environments, including conditions not anticipated by manufacturers of civilian dental supplies or devices. Supplies exposed to extreme temperature and relative humidity conditions during military transport and storage are not reflected in their manufacturer's estimates of performance or shelf life.

Objective: The main objective of this study was to determine, in a short period of time, if certain antibiotics and anesthetics used in dental procedures and oral surgeries were susceptible to degradation in hot and humid conditions set forth by military standards for testing.

Methods: We achieved our objective by artificially inducing degradation through simulated austere conditions in an environmental chamber for 10 days. Liquid Chromatography-Mass Spectrometry was then used to compare the degradation of these pharmaceutical compounds that were environmentally stressed to those stored at manufacturer recommended conditions.

Results: The difference between Marcaine and mepivacaine was statistically significant (0.6% ± 3.1 for Marcaine, 5.7% ± 1.1 for mepivacaine, $p=0.047$).

Conclusions: All drugs in this study exhibited degradation less than 10%, and only three experienced more than 5%. Further studies should focus on realistic simulations of field storage conditions for extended periods of time up to 90 days. This would more accurately represent austere exposure patterns experienced by warfighters and logistics.

INTRODUCTION

Dental restorations and oral-facial surgeries rely heavily on pharmaceuticals for successful treatment. Local pain management is essential in dental restorations and general anesthesia is the cornerstone of more invasive oral-facial surgeries. For recovery, a similarly important focus is infection prevention with the use of antibiotics. Fortunately, many local anesthetics, general anesthetics and antibiotics are available for pain management and infection control.

Unfortunately, some of these are known to be susceptible to degradation above room temperature, while the temperature-related drug degradation profiles of others are unknown (Ondrak, Jones, & Fajt, 2015). Epinephrine, a vasoconstrictor that helps keep local anesthetics concentrated at the injection site has been shown to sometimes degrade rapidly when stored at elevated temperatures (Fry & Ciarlone, 1980a, 1980b; Larson et al., 1991). If a large amount of a local anesthetic's epinephrine degrades, the drug will leave the injection site more rapidly, decreasing the drug's efficacy. If this drop in epinephrine is coupled with a similar degradation of the anesthetic itself, as previous research suggest it could (Gottwald et al., 1999), in-theater oral surgeries may be reliant on drug formulations that decrease week-to-week with continued storage in aggravated temperatures. In a study by E. Samara et al., the authors reported that certain antibiotic classes degraded rapidly at 37°C (98°F) (Samara et al., 2017).

The U.S. military operates in a variety of environments, including conditions not anticipated by manufacturers of civilian dental supplies or devices (Defense, 2008). Most vendors recommend their materials be stored at room temperature or cooler, in dry places, and away from direct sunlight. Accordingly, supplies exposed to extreme temperature and relative humidity conditions during military transport and storage are not reflected in their manufacturer's estimates of performance or shelf life (Table 1). The potential for unexpected and rapid declines in performance due to these difficult conditions must be evaluated ("Packaging of Materials Preservation," 1999). Even when drugs are shipped and stored in climate-controlled containers, temperature excursions from disruptions in power or location changes are still a concern.

Table 1. Manufacturer Recommended Storage Conditions

Drug	Category	Recommended Storage	Notes
Clindamycin (Cleocin Phosphate, Pfizer Inc., NY)	Antibiotic	20-25°C	Exposure to heat should be minimized, avoid temperatures above 30°C
Ampicillin with Sulbactam (Sagent Pharmaceutical, IL)	Antibiotic	20-25°C	Storage based on sterile powder prior to reconstitution
Mepivacaine (1% Carbocaine, Hospira Inc, IL)	Local Anesthetic	20-25°C	Excursions permitted between 15°C and 30°C
Bupivacaine (Hospira Inc., IL)	Local Anesthetic	20-25°C	Excursions permitted between 15°C and 30°C
0.25% Bupivacaine with 1:200,000 Epinephrine (Marcaine, Hospira Inc., IL)	Local Anesthetic	20-25°C	Excursions permitted between 15°C and 30°C
1% Lidocaine with 1:100,000 Epinephrine (Hospira Inc., IL)	Local Anesthetic	20-25°C	Store below 40°C, 25°C recommended
Propofol (Diprivan, Fresenius Kabi, Germany)	General Anesthetic	4-25°C	Do not freeze, shake well before use.

Antibiotics, local anesthetics, and general anesthetics are fundamental for dental emergencies and oral surgeries and require thorough examination to best support warfighters. The aim of our study was to determine if the antibiotics and anesthetics used in dental procedures by the military are potentially subjected to degradation due to environmental factors based on different operating climates. The most common standard to determine if a product can withstand the difficult environmental conditions that military operations experience is the Department of Defense Test Method Standard for Environmental Engineering Considerations and Laboratory Tests (MIL-STD-810G) (Defense, 2008). This document is reviewed and updated regularly and states that extreme environment considerations for materiel intending to be deployed or used in extreme climates (hot, cold, and severe cold), in areas with extreme non-thermal weather conditions (such as blowing sand and dust), or in areas with mobility-restricting terrain conditions (such as tundra soil and heavily forested areas) will require additional planning, design, and testing

considerations. In addition to being prepared for basic climate, most materiel will need to be designed, developed, tested, and evaluated for operation, storage, and transit conditions in areas of the world that experience extreme temperatures. There are multiple guidelines set forth by the North Atlantic Treaty Organization (NATO) which help to identify potential damaging effects that natural and induced environmental conditions have on materials and provide guidelines on appropriate test methods (NATO STANAG 4370; AECTP 230, MIL-HDBK-310; and AR 70-38). According to these guidelines, to qualify as an area of extreme temperature, the area must meet one of the following two conditions: (1) have one percent or more of the hours in the hottest month equal to or exceeding 43°C (109°F); (2) have one percent or more of the hours in its coldest month equal to or lower than -32°C (-26°F) (Defense, 2008). Hot and humid conditions are found in the Niger Delta region, Mainland and Maritime Southeast Asia, the Arabian Gulf, and the Red Sea regions, among others. Hot conditions are found in North Africa, South Asia, and the Middle East, as well as many others. Many of these areas are strategically important or militarily relevant, and medical material transported through, deployed to, or stored at these locations must not degrade due to climate.

While there are many types of antibiotics and anesthetics available to medical clinicians, this project assessed those that were relevant to dental procedures and oral surgeries. We characterized selected drugs into three categories: antibiotics, local anesthetics, and general anesthetics. Clindamycin (Cleocin Phosphate, Pfizer Inc, NY) and ampicillin-sulbactam (Ampicillin-Sulbactam, Sagent Pharmaceuticals, IL) were chosen to represent antibiotics commonly used in dental care and emergencies. Cleocin phosphate vials contain clindamycin phosphate, a water-soluble ester of clindamycin and phosphoric acid. Each ml contains the equivalent of 150 mg clindamycin, 0.5 mg disodium edetate and 9.45 mg benzyl alcohol added as preservative. Clindamycin works by inhibiting ribosomal translocation in the target bacteria, which reduces their ability to make proteins. The ampicillin tested contained sulbactam in a two parts ampicillin to one-part sulbactam ratio. Ampicillin works by interfering with the ability of bacteria to form a cell wall. Many bacteria have developed proteins like beta-lactamase which destroy ampicillin, so sulbactam is added to inhibit beta-lactamase and allow the ampicillin to kill the bacteria. Bupivacaine (Hospira Inc., IL), mepivacaine (1% Carbocaine, Hospira Inc., IL), 1% lidocaine with 1:100,000 epinephrine (Hospira Inc., IL), and 0.25% bupivacaine with 1:200,000 epinephrine (Marcaine, Hospira Inc., IL) were tested to represent the local anesthetics. Local

anesthetics work by reversibly inhibiting nerve transmission by binding voltage-gated sodium channels in the nerve plasma membrane (Yanagidate & Strichartz, 2007). Propofol (Diprivan, Fresenius Kabi, Germany) was tested to represent the general anesthetics. Each local anesthetic has its own advantages and disadvantages which the clinicians rely on to treat a variety of situations and conditions. For example, when comparing bupivacaine with lidocaine, lidocaine has a shorter onset time and shorter duration of action when compared to bupivacaine.

The chosen drugs are listed on the Authorized Medical/Dental Allowance List (AMAL/ADAL), which are lists produced by the Navy that outline required medical/dental equipment and supplies sufficient to provide support to fleet forces for 60 days. For this project, unopened samples of each drug were exposed to aggravated hot and humid conditions in accordance with the MIL-STD-810G using the environmental chamber at the Naval Medical Research Unit San Antonio (NAMRU-San Antonio).

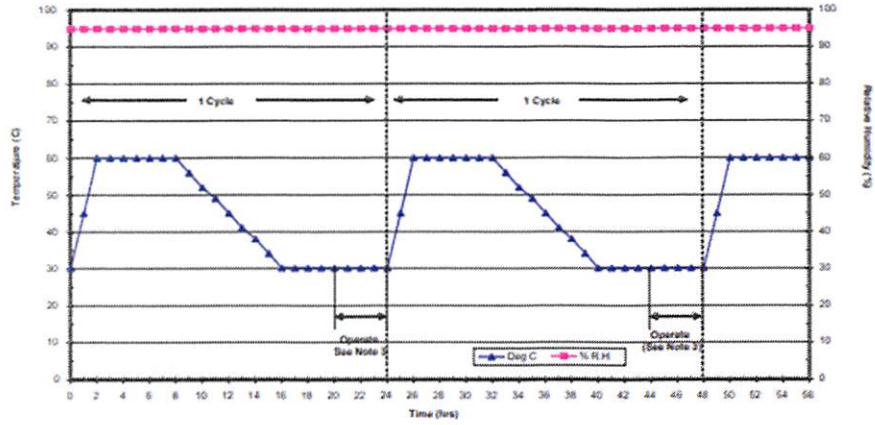
Although the combined temperature and humidity of this test is extreme, and does not occur in nature, this combination of temperature and relative humidity has historically proven adequate to reveal potential effects in most materiel. After the environmental challenge conditions, the susceptibility to degradation of each drug was compared with those stored at manufacturer recommendation to determine the amount of degradation over time. The purpose of this project was to force a scenario of drug degradation to better understand the stability of the active molecules within each drug as it related to environmental stability in an austere setting.

MATERIALS AND METHODS

Simulated Environmental Conditions

Samples of each drug were subjected to aggravated hot and humid field conditions via one of our environmental chambers (TE 1007H CSA, TestEquity LLC, Moorpark, CA), which has an internal footprint of 7 cubic feet. Unopened samples of each drug were subjected to a constant relative humidity of 95%, and fluctuating temperature of 30-60°C per cycle here at the NAMRU-San Antonio (Figure 1). The storage conditions of a steady relative humidity and temperature fluctuation cycle was repeated daily for 10 days. These conditions, from MIL-STD-810G, are intended to reveal any propensity for degradation due to temperature and humidity with greater confidence.

A



B

Time	Temp. °F	Temp. °C	RH %
0000	86	30	Constant at 95%
0200	140	60	
0800	140	60	
1600	86	30	
2400	86	30	
0200	140	60	
0800	140	60	
1600	86	30	
2400	86	30	

Figure 1: Figures from the Department of Defense Test Method Standard for Environmental Engineering Considerations and Laboratory Tests. A) Graphical image of aggravated temperature-humidity cycles. B) Aggravated cycle temperature and humidity settings based on a 24-hour time frame (Defense, 2008).

Liquid Chromatography Mass Spectrometry

Liquid chromatography-mass spectrometry (LC-MS) was performed on a Shimadzu HPLC system LC-20AD (Shimadzu Corporation, Kyoto, Japan). For each sample, a 10 µl aliquot of the sample was injected into an Agilent ZORBAX Eclipse XDB 80Å C18 column (2.1 x 50 mm, 5 µm). Mass spectrometric analysis was carried out on an AB Sciex API 4000 mass spectrometer (AB Sciex, Framingham, MA) with an electrospray ionization (ESI) interface and triple quadrupole mass analyzer. Liquid chromatography-mass spectrometry analyses were performed using a two-component system composed of mobile phase A (0.1% formic acid in water) and mobile phase B (0.1% formic acid in acetonitrile). Samples were bound to a C18 column for 0.5 min with 100% mobile phase A, and then eluted with a linear gradient from 0 to 90% mobile phase B for 2.5 min. Between 3.0 and 4.5 min, the mobile phase was maintained at 90% B. From 4.51 to 7.0 min, the mobile phase was switched back to 100% A. The flow rate of mobile phase was set at 0.4 ml/min. The total chromatographic analysis time was 7.0 min. All drugs were prepared and serially diluted to 10 µg/ml stock solution. Internal standard (IS) – spiked standards at six concentrations over the range 0-1 µg/ml were prepared and analyzed in LC-MS runs. The calibration plots were constructed by linear regression analysis using the Toolpak extension from Microsoft Excel (Version 7, Microsoft, WA) of observed drug to IS

peak-area ratios against concentration. Various military storage-treated drugs were spiked with 1 μg/ml IS and 10 μl of samples and injected for LC-MS identification and quantification. All drugs and IS were measured in multiple reaction monitoring (MRM) in electrospray positive ionization or electrospray negative ionization depending on their chemical properties on AB Sciex API 4000 triple quadrupole mass analyzer. Multiple reaction monitoring transitions were m/z 505.2/126.1 in the positive mode for clindamycin (at min 2.69), m/z 455.1/323.2 in the positive mode for cefazolin (at min 2.65), m/z 348.0/206.9 in the negative mode for ampicillin (at min 2.51), m/z 231.9/188.0 in the negative mode for sulbactam (at min 1.78), m/z 177.4/161.0 in the negative mode for propofol (at min 3.49), m/z 289.2/140.3 in the positive mode for bupivacaine (at min 2.79), m/z 247.2/98.2 in the positive mode for mepivacaine (at min 2.58), m/z 235.2/86.2 in the positive mode for lidocaine (at min 2.57), and m/z 184.1/166.1 in the positive mode for epinephrine (at min 0.03). These methods were validated over concentrations ranging at 10 - 1000 ng/ml. The Tandem mass spectrometry settings were: collision energy 49.0 V and collision cell exit potential 5.6 V for m/z 505.2/126; collision energy 16.0 V and collision cell exit potential 14.3 V for m/z 455.1/323.2; collision energy -17.0 V and collision cell exit potential -18.0 V for m/z 348.0/206.9; collision energy -14.0 V and collision cell exit potential -10.0 V for m/z 231.9/188.0; collision energy -30.0 V and collision cell exit potential -11.0 V for m/z 177.4/161.0; collision energy 30.6 V and collision cell exit potential 7.0 V for m/z 289.2/140.3; collision energy 25.8 V and collision cell exit potential 3.3 V for m/z 247.2/98.2; collision energy 29.0 V and collision cell exit potential 16.0 V for m/z 235.2/86.2; collision energy 14.0 V and collision cell exit potential 9.9 V for m/z 184.1/166.1. Capillary voltage was set at 4.5 kV.

Statistical Analysis

All statistical analyses were run using Statistical Analysis System software (SAS Institute, NC), p-values ≤ 0.05 were treated as statistically significant unless otherwise stated. Each 0-day and 10-day sample had an n=3. Small sample sizes are usually analyzed using non-parametric tests, but non-parametric testing assumes n=5 at minimum. Parametric t-tests are therefore used to analyze differences between groups. Parametric one-way Analysis of Variance (ANOVA) F-test was performed comparing the mean percents of anesthetic remaining at 10 days. Post-hoc Tukey's t-tests were performed to determine sources of significance. Additional t-tests were also performed

to compare the mean concentrations and mean percents of epinephrine remaining within the lidocaine and Marcaine at 10 days, and to compare the mean concentrations and mean percents of ampicillin and clindamycin remaining at 10 days.

RESULTS

After 10 days of storage in aggravated conditions using the MIL-STD-810 (Figure 1A), samples were tested for degradation using an LC-MS. Results of the study are shown in Figure 2. Stressed drugs were compared to the control samples (stored per manufacturer directions), and total drug percent remaining was calculated. Each drug underwent three separate trials in the environmental chamber, and the three trials were averaged together. Minor degradation is defined as under 10%.

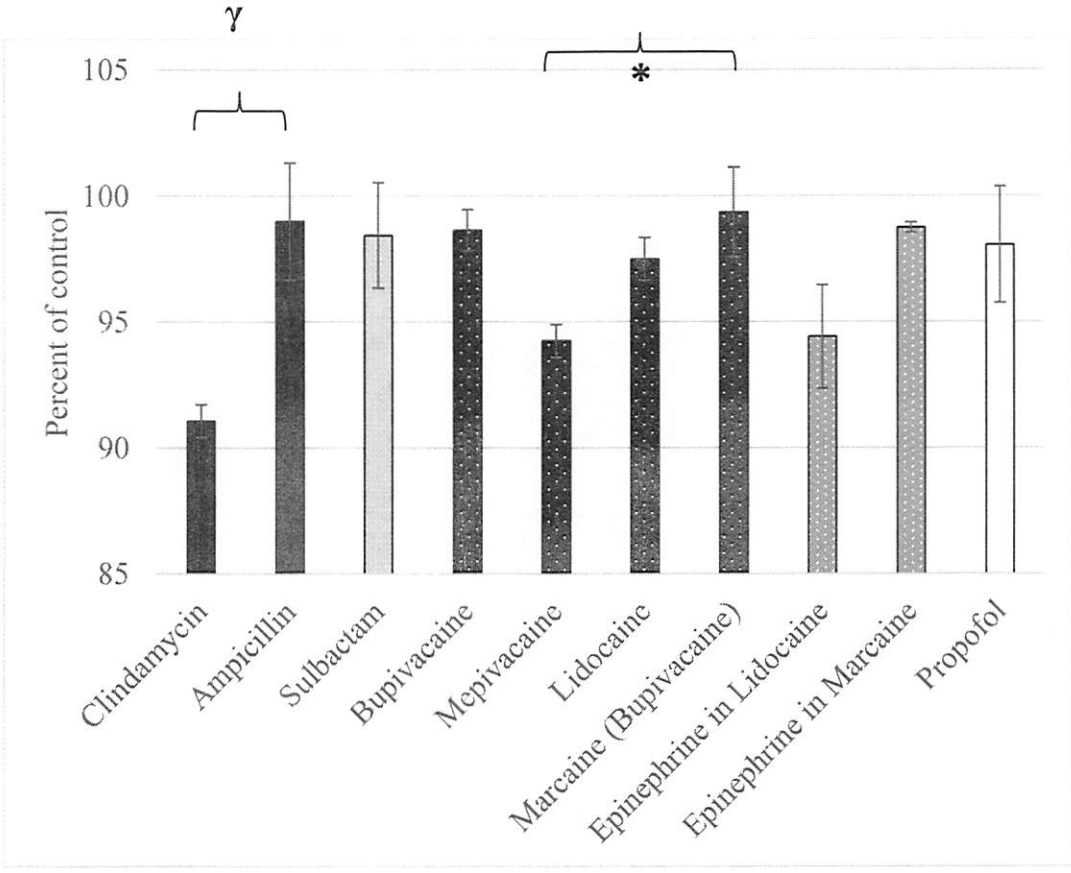


Figure 2. 10-Day Drug degradation. Shown as a percent of total drug remaining compared to day 0 control. Solid black indicates antibiotics (**γ:** clindamycin vs. ampicillin, p=0.054), solid grey is the antibiotic additive sulbactam, black bars with white dots indicate local anesthetics (*:

mepivacaine vs. Marcaine, p=0.047), grey bars with white dots are the epinephrine additive, and solid white represents the general anesthetic. Error bars indicate SEM, n=3 for all samples.

Antibiotics

Two antibiotics were environmentally stressed, ampicillin and clindamycin, and the percent of degradation was compared. After 10 days of storage in aggravated conditions, there was minor degradation of clindamycin (Figure 3) and ampicillin with sulbactam (Figure 4), the comparison approached significance (8.9% ± 1.1 for clindamycin, 1.0% ± 4.0 for ampicillin, p=0.054). The sulbactam in the ampicillin degraded 1.5% ± 3.6.

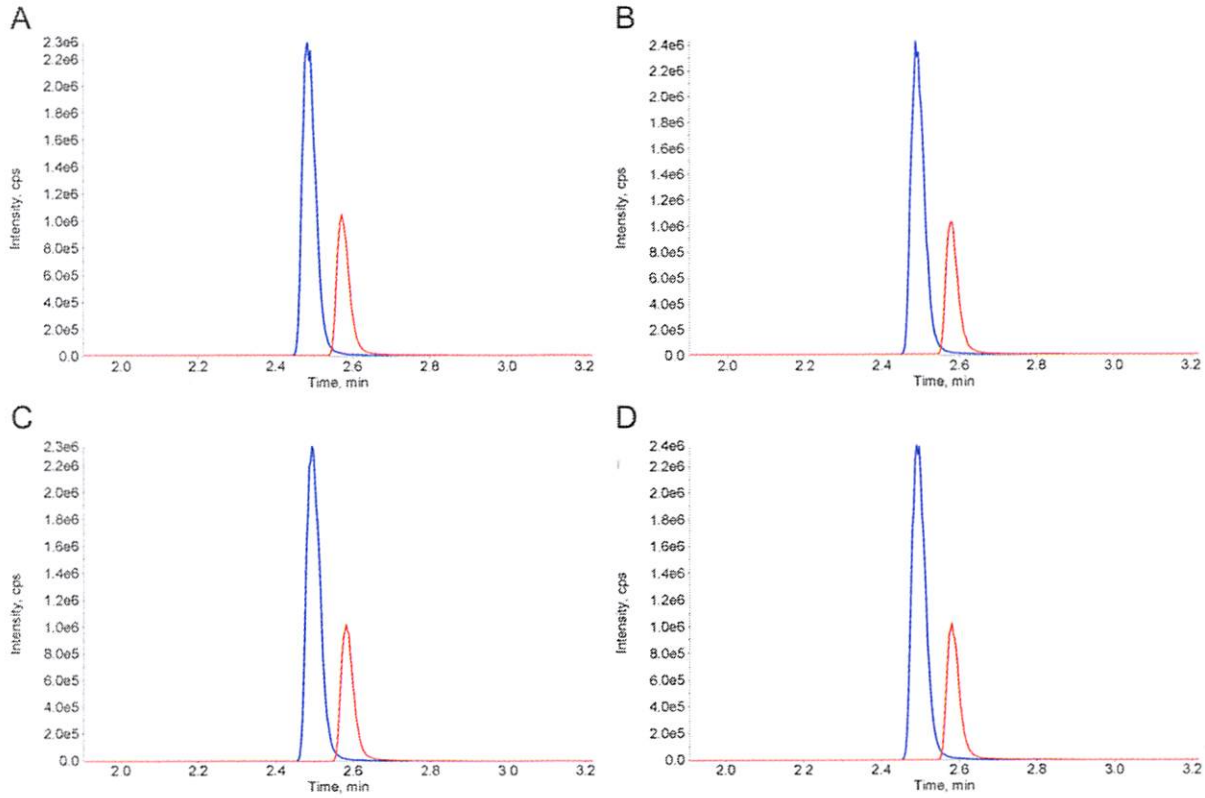


Figure 3. LC-MS MRM quantification of clindamycin (red) with cefazolin (blue) as Internal Standard. Day 0 (A) sample was used as control and three independent repetitions of day 10 sample in simulated field storage were shown as in B, C and D, respectively. Degradation was calculated by comparing the peak area ratios.

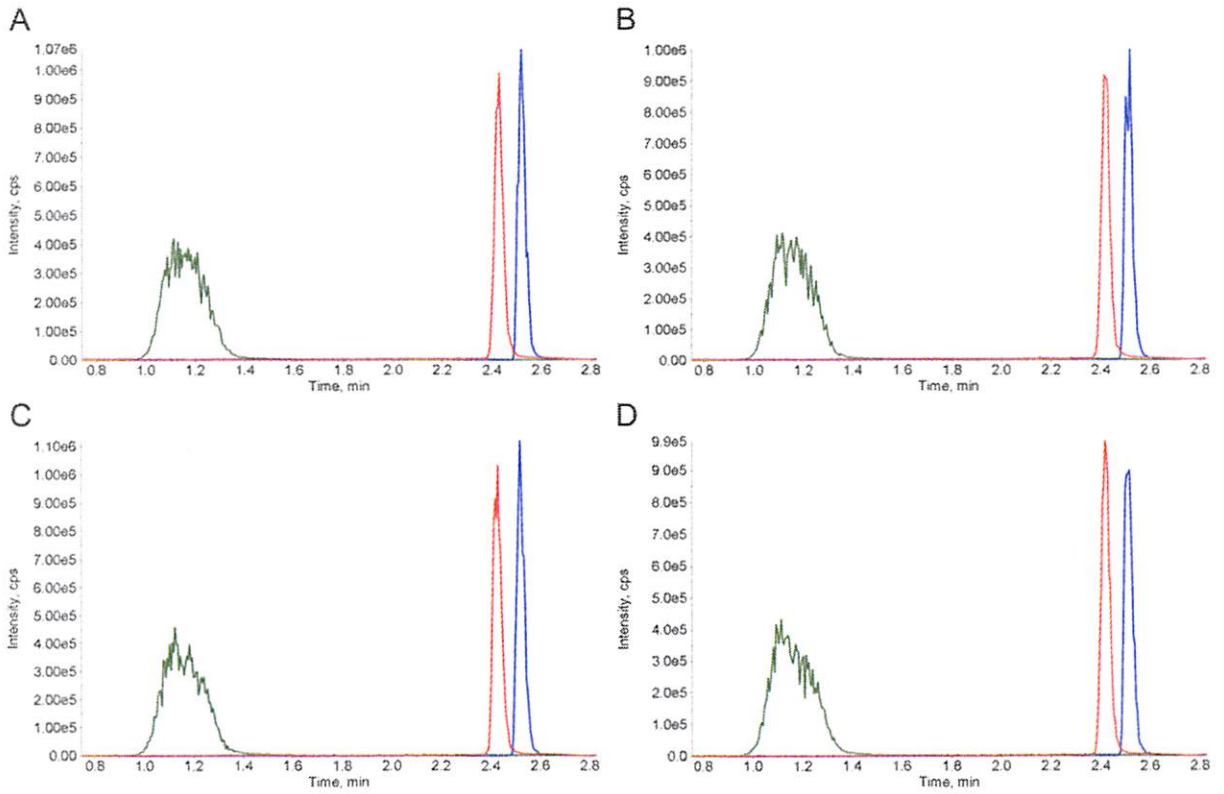


Figure 4. LC-MS MRM quantification of ampicillin (blue) and sulbactam (red) with gallic acid (green) as Internal Standard. Day 0 (A) sample was used as control and three independent repetitions of day 10 sample in simulated field storage were shown as in B, C and D, respectively. Degradation was calculated by comparing the peak area ratios.

Local Anesthetics

Four local anesthetics were environmentally stressed, two contained the additive epinephrine. When comparing the degradation of the four local anesthetics using a one-way ANOVA F-test, we found there was some significant difference between the anesthetics ($p=0.048$). Post-hoc analysis using Tukey's t-test determined that Marcaine (Figure 6) had degraded more than mepivacaine (Figure 8) ($0.6\% \pm 3.1$ for Marcaine, $5.7\% \pm 1.1$ for mepivacaine, $p=0.047$). Although no other comparison between the local anesthetics were statistically significant, measurable degradation had occurred for bupivacaine (Figure 5) ($1.3\% \pm 1.4$) and lidocaine (Figure 7) ($2.5\% \pm 1.5$). An approach towards significance was seen in the difference of degradation between bupivacaine and mepivacaine ($p=0.089$). We also measured the degradation of the epinephrine additive in our lidocaine (Figure 9) and Marcaine (Figure 10) on a separate run

measuring minimal degradation (5.6% ± 3.6 and 1.2% ± 0.3, respectively), but no statistical significance was found when they were compared.

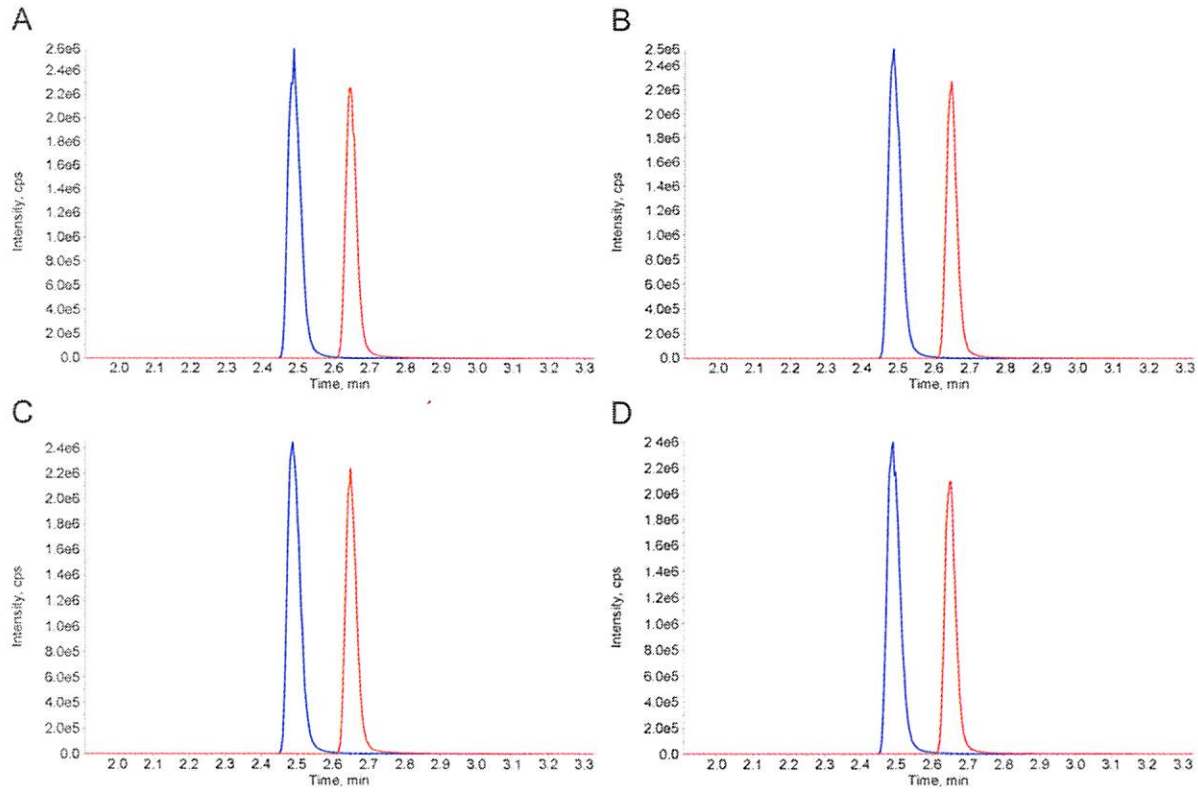


Figure 5. LC-MS MRM quantification of bupivacaine (red) with cefazolin (blue) as Internal Standard. Day 0 (A) sample was used as control and three independent repetitions of day 10 sample in simulated field storage were shown as in B, C and D, respectively. Degradation was calculated by comparing the peak area ratios.

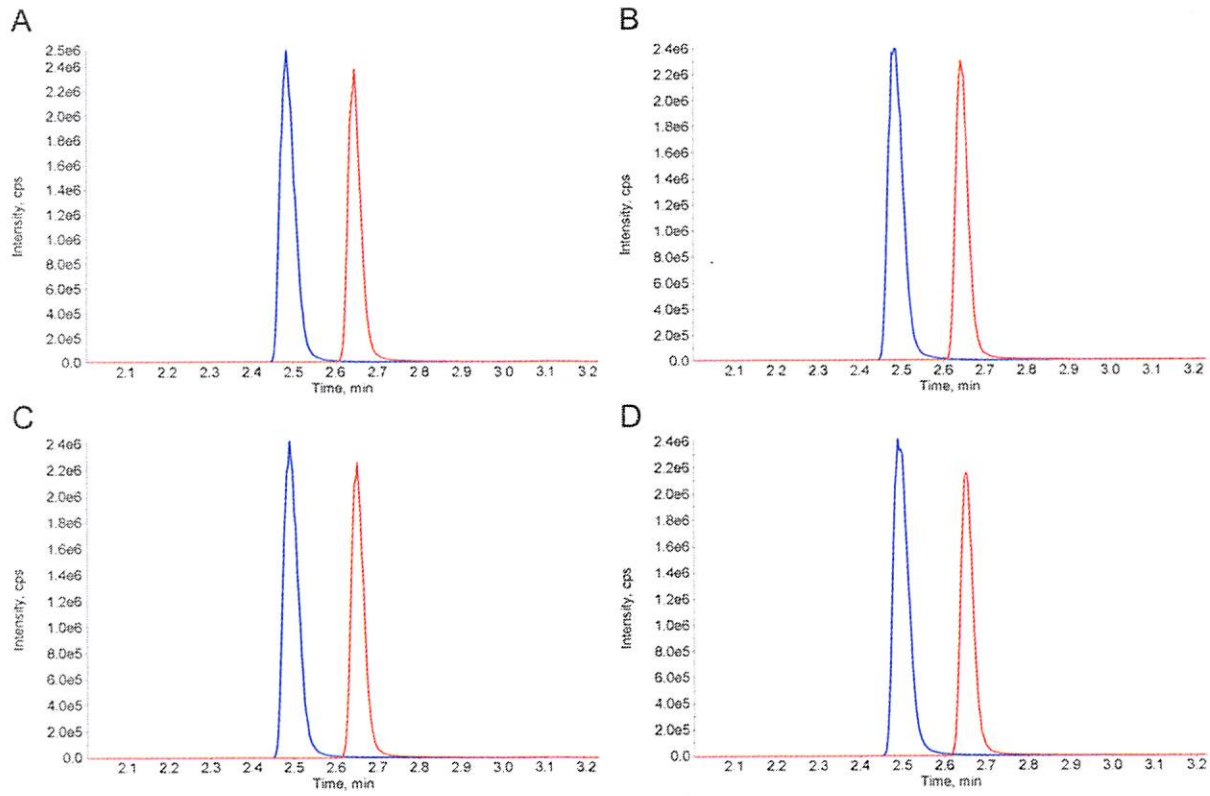


Figure 6. LC-MS MRM quantification of Marcaine (red) with cefazolin (blue) as Internal Standard. Day 0 (A) sample was used as control and three independent repetitions of day 10 sample in simulated field storage were shown as in B, C and D, respectively. Degradation was calculated by comparing the peak area ratios.

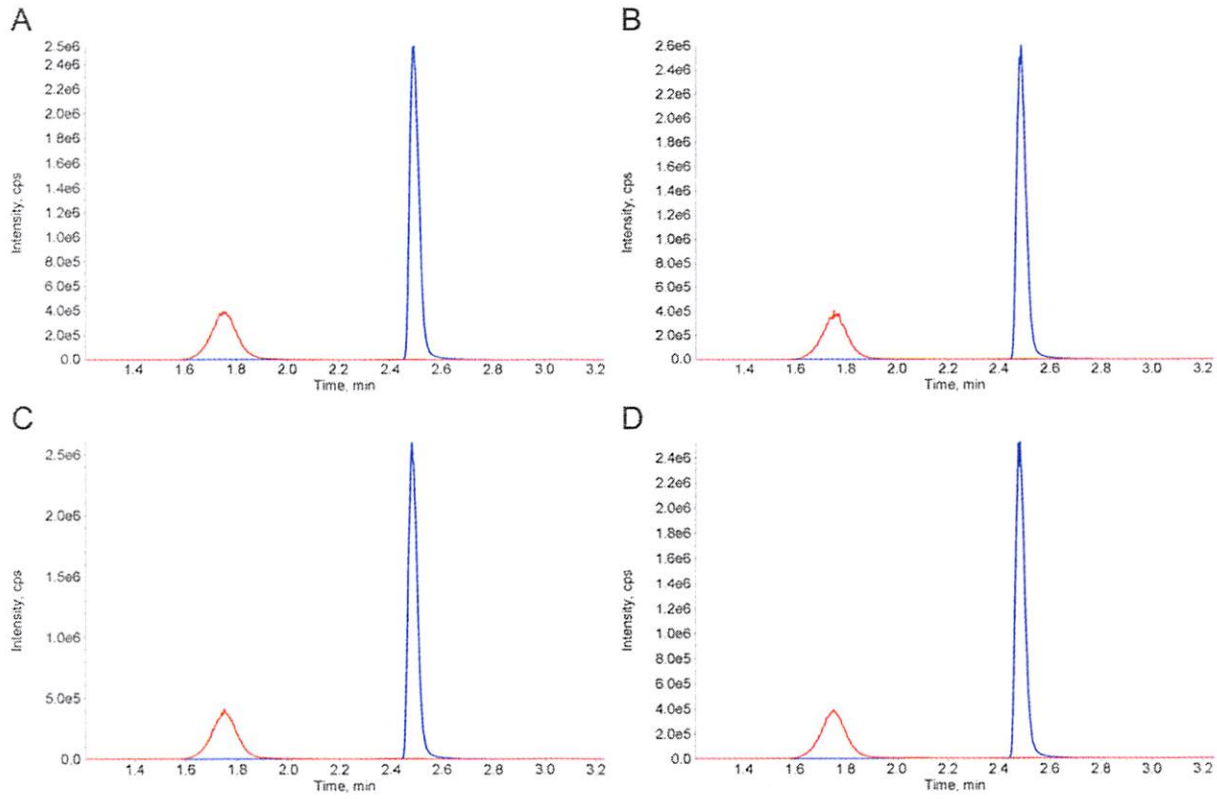


Figure 7. LC-MS MRM quantification of lidocaine (red) with cefazolin (blue) as Internal Standard. Day 0 (A) sample was used as control and three independent repetitions of day 10 sample in simulated field storage were shown as in B, C and D, respectively. Degradation was calculated by comparing the peak area ratios.

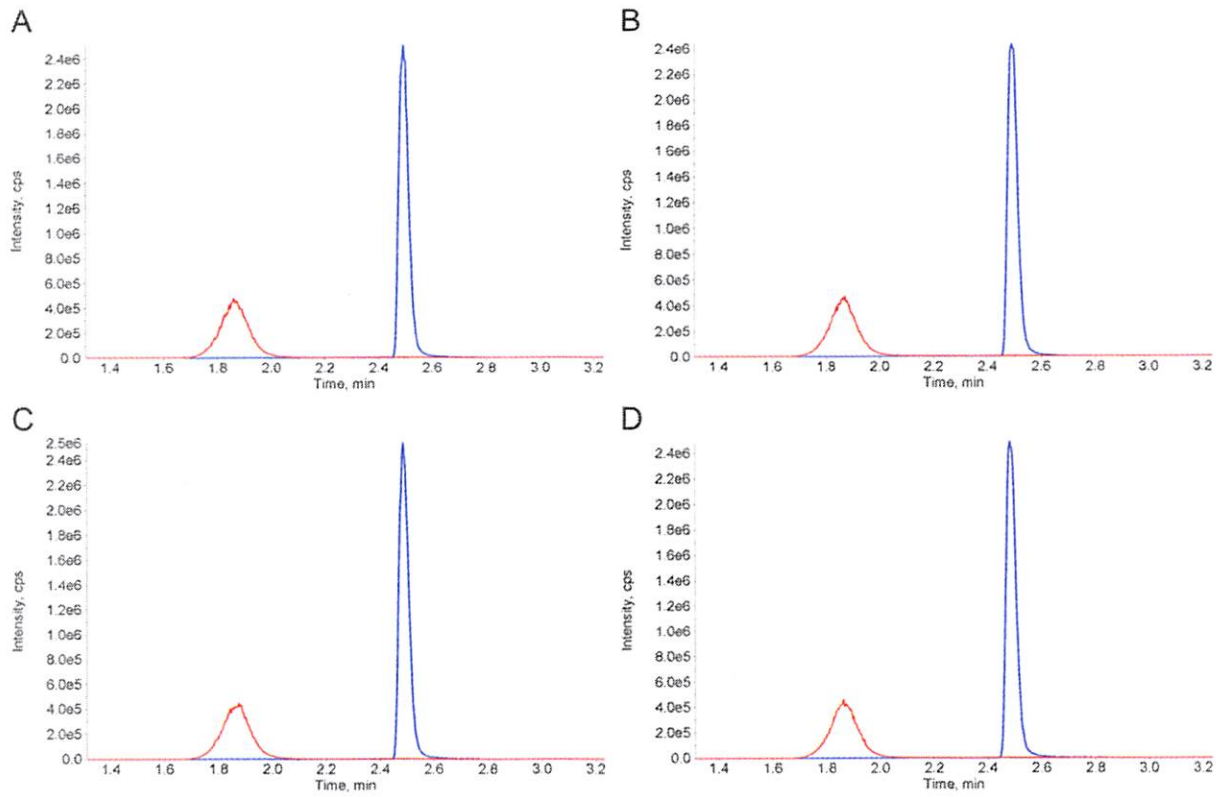


Figure 8. LC-MS MRM quantification of mepivacaine (red) with cefazolin (blue) as Internal Standard. Day 0 (A). sample was used as control and three independent repetitions of day 10 sample in simulated field storage were shown as in B, C and D, respectively. Degradation was calculated by comparing the peak area ratios.

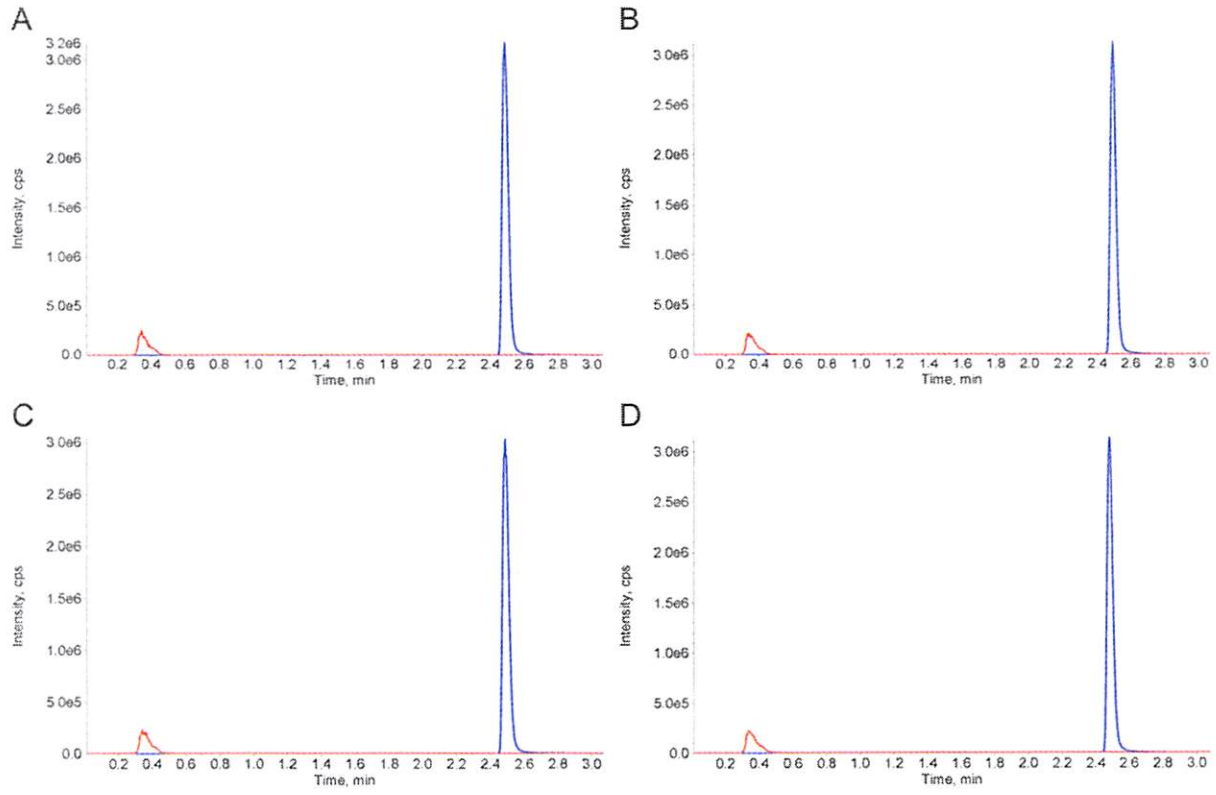


Figure 9. LC-MS MRM quantification of epinephrine in lidocaine (red) with cefazolin (blue) as Internal Standard. Day 0 (A) sample was used as control and three independent repetitions of day 10 sample in simulated field storage were shown as in B, C and D, respectively. Degradation was calculated by comparing the peak area ratios.

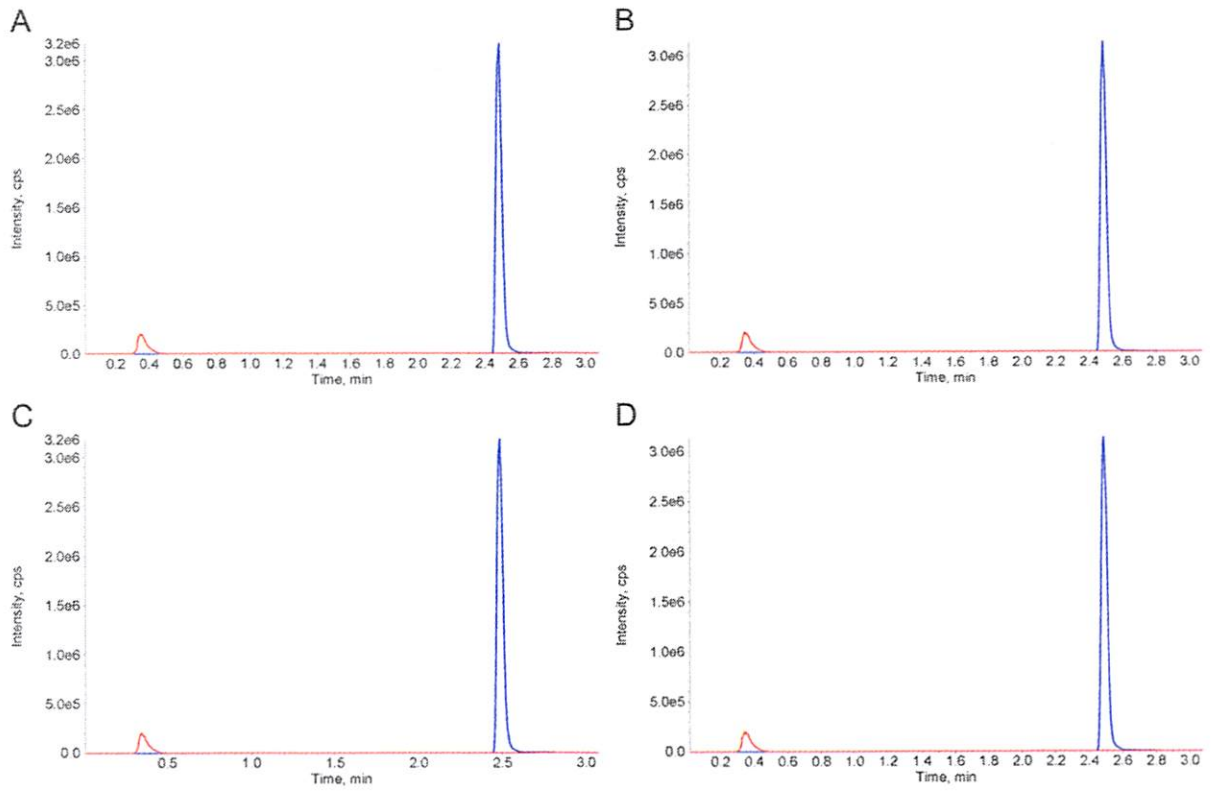


Figure 10. LC-MS MRM quantification of epinephrine in Marcaine (red) with cefazolin (blue) as Internal Standard. Day 0 (A) sample was used as control and three independent repetitions of day 10 sample in simulated field storage were shown as in B, C and D, respectively. Degradation was calculated by comparing the peak area ratios.

General Anesthetic

Propofol was the only general anesthetic tested during this project. After 10 days 1.9% ± 4 degradation had occurred (Figure 11). No inferential statistics were run to compare this degradation to other drugs in this project.

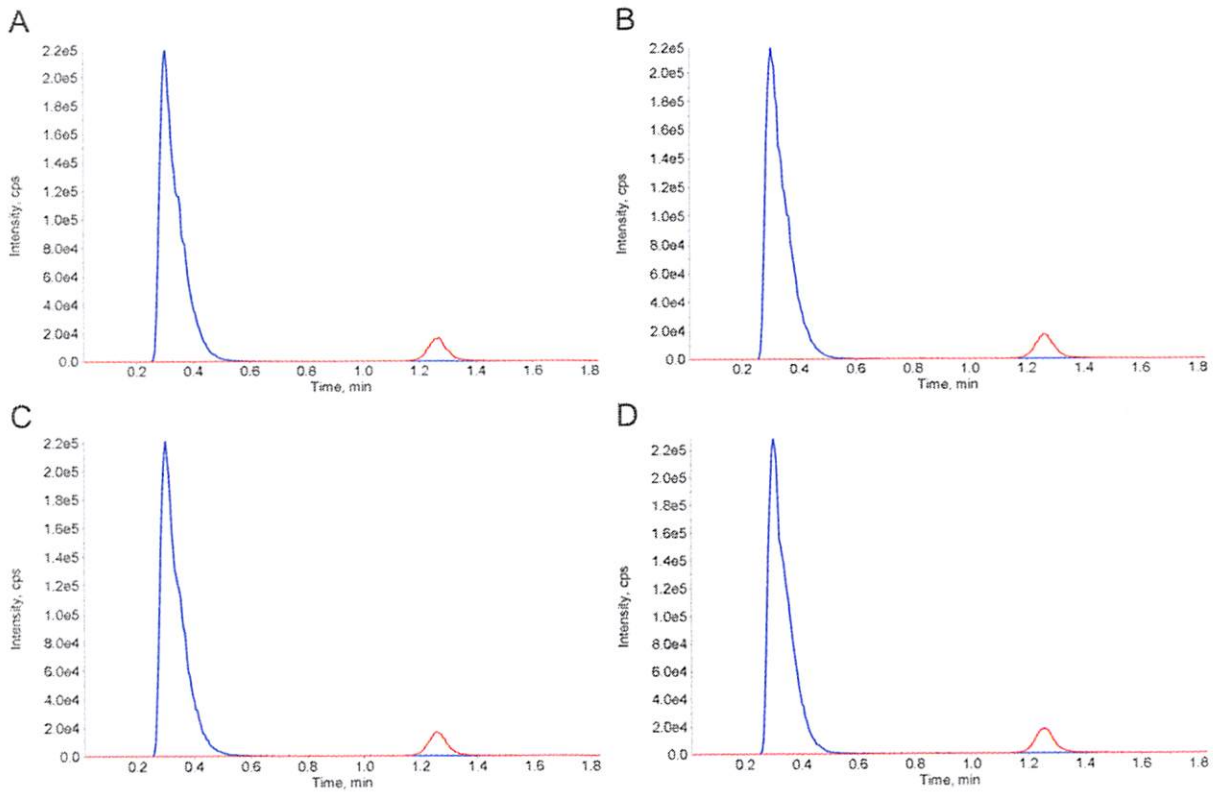


Figure 11. LC-MS MRM quantification of propofol (red) with ampicillin (blue) as Internal Standard. Day 0 (A) sample was used as control and three independent repetitions of day 10 sample in simulated field storage were shown as in B, C and D, respectively. Degradation was calculated by comparing the peak area ratios.

DISCUSSION

The main objective of this study was to determine, in a short period of time, if certain antibiotics and anesthetics used in dental procedures and oral surgeries were susceptible to degradation in hot and humid conditions experienced in a military setting. Drug manufacturers perform stability testing within the narrow range of a climate-controlled scenario, and to our knowledge no testing had been done previously to assess the result of exposure to hot and humid conditions. We achieved our objective by artificially inducing degradation through simulated austere conditions in an environmental chamber for 10 days. The military standard of testing we followed advised that 10 days under aggravated conditions has historically been sufficient to artificially induce degradation in medical drugs and materials. The advantage of this method is to produce results quickly, which would allow us to identify drugs that generally exhibit

temperature/humidity effects sooner than in a natural setting or other induced procedures. This allows us to test a broad range of drugs and potentially narrow down a small number that require further analysis. The disadvantage is that the effects may not accurately represent those that would be experienced in actual service. The intention of this study is not to establish new standards of use for these drugs or justify the use of drugs that were known to have extreme temperature excursions beyond manufacturer recommendations.

There are multiple ways a clinician can deliver antibiotics to a patient during or following a dental procedure or oral surgery. After dental procedures, solid pills are generally the standard delivery method, while after oral surgeries, like implants, an antibiotic is injected prophylactically. We chose to test injectable antibiotics since they are less stable than the solid pill forms and more susceptible to degradation from environmental factors. Clindamycin and ampicillin with sulbactam both exhibited minor degradation after the 10-day trial. Clindamycin was the most susceptible drug during this study (8.9% degradation), and we did see an approach towards significance in comparing clindamycin and ampicillin degradation ($p=0.054$).

We expected greater degradation from the test conditions based on environmental exposure and body temperature research that had be done previously on similar drugs, especially with regards to epinephrine (Larson et al., 1991). We measured very little degradation from each of the local anesthetics and only the degradations comparing mepivacaine and Marcaine had a p value less than 0.05 when local anesthetics were compared to each other ($p=0.047$), while bupivacaine and mepivacaine had approached significance ($p=0.089$). While the small difference in epinephrine degradation was measurable, it was not statistically significant. Due to time constraints, we were only able to run a single control test for propofol.

As mentioned above, the purpose of this study was to determine if certain drugs used in dental procedures and oral surgeries were susceptible to degradation in austere hot and humid conditions. We chose to test under aggravated testing standards with the idea that it would sufficiently cause between 5% and 20% degradation over a short period of time (Blessy, Patel, Prajapati, & Agrawal, 2014). These conditions however resulted in only three drugs deteriorating to that level (clindamycin at 8.9%, mepivacaine at 5.7%, and the epinephrine in the lidocaine at 5.6%). Our next objective will be to use different conditions within the standard to better define degradation susceptibility during transit and storage of dental and medical materials. These conditions would extend the timeframe of exposure from 10 days up to 90 days; however, the

temperature and humidity would be slightly less severe and closer simulate actual conditions in the field. We also plan to test antibiotics and anesthetics under polar conditions including freeze-thaw cycles. With recent conflicts in Eastern Europe and in Asia, many issues have resurfaced unique to cold weather operations that require future studies that facilitate military readiness. We will also expand the number of antibiotics and general anesthetics to cover all that are available and used in oral and medical surgeries.

Military Significance

The U.S. military operates in a variety of environments, including conditions not anticipated by manufacturers of civilian dental supplies or devices. Accordingly, supplies exposed to extreme temperature and relative humidity conditions during military transport and storage are not reflected in their manufacturer's estimates of performance or shelf life. The potential for unexpected and rapid declines in performance due to these difficult conditions must be evaluated. Even when drugs are shipped and stored in climate-controlled containers, temperature excursions from disruptions in power or location changes are still a concern. Injectable antibiotics, local anesthetics, and general anesthetics are fundamental for dental procedures and oral surgeries and require thorough examination to aid the clinician in supporting the warfighters return to duty. The information provided by this study demonstrates the effect of heat and humidity on some of these drugs and clinicians should understand this when deciding dosages and administration methods of these drugs.

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14. ABSTRACT

Dental restorations and oral-facial surgeries rely heavily on pharmaceuticals for successful treatment. Local pain management is essential in dental restorations and general anesthesia is the cornerstone of more invasive oral-facial surgeries. For recovery, a similarly important focus is infection prevention with the use of antibiotics. Some pharmaceuticals are known to be susceptible to degradation above room temperature, while the temperature-related drug degradation profiles of others are unknown. The U.S. military operates in a variety of environments, including conditions not anticipated by manufacturers of civilian dental supplies or devices. We achieved our objective by artificially inducing degradation through simulated austere conditions in an environmental chamber for 10 days. Liquid Chromatography-Mass Spectrometry was then used to compare the degradation of these pharmaceutical compounds that were environmentally stressed to those stored at manufacturer recommended conditions.All drugs in this study exhibited degradation less than 10%, and only three experienced more than 5%.

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